Statistical Methods in Cancer Epidemiology using R

Karri Seppä

Finnish Cancer Registry

Lecture 5

karri.seppa@cancer.fi

Mar 2, 2020

More than one time scale and SIR & SMR

Contents

1. Special exposure cohorts
2. Observed and expected cases, SIR & SMR
3. Lexis diagram and life lines
4. Splitting follow-up time simultaneously by age and period
5. Merging reference rates with the cohort data and performing SIR/SMR computations

Main R functions to be covered

- `Lexis.diagram()` and other Lexis tools in `Epi`
- `merge()`
- `sir()` and `sirspline()` in `popEpi`

Special cohorts of exposed subjects

- Occupational cohorts, exposed to potentially \ hazardous agents
- Cohorts of patients on chronic medication, which may have harmful long-term side-effects

No internal comparison group of unexposed subjects.

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)

Accounting for age distribution

- 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 (or standardized mortality ratio SMR)

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

Example: HT and breast ca.

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

Age	Y_a	λ_a^*	E_a
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

Example: HT use and breast ca. (cont'd)

- "Expected" number of cases at ages 40–44:

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

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

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

A statistical model for SIR

- The theoretical rates λ_{ap} by age (a) and calendar period (p) in the cohort are assumed to be proportional to the rates λ^*_{ap} in the reference population:

$$\lambda_{ap} = \rho \times \lambda^*_{ap}$$

  $\rho =$ hazard ratio btw the cohort and the reference pop'n.

- The population rates λ^*_{ap} are assumed to be known.
- Cohort data: numbers of cases D_{ap} and p-years Y_{ap} by $a$ge and $p$eriod are computed.
- It can be shown that the likelihood of ρ is of Poisson type, and the maximum likelihood estimator of ρ is:

$$\widehat{\rho} = \frac{D}{\sum \lambda^*_{ap} Y_{ap}} = \frac{\text{Observed}}{\text{Expected}} = \text{SIR}$$

Example: The Welsh Nickel Workers' Study

- A cohort of 679 men working in nickel smelters in South Wales first employed 1903-25 (for details see **B&D**).
- Outcomes of interest: deaths from nasal (ICD code 160) and lung cancer (ICD 162 and 163) during follow-up 1934-76.
- Outcome event indicator and basic time variables:

$$
\begin{aligned}
\texttt{icd} &= \text{code for cause of death, 0 if not yet dead} \\
\texttt{date.bth} &= \text{date of birth} \\
\texttt{date.in} &= \text{date of starting follow-up} \\
\texttt{date.out} &= \text{date when follow-up ended}
\end{aligned}
$$

Example (cont'd)

- Interesting risk factors in the original data frame:

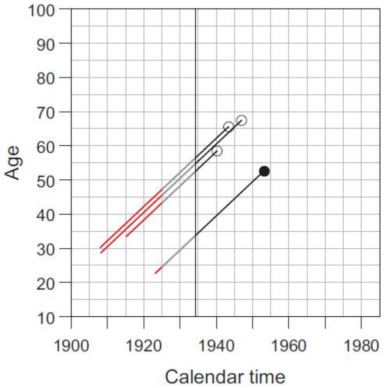
$$\begin{aligned} \texttt{expos} &= \text{exposure index based on years employed in} \\ & \text{high-risk areas in the smelter by 1925} \\ & \rightarrow \text{ categorized version EXP} \\ \texttt{date.1st} &= \text{date when first employed } \rightarrow \text{ AFE} \end{aligned}$$

- Risk factors to be formed from original variables:

$$\begin{aligned} \texttt{age.1st} &= \text{age when first employed } \rightarrow \text{ AFE} \\ \texttt{year.1st} &= \text{year of first employment } \rightarrow \text{ YFE} \\ \texttt{time.1st} &= \text{time since first exposure } \rightarrow \text{ TFE} \end{aligned}$$

Lexis diagram & 4 lifelines from the nickel cohort

Diagram invented by *Wilhelm Lexis* (1837-1914), German mathematician and demographer, professor in Tartu 1874-76.

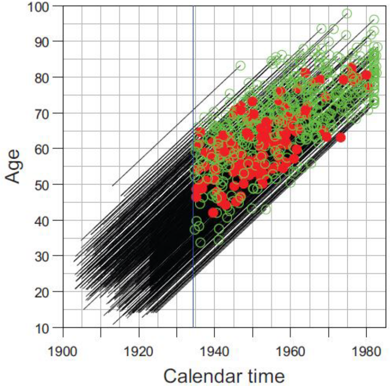


Individual lifelines run diagonally from a given (age, time) starting point to an endpoint.

