Nordic Summer School in Cancer Epidemiology
12 to 23 August, 2024
Danish Cancer Society, Copenhagen

Measures of disease frequency and effects

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Key references

IS: dos Santos Silva, I. (1999).
Cancer Epidemiology: Principles and Methods. International Agency for Research on Cancer, Lyon.

B&D: Breslow, N.E., Day, N.E. (1986).
Statistical Methods in Cancer Research Vol. II – The Design and Analysis of Cohort Studies. IARC, Lyon.

C&H: Clayton, D., Hills, M. (1993).
Statistical Models in Epidemiology. OUP, Oxford.

Internet resources on cancer statistics

- **NORDCAN:** Incidence, mortality, prevalence and survival statistics from 41 major cancers in the Nordic countries.

  Association of the Nordic Cancer Registries (ANCR), Danish Cancer Society `https://nordcan.iarc.fr/en`

  Engholm, G. *et al.* (2010) NORDCAN – a Nordic tool for cancer information, planning, quality control and research. *Acta Oncol* **49**: 725-736.

- **Global Cancer Observatory (GCO):** An interactive web-based platform presenting global cancer statistics to inform cancer control and research.

  International Agency for Research on Cancer (IARC); `http://gco.iarc.fr/`

INTRODUCTION

What is epidemiology?

Some textbook definitions:

- "study of the **distribution** and **determinants** of disease **frequency** in man"
  (MacMahon and Pugh (1970). *Epidemiology*)
- "study of the distribution and determinants of health related **states** and **events** in specified populations, . . ."
  (Porta *et al.* (ed.) (2014). *Dictionary of Epidemiology*)
- "discipline on principles of **occurrence** research in medicine"
  (Miettinen (1985). *Theoretical Epidemiology*)

Different epidemiologies

- **descriptive** epidemiology – monitoring & surveillance of diseases for planning of health services
  – a major activity of cancer registries.
- **etiologic** or "analytic" epidemiology – study of cause-effect relationships
- **disease** epidemiologies – *e.g.* of cancer, cardiovascular diseases, infectious diseases, mental disorders, . . .
- **determinant-based** epidemiologies
  – *e.g.* occupational epidemiology, nutritional epidemiology, . . .
- **clinical** epidemiology: study of diagnosis, prognosis and effectiveness of therapies in patient populations
  – basis of evidence-based medicine

Frequency (from Webster's Dictionary)

Etymology: < L *frequentia* = assembly, multitude, crowd.

2. rate of occurrence
3. *Physics*. number of . . . regularly occurring events . . . in unit of time,
5. *Statistics*. the number of items occurring in a given category. Cf. **relative frequency**.

These meanings are all relevant in epidemiology.

But what are **rate** and **occurrence**?

Cancer in Norden 1997 (NORDCAN)

Frequency of cancer (all sites excl. non-melanoma skin) in Nordic male populations expressed by different measures.

	New cases	Crude rate	ASR (World)	Cumul. risk	SIR
Denmark	11 787	452	281	27.8	104
Finland	10 058	401	269	26.5	101
Iceland	633	464	**347**	**32.6**	**132**
Norway	10 246	**469**	294	29.4	109
Sweden	**19 908**	455	249	25.4	93

- Where is the frequency truly **highest**, where lowest?
- What do these measures mean?

Questions on frequency & occurrence

How many women in Denmark

- are carriers of breast cancer today at 12? – **prevalence**
- will contract a new breast ca. during 2024? – **incidence**
- die from breast ca. in 2024? – **mortality**
- will be alive after 5 years since diagnosis among those getting breast ca. in 2024? – **survival**
- are cured of breast cancer during 2024? – **cure**

What are the **proportions** or/and **rates** of the occurrence of these **states** and **events**?

Questions on risk

- How great are the **risks** of these events?
- Is the risk of breast ca. among nulliparous **greater than** among parous women?
- What are the **excess** and **relative risks** for nulliparous compared to parous women?
- Does long-term use of menopausal hormone therapy (MHT) have a **causal effect** on the risk of breast cancer, and how strong is this effect?
- What is the **exposure-response relationship** between MHT use and breast cancer in terms of type, level and duration of exposure?

Descriptive and causal questions

- **Descriptive**: What is the occurrence in the next 10 y of breast cancer in 50-59 y old women having been $>$ 5 y on specific MHT as compared with women who had no MHT at all?
- **Causal**: What is the 10-y risk of breast cancer in a population of 50-59 y old women, *if they initiated* MHT *as compared with* what the risk in these women *would be, if they did not* start MHT at all?

NB. Causal question comparison of **potential outcomes** or **counterfactual conditionals**.

Challenge: *How to find a* **comparable** *group of unexposed to an exposed group in real life*?

What is risk?

Phrase "Risk of disease S" may refer to different concepts:

(i) **probability** of *getting* S during a given **risk period**
→ **incidence** probability,

(ii) **rate** of change of that probability
→ **hazard** or intensity, or

(iii) **probability** of *carrying* S at a given *time point*
→ **prevalence** probability.

Most commonly meaning (i) is attached with risk.

NB. "Risk" should not be used in the meaning of **risk factor**.

However, in **risk assessment** literature: "hazard" is often used in that meaning.

In statistics, though, hazard refers to (ii): change of probability per unit time.

Risks are conditional probabilities

- There are no “absolute risks”.
- All risks are conditional on a multitude of factors, like
  - length of risk period (*e.g.* next week or lifetime),
  - age and gender,
  - genetic constitution,
  - health behaviour & environmental exposures.
- In principle each individual has an own quantitative value for the risk of given disease in any defined risk period, depending on his/her own risk factor profile.
- Yet, these individual risks are latent and unmeasurable.
- **Average risks** of disease in large groups sharing common characteristics (like gender, age, smoking status) are estimable from appropriate epidemiologic studies by pertinent **measures of occurrence**.

BASIC MEASURES OF FREQUENCY OR OCCURRENCE

Quantification of the occurence of disease (or any other health-related state or event) requires specification of:

(1) what is meant by a **case**, *i.e.*, an individual in a population who has or gets the disease

– more generally: possesses the state or undergoes the event of interest.

⇒ challenge to accurate diagnosis and classification!

(2) the **population** from which the cases originate.

(3) the **time point** or **period** of observation.

Types of occurrence measures

- Longitudinal – **incidence** measures: incidence rate & incidence proportion
- Cross-sectional – **prevalence** measures.

General form of frequency or occurrence measures

$$\frac{\text{numerator}}{\text{denominator}}$$

Numerator: number of cases observed in the population.

Denominator: generally proportional to the size of the population from which the cases emerge.

Numerator and denominator must cover the
same population, and the *same period* or *same time point*.

Incidence measures

- **Incidence proportion** (Q) over a fixed *risk period*:

$$Q = \frac{\text{number of incident (new) cases during period}}{\text{size of pop'n at risk at start of the period}}$$

Also called **cumulative incidence** (even "risk"; *e.g.* in **IS**).

NB. "Cumulative incidence" has other meanings, too.

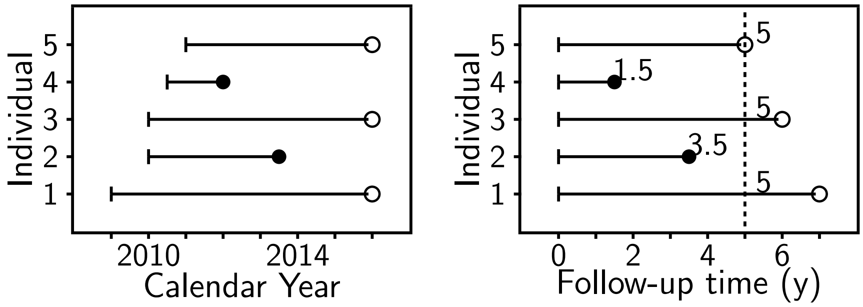
- **Indidence rate** (I) over a defined observation period:

$$I = \frac{\text{number of incident (new) cases during period}}{\text{sum of follow-up times of pop'n at risk}}$$

Also called **incidence density**.

Example: Follow-up of a small cohort

| = entry, ○ = exit with censoring; outcome not observed,
● = exit with outcome event (disease onset) observed



Complete follow-up in the 5-year risk period ⇒ can calculate both:

$$\begin{aligned}\text{Inc. rate} &= \frac{2 \text{ cases}}{5+3.5+5+1.5+5 \text{ years}} = 10 \text{ per } 100 \text{ years},\\ \text{Inc. prop.} &= 2/5 = 0.4 \text{ or } 40 \text{ per cent.}\end{aligned}$$

Properties of incidence proportion

- Dimensionless quantity ranging from 0 to 1 (0% to 100%) = *relative frequency*,
- Estimates the average theoretical **risk**, *i.e.* the probability of the outcome occurring during the risk period, in the **population at risk** – *i.e.* among those who are still free from the outcome at the start of the period.
- Simple formula valid when the follow-up time is fixed & equals the risk period, and when there are no **competing events** or **censoring**.
- Competing events & censoring ⇒
Calculations need to be corrected using special methods of survival analysis.

Properties of incidence rate

- Like *a frequency* quantity in physics; measurement unit: *e.g.* Hz = 1/second, 1/year, or 1/1000 y.
- Estimates the average underlying **intensity** or **hazard rate** of the outcome in a population,
- Estimation accurate in the **constant hazard model**,
- Calculation straightforward also with competing events and censored observations.
- Hazard usually depends on age ⇒ **age-specific** rates needed.
- Incidence proportions can be estimated from rates. In the constant hazard model with no competing risks:

$$Q = 1 - \exp(-I \times \Delta) \approx I \times \Delta$$

Competing events and censoring

The outcome event of interest (*e.g.* onset of disease) is not always observed for all subjects during the chosen risk period.

