Fitting smooth-in-time prognostic risk functions via logistic regression

James A. Hanley[1] Olli S. Miettinen[1]

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University

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OUTLINE

WHY PROFILE-SPECIFIC RISK FUNCTIONS?

- 5-year Cumulative Incidence or 5-year Risk, of stroke for 78 yr. white female with isolated hypertension (Systolic Pressure=180) if treat / do not treat hypertension ???
- Most reports of RCTs are for "average" profile, and use hazard/incidence ratios (HRs) rather than risk differences
- For an individual patient, $\widehat{HR} = \widehat{IDR} = 0.65$ not helpful.
- $\widehat{Risk_{0-5}} = \widehat{CI_{0-5}} = 8.2\%$ *if* $Tx = 0$ (don't treat);
  $\widehat{Risk_{0-5}} = \widehat{CI_{0-5}} = 5.2\%$ *if* $Tx = 1$ (treat),

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- but need risks specific to the profile (unless profile is near the centre of profiles included in trial).

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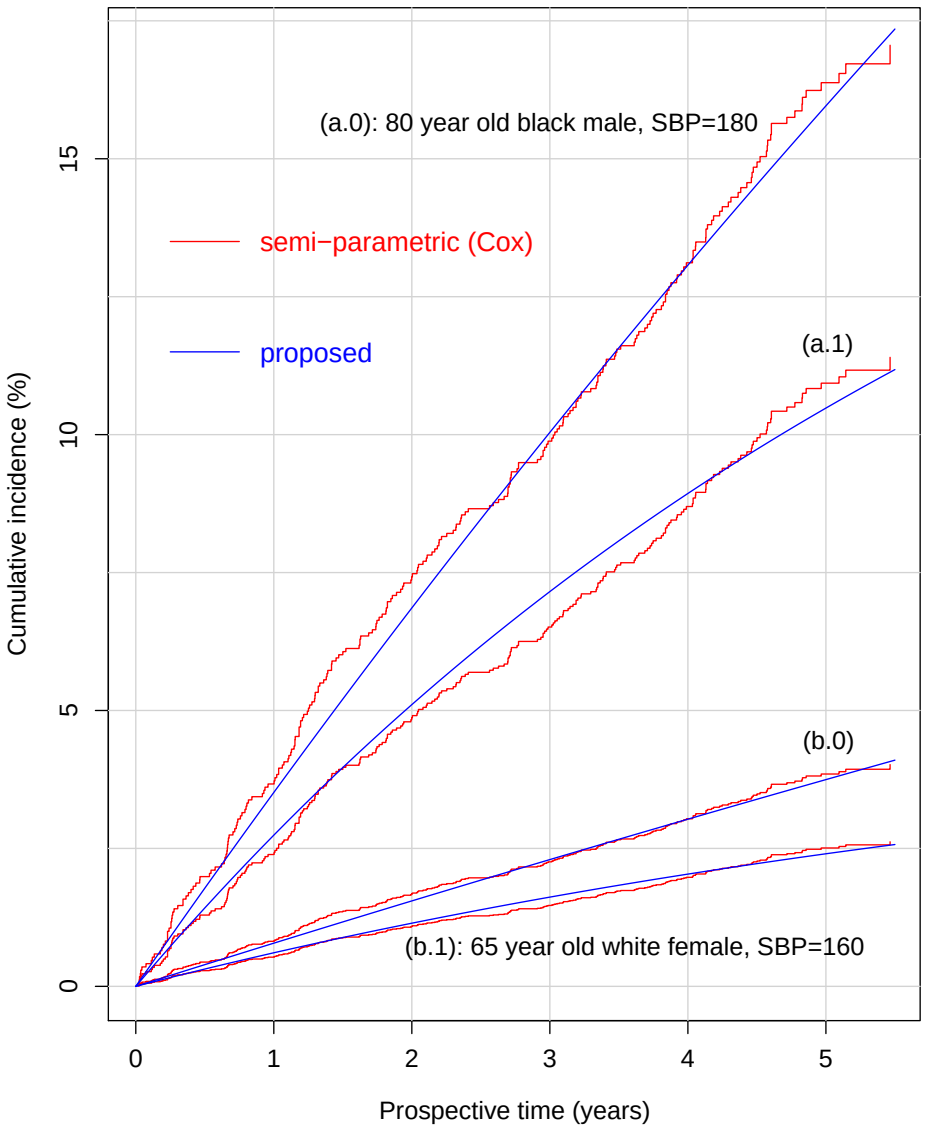
5-year Cumulative Incidence / Risk of Stroke:



<- High-risk, untreated

<- High-risk, treated

<- Low-risk, untreated

<- Low-risk, treated

WHAT WE WISHED TO DO

- Model the hazard (h), or incidence density (ID), as a smooth function of
  - set of prognostic indicators
  - choice of intervention
  - prospective time.
- Estimate the parameters of this function.
- Calculate profile-specific risk/cumulative incidence, $\widehat{CI_x(t)}$ from this function:

$$\widehat{CI_x(t)} = 1 - \exp\{-\widehat{H_x(t)}\} = 1 - \exp\{-\int_0^t \widehat{h_x(u)}du\}.$$

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FULLY-PARAMETRIC MODEL: FORM

$$\log\{h(x,t)\} = g(x,t,\beta) \quad \Longleftrightarrow \quad h(x,t) = e^{g(x,t,\beta)}$$

- x is a realization of the covariate vector X, representing the patient profile P, and possible intervention I.
- β : a vector of parameters with unknown values,
- $g()$ includes constant 1, variates for P, I and t;
- $g()$ can have product terms involving P, I, and t.
- $g()$ must be 'linear' in parameters, in '*linear* model' sense.