Here the lines go from start of exposure till the age and time of exit.

Mortality follow-up started in 1934.

Nickel cohort: All lifelines in the Lexis diagram



Follow-up starts not until 1934 for all subjects.

- dot (red) = lung ca. death,
- circle (green) = censoring

Function `splitLexis()` splits individual follow-up times into rectangles defined by agebands and calendar periods.

Splitting follow-up by age & calendar time

from the registration of:

- Entry,
- Exit,
- Failure status

of the individuals in the cohort,
and the definition of the scale by:

- **O**rigin
- **S**cale
- **C**utpoints

to the table of:

- D = events,
- Y = person time,

by age and period.

Expected numbers in practice

- From the records of age-period split & expanded cohort data:

  $y_{i,ap}$ = person-time slot in a record defined by

  a = ageband of the record

  p = period of the record

- From the file containing the reference rates:

  λ^*_{ap} = age & period specific rate

  a = ageband of the population rate

  p = period of the population rate

Expected numbers in practice (cont'd)

Population rates are matched up to the expanded cohort data, and expected numbers individually are computed as:

$$e_{i,ap} = \lambda^*_{ap} \times y_{i,ap}$$

and these are eventually summed: $E = \sum e_{i,ap}$

Always two datasets are needed for SIR:

1. the *cohort* data with follow-up information on its individual members. This must be split & expanded to match with

2. the *reference rate* data with age & period specific rates in the chosen reference population.

SMR-calculations in R using Lexis tools:

1. Read in the cohort data (Welsh Nickel Workers)

and convert the dates `dd/mm/yyyy` into "decimal years"

```
library(Epi)
nick <- read.table( "nickel.txt", header=T, as.is=T )
for (j in 4:7) nick[ , j] <-
   cal.yr( nick[ , j], format = "%d/%m/%Y" )
```

List the records for the 4 men in a previous Lexis diagram

```
round(nick[11:14, ],2)
```

```
   id icd expos date.bth date.1st date.in date.out
11 19 160  10.0  1881.73  1915.18 1934.25  1940.21
12 21  14   0.0  1877.80  1908.00 1934.25  1943.37
13 22 177   2.5  1879.50  1908.17 1934.25  1946.98
14 23 162   0.0  1900.50  1923.15 1934.25  1953.20
```

2. Reference rates in E & W read in

```r
ewrates <- read.table("ewrates.txt",header=T)
```

8 first and last rows checked

```r
ewrates[c(1:8, 143:150), ]
```

```
    year age lung nasal  other
1   1931  10    1     0   1269
2   1931  15    2     0   2201
3   1931  20    6     0   3116
4   1931  25   14     0   3024
5   1931  30   30     1   3188
6   1931  35   68     1   4165
7   1931  40  149     3   5651
8   1931  45  274     5   8326
143 1976  45  403     3   4311
144 1976  50 1003     9   7687
145 1976  55 1896     9  12544
146 1976  60 3342    15  20787
147 1976  65 4985    17  33729
148 1976  70 6718    20  55480
149 1976  75 8068    38  89199
150 1976  80 7744    33 137360
```

E & W lung ca. death rates by age and period}

```r
tapply(ewrates$lung, list("age" = ewrates$age,
         "year" = ewrates$year),sum)
```

```
    year
age  1931 1936 1941 1946 1951 1956 1961 1966 1971 1976
  10    1    1    1    1    0    0    0    0    0    0
  15    2    2    2    3    2    2    2    2    1    1
  20    6    6    6    8    7    4    5    4    4    2
  25   14   14   16   18   13   12   11   10   10    7
  30   30   30   34   36   35   35   34   25   24   17
  35   68   68   81   94   98   93   90   76   58   56
  40  149  149  191  236  248  251  223  216  177  139
  45  274  274  384  544  579  590  563  531  503  403
  50  431  431  597  954 1224 1248 1221 1160 1070 1003
  55  586  586  883 1350 2003 2317 2284 2201 2077 1896
  60  646  646 1021 1717 2555 3315 3663 3695 3546 3342
  65  636  636  970 1763 2926 3926 4844 5273 5174 4985
  70  533  533  748 1400 2624 3878 4977 6210 6820 6718
  75  464  464  631 1085 2069 3332 4513 5914 7273 8068
  80  324  324  385  765 1416 2258 3417 4563 6089 7744
```