- Some subjects die (from other causes) before the event.

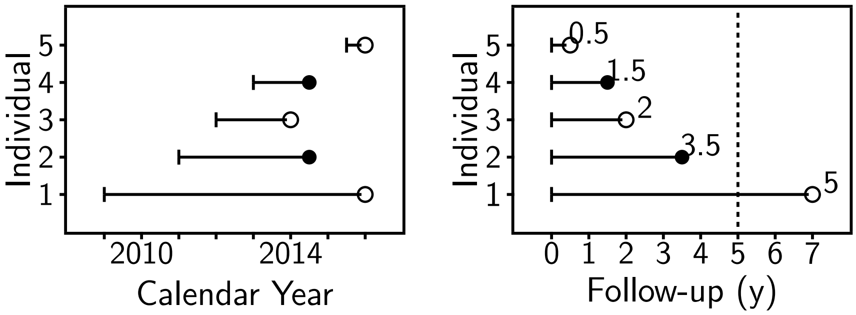
  ⇒ **Competing event**, after which the outcome can no more occur.

- Others emigrate and escape national disease registration, or the whole study is closed "now", prematurely interrupting the follow-up of them.

  ⇒ **Censoring**, **withdrawal**, or **loss to follow-up**

Competing events and censorings require special statistical treatment in estimation of incidence and risk.

Follow-up of another small cohort



Two censored observations ⇒ the rate can be calculated:

$$I = 2/12.5 \text{ y} = 16 \text{ per } 100 \text{ years}$$

but the 5-year incidence proportion Q **IS NO MORE** 2/5 !

Yet, with constant rate and no competing risks, the incidence proportion is:

$$Q = 1 - \exp(-5 \times 2/12.5) = 0.55 \text{ (or 55\%)}$$

Person-years in dynamic populations

With a **dynamic** study population, individual follow-up times are always variable and impossible to measure accurately.

Common approximation – **mid-population** principle:

(1) Let the population size be N_{t-1} at start and N_t at the end of the observation period t with length u_t years,

(2) Mid-population for the period: $\bar{N}_t = \frac{1}{2} \times (N_{t-1} + N_t)$.

(3) Approximate person-years: $\widetilde{Y}_t = \bar{N}_t \times u_t$.

NB. The actual study population often contains some already affected, thus not belonging to the population at risk. With rare outcomes their influence is small.

Male person-years in Finland 1991-95

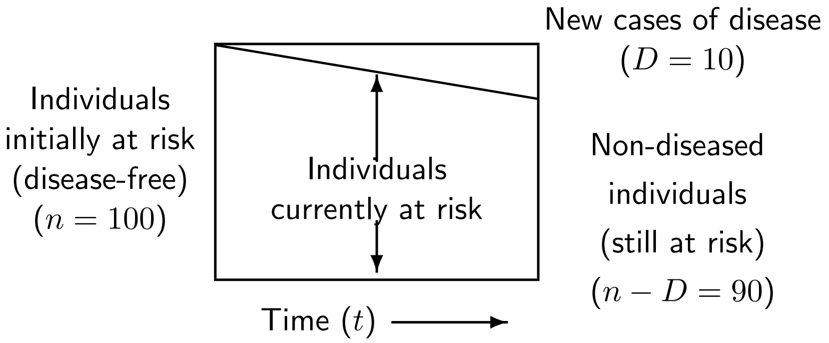
Total male population (1000s) on 31 December by year:

1990	1991	1992	1993	1994	1995
2431	2443	2457	2470	2482	2492

Approximate person-years (1000s) in various periods:

1992:	$\frac{1}{2} \times (2443 + 2457) \times 1 =$	2450
1993-94:	$\frac{1}{2} \times (2457 + 2482) \times 2 =$	4937
1991-95:	$\frac{1}{2} \times (2431 + 2492) \times 5 =$	12307.5

Incidence proportion, rate, and odds (IS, Ex 4.5)



Assuming a risk period of 1 year with complete follow-up:

$$\begin{aligned} \text{Incidence proportion } Q &= 10/100 = 0.10 = 10\% \\ \text{Incidence rate } I &= 10/95 \text{ y} = 10.5 \text{ per } 100 \text{ y} \\ \textbf{Incidence odds } Q/(1-Q) &= 10/90 = 0.11 = 11 \text{ per } 100 \end{aligned}$$

Approximate relations btw measures

With sufficiently

- "short" length Δ of risk period and
- "low" risk (say $Q < 5\%$)

the incidence proportion Q, rate I and odds are approximately related as follows:

$$\frac{Q}{1-Q} \approx Q \approx I \times \Delta$$

The "**rare disease assumption**".

Mortality

Cause-specific mortality from disease S is described by **mortality rates** defined like incidence rates, but

- cases are *deaths* from S, and
- follow-up is extended until death or censoring.

Cause-specific **mortality proportions** must be corrected for the incidence of **competing causes of death**

Total mortality:

- cases are deaths from any cause.

Mortality depends on the incidence and the **prognosis** or **case fatality** of the disease, *i.e.* the **survival** of those affected by it.

Prevalence measures

Point prevalence or simply **prevalence** P of a health state C in a population at a given **time point** t is defined

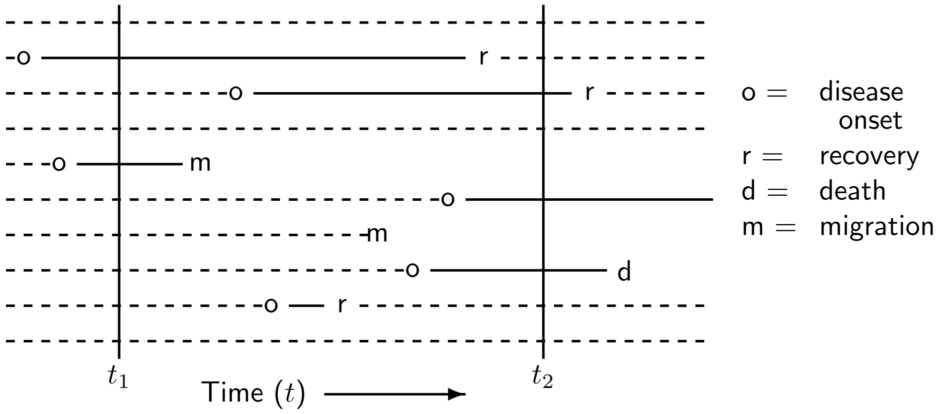
$$P = \frac{\text{number of existing or prevalent cases of } C}{\text{size of the whole population}}$$

This is calculable from a cross-sectional study base.

Period prevalence for period from t_1 to t_2 is like P but

- numerator refers to all cases prevalent already at t_1 plus new cases occurring during the period, and
- denominator is the population size at t_2.

Example 4.1 (IS: p. 59)



Prevalence at time t_1 : $2/10 = 0.2 = 20\%$
Prevalence at time t_2 : $3/8 = 0.38 = 38\%$
Period prevalence: $5/8 = 0.62 = 62\%$

Prevalence and incidence are related

Point prevalence of S at given time point t depends on the

(a) *incidence* of new cases of S before t, and the
(b) *duration* of S, depending in turn on the probability of *cure* or recovery from S, or *survival* of those affected

typically in a complicated way.

Simple special case: In a **stationary** ("stable") population, the

prevalence (P), incidence (I), and average duration ($\bar{d}$) of S

are related

$$P = \frac{I \times \bar{d}}{I \times \bar{d} + 1} \quad \approx \quad I \times \bar{d}$$

The approximation works well, when $P < 0.1$ (10%).

Prevalence of cancer?

- How do we know, whether and when cancer is cured?

  ⇒ Existing or prevalent case problematic to define.

- NORDCAN: Prevalence of cancer C at time point t in the target population refers to the

  - number & proportion of population members who

  (a) are alive and resident in the population at t, and

  (b) have a record of an incident cancer C diagnosed before t.

- **Partial prevalence:** Cases limited to those diagnosed during a fixed time in the past; *e.g.* within 1 y (initial treatment period), 3 y (clinical follow-up), or 5 y (cure?).

Ex: Cancer with poor and with good prognosis

Age-standardized[a] incidence, mortality, prevalence, and survival for cancers of kidney and thyroid in women of Finland.

	Kidney	Thyroid
Incidence rate in 2011 (per 10^5 y)	12	11
Mortality rate in 2011 (per 10^5 y)	5	1
Prevalence on 31.12.2011 (per 10^5)	92	198
– diagnosed $<$ 1 y ago	*9*	*10*
– diagnosed $<$ 3 y ago	*24*	*29*
– diagnosed $<$ 5 y ago	*35*	*47*
– diagnosed $>$ 5 y ago	*57*	*151*
5-y relative survival; cases 2004–8 (%)	64	90

[a] Standard: Nordic population in 2000

MEASURES OF EFFECT – COMPARATIVE MEASURES

- Quantification of the **association** between a determinant (risk factor) and an outcome (disease) is based on

  comparison of occurrence between the *index* ("exposed") and the *reference* ("unexposed") groups by
  - relative comparative measures (ratio)
  - absolute comparative measures (difference)
- In causal studies these are used to estimate the **causal effect** of the factor on the disease risk.