- 'proportional hazards' if no product terms involving t & I
- If t is represented by a linear term (so that 'time to event' $\sim$ *Gompertz*), then $\widehat{CI_{p,\,i}(t)}$ has a closed smooth form.
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- Unable to find a ready-to-use ML procedure within the common statistical packages.
- Likelihood becomes quite involved even if no censored observations.
- Albertsen & Hanley('98); Efron('88, '02); Carstensen('00):

  - divide 'survival time' of each subject into time-slices;

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FITTING: OUR APPROACH

- An extension of the method of Mantel (1973) to binary outcomes that deals with time dimension.
- Mantel's problem:
  - $(c =)165$ 'cases' of $Y = 1$,
  - 4000 instances of $Y = 0$.
  - Associated regressor vector X for each of the 4165
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MANTEL'S SOLUTION

- Form a reduced dataset containing...
  - All c instances (cases) of $Y = 1$
  - Random sample of the $Y = 0$ observations
- Fit the same logistic model to this reduced dataset.

  "Such sampling will tend to leave the dependence of the log odds on the variables unaffected except for an additive constant."

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DATA TO EXPLAIN OUR APPROACH

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..... SHEP Cooperative Research Group (1991).

..... Journal of American Medical Association 265, 3255-3264.

- 4,701 persons with complete data on $P = \{\underline{\text{age}}, \underline{\text{sex}}, \underline{\text{race}}, \text{and systolic } \underline{\text{blood pressure}}\}$ and $I = \{\underline{\text{active/placebo}}\}$.
- Study base of $B = 20,894$ person-years of follow-up; $c = 263$ events ("cases") of stroke identified.

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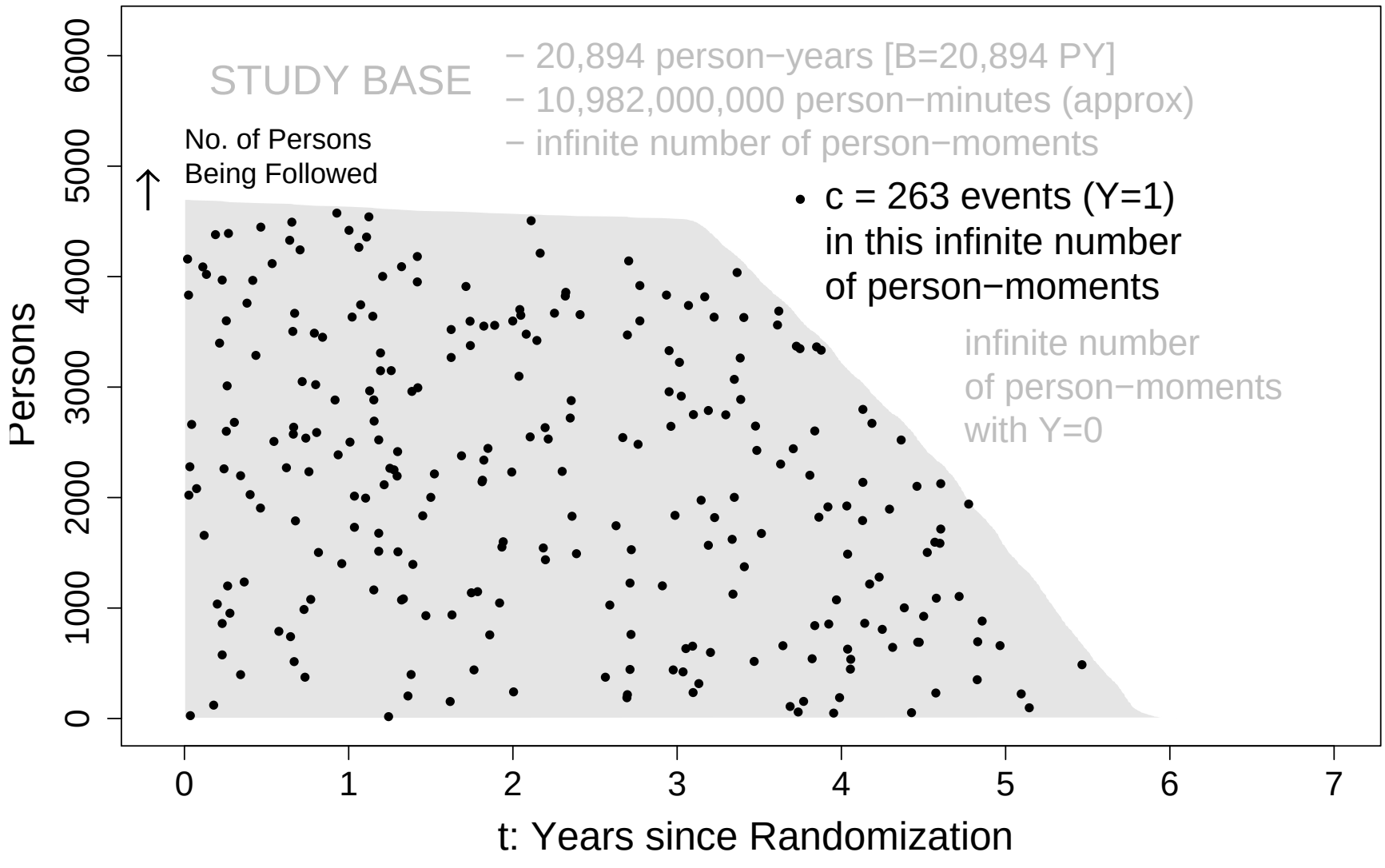
STUDY BASE, and the 263 cases