3. Creating and expanding the Lexis object}

The data frame converted to a Lexis object in two time scales: year (calendar time) and age:

```
nickL <- Lexis( entry = list( year = date.in ),
                exit = list( year = date.out,
                             age = date.out - date.bth ),
    exit.status = as.numeric( nick$icd %in% c(162, 163) ),
           data = nick )
```

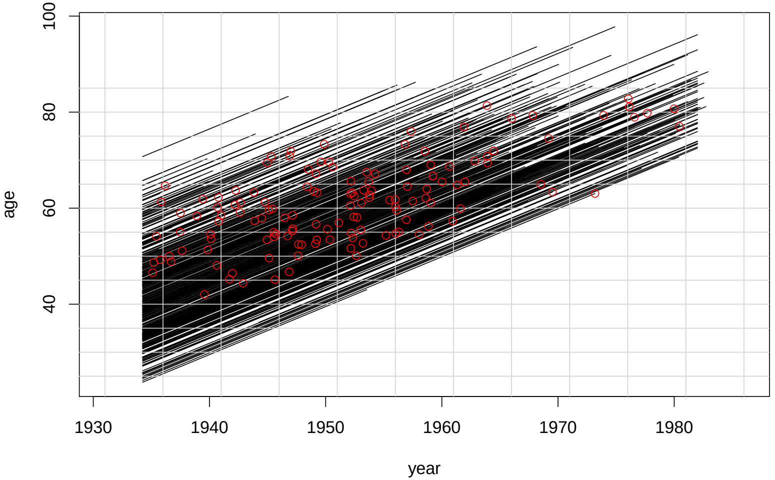
```
NOTE: entry.status has been set to 0 for all.
```

The Lexis object jointly split by age and period. Agebands and period bands are named like in the ewrates file – "left" means the lower cutpoint (1st year) of a band.

```
nickL.a <- splitLexis(nickL, "age", br=seq(10,85,5) )
nickL.ap<- splitLexis(nickL.a,"year",br=seq(1931,1986,5))
```

Splitting follow up time by age and calendar year

```
plot( nickL.ap, c("year","age"), col=c("black"), xlim=c(1931,1986) )
points( nickL.ap, c("year","age"), pch=c(NA,1)[nickL.ap$lex.Xst+1], col="red" )
```




```
nickL.ap$year <- timeBand(nickL.ap, "year", "left")
nickL.ap$age <- timeBand(nickL.ap, "age", "left")
```

The expanded data frame viewed

```
dim(nickL.ap)  # 10-fold expansion!
```

```
[1] 6949   13
```

```
round( subset( nickL.ap, lex.id %in% 13:14)
       [ , c(1:4,6,8,10,12,13)] ,2)
```

```
    lex.id year age lex.dur lex.Xst icd date.bth date.in date.out
90      13 1931  50    0.25       0 177   1879.5 1934.25  1946.98
91      13 1931  55    1.50       0 177   1879.5 1934.25  1946.98
92      13 1936  55    3.50       0 177   1879.5 1934.25  1946.98
93      13 1936  60    1.50       0 177   1879.5 1934.25  1946.98
94      13 1941  60    3.50       0 177   1879.5 1934.25  1946.98
95      13 1941  65    1.50       0 177   1879.5 1934.25  1946.98
96      13 1946  65    0.98       0 177   1879.5 1934.25  1946.98
97      14 1931  30    1.25       0 162   1900.5 1934.25  1953.20
98      14 1931  35    0.50       0 162   1900.5 1934.25  1953.20
99      14 1936  35    4.50       0 162   1900.5 1934.25  1953.20
100     14 1936  40    0.50       0 162   1900.5 1934.25  1953.20
101     14 1941  40    4.50       0 162   1900.5 1934.25  1953.20
102     14 1941  45    0.50       0 162   1900.5 1934.25  1953.20
103     14 1946  45    4.50       0 162   1900.5 1934.25  1953.20
104     14 1946  50    0.50       0 162   1900.5 1934.25  1953.20
105     14 1951  50    2.20       1 162   1900.5 1934.25  1953.20
```