  $\Rightarrow$ **comparative measure** $\approx$ **effect measure**
- Yet, caution is needed in inferences on causal effects, as often the groups to be compared suffer from **poor comparability** $\Leftrightarrow$ **Confounding**.

Relative comparative measures

Generic name **"relative risk"** (RR) comparing occurrences between exposed (1) and unexposed (0) groups can refer to

- incidence rate ratio IR $= I_1/I_0$,
- incidence proportion ratio IPR $= Q_1/Q_0$,
- incidence odds ratio IOR $= [Q_1/(1-Q_1)]/[Q_0/(1-Q_0)]$,
- prevalence ratio PR $= P_1/P_0$, or
- prevalence odds ratio POR $= [P_1/(1-P_1)]/[P_0/(1-P_0)]$,

depending on study base and details of its design.

Incidence rate ratio IR $= I_1/I_0$ is the most commonly used comparative measure in cancer epidemiology.

Absolute comparative measures

Generic term **“excess risk”** or **“risk difference”** (RD) btw exposed and unexposed can refer to

- incidence rate difference ID $= I_1 - I_0$,
- incidence proportion difference IPD $= Q_1 - Q_0$, or
- prevalence difference PD $= P_1 - P_0$.

Use of relative and absolute comparisons

- Ratios – describe the **biological strength** of the exposure
- Differences – inform about its **public health importance**.

Example (IS, Table 5.2, p.97)

Relative and absolute comparisons between the exposed and the unexposed to risk factor X in two diseases.

	Disease A	Disease B
Incidence rate among exposed[a]	20	80
Incidence rate among unexposed[a]	5	40
Rate ratio	4.0	2.0
Rate difference[a]	15	40

[a] Rates per 100 000 pyrs.

Factor X has a stronger biological potency for disease A, but it has a greater public health importance for disease B.

Ratio measures in “rare diseases” (IS: Ex 5.13)

	Exposure	
	Yes	No
No. initially at risk	4 000	16 000
No. of cases	30	60
Person-years at risk	7 970	31 940

$$\begin{aligned}
\text{Inc. prop'n ratio} &= \frac{30/4\,000}{60/16\,000} &&= \frac{7.5 \text{ per } 1\,000}{3.75 \text{ per } 1\,000} &&= \mathbf{2.0000} \\
\text{Inc. rate ratio} &= \frac{30/7\,970 \text{ y}}{60/31\,940 \text{ y}} &&= \frac{3.76 \text{ per } 1\,000 \text{ y}}{1.88 \text{ per } 1\,000 \text{ y}} &&= \mathbf{2.0038} \\
\text{Inc. odds ratio} &= \frac{30/(4\,000-30)}{60/(16\,000-60)} &&= \frac{0.00756}{0.00376} &&= \mathbf{2.0076}
\end{aligned}$$

With low incidence these ratios are very similar.

Attributable fraction (excess fraction)

- **Measures of potential impact**:
  Combination of absolute and relative comparisons.
- When the incidence is higher in the exposed, the **attributable fraction** (AF) for the exposure or risk factor is defined as:

$$\mathsf{AF} = \frac{I_1 - I_0}{I_1} = \frac{\mathsf{RR} - 1}{\mathsf{RR}}.$$

  Also called **excess fraction** (or even “attributable risk” in old texts).
- This measure estimates the fraction out of all new cases of disease *among those exposed*, which are attributable to (or “caused” by) the exposure itself, and which thus could be avoided if the exposure were absent.

Population attributable fraction

- Suppose we ask instead:
  “How large a fraction of all cases in the population would be prevented, if the exposure were eliminated?”
- The answer to this question depends in addition on

$$p_{\mathsf{E}} = \text{ proportion of exposed in the population.}$$

- **Population attributable (excess) fraction** (PAF) is defined:

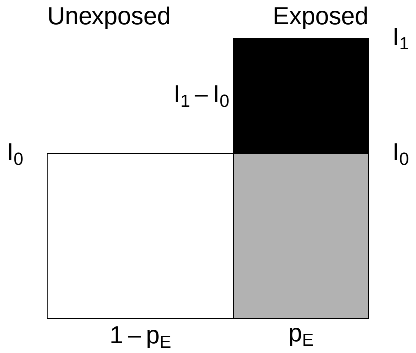
$$\mathsf{PAF} = \frac{I - I_0}{I} = \frac{p_{\mathsf{E}}(\mathsf{RR} - 1)}{1 + p_{\mathsf{E}}(\mathsf{RR} - 1)}$$

- AF: biological impact of exposure,
- PAF: impact of exposure on the population level.

Attributable fraction illustrated

- The population is divided into exposed and unexposed.
- The rate I_1 among the exposed would be I_0, *i.e.* the same as in the unexposed, if the exposure had no effect.
- The excess incidence $I_1 - I_0$ is caused by the exposure.
- $\mathsf{AF} = \dfrac{I_1 - I_0}{I_1}$,

$=$ fraction of black area out of total black + gray area.



PAF illustrated

- Total incidence I in the population – a weighted average:

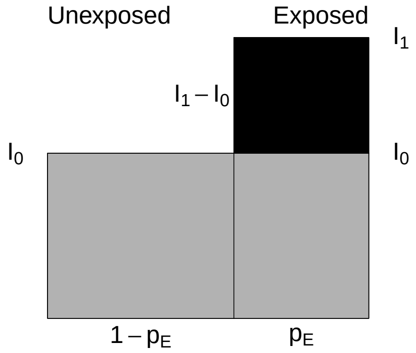
$$I = p_{\mathsf{E}} \times I_1 + (1 - p_{\mathsf{E}}) \times I_0 \quad \text{(total area)}$$

would equal I_0, if exposure had no effect

- Excess incidence caused by exposure: $I - I_0 = p_{\mathsf{E}} \times (I_1 - I_0)$ (black area).

- PAF $= \dfrac{I - I_0}{I}$,

$=$ fraction of black area out of total black + gray area.



Prevented fractions

- When the incidence in exposed is lower, we define the **prevented fraction**:

$$\text{PF} = \frac{I_0 - I_1}{I_0} = 1 - \text{RR}$$

also called **relative risk reduction**
$=$ percentage of cases prevented among the exposed due to the exposure.

- Used to evaluate the relative effect of a preventive intervention ("exposure") vs. no intervention.
- **Population prevented fraction** (PPF) combines this with the prevalence of exposure in the population:

$$\text{PPF} = \frac{I_0 - I}{I_0} = p_{\mathsf{E}} \times (1 - \text{RR}),$$

measuring the relative reduction in caseload attributable to the presence of preventive factor in the population.

Smoking on mortality by cause (IS: Ex 5.14, p. 98)

Underlying cause of death	Never smoked regularly Rate[b]	Current cigarette smoker Rate[b]	Rate ratio	Rate differ-ence[b]	Attributable fraction (%)
	(1)	(2)	(2)/(1)	(2) − (1)	$\frac{(2)-(1)}{(2)} \times 100$
Cancer					
All sites	305	656	2.2	351	54
Lung	14	209	14.9	195	93
Oesophagus	4	30	7.5	26	87
Bladder	13	30	2.3	17	57
Respiratory diseases	107	313	2.9	206	66
Vascular diseases	1037	1643	1.6	606	37
All causes	1706	3038	1.8	1332	44

[a] Data from Doll *et al.*, 1994a. [b] Age-adjusted rates per 100 000 pyrs.

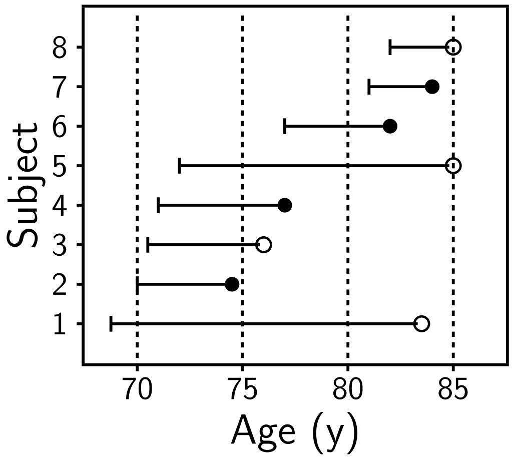
RATES IN MANY TIME SCALES

Incidence can be studied on various distinct time scales, *e.g.*

Time scale	Origin: date of ...
age	birth
exposure time	first exposure
follow-up time	entry to study
duration of disease	diagnosis

- Age is usully the strongest time-dependent determinant of health outcomes.
- Age is also often correlated with duration of "chronic" exposure (*e.g.* years of smoking).

Follow-up of a small geriatric cohort



Overall rate: 4 cases/53.5 person-years = 7.5 per 100 y.

Hides the fact that the "true" rate varies by age, being higher among the old.