OUR APPROACH

- Base series: representative (unstratified) sample of base.
- b: size of base series
- B: amount of population-time constituting study base.
- $B(x,t)$: population-time element in study base

$$\frac{\Pr(Y=1|x,t)}{\Pr(Y=0|x,t)} = \frac{h(x,t) \times B(x,t)}{b \times [B(x,t)/B]} = h(x,t) \times (B/b),$$

- $\log(B/b)$ is an offset [a regression term with *known* coefficient of 1].

$\longrightarrow$ logistic model, with t having same status as x, and offset,

directly yields $\widehat{h(x,t)} = \widehat{ID}_{x,t} = \exp\{\widehat{g(x,t)}\}$.

How large should b be on relation to c?

b: no. of instances of $Y = 0$;
c: no. of instances of $Y = 1$

- Mantel (1973)...

  little to be gained by letting the size of one series, b, become arbitrarily large if the size of the other series, c, must remain fixed.

- With 2008 computing, we can use a b/c ratio as high as 100, and thereby extract virtually all of the information in the base.

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$\log[h] = \Sigma \beta_k X_k$, where

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X_2 = Indicator of male gender
X_3 = Indicator of Black race
X_4 = Systolic BP (in mmHg) - 140

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- Formed person-moments dataset pertaining to:
  - case series of size $c = 263$ ($Y = 1$)
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  - (randomly-selected) base series of size $b = 26,300$ ($Y = 0$).
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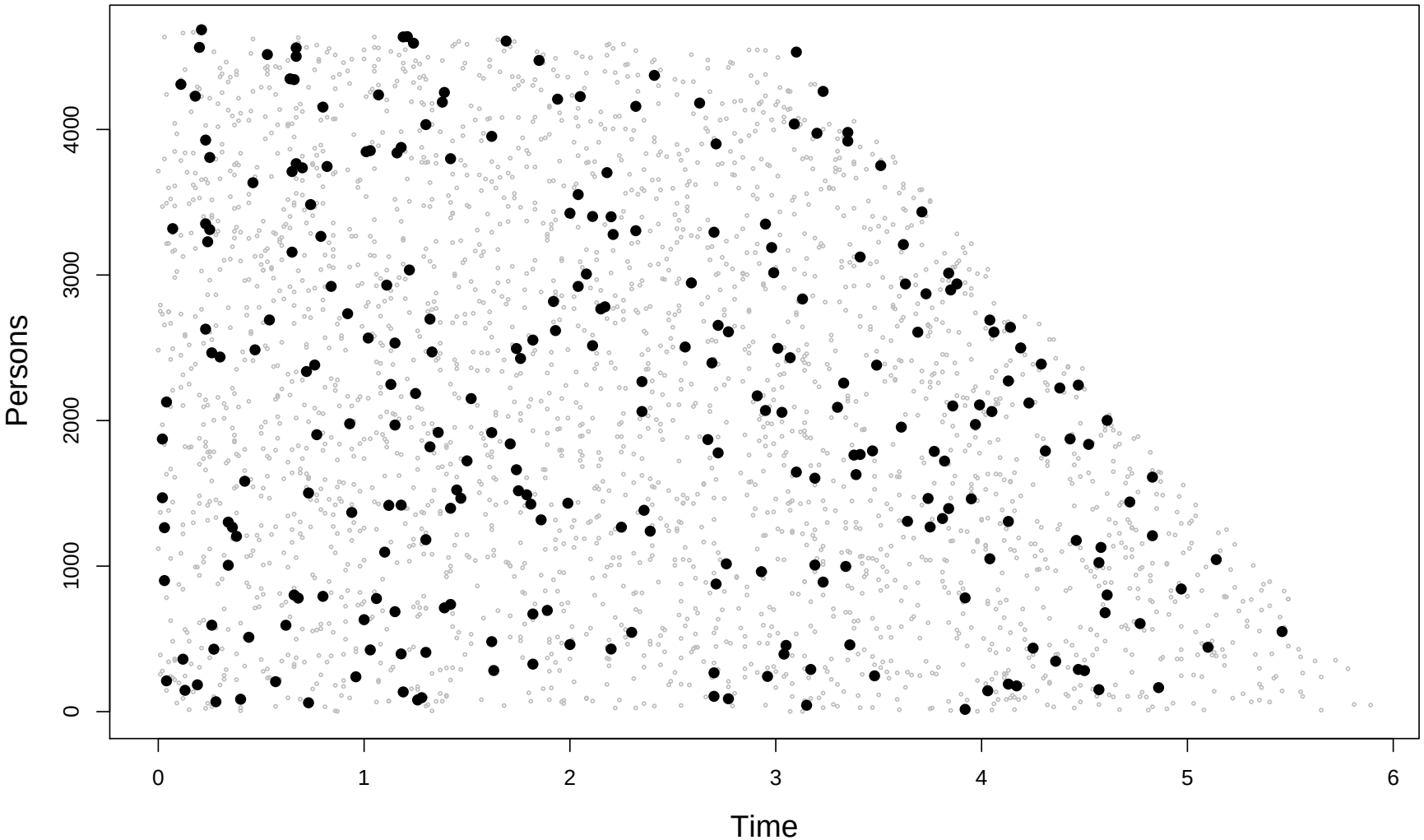

