Alternatives to Net and Relative Survival for Comparison of Survival between Populations

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Problem

- To describe the survival in patients diagnosed with cancer reflecting only the mortality in excess of what they would have experienced in any case
- Two approaches
  - Cause-specific survival (death from cancer)
    - Problem 1: non-independence of causes of death
    - Problem 2: difficulty determining cause of death
  - Adjust for expected mortality

Why not simply use overall survival?

- Survival in patients diagnosed aged 75 plus will be much worse that in patients aged 55-74
  - Is that because elderly patients:
    - Aren’t treated properly?
    - Have co-morbidities and are more frail?
    - Simply die more often from completely unrelated diseases?

- Survival of cancer patients diagnosed in 2000-2004 much better than in those diagnosed in 1970-1974
  - Better treatment, earlier diagnosis
  - Fewer dying from cardiovascular disease, infections, …

How should one adjust survival using expected rates?

- Method 1: Relative survival

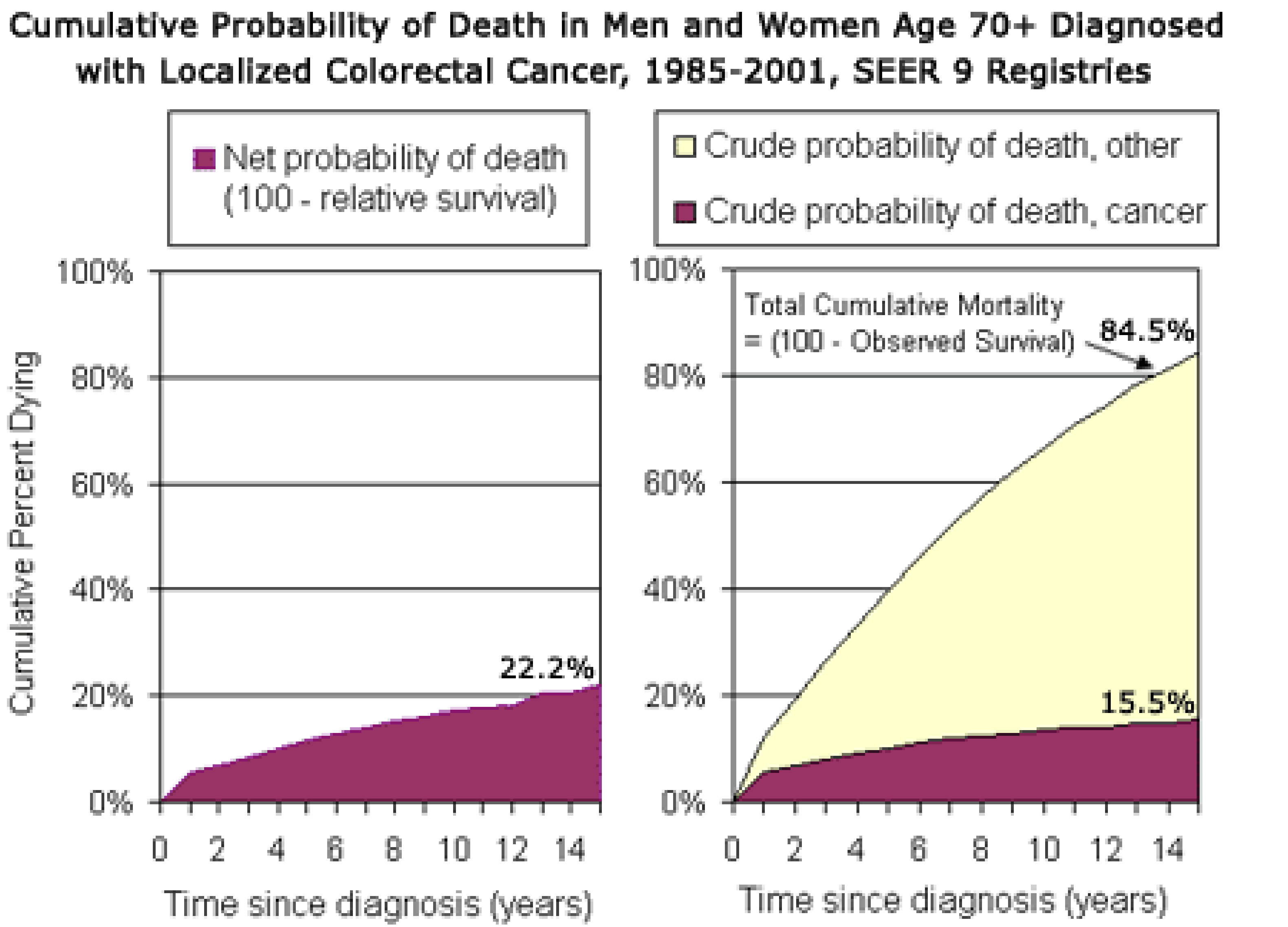
$$S_r(t)=S_O(t)/S_E(t)$$

r=relative

O=Observed

E=Expected

Example: Relative and cause-specific fatality



What is net survival?