Splitting follow-up into agebands

- To describe, how incidence varies by age, individual person-years from age of entry to age of exit must first be split or divided into narrower agebands.
- Usually these are based on common 5-year age grouping.
- Numbers of cases are equally divided into same agebands.
- **Age-specific incidence rate** for age group k is

$$I_k = \frac{\text{number of cases observed in ageband}}{\text{person-years contained in ageband}}$$

- Underlying assumption: **piecewise constant rates**

P-years and cases in agebands: age-specific rates

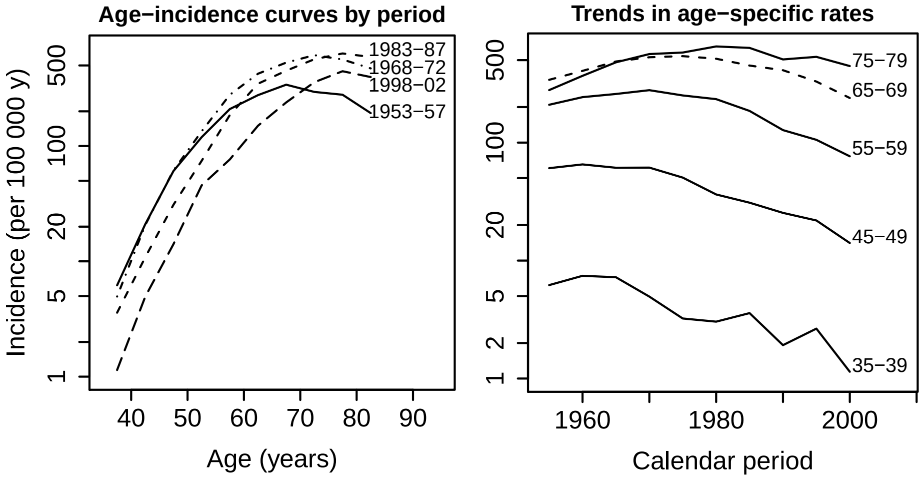
	Ageband			
Subject	70-74	75-79	80-84	Total
1	5.0	5.0	3.5	13.5
2	4.5	-	-	4.5
3	4.5	1.0	-	5.5
4	4.0	2.0	-	6.0
5	3.0	5.0	5.0	13.0
6	-	3.0	2.0	5.0
7	-	-	3.0	3.0
8	-	-	3.0	3.0
Sum of person-years	21.0	16.0	16.5	53.5
Cases	1	1	2	4
Rate (/100 y)	4.8	6.2	12.1	7.5
	Age-specific rates			overall

Ex. Lung cancer incidence in Finland by age and period (compare IS, Table 4.1)

Calendar	Age group (y)									
period	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
1953-57	21	61	119	209	276	340	295	279	193	93
1958-62	22	65	135	243	360	405	429	368	265	224
1963-67	24	61	143	258	395	487	509	479	430	280
1968-72	21	61	134	278	424	529	614	563	471	358
1973-77	16	50	134	251	413	541	629	580	490	392
1978-82	13	36	115	234	369	514	621	653	593	442
1983-87	11	31	74	186	347	450	566	635	592	447
1988-92	9	25	57	128	262	411	506	507	471	441
1993-97	7	22	48	106	188	329	467	533	487	367
1998-02	5	14	46	77	150	239	358	445	396	346

- Rows: age-incidence pattern in different calendar periods.
- Columns: Trends of age-specific rates over calendar time.

Lung cancer rates by age and period



- Age-incidence curves: overall level and peak age variable across periods.
- Time trends inconsistent across age groups.

Incidence by age, period & cohort

- **Secular trends** of specific and adjusted rates show, how the "cancer burden" has developed over periods of calendar time.

Birth cohort = people born during the same limited time interval, *e.g.* single calendar year, or 5 years period.

- Analysis of rates by birth cohort reveals, how the level of incidence (or mortality) differs between successive generations.
  – May reflect differences in risk factor levels across the cohorts.
- Often more informative about "true" age-incidence pattern than age-specific incidences of single calendar period.

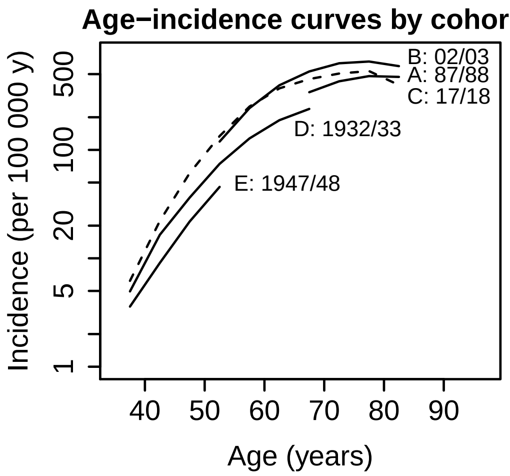
Age-specific rates by birth cohort

Calendar	Age group (y)							
period	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	
1953-57	21	61	$\boxed{119}$	209	276	$\boxed{340}$	295	279	
1958-62	$\boxed{22}$	65	135	$\boxed{243}$	360	405	$\boxed{429}$	368	
1963-67	24	$\boxed{61}$	143	258	$\boxed{395}$	487	509	$\boxed{479}$	A
1968-72	21	61	$\boxed{134}$	278	424	$\boxed{529}$	614	563	
1973-77	$\boxed{16}$	50	134	$\boxed{251}$	413	541	$\boxed{629}$	580	
1978-82	13	$\boxed{36}$	115	234	$\boxed{369}$	514	621	$\boxed{653}$	B
1983-87	11	31	$\boxed{74}$	186	347	$\boxed{450}$	566	635	
1988-92	$\boxed{9}$	25	57	$\boxed{128}$	262	411	$\boxed{506}$	507	
1993-97	7	$\boxed{22}$	48	106	$\boxed{188}$	329	467	$\boxed{533}$	C
1998-02	5	14	$\boxed{46}$	77	150	$\boxed{239}$	358	445	
			E: 1947/48			D: 1932/33			

A = synthetic cohort born around 1887/88, B: 1902/03, C: 1917/18

Diagonals reflect age-incidence patterns in various birth cohorts.

Age-incidence curves in 5 birth cohorts



Variable overall levels but fairly consistent form and similar peak age across different birth cohorts.

Split of follow-up by age and period

- Incidence of (or mortality from) disease C in special **cohort of exposed** (*e.g.* occupational group, patients on certain treatment)
  - → often compared to incidence in an external **reference** or "general" population.
- Some examples will be presented in Jóhanna's lecture on cohort studies on Thursday.
- Adjustment for age and calendar time needed, *e.g.* by comparing **observed** to **expected** cases with SIR (see p. 70-74).
  - ⇒ Cases and person-years in the study cohort must be split by more than one time scale (age).

Example (adapted from C&H, Tables 6.2 & 6.3, p. 54)

Entry and exit dates for a small cohort of four subjects

Subject	Born	Entry	Exit	Age at entry	Outcome
1	1954	1993	2002	39	Migrated
2	1974	1998	2005	24	Disease C
3	1964	1995	2011	31	Study ends
4	1970	1998	2006	28	Unrelated death

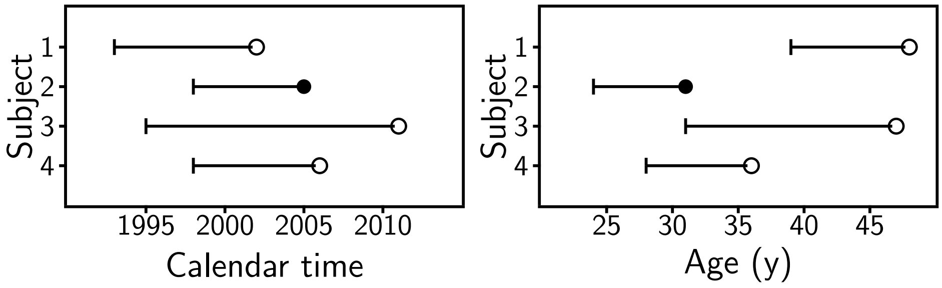
Subject 1: Follow-up time spent in each ageband

Age band	Date in	Date out	Time (years)
35–39	1993	1994	1
40–44	1994	1999	5
45–49	1999	2002	3

Example: (*cf.* C&H, Figures 6.1 & 6.2, p. 55)

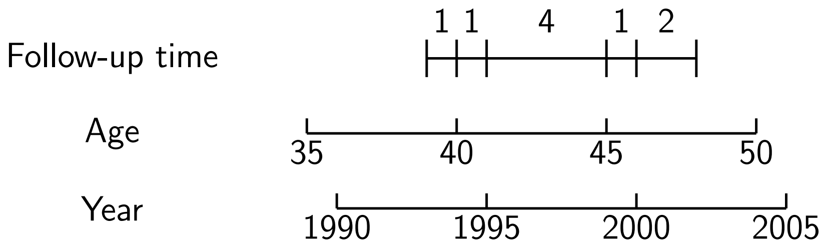
Follow-up of cohort members by calendar time and age

| entry
• exit because of disease onset (outcome of interest)
○ exit due to other reason (censoring)



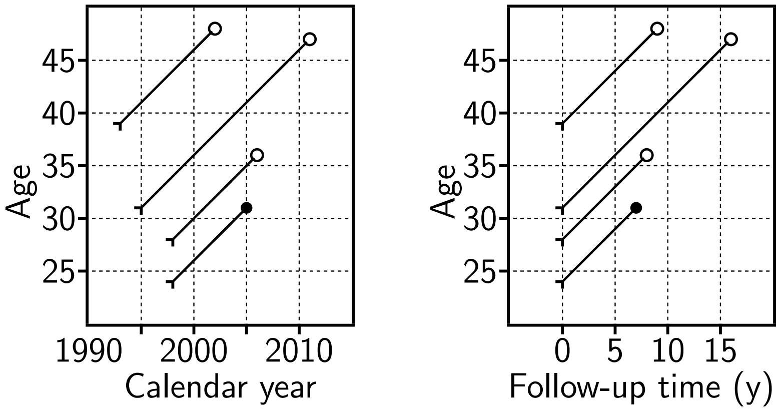
Person-years by age and period (*cf.* C&H, Figure 6.4)

Subject 1: Follow-up jointly split by age and calendar time:



This subject contributes person-time into 5 different cells defined by ageband & calendar period

Follow-up in Lexis-diagrams (*cf.* C&H, pp. 58-59)



Follow-up lines run diagonally through different ages and calendar periods.