FITTED VALUES

	Proposed logistic regression		Cox regression
β_{age-60}	0.041	0.041	0.041
$\beta_{I_{male}}$	0.257	0.258	0.259
$\beta_{I_{black}}$	0.302	0.301	0.303
$\beta_{SBP-140}$	0.017	0.017	0.017
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$\beta_{I_{Active\ treatment}}$	-0.200	-0.435	-0.435
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β_0	*-5.390*	*-5.295*	
β_t	-0.014	-0.057	
$\beta_{t \times I_{Active\ treatment}}$	-0.107		

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Risk	I	$h(t)$ [ID(t)]	$H(5)$ [$\int_0^5 h_x(t)dt$]	$CI(5)$ [$1 - e^{-H(5)}$]	Δ
Low	0	$e^{-4.86-0.014t}$	0.037	0.036	
	1	$e^{-5.06-0.124t}$	0.024	0.024	1.2%
High	0			0.16	
	1			0.10	6%
Overall	0			0.076	
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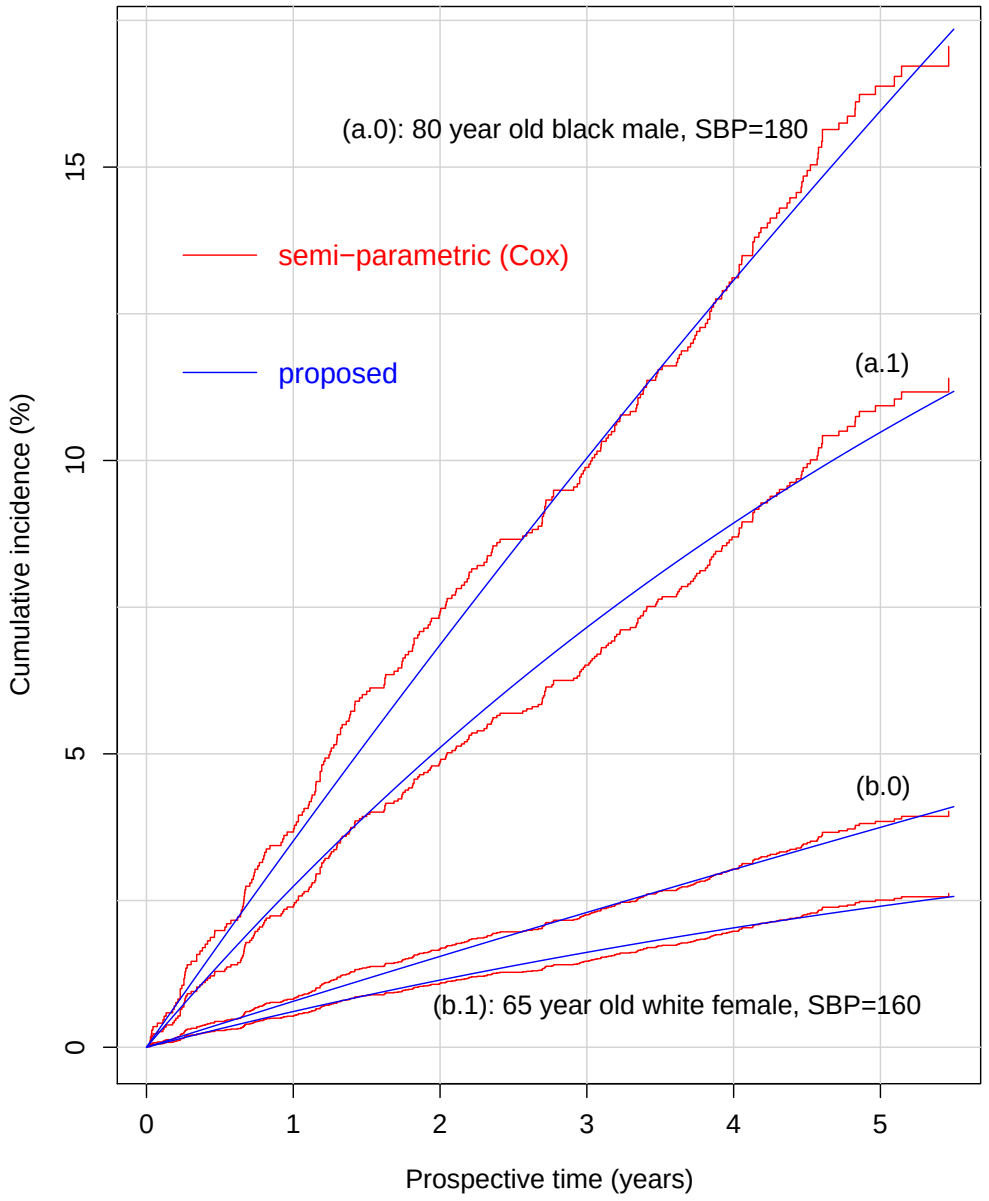
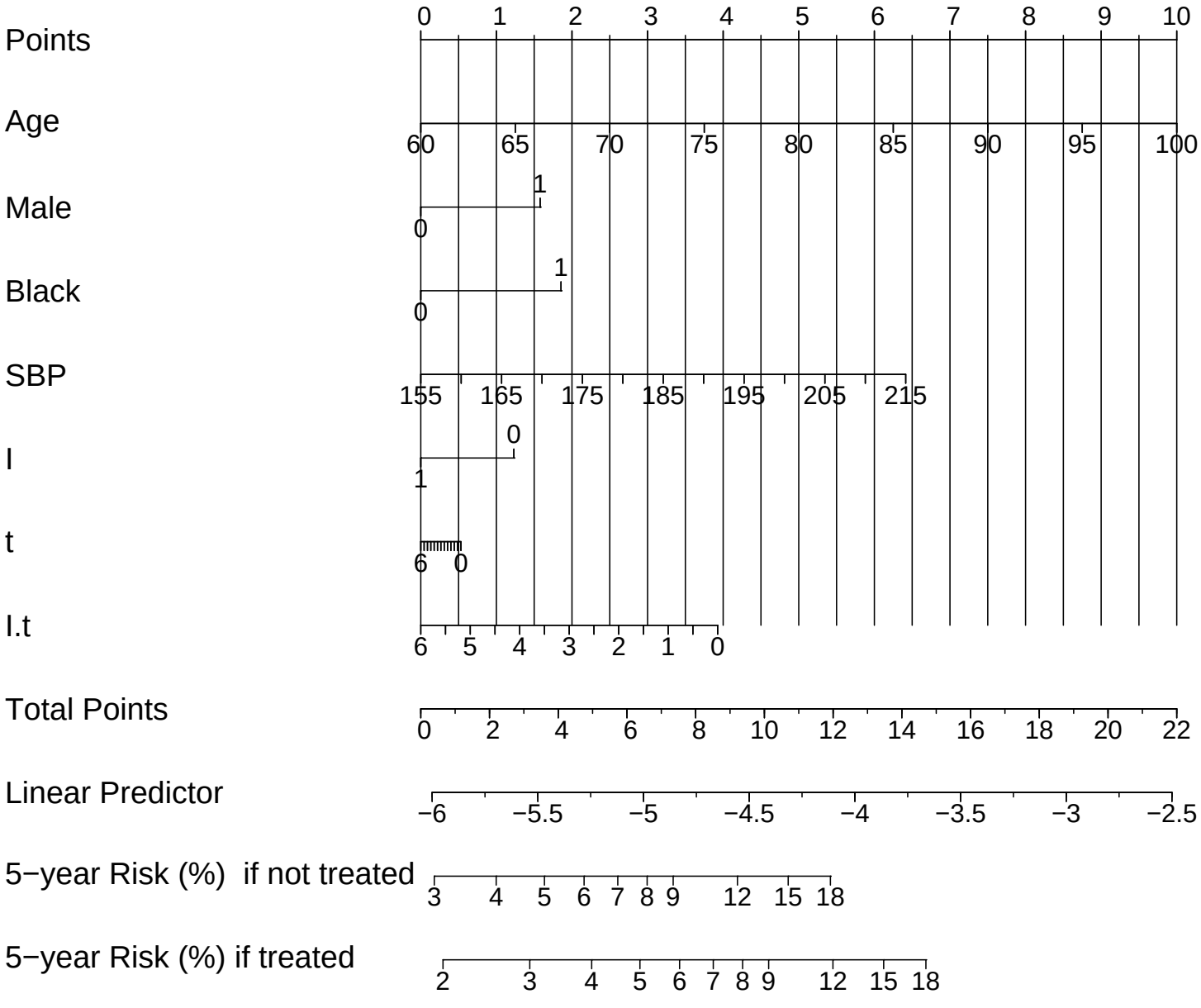