1. Cause-specific survival

The survival that would be observed if the patients were only subject to the mortality from the disease of interest

If T & U competing survival times:

- net-hazard

$$\lambda(t)=\lim P\{t\leq T<t+\Delta|T\geq t\}/\Delta$$

- crude-hazard

$$\lambda^{\#}(t)=\lim P\{t\leq T<t+\Delta|T\geq t, U\geq t\}/\Delta$$

Would like net-hazard but can only estimate crude-hazard

What is net survival?

1. Cause-specific survival
2. **Relative survival**

The survival that would be observed if the patients were not subject to the mortality in the background population

Excess hazards

- Excess hazard is the difference between the observed and the expected hazard

$$\lambda_e(t)=\lambda_O(t)-\lambda_E(t)$$

- Note that the excess hazard is the logarithmic derivative of the relative survival:

$$S_r(t)=S_O(t)/S_E(t)$$

where

$\lambda_O(t)=-d \ln\{S_O(t)\}/dt$; $\lambda_E(t)=-d \ln\{S_E(t)\}/dt$;

and hence $\lambda_e(t)=-d \ln\{S_O(t)/S_E(t)\}/dt$

So….

- The excess hazard corresponds to the relative survival

Classical solution

- **Ederer-II** (Ederer 1959, 1961)
  - Estimate the relative survival:

$$S_r(t)=S_O(t)/S_E(t)$$

where $S_O(t)$ is the observed (Kaplan-Meier) survival function, and

$$d \ln\{S_E(t)\}/dt = -\sum_{i=1}^{n} Y_i(t)\lambda_{Ei}(t) \,/\, \sum_{i=1}^{n} Y_i(t)$$

where $Y_i(t)$ indicates whether or not the i'th individual is at risk at time t

  - It uses the expected hazard for the i'th individual only whilst that individual is at risk

For homogeneous data…

Net survival and relative survival are the same

But for heterogeneous data …

- The mean relative survival:

$$(1/n) \sum_{i=1}^{n} S_{ri}(t)$$

is **not** the same as

- The relative (mean) survival:

$$\sum_{i=1}^{n} S_{Oi}(t) \,/\, \sum_{i=1}^{n} S_{Ei}(t)$$

- *It is the mean relative survival that corresponds to the marginal net survival*

What happens with heterogeneous data?

- For the i'th individual we have $S_{ri}(t)$ corresponding to $\lambda_{ei}(t)$
- But how should we combine these to obtain an overall measure?
  - If the i'th individual dies at T_i should we still try to estimate $S_{ri}(t)$ or $\lambda_{ei}(t)$ beyond T_i?
  - If we don't then the overall estimate will depend on the expected mortality

Traditional approach to heterogeneity

- Stratify
  - Assume homogeneous within strata
  - Take a weighted average of the estimates within each strata
  - Note: traditionally the stratum-specific weights were fixed, but Brenner & Hakulinen (2003) allowed time-dependent weights

Problems with stratification

- If strata too broad then not homogeneous
- If strata too narrow then unable to estimate (for large t) because no one still at risk in stratum

Recent quotations

- “In estimating net survival, cancer registries should abandon all classical methods”
- “Due to inherent biases, most of the statistical methods used to estimate net survival are quite inaccurate.”

But …

- If the excess hazard is homogenous within strata then the stratified Ederer-II estimator is consistent
  - The classical approaches are not so bad so long as one stratifies

How can we estimate the marginal net survival?