STANDARDIZATION OF RATES

- Incidence of most cancers (and many other diseases) increases strongly by age in all populations.

  ⇒ Most of the caseload comes from older age groups.

- **Crude incidence rate** $= \dfrac{\text{total no. of new cases}}{\text{total person-years}}$,
  - numerator = sum of age-specific numbers of cases,
  - denominator = sum of age-specific person-years.

- This is generally a poor summary measure.

- Comparisons of crude incidences between populations can be very misleading, when the age structures differ.

- **Adjustment** or **standardization** for age needed!

Ex. Male stomach cancer in Cali and Birmingham (IS, Table 4.2, p. 71)

	Cali			Birmingham			
		Male	Incid.		Male	Incid.	
	Male	Popu-	Rate	Male	Popu-	Rate	
	cases	lation	$(/10^5 \mathrm{y})$	cases	lation	$(/10^5 \mathrm{y})$	
Age	1982	1984	1982	1983	1985	1983	Rate
(y)	-86	$(\times 10^3)$	-86	-86	$(\times 10^3)$	-86	ratio
0–44	39	524.2	**1.5**	79	1 683.6	**1.2**	*1.25*
45-64	266	76.3	**69.7**	1037	581.5	**44.6**	*1.56*
65+	315	22.4	**281.3**	2352	291.1	**202.0**	*1.39*
Total	620	622.9	**19.9**	3468	2 556.2	**33.9**	*0.59*

- In each age group Cali has a higher incidence
  – but the crude incidence is higher in Birmingham.
- **Is there a paradox?**

Comparison of age structures (IS, Tables 4.3, 4.4)

	% of male population			
Age	Cali	B'ham	Finland	World
(years)	1984	1985	2011	Stand.
0–44	84	66	56	74
45–64	12	23	29	19
65+	4	11	15	7
All ages	100	100	100	100

The fraction of old men greater in Birmingham than in Cali.

⇒ Crude rates are **confounded** by age.

⇒ Any summary rate must be **adjusted for age**.

Adjustment by standardisation

Age-standardised incidence rate (ASR):

$$\text{ASR} = \sum_{k=1}^{K} \text{weight}_k \times \text{rate}_k \ / \ \text{sum of weights}$$

= **Weighted average** of age-specific rates over the age-groups $k = 1, \ldots, K$.

- Weights describe the age distribution of some **standard population**.
- Standard population can be
  - real (*e.g.* one of the populations compared, or their total), or
  - fictitious (*e.g.* World Standard Population, WSP)
- Choice of standard population always more or less arbitrary.

Some standard populations:

Age group (years)	African	World	European	Nordic[a]
0–4	10 000	12 000	8 000	5 900
5–9	10 000	10 000	7 000	6 600
10–14	10 000	9 000	7 000	6 200
15–19	10 000	9 000	7 000	5 800
20–24	10 000	8 000	7 000	6 100
25–29	10 000	8 000	7 000	6 800
30–34	10 000	6 000	7 000	7 300
35–39	10 000	6 000	7 000	7 300
40–44	5 000	6 000	7 000	7 000
45–49	5 000	6 000	7 000	6 900
50–54	3 000	5 000	7 000	7 400
55–59	2 000	4 000	6 000	6 100
60–64	2 000	4 000	5 000	4 800
65–69	1 000	3 000	4 000	4 100
70–74	1 000	2 000	3 000	3 900
75–79	500	1 000	2 000	3 500
80–84	300	500	1 000	2 400
85+	200	500	1 000	1 900
Total	100 000	100 000	100 000	100 000

[a] NORDCAN population in 2000.

Stomach cancer in Cali & Birmingham

Age-standardized rates by the World Standard Population:

	Cali		Birmingham	
Age	Rate[a]	Weight	Rate[a]	Weight
0–44	1.5 ×	0.74 = 1.11	1.2 ×	0.74 = 0.89
45–64	69.7 ×	0.19 = 13.24	44.6 ×	0.19 = 8.47
65+	281.3 ×	0.07 = 19.69	202.0 ×	0.07 = 14.14
Age-standardised rate		**34.04**		**23.50**

- ASR in Cali higher – coherent with the age-specific rates.
- Summary rate ratio estimate: **standardized rate ratio**

$$\text{SRR} = \mathbf{34.0/23.5 = 1.44}.$$

- This is also called as **comparative mortality figure (CMF)**, when the outcome is death (from cause C or from all causes).

Cumulative rate and "cumulative risk"

- A neutral alternative to arbitrary standard population for age-adjustment is provided by **cumulative rate**:

$$\text{CumRate} = \sum_{k=1}^{K} \text{width}_k \times \text{rate}_k,$$

- Weights are now widths of the agebands to be included, usually up to 75 y.
- NORDCAN & GLOBOCAN use a transformation:

$$\text{CumRisk} = 1 - \text{exp}(-\text{CumRate}),$$

calling it as the **cumulative risk** of getting the disease by given age, in the absence of competing causes.

- Yet, in reality competing events are present, so the probability interpretation of CumRisk is somewhat problematic.

Stomach cancer in Cali & Birmingham

From age-specific rates of Table 4.2. the cumulative rates up to 65 years and their ratio are

$$\begin{aligned}
\text{Cali:}\quad & 45\ y \times \tfrac{1.5}{10^5 y} + 20\ y \times \tfrac{69.7}{10^5 y} = 0.0146 = \mathbf{1.46} \text{ per } 100 \\
\text{B'ham:}\quad & 45\ y \times \tfrac{1.2}{10^5 y} + 20\ y \times \tfrac{44.6}{10^5 y} = 0.0095 = \mathbf{0.95} \text{ per } 100 \\
\text{ratio:}\quad & \mathbf{1.46/0.95 = 1.54}
\end{aligned}$$

"Cumulative risks" & their ratio up to 65 y:

$$\begin{aligned}
\text{Cali:}\quad & 1 - \exp(-0.0146) = 0.0145 = \mathbf{1.45}\% \\
\text{B'ham:}\quad & 1 - \exp(-0.0095) = 0.0094 = \mathbf{0.94}\% \\
\text{ratio:}\quad & \mathbf{1.45/0.94 = 1.54}
\end{aligned}$$

NB. For more appropriate estimates of cumulative risks, correction for total mortality (competing event) needed.

Cum. measures in B'ham with 5-y groups (IS, Fig 4.11)

Age-group (years)	Incidence rate (per 100 000 pyrs)
0–4, . . . , 15–19	0.0
20–24, 25–29	0.1
30–34	0.9
35–39	3.5
40–44	6.7
45–49	14.5
50–54	26.8
55–59	52.6
60–64	87.2
65–69	141.7
70–74	190.8
Sum	524.9

$$\begin{aligned}
\text{Cumulative rate 0-75 y} \quad &= \quad 5 \text{ y} \times \frac{524.9}{10^5 \text{ y}} = 0.0262 = \mathbf{2.6} \text{ per } 100 \\
\text{"Cumulative risk" 0-75 y} \quad &= \quad 1 - \exp(-0.0262) = 0.0259 = \mathbf{2.6}\%.
\end{aligned}$$

Cumulative and life-time risks

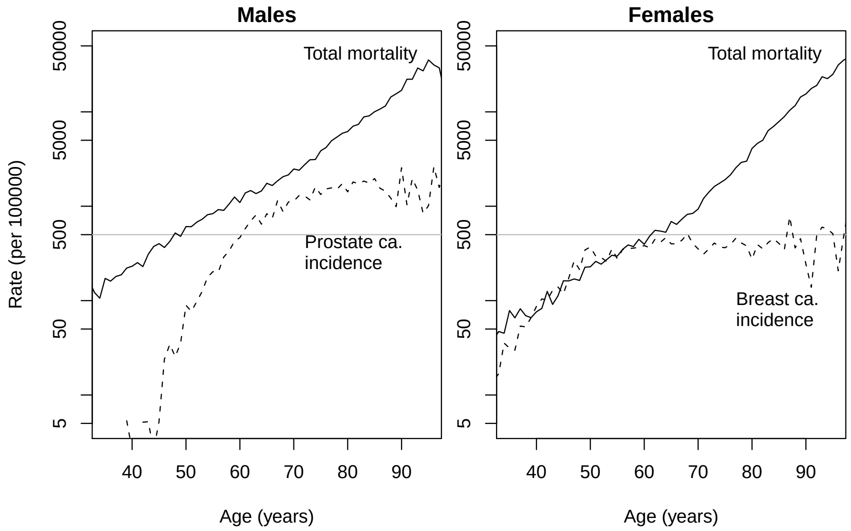
It is, of course, an interesting and relevant question to ask:

> *"What are my chances of getting cancer C, say, in the next 10 years, between ages 50 to 75 years, or during the whole lifetime?"*

However, this is difficult to answer.

- Fully individualized risks are unidentifiable.
- Age-specific and standardized rates are not very informative as such.
- Average cumulative risks are often estimated from cumulative rates using the simple formula above.
- Yet, these naive estimates fictitiously presume that a person would not die from any cause before cancer hits him/her, but could even survive forever!