4. Merging the cohort data with E&W rates

```
nickLew.ap <- merge(nickL.ap, ewrates,
        by = c("age", "year"))  # key columns
round(nickLew.ap[1:20, c(1:4,6:8,10,12,13,14) ],1)
```

```
   year age lex.id lex.dur lex.Xst  id icd date.bth date.in date.out lung
1  1931  20    400     0.5       0 574 491   1909.7  1934.2   1980.4    6
2  1931  20    197     0.3       0 273 154   1909.5  1934.2   1965.4    6
3  1931  20    156     0.9       0 213 162   1910.1  1934.2   1973.2    6
4  1931  20    384     0.3       0 546   0   1909.5  1934.2   1982.0    6
5  1931  20    236     1.3       0 325 434   1910.5  1934.2   1953.5    6
6  1931  20     84     0.0       0 110   0   1909.2  1934.2   1982.0    6
7  1931  25    274     1.8       0 380 411   1907.2  1934.2   1960.8   14
8  1931  25    315     1.1       0 443 420   1905.3  1934.2   1971.1   14
9  1931  25    197     1.5       0 273 154   1909.5  1934.2   1965.4   14
10 1931  25     52     1.2       0  75   0   1905.4  1934.2   1982.0   14
11 1931  25    478     1.8       0 690 420   1906.5  1934.2   1961.6   14
12 1931  25     17     1.6       0  28 420   1905.8  1934.2   1967.4   14
13 1931  25    569     1.8       0 828   0   1908.7  1934.2   1982.0   14
14 1931  25    543     1.8       0 792   0   1908.5  1934.2   1982.0   14
15 1931  25    609     0.1       0 884   0   1904.4  1934.2   1982.0   14
16 1931  25    138     1.8       0 187 999   1906.5  1934.2   1941.0   14
17 1931  25    368     1.8       0 523   0   1906.0  1934.2   1982.0   14
18 1931  25    285     0.3       0 394 237   1904.6  1934.2   1970.4   14
19 1931  25    400     1.3       0 574 491   1909.7  1934.2   1980.4   14
20 1931  25    156     0.9       0 213 162   1910.1  1934.2   1973.2   14
```

5. Calculation of observed and expected

Cases & person-time slots renamed, expectations $\lambda^*_{ap} y_{i,ap}$ of becoming a case computed, and tables by a and p produced.

```
nickLew.ap <- transform( nickLew.ap,
          d_iap = lex.Xst, y_iap = lex.dur,
          e_iap = lex.dur * lung/1.0E6 )

Obs.lung <- with(nickLew.ap, tapply(d_iap,
  list("age" = age, "year" = year), sum))

Exp.lung <- with(nickLew.ap, tapply(e_iap,
  list("age" = age, "year" = year), sum))
```

```
Obs.lung ; round(Exp.lung,3)
```

Observed and expected numbers printed

age \ year	1931	1936	1941	1946	1951	1956	1961	1966	1971	1976
30	0	0	0	NA	NA	NA	NA	NA	NA	NA
35	0	0	0	0	NA	NA	NA	NA	NA	NA
40	0	1	1	0	0	NA	NA	NA	NA	NA
45	3	2	4	1	0	0	NA	NA	NA	NA
50	1	5	3	7	6	2	0	NA	NA	NA
55	0	5	6	6	4	5	1	0	NA	NA
60	1	4	5	3	11	6	1	2	1	NA
65	0	0	1	5	4	6	3	0	0	0
70	0	0	1	3	0	2	2	1	0	0
75	NA	0	0	0	0	1	1	2	1	3
80	NA	NA	0	0	0	0	1	0	0	3

age \ year	1931	1936	1941	1946	1951	1956	1961	1966	1971	1976
30	0.004	0.005	0.001	NA	NA	NA	NA	NA	NA	NA
35	0.012	0.032	0.015	0.004	NA	NA	NA	NA	NA	NA
40	0.027	0.075	0.090	0.045	0.011	NA	NA	NA	NA	NA
45	0.054	0.135	0.184	0.246	0.110	0.025	NA	NA	NA	NA
50	0.082	0.231	0.281	0.438	0.511	0.220	0.046	NA	NA	NA
55	0.070	0.263	0.411	0.557	0.789	0.834	0.343	0.069	NA	NA
60	0.035	0.162	0.362	0.644	0.880	1.108	1.155	0.502	0.104	NA
65	0.004	0.045	0.178	0.481	0.775	1.015	1.314	1.240	0.539	0.122
70	0.001	0.004	0.041	0.157	0.486	0.682	0.796	1.172	1.203	0.519
75	NA	0.001	0.003	0.039	0.136	0.342	0.470	0.498	0.954	0.885
80	NA	NA	0.001	0.001	0.037	0.098	0.158	0.218	0.293	0.536