- Horvitz–Thompson / inverse probability weighting
  - Divide the indicator of "at-risk", $Y_i(t)$, by $EY_i(t) = S_{Ei}(t)$
  - Pohar-Perme
    - Must use the same weights to estimate the "observed" hazard as well as the expected hazard
    - Yields a consistent estimators of the excess hazard and hence of the (marginal) net survival

Roche (2012) on Pohar-Perme

- “In estimating net survival, cancer registries should abandon all classical methods and adopt the new Pohar-Perme estimator.”
- “Due to inherent biases, most of the statistical methods used to estimate net survival are quite inaccurate.”
- “We see no reason to favour any classically used method … because, unlike the PPE, they are all biased”

Dickman (2013) on Roche

- “The approach used by Roche et al. to calculate the `bias with the classical methods’ is fundamentally flawed.”
- “Researchers should also be aware that the lack of bias in the PP estimator comes at a price of higher variance.”

Also note:

- If the stratification is so fine that within strata the expected survival is homogenous, $S_E(.|Z)=S_E(.)$, then
  - The stratified Pohar-Perme estimator is identical to the stratified Ederer-II estimator

Take a step back: What are we trying to do?

What are we trying to do?

- Compare the survival corresponding to the excess hazard in cancer patients in different populations
- Estimate the relative survival when it is the same as the net survival

Measures of net survival

- $S_E(.|z)$ is the expected survival conditional on covariates
- H is the distribution of Z
- Define $S_r(.|z)=S_O(.|z)/S_E(.|z)$
- Functionals of S_r, S_E, H
  - $R(S_r,S_E,H)(t)$

Requirements of $R(S_r,S_E,H)$

1. It **estimates** the net survival when the net survival is homogeneous. If $S_r(.|z)= S_r(.)$ then

$$R(S_r,S_E,H)(t)= S_r(t)$$

2. It is **invariant** under changes of the expected survival and the covariate distribution

$$R(S_r,S_E,H) = R(S_r,S_{E*},H^*)$$

3. Ordering: If $S_r(.|z) < S_{r*}(.|z)$ for all z, then

$$R(S_r,S_E,H)(.) < R(S_{r*},S_E,H)(.)$$

Desirable properties

- **Robustness**
- **Precision** (efficient estimators will have small variance)

Families of measures

- Ratio of weighted average observed to weighted average expected survival

$$E_H\{w(t,Z)S_O(t|Z)\}/E_H\{w(t,Z)S_E(t|Z)\}$$

  - In order for the measure to depend on S_O only through S_r the weights must be proportional to $1/S_E$:

$$E_H\{v(t,Z)S_O(t|Z)/S_E(t|Z)\}/E_H\{v(t,Z)\}$$
$$= E_H\{v(t,Z)S_r(t|Z)\}/E_H\{v(t,Z)\}$$

- Weighted mean of the relative survival
  - Note that v(t,z) must be proportional to $h_0(z)/h(z)$ in order for the measure not to depend on H.

$E_{H_0}\{v^*(t,Z)S_r(t|Z)\}$ where $E_{H_0}\{v^*(t,Z)\}=1$

Families of measures

- Weighted mean of the relative survival

$$R_w^1 = \frac{\mathrm{E_H}\{\mathrm{w(t,Z)S}_r\mathrm{(t|Z)\ h_0(Z)/h(Z)}\}}{\mathrm{E_H}\{\mathrm{w(t,Z)\ h_0(Z)/h(Z)}\}}$$

Families of measures (2nd family)

- Weighted excess hazard

$$R_w^2 = exp\left\{-\int_0^t \frac{\mathrm{E_H}\{\mathrm{w(u,Z)h_0(Z)/h(Z)\ d}\Lambda_e(\mathrm{u|Z})\}}{\mathrm{E_H}\{\mathrm{w(u,Z)\ h_0(z)/h(z)}\}}\right\}$$

Or

$$R_v^2 = exp\left\{-\int_0^t \frac{E_{H_0}\{\mathrm{v(u,Z)S}_r(\mathrm{u|Z})\mathrm{d}\Lambda_e(\mathrm{u|Z})\}}{E_{H_0}\{\mathrm{v(u,Z)\ S}_r(\mathrm{u|Z})\}}\right\}$$

Two families of measures

- Weighted mean of the relative survival

$$R_w^1(t) = \frac{E_{H_0}\{\mathrm{w(t,Z)S}_r\mathrm{(t|Z)}\}}{E_{H_0}\{\mathrm{w(t,Z)}\}}$$

- Weighted excess hazard

$$R_w^2(t) = exp\left\{\int_0^t \frac{E_{H_0}\{\mathrm{w(u,Z)S}_r\mathrm{(u|Z)d}\Lambda_e\mathrm{(u|Z)}\}}{E_{H_0}\{\mathrm{w(u,Z)\ S}_r\mathrm{(u|Z)}\}}\right\}$$