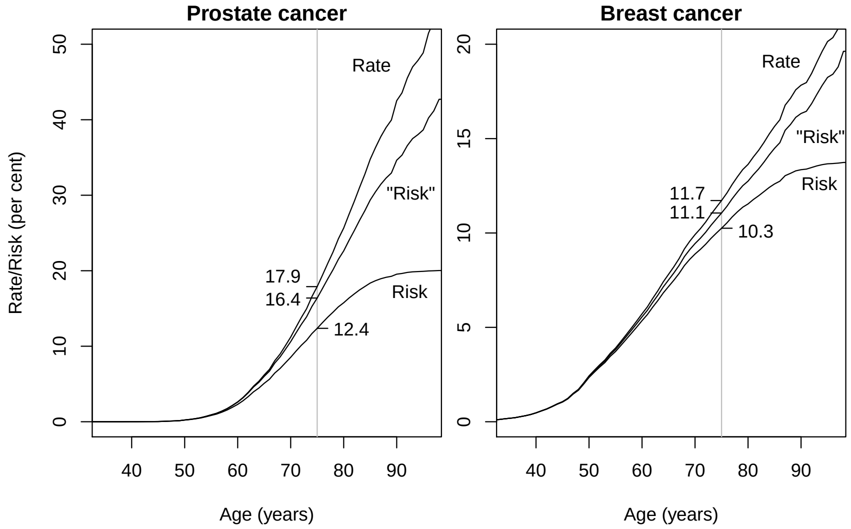
Total mortality and incidence of two common cancers by age, Finland 2005



Estimation of cumulative risks

- The probability of contracting cancer during realistic lifespan or in any age range depends not only on age-specific hazard rates of cancer itself but also of probabilities of overall survival up to relevant ages,
- Hence, the dependence of total mortality by age in the population at risk must be incorporated in the estimation of cumulative risks of cancer.
- When this is properly done, the corrected estimates of cumulative risk will always be lower than the uncorrected “risks”.
- The magnitude of bias in the latter grows by age, but is reduced with increased life expectancy.

Cumulative measures, Finland 2005



Greater differences in males reflect shorter life expectancy and relatively high rates of prostate ca. in old ages.

Special cohorts of exposed subjects

- Occupational cohorts, exposed to potentially hazardous agents, *e.g.* asbestos workers, uranium miners (see Jóhanna's lecture on cohort studies)
- Cohorts of patients on intensive treatment, which may have harmful long-term side-effects, *e.g.* people with a history of childhood cancer.
- Often no internal comparison group of unexposed subjects available.

Question: Do incidence or mortality rates in the **exposed** target cohort differ from those of a roughly comparable **reference** population?

Reference rates obtained from:

- population statistics (mortality rates)
- disease & hospital discharge registers (incidence)

Observed and expected cases – SIR

- Compare rates in a study cohort with a standard set of age–specific rates from the reference population.
- Reference rates normally based on large numbers of cases, so they are assumed to be "known" without error.
- Calculate **expected** number of cases, E, if the standard age-specific rates had applied in our study cohort.
- Compare this with the **observed** number of cases, D, by the **standardized incidence ratio** (SIR)

$$\text{SIR} = D/E, \qquad \text{SE}(\log[\text{SIR}]) = 1/\sqrt{D}$$

- Analogously, **standardized mortality ratio** (SMR) with death as outcome.

Example: Hormone therapy and breast cancer

- A cohort of 974 women treated with hormone (replacement) therapy (HT) were followed up.
- $D =$ 15 incident cases of breast cancer were observed.
- Person-years (Y) and reference rates (λ^*_a, per 100000 y) by age group:

Age	Y	λ^*_a	E
40–44	975	113	1.10
45–49	1079	162	1.75
50–54	2161	151	3.26
55–59	2793	183	5.11
60–64	3096	179	5.54
$\sum$			16.77

Ex: HT and breast ca. (cont'd)

- "Expected" cases at ages 40–44:

$$975 \times \frac{113}{100\,000} = 1.10$$

- Total "expected" cases is $E = 16.77$
- SIR $= 15/16.77 = \mathbf{0.89}$.
- Error-factor: $\exp(1.96 \times \sqrt{1/15}) = 1.66$
- 95% confidence interval is:

$$0.89 \overset{\times}{\div} 1.66 = (0.54, 1.48)$$

SIR for Cali with Birmingham as reference (IS: Fig. 4.9)

Total person-years at risk and expected number of cases in Cali 1982-86 based on age-specific rates in Birmingham

Age	**Person-years**	**Expected cases in Cali**
0–44	524 220 × 5 = 2 621 100	0.000012 × 2 621 100 = 31.45
45–64	76 304 × 5 = 381 520	0.000446 × 381 520 = 170.15
65+	22 398 × 5 = 111 990	0.002020 × 111 990 = 226.00
All ages	= **3 114 610**	**Total expected (E) 427.82**

Total observed number $O = \mathbf{620}$.

Standardised incidence ratio:

$$\text{SIR} = \frac{O}{E} = \frac{\mathbf{620}}{\mathbf{427.8}} = \mathbf{1.45} \quad \text{(or } 145 \text{ per } 100\text{)}$$

Crude and adjusted rates compared (IS: Table 4.6)

	Cali, 1982-86	B'ham, 1983-86	Rate ratio
Crude rates ($/10^5$ y)	19.9	33.9	*0.59*
ASR ($/10^5$ y)^B with 3 broad age groups	48.0	33.9	*1.42*
ASR ($/10^5$ y)^C –"–	19.9	14.4	*1.38*
ASR ($/10^5$ y)^W –"–	34.0	23.5	*1.44*
Cum. rate $<$ 65 y (per 1000) –"–	14.6	9.5	*1.54*
ASR ($/10^5$ y)^W with 18 5-year age groups	36.3	21.2	*1.71*
Cum. rate $<$ 75 y (per 1000) –"–	46.0	26.0	*1.77*

Standard population: ^{B} Birmingham 1985, ^{C} Cali 1985, ^{W} World SP

NB: The ratios of age-adjusted rates appear less dependent on the choice of standard weights than on the coarseness of age grouping.
– 5-year age groups are preferred.

SURVIVAL ANALYSIS

Questions of interest on the **prognosis** of cancer:

- what are the patients' chances to **survive** at least 1 year, or 5 years *etc.*, since diagnosis?

Survival analysis: In principle like incidence analysis but

- population at risk = patients with cancer,
- basic time variable = time since the date of diagnosis, on which the follow-up starts,
- outcome event of interest = death,
- measures and methods used somewhat different from those used in incidence analysis.

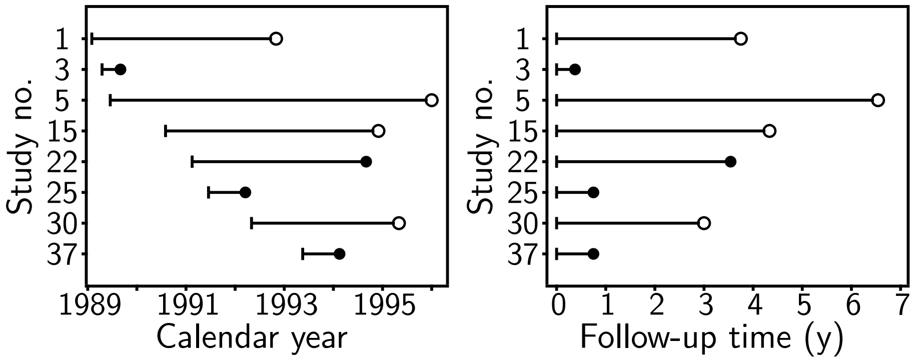
Follow-up of 8 out of 40 breast cancer patients (from IS, table 12.1., p. 264)

No.	Age (y)	Stage[a]	Date of diagnosis	Date at end of follow-up	Vital status at end of follow-up	Cause of death[c]	Full years from diagn's up to end of follow-up	Days from diagn's up to end of follow-up
1	39	1	01/02/89	23/10/92	A	–	3	1360
3	56	2	16/04/89	05/09/89	D	BC	0	142
5	62	2	12/06/89	28/12/95	A	–	6	2390
15	60	2	03/08/90	27/11/94	A	–	4	1577
22	64	2	17/02/91	06/09/94	D	O	3	1297
25	42	2	20/06/91	15/03/92	D	BC	0	269
30	77	1	05/05/92	10/05/95	A	–	3	1100
37	45	1	11/05/93	07/02/94	D	BC	0	272

[a] 1 = absence of regional lymph node involment and metastases
2 = involvement of regional lymph node and/or presence of metastases
[b] A = alive; D = dead; [c] BC = breast cancer; O = other causes

Follow-up of breast ca. patients (cont'd)

| entry = diagnosis; ● exit = death; ○ exit = censoring



(**IS**: Figure 12.1, p. 265)

Life table or actuarial method

Commonly used in population-based survival analysis by cancer registries.
(In clinical applications the **Kaplan-Meier** method is more popular.)

(1) Divide the follow-up time into subintervals $k = 1, \dots K$;
most of these having width of 1 year.

Often the first year is divided into monthly intervals, or at two intervals with widths of 3 mo and 9 mo, respectively.