(a.0): 80 year old black male, SBP=180
semi−parametric (Cox)
proposed
(a.1)
(b.0)
(b.1): 65 year old white female, SBP=160
Cumulative incidence (%)
0
5
10
15
0
1
2
3
4
5
Prospective time (years)


Points
0 1 2 3 4 5 6 7 8 9 10
Age
60 65 70 75 80 85 90 95 100
Male
1
0
Black
1
0
SBP
155 165 175 185 195 205 215
I
0
1
t
6 0
I.t
6 5 4 3 2 1 0
Total Points
0 2 4 6 8 10 12 14 16 18 20 22
Linear Predictor
−6 −5.5 −5 −4.5 −4 −3.5 −3 −2.5
5−year Risk (%) if not treated
3 4 5 6 7 8 9 12 15 18
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FUNDING / CO-ORDINATES / SOFTWARE

Natural Sciences and Engineering Research Council of Canada

James.Hanley@McGill.CA
http://www.biostat.mcgill.ca/hanley

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- All instances of event in study base identified $\rightarrow$ study's 'case series' of person-moments, characterized by $Y = 1$.
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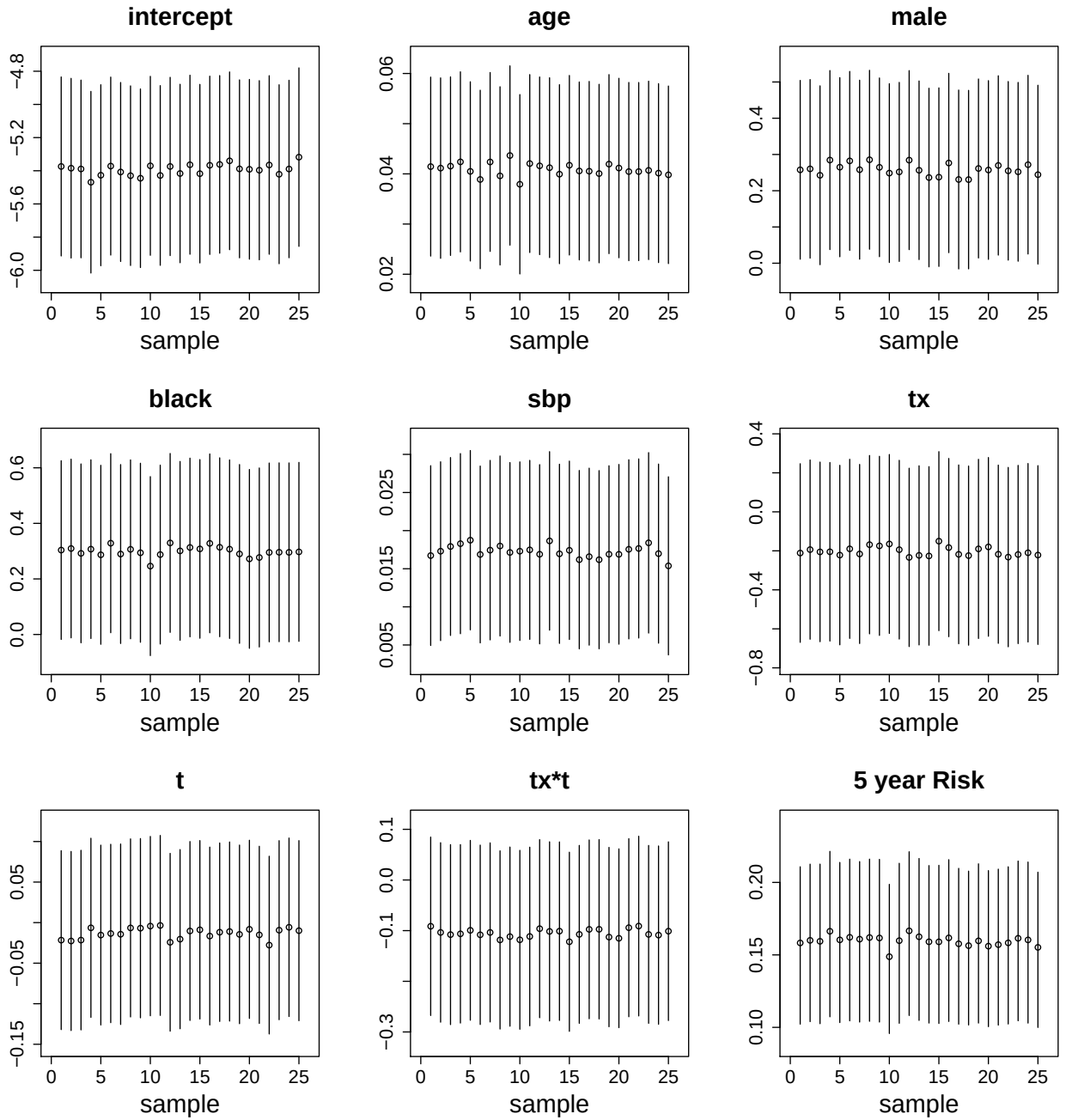
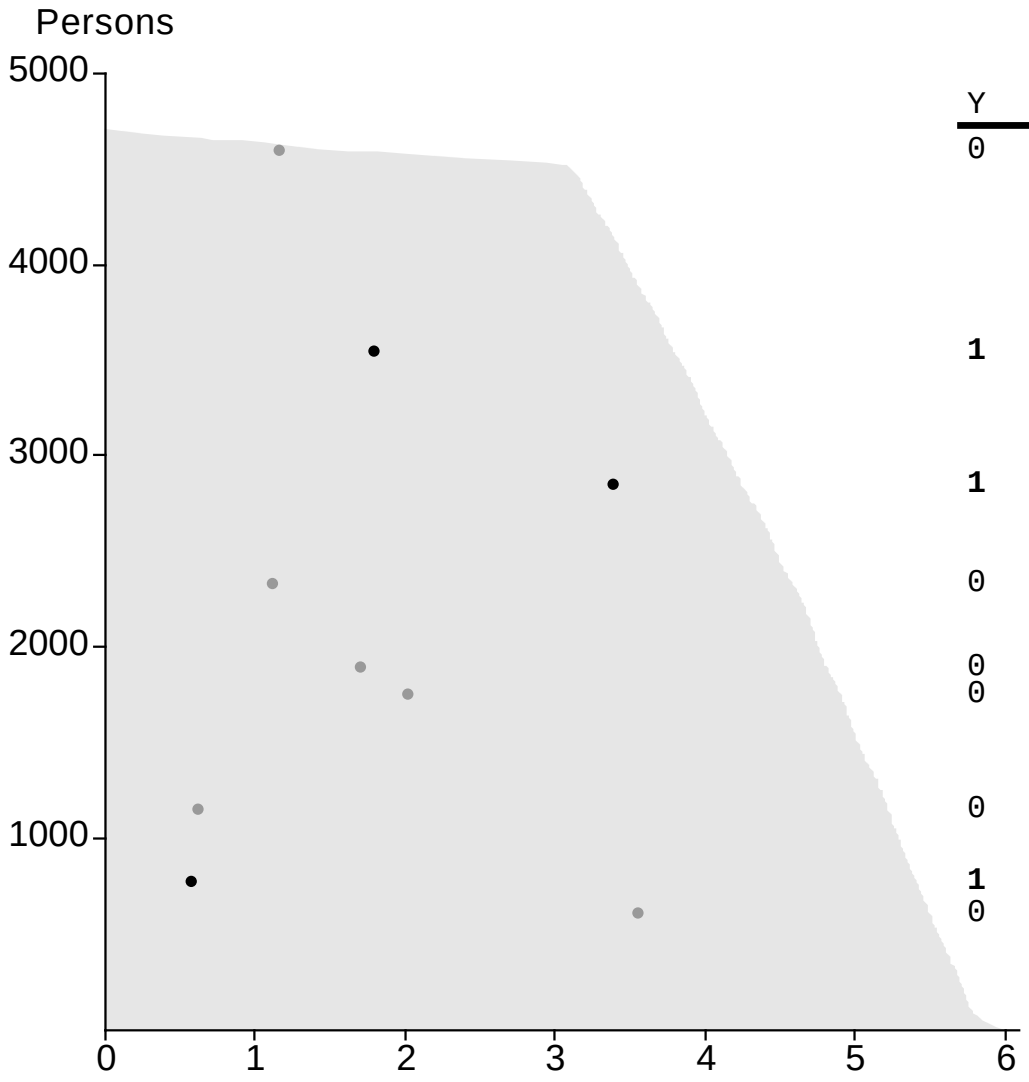