  - NB The weights are not a function of S_r, S_P or H

Estimators

$$Q_v^2 = exp\left\{-\int_0^t \frac{\sum \mathrm{v_i(u)h_0}(z_i)/\mathrm{h_n}(z_i)\mathrm{Y_i(u)/S_{Ei}(u)\{dNi(u)-d}\Lambda_{Ei}(\mathrm{u})\}}{\sum \mathrm{v_i(u)h_0}(z_i)/\mathrm{hn}(z_i)\mathrm{Yi(u)/SEi(u)}}\right\}$$

Here: h_n is the “empirical density”

$N_i(t)$ is the counting process (of death)

With: v=1 and h_0/h_n=1 we have the Pohar-Perme estimator

Note: h_0/h_n standardises inside the exponential

Estimators

$$Q_v^2 = exp\left\{-\int_0^t \frac{\sum v_i(u) h_0(z_i)/h_n(z_i) Y_i(u)/S_{Ei}(u)\{dNi(u) - d\Lambda_{Ei}(u)\}}{\sum v_i(u) h_0(z_i)/hn(z_i) Yi(u)/SEi(u)}\right\}$$

With: $v_i(u)=S_{Pi}(u)$ and $h_0/h_n=1$ we have the Ederer-II estimator

Estimators

$$Q_v^2 = exp\left\{-\int_0^t \frac{\sum v_i(u)h_0(z_i)/h_n(z_i)Y_i(u)/S_{Ei}(u)\{dNi(u)-d\Lambda_{Ei}(u)\}}{\sum v_i(u)h_0(z_i)/hn(z_i)Yi(u)/SEi(u)}\right\}$$

When S_E=1 (no competing risk):

- Both Ederer-II and Pohar-Perme give the Kaplan-Meier estimator, while Q_v^2 is a stratum weighted Kaplan-Meier estimator

Variance of ln(Q)

$$\int_0^t \frac{J(u)\sum_{i=1}^{n}\{\mathrm{v_i(u)(h_0/hn)}(z_i)\mathrm{/SEi(u)}\}^2 \mathrm{dN_i(u)}}{\{\sum_{i=1}^{n}\mathrm{v_i(u)(h_0/hn)}(z_i)\mathrm{/SEi(u)}\}^2}$$

Where J(u) is an indicator of at least one individual at risk at u.

In order to control the variance we want to counter balance the $1/S_{Ei}$ term which could cause the variance to “blow up” when S_{Ei} is very small (for some i)

Set $v_i(u)=S_{0i}(u)$ using a “standard” survival function

$v_i(u)=S_{0i}(u)$: Choice of S_0

- S-zero (not S-Oh)
- If $S_0=S_E$ (and $h_0=h$) then have Ederer-II
- Want S_0 to be the minimum of S_E (or even S_O) in each of the populations being compared

- Also for robustness want $S_0(t|z)$ to be zero for values of t for which $S_E(t|z)$ can be very small for some z in one of the populations of interest
- But for precision do not want $S_0(t|z)$ to be zero unnecessarily

What does $Q^2_{S_0}$ estimate?

- The ratio of observed to expected survival that would be observed in a standard population in which the covariate distribution at diagnosis matched the standard covariate distribution and the expected mortality matched the standard mortality