6. Calculation of SMR

We can sum either over individual time slots:

```
D <- sum(nickLew.ap$d_iap)
E <- sum(nickLew.ap$e_iap)
```

or over the newly formed tables:

```
D <- sum(Obs.lung, na.rm=T)
E <- sum(Exp.lung, na.rm=T)
```

Either way, the calculation proceeds:

```
SMR <- D/E; SE <- 1/sqrt(D); EF <- exp(1.96*SE)
round(c(D, E, SMR, SMR/EF, SMR*EF), 2)
```

```
[1] 137.00  26.62   5.15   4.35   6.08
```

6. Fit model for SMR

```r
m <- glm( d_iap ~ 1+offset(log(e_iap)),
 family=poisson, data=nickLew.ap )
round( ci.exp( m ), 2 )
```

```
            exp(Est.) 2.5% 97.5%
(Intercept)      5.15 4.35  6.08
```

6. Fit model for SMR by age group

```
nickLew.ap$agegrp <- cut(nickLew.ap$age,c(20,50,65,100),right=F)
m <- glm( d_iap ~ -1+agegrp+offset(log(e_iap)),
 family=poisson, data=nickLew.ap )
round( ci.exp( m ), 2 )
```

```
                exp(Est.) 2.5% 97.5%
agegrp[20,50)       11.13 6.32 19.60
agegrp[50,65)        8.42 6.80 10.41
agegrp[65,100)       2.59 1.90  3.53
```

6. Fit model for SMR using popEpi package

```
library(popEpi)
nickLew.ap$ref.rate <- nickLew.ap$e_iap/nickLew.ap$y_iap
m <- sir( coh.data = nickLew.ap, coh.obs = 'd_iap', coh.pyrs = 'y_iap',
          ref.data = nickLew.ap, ref.rate = 'ref.rate',
          adjust = c('age', 'year'), print = 'agegrp', conf.type = "wald")
m
```

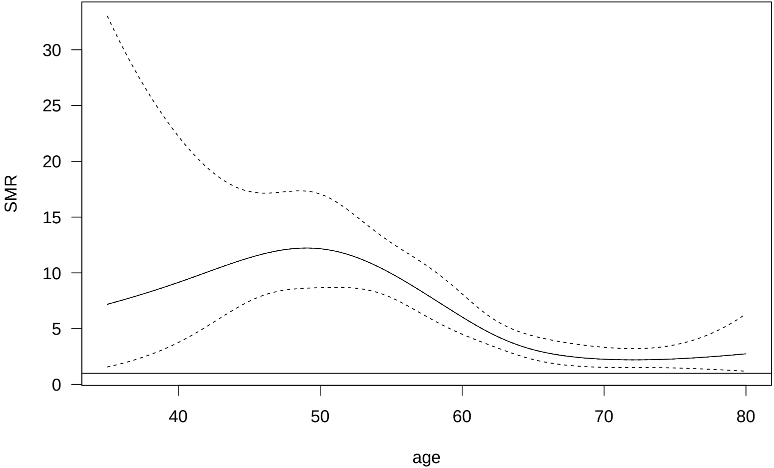
```
SIR (adjusted by age, year) with 95% confidence intervals (wald)
Test for homogeneity: p < 0.001

 Total sir: 5.15 (4.32-6.08)
 Total observed: 137
 Total expected: 26.62
 Total person-years: 15199

    agegrp observed expected    pyrs   sir sir.lo sir.hi p_value
1:  [20,50)       12     1.08 4576.71 11.13   6.32  19.60       0
2:  [50,65)       85    10.10 6864.99  8.42   6.80  10.41       0
3: [65,100)       40    15.45 3757.27  2.59   1.90   3.53       0
```

6. Fit model for SMR using popEpi package

```
m <- sirspline(
  coh.data = nickLew.ap, coh.obs = 'd_iap', coh.pyrs = 'y_iap',
  ref.data = nickLew.ap, ref.rate = 'ref.rate',
  adjust = c('age', 'year'), spline = 'age', knots=5, subset = age>30)
plot(m, conf.int = F)
lines(m, conf.int = T, lty=2)
```



Concluding remarks

- If specific exposure factors exist that have variable values within the target cohort, the estimation of rate ratios associated with them may be efficiently adjusted for age and calendar period by taking the age- and period-specific expected number as the baseline in Poisson-modelling.
- Follow-up time could be split yet by another relevant time axis, like time passed since start of exposure, which may be taken as an explanatory variable when modelling the effects of exposure within a cohort.
- The main challenge is to identify a sufficiently comparable reference population. The "general" population is rarely an ideal one.