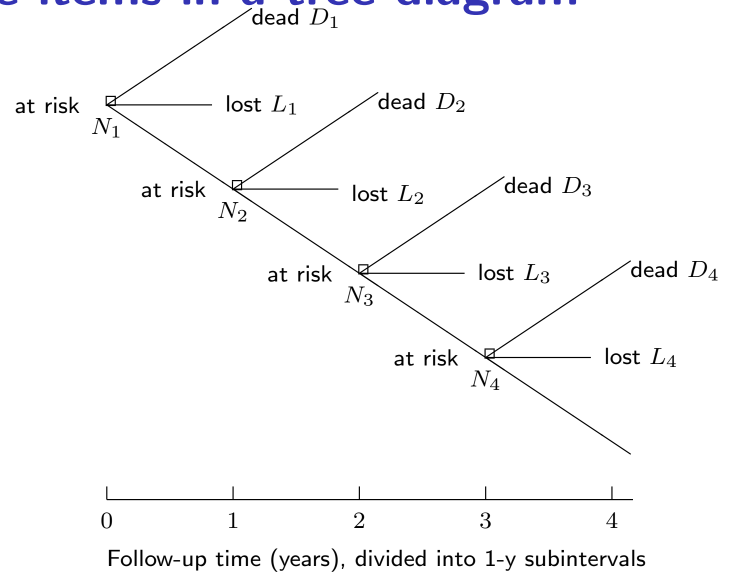
(2) Tabulate from original data for each interval

$N_k =$ size of the **risk set**, *i.e.* the no. of subjects still alive and under follow-up at the start of interval,

$D_k =$ no. of **cases**, *i.e.* deaths observed in the interval,

$L_k =$ no. of **losses**, *i.e.* individuals **censored** during the interval before being observed to die.

Life table items in a tree diagram



$N_k =$ population at risk at the start of the kth subinterval

$D_k =$ no. of deaths, $L_k =$ no. of losses or censorings in interval k

Life table items for breast ca. patients

(**IS**: Table 12.2., p. 273, first 4 columns)

Inter- val (k)	Years since diagnosis	No. at start of interval (N_k)	No. of deaths (D_k)	No. of losses (L_k)
1	0– < 1	40	7	0
2	1– < 2	33	3	6
3	2– < 3	24	4	3
4	3– < 4	17	4	4
5	4– < 5	9	2	3
6	5– < 6	4	1	2
7	6– < 7	1	0	1
Total			21	19

Life table calculations (cont'd)

(3) Calculate and tabulate for each interval

$N'_k = N_k - L_k/2$ = corrected size of the risk set, or "effective denominator" at start of the interval,

$q_k = D_k/N'_k$ = estimated conditional probability of dying during the interval given survival up to its start,

$p_k = 1 - q_k$ = conditional survival proportion over the int'l,

$S_k = p_1 \times \cdots \times p_k$ = **cumulative survival proportion** from date of diagnosis until the end of the kth interval

= estimate of **survival probability** up to this time point.

Follow-up of breast ca. patients (cont'd)

Actuarial life table completed (IS, table 12.2, p. 273)

Interval	Years since diagnosis	No. at start of interval	No. of deaths	No. of losses	Effective denominator	Cond'l prop'n of deaths during int'l	Survival prop'n over int'l	Cumul. survival; est'd survival prob'ty
(k)		(N_k)	(D_k)	(L_k)	(N'_k)	(q_k)	(p_k)	(S_k)
1	0– < 1	40	7	0	40.0	0.175	0.825	0.825
2	1– < 2	33	3	6	30.0	0.100	0.900	0.743
3	2– < 3	24	4	3	22.5	0.178	0.822	0.610
4	3– < 4	17	4	4	15.0	0.267	0.733	0.447
5	4– < 5	9	2	3	7.5	0.267	0.733	0.328
6	5– < 6	4	1	2	3.0	0.333	0.667	0.219
7	6– < 7	1	0	1	0.5	0.0	1.0	0.219

1-year survival probability is thus estimated 82.5% and 5-year probability 32.8%.

Comparison to previous methods

- Complement of survival proportion $Q_k = 1 - S_k$ = incidence proportion of deaths.

  Estimates the cumulative risk of death from the start of follow-up till the end of kth interval.

- Indidence rate in the kth interval is computed as:

$$I_k = \frac{\text{number of cases } (D_k)}{\text{approximate person-time } (\widetilde{Y}_k)}$$

where the approximate person-time is given by

$$\widetilde{Y}_k = \left[N_k - \frac{1}{2}(D_k + L_k) \right] \times \text{width of interval}$$

The dead and censored thus contribute half of the interval width.

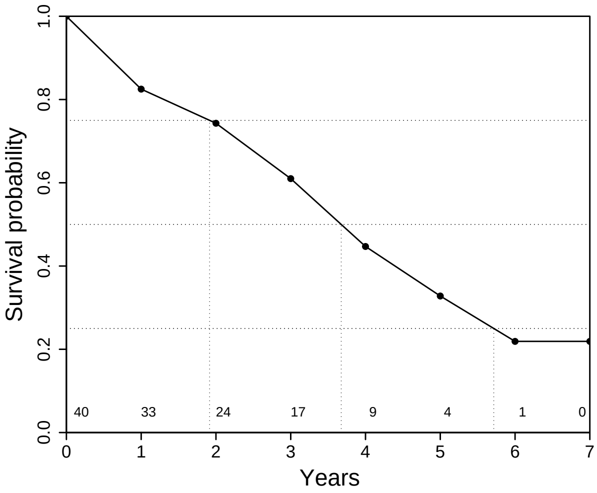
Survival curve and other measures

Line diagram of survival proportions through interval endpoints provides graphical estimates of interesting parameters of the survival time distribution, *e.g.*:

- **median** and **quartiles**: time points at which the curve crosses the 50%, 75%, and 25% levels
- **mean residual lifetime**: area under the curve, given that it decreases all the way down to the 0% level.

NB. Often the curve ends at higher level than 0%, in which case some measures cannot be calculated.

Survical curve of breast ca. patients (IS: Fig 12.8)



Numbers above x-axis show the size of population at risk.

Relative survival analysis

- Another interesting and relevant question:

  "How much worse are the chances of a cancer patient to survive, say, 5 years, as compared with a comparable person without the disease?"

- An answer is provided by **relative survival proportions**:

$$R_k = S_k^{\text{obs}} / S_k^{\text{exp}}, \qquad \text{where}$$

- S_k^{obs} = **observed** survival proportion in cancer patient group k by age, gender and year of diagnosis,
- S_k^{exp} = **expected** survival proportion based on the age-specific mortality rates of the same gender and calendar time in a reference population (compare with calculations of SIR!)

+ No information on causes of death needed.

CONCLUSION

Measuring and comparing disease frequencies

- not a trivial task but
- demands expert skills in epidemiologic methods.

Major challenges:

- obtain the right denominator for each numerator,
- valid calculation of person-years,
- appropriate treatment of time and its various aspects,
- removal of confounding from comparisons.

APPENDIX: Introduction to Rand how we use it

What is R?

- A practical calculator:
  - You can see what you compute
  - . . . and change easily to do similar calculations.
- A statistical program.
- An environment for data analysis and graphics.
- A programming language
- Developed by international community of volunteers.
- Free.
- Runs on any computer.
- Updated every 6 months.

What does R offer for epidemiologists?

- Descriptive tools
  - Versatile tabulation
  - High-quality graphics
- Analytic methods
  - Basic epidemiologic statistics
  - Survival analysis methods
  - Common regression models and their extensions
  - Other. . .

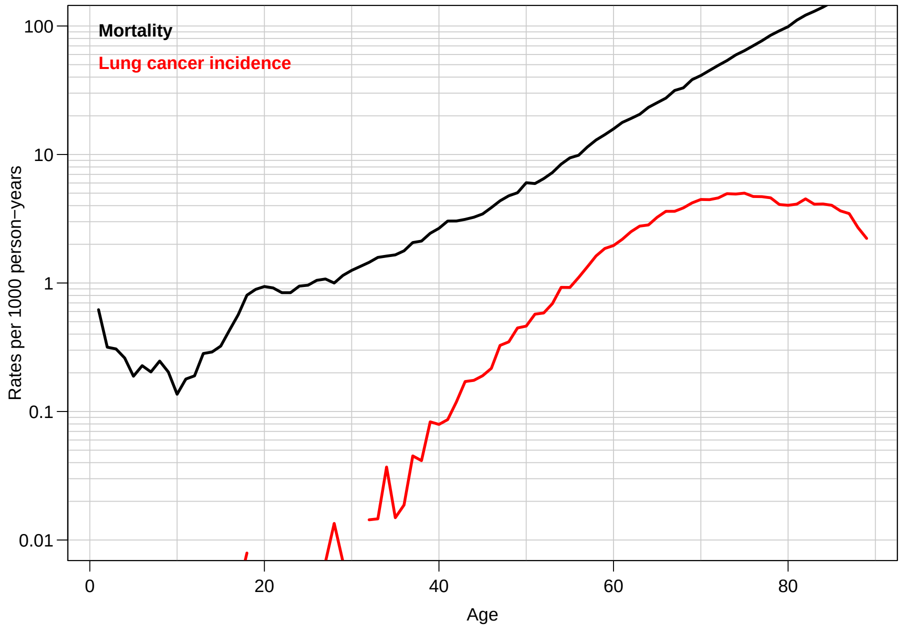
These are provided by *e.g.* SPSS, SAS and Stata, too, so . . . ?

Many features of R are more appealing in the long run.