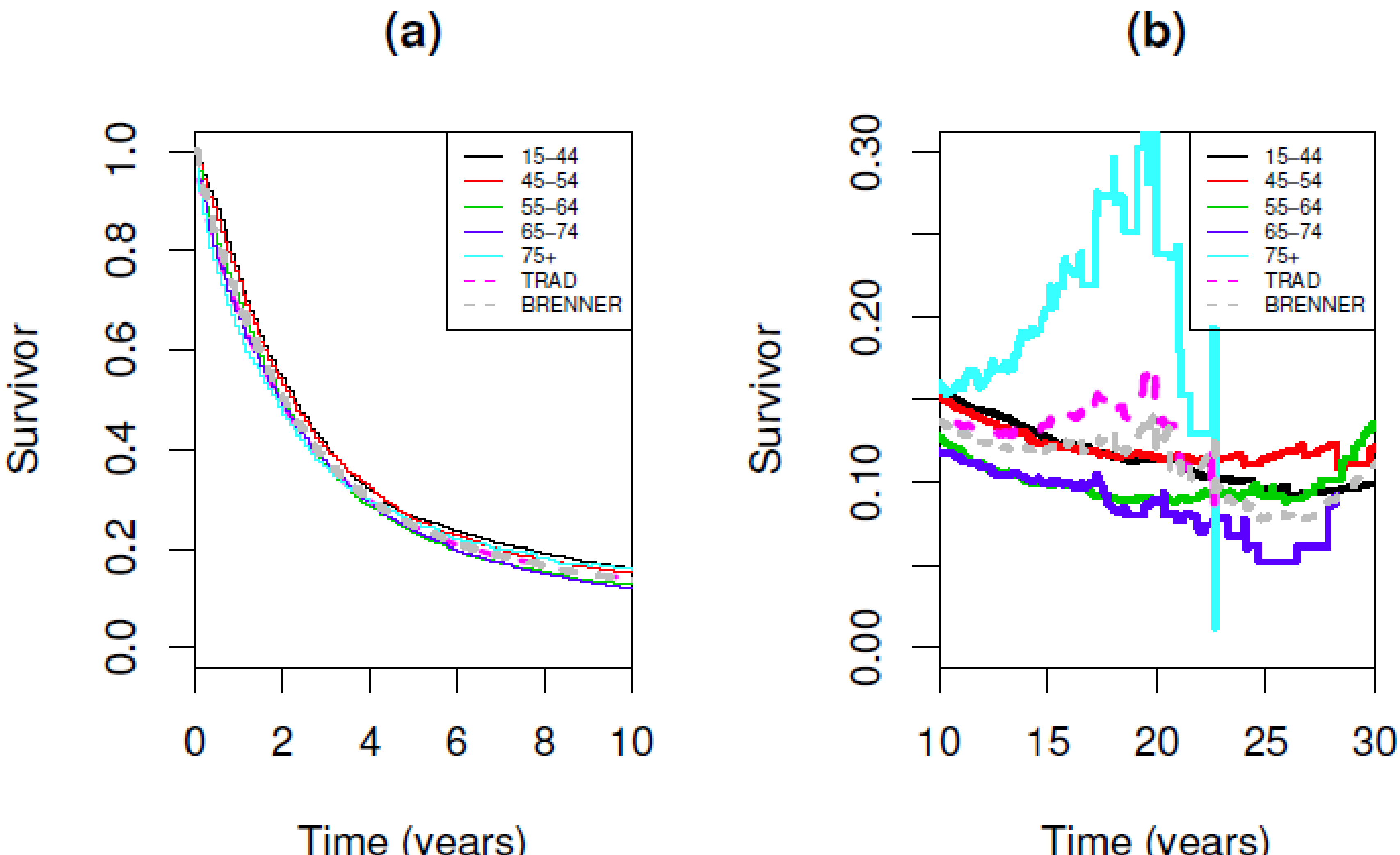
An estimator for R[1]

$$\frac{\sum_{i=1}^{n}\{(S_{0i}/SEi)(t))(h_0/hn)(z_i)\}Y_i(t)}{\widehat{S(t)}\sum_{i=1}^{n}\{S_{0i}(t))(h_0/hn)(z_i)\}}$$

Here $\widehat{S(t)}$ is the Kaplan-Meier estimator of the censoring distribution

Note: $EY=S_O$ so Y_i/S_E is an "estimate" of the i'th relative survival. Hence this estimator can be viewed as a (very finely) stratified estimator (with stratification weights that are time-dependent)

EXAMPLE: SURVIVAL FROM BREAST CANCER WITH DIST. METS, USA 1973-2010 ($n = 16,597$)