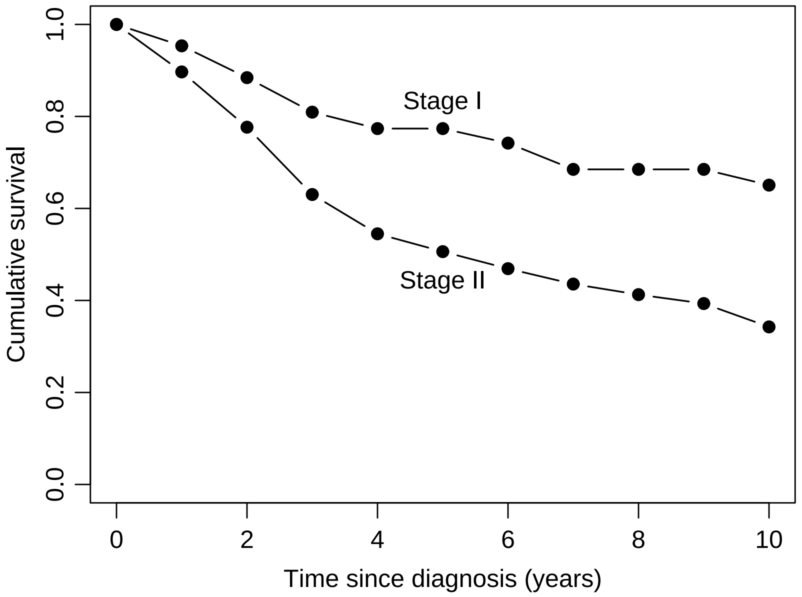
Graphics in R

- Versatile, flexible, high quality, . . .
- Various **high-level** graphic functions available.
- Easy to add items (points, lines, text, legends . . .) to an existing graph by **low-level** plotting commands.
- Fine tuning of symbols, lines, axes, colours, etc. by *graphical parameters* (> 67 of them!)
- Interactive tools using the mouse
  - Put new things on a graph
  - Identify points

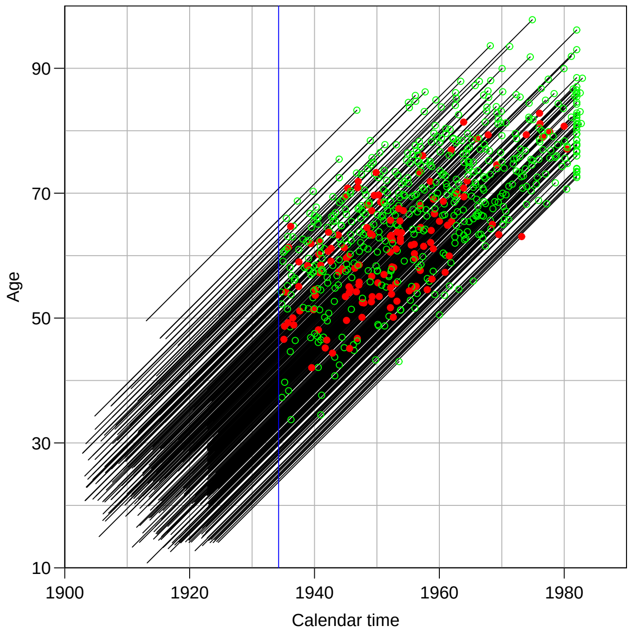
Example: Total mortality and lung ca incidence in DK



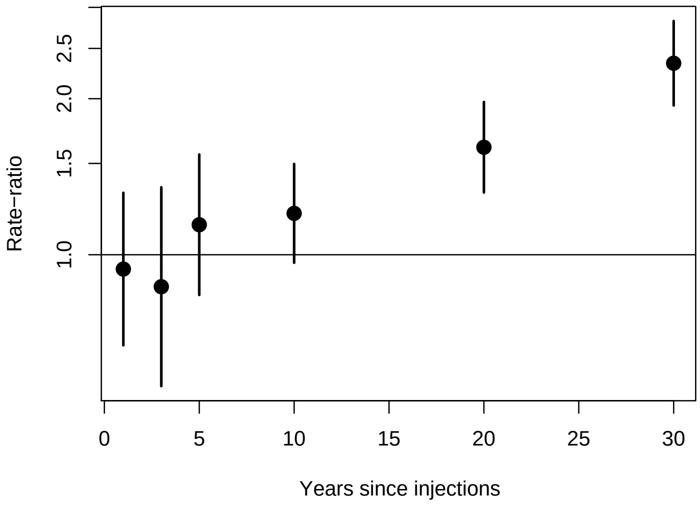
Example: Survival of cervix ca patients (C&H, 34)



Example Lexis diagram of Welsh nickel cohort



Example: Rate ratios with confidence intervals



Getting your graphs out

- Graphs can be saved to disk in almost any format

  `.eps`, `.pdf`, `.bmp`, `.jpg`, `.png`, . . .
- Save graphs from the screen or write directly to a file.
- You can also directly transport an R graph as a metafile into a Word document!

Tools for nearly anything!

- Thousands of add-on packages.
- Several packages for epidemiological analyses and modelling.
  Most on them focus on infectious disease epidemiology.
- Packages of interest for cancer epidemiologist
  - `Epi`: extensive set of functions for *e.g.* splitting follow-up time by several timescales, cohort and case-control studies, multistate models, advanced tabulation, informative reporting of estimation results.
  - See Carstensen: *Epidemiology with R*
  - `survival`: *e.g.* Kaplan-Meier curves, Cox regression model.
  - `popEpi`: additional tools for, *e.g.* standardized rates and ratios, population-based relative survival analysis.
- Packages may be installed and updated from within R.

Running R

- Interactive but not mouse-driven!
- Commands typed from keyboard.
- More practical: commands written and saved in a **script file** from which they are run.
- Execution of tasks:
  - evaluation of **expressions** contained in commands,
  - based on calls of **functions**.

Difficult to learn & slow to use?

- Maybe in the beginning.
- Versatility and flexibility rewarding in the long run.

Running R on Windows

- Start by double-clicking the R-icon.
- `R Console`: the **console window**
  - command lines to be typed – or pasted from a script file – after prompt '>',
  - prompt '+' marks continuation of an incomplete command line,
  - output follows a completed command requesting it,
  - arrow key $\boxed{\uparrow}$ leads to previous command lines.
- Menu bar for a few useful pull-down menus.
- On-line help in HTML form.

R as a simple calculator

Write the arithmetic expression on the empty line after the prompt and press `Enter`. The result is displayed immediately.

```
> 2+2
[1] 4
> 3*5 - 6/2
[1] 12
> (2+3)^2
[1] 25
> sqrt( 1/12 + 1/17 )
[1] 0.3770370
> exp( 1.96 * sqrt( 1/12 + 1/17 ) )
[1] 2.093825
```

R as a smart calculator

Simple summary of results from a cohort study:

	Exposed	Unexposed
No. of cases/Person-years	20/2000	25/5000

- No's of cases and p-years are first assigned & saved into vectors `D` and `Y`;
- Incidence rates in the two groups as well as their ratio and difference are then calculated and printed:

```
> D <- c(20, 25) ; Y <- c(2000, 5000)
> rate <- 1000*D/Y ; rate
[1] 10  5
> ratio <- rate[1]/rate[2] ; diff <- rate[1]-rate[2]
> c(ratio, diff)
[1] 2 5
```

A couple of important things

- Names of **variables** (or any other **objects**)
  - Start with a letter from `A,...,Z` or `a,..., z`;
    lower case separated from upper case, *e.g.* '`x`' $\neq$ '`X`'
  - Letters, integers `0, ..., 9`, dots '`.`', and underlines '_' allowed after 1st letter.
- **Assignment operator** '`<-`' (consists of '`<`' and '`-`')
  - assigns a value to an object, for example

    ```
    > A <- 5+2 ; A
    [1] 7
    ```

    means that a numeric variable '`A`' is given $5+2 = 7$ as its value, and is then printed,
  - the equal sign '=' is also allowed as assignment operator.

Vectors and their arithmetics

Vector = ordered set of numbers (or other similar elements)

- Can be assigned values elementwise by function `c()`
- Vector `x` with 4 elements 1, 2, 4, 7 assigned and printed:

```
> x <- c(1,2,4,7)
> x
[1] 1 2 4 7
```

- Arithmetic operations `+, -, *, /, ^` (power) for vectors of same **length** *i.e.* same number of elements.

⇒ Outcome: a new vector whose elements are results of the operation on the corresponding elements in original vectors.

- Common mathematical functions, like `sqrt(), log(), exp()` work in the same way for numeric vectors.

R script – commands in a file

R script file is an ASCII file containing a sequence of R commands to be executed.

The **script editor** of R works as follows:

1. In `RGui` open the script editor window: *File - New script*, or when editing an existing script file: *File - Open script*,
2. Write the command lines without prompt '>' or '+'.
3. Save the script file: *File - Save e.g.* as `c:\...\mycmds.R` or with some other file name having extension `.R`

R script (cont'd)

4. Paint the lines to be excecuted and paste them on the console window using the third icon on the toolbar.
5. Edit the file using *Edit* menu, save & continue.

- To run a whole script file, write in console window:

```
> source("c:/.../mycmds.R", echo=TRUE)
```

An effective alternative: **R Studio** – a handy interface for writing and running R scripts; see http://www.rstudio.com/.

R in this course

- The main purpose is to inform you about the existence and potential of R, which you might find useful in any future work involving serious epidemiologic data analysis.
- Here, R will be used only as a simple calculator.
- No need for a lot of the more fancy stuff.
- The script editor will help you keep your solutions for future reference.
- After the course, solutions to all exercises will be provided.
- There is a good workbook introduction to R