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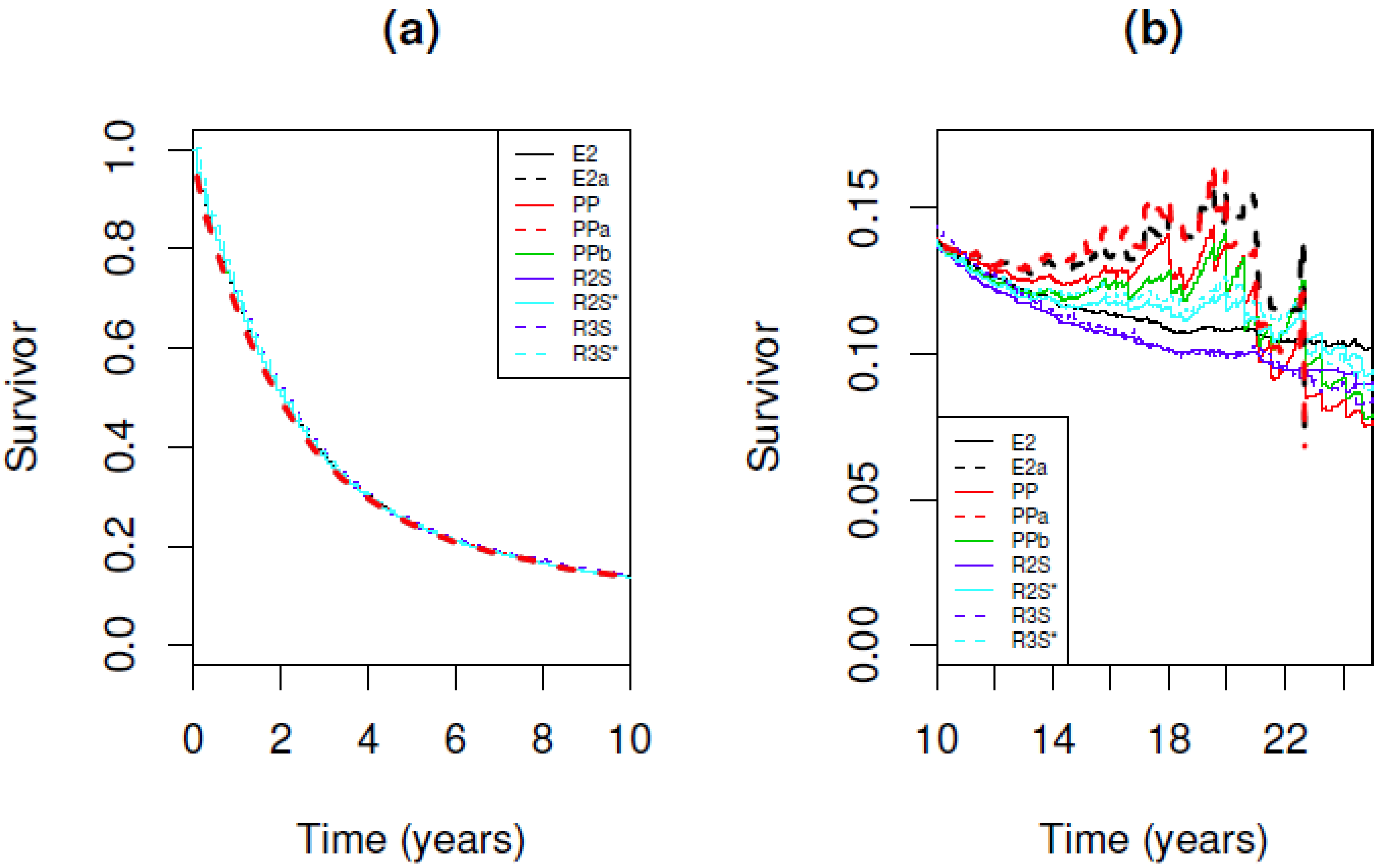
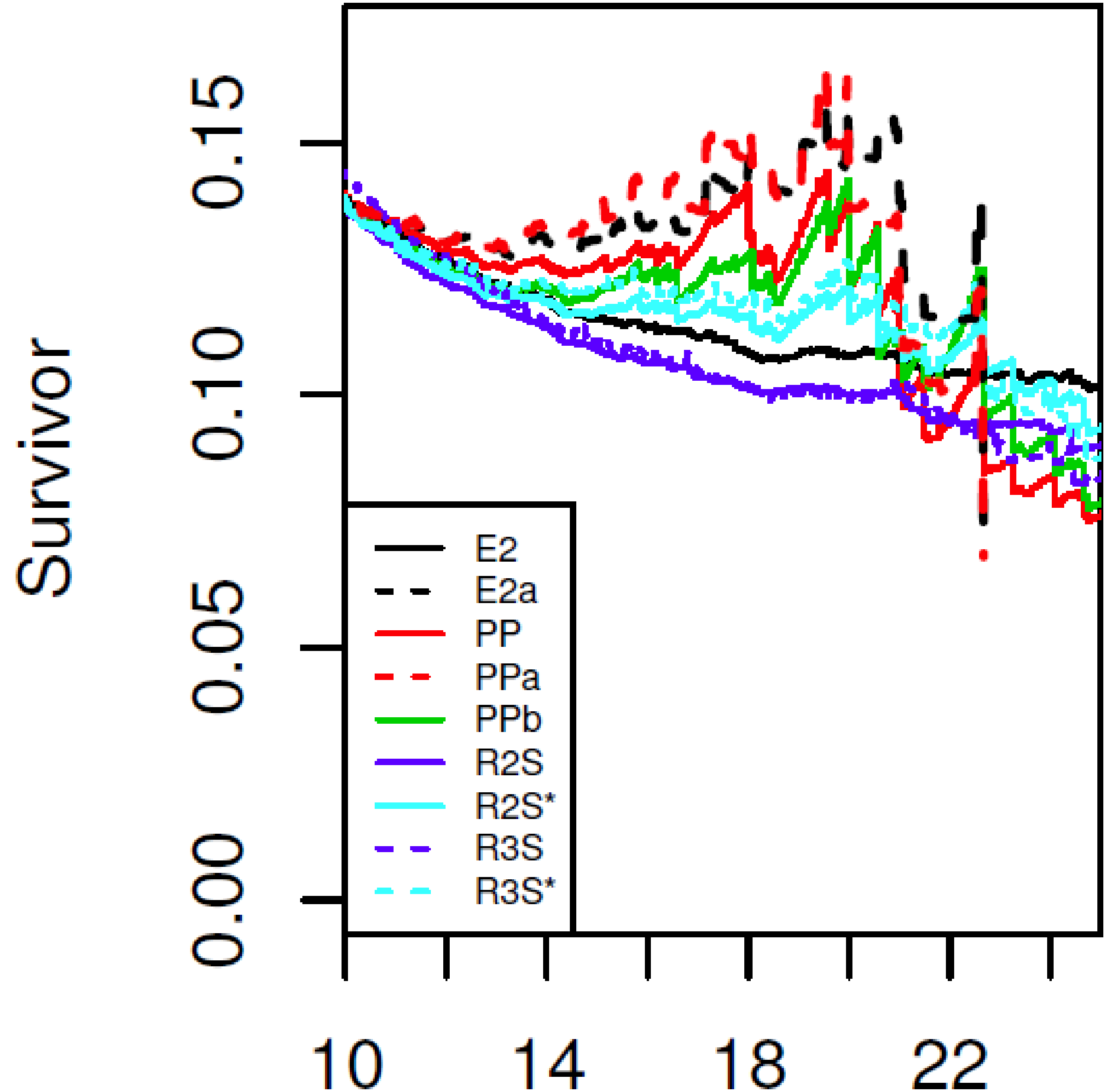


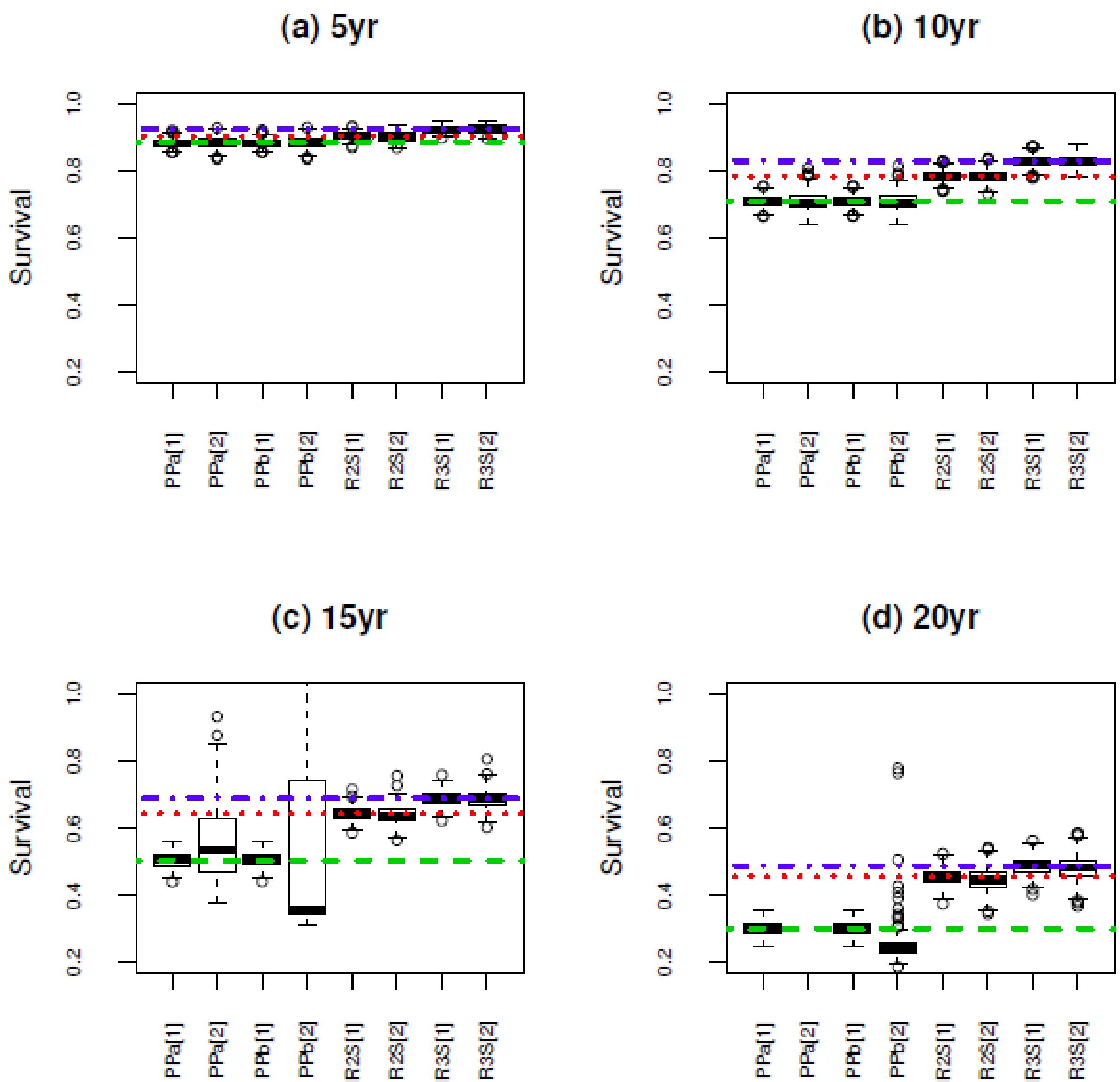

Survivor
0.00
0.05
0.10
0.15
10
14
18
22
E2
E2a
PP
PPa
PPb
R2S
R2S*
R3S
R3S*

SIMULATION: SETUP ($n = 2,000$)

Population	Mortality rate aged 65-69	Mortality rate aged 70-85	Mortality rate aged 86+	Percent in Group 1
1: women USA 1980	Ref	Ref	Ref	60%
2: higher mortality	x1.2	x2.0	x4.0	70%
Standard population	x2.0	x4.0	x100.0	50%

- Two groups in population
  1. Aged 65 at diagnosis
  2. Aged 75 at diagnosis
- Same excess hazard all populations (3% per year)
- No censoring considered here (does not change findings)

SIMULATION RESULTS



RESULTS

Measure	Pop	Mean bias (%)	SD (×100)	Var($\hat{R}$)/R^2 (×10000)		Mean bias (%)	SD (×100)	Var($\hat{R}$)/R^2 (×10000)
(a) 5-yr					(c) 15-yr			
net-strata	1	-0.1	1.2	1.7		0.0	1.9	13.9
net-brenner	1	-0.1	1.2	1.7		0.1	1.9	13.8
std-r2	1	0.0	1.0	1.2		0.0	1.9	8.9
std-r3	1	0.0	0.9	1.0		0.1	2.1	9.3
net-strata	2	-0.3	1.6	3.3		****	****	****
net-brenner	2	-0.2	1.6	3.3		-0.8	25.4	2549.9
std-r2	2	-0.1	1.2	1.8		-0.7	2.7	17.4
std-r3	2	-0.1	1.0	1.1		-0.3	2.9	18.0
(b) 10-yr					(d) 20-yr			
net-strata	1	-0.2	1.6	5.1		0.6	2.2	51.8
net-brenner	1	-0.1	1.6	5.1		1.0	2.2	52.8
std-r2	1	-0.1	1.5	3.9		-0.2	2.4	28.6
std-r3	1	0.0	1.7	4.0		0.1	2.6	28.6
net-strata	2	-0.8	2.8	15.5		****	****	****
net-brenner	2	-0.5	2.8	15.4		7.3	130.1	188389.5
std-r2	2	-0.3	1.7	4.8		-1.4	3.9	71.7
std-r3	2	-0.2	1.7	4.4		-0.6	4.1	70.9