STABILITY ?

Point and (95% confidence) interval estimates of hazard function, and of 5-year risk for a specific (untreated) high-risk profile. Fits are based on 25 different random samples of b =26,300 from the infinite number of person-moments in the study base, and same $c = 263$ cases each run.

DATASET FOR LOGISTIC REGRESSION (SCHEMATIC)

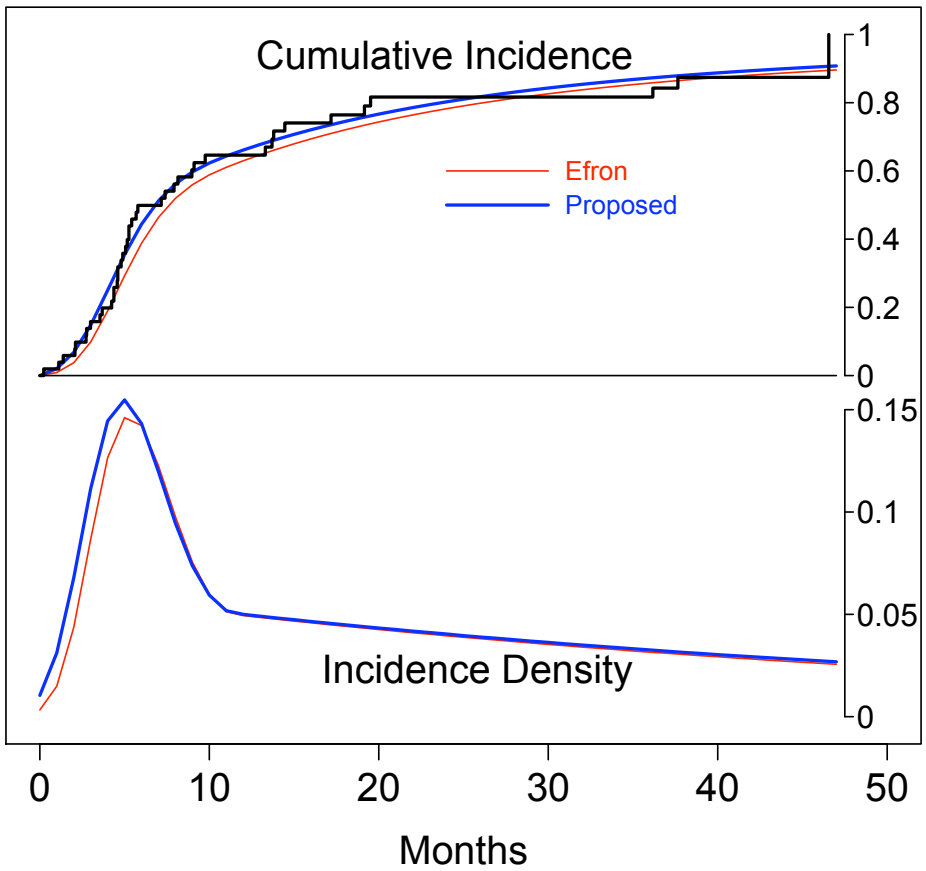


Y	Age	B	M	SBP	I	t
0	81	1	0	161	0	1.16
1	**69**	**0**	**1**	**161**	**0**	**1.79**
1	**85**	**0**	**1**	**184**	**0**	**3.39**
0	70	0	1	185	0	1.11
0	69	0	0	182	0	1.70
0	73	0	1	167	1	2.02
0	73	1	0	199	0	0.62
1	**69**	**1**	**0**	**166**	**1**	**0.57**
0	72	0	0	172	1	3.56

DATA ANALYZED BY EFRON, 1988

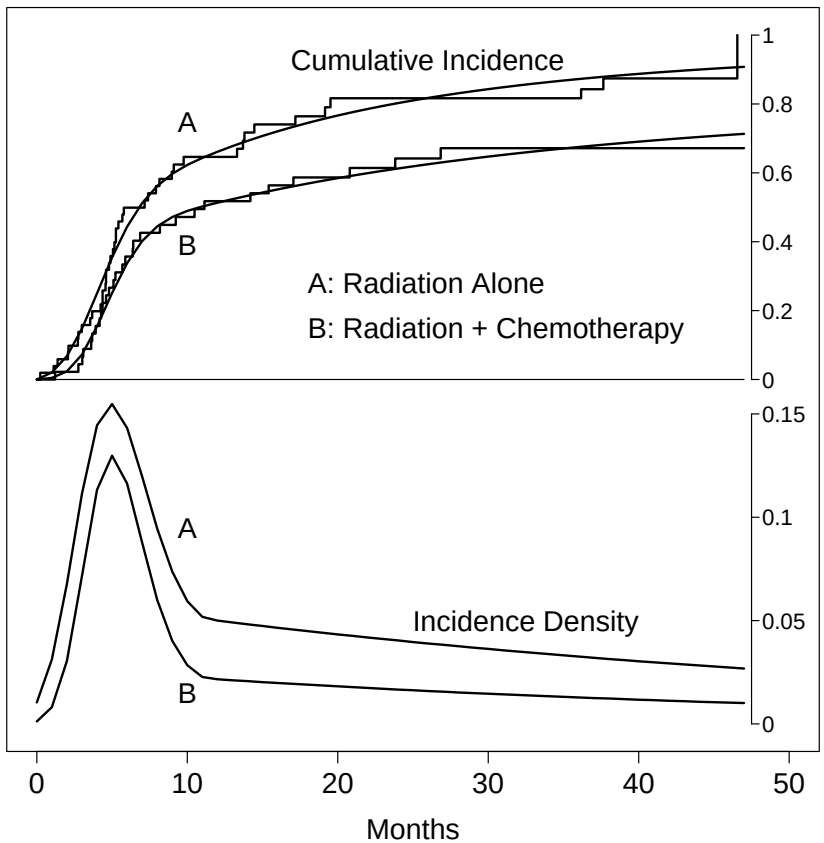
Arm A [time-to-recurrence of head & neck cancer]

Cum. Inc. estimates – K-M, Efron & Proposed



Inc. density estimates – Efron & Proposed

Arm A *vs.* Arm B



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Predominant use of the semi-parametric 'Cox model.'

- Time is considered as a non-essential element.
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- Estimates can be based on logistic regression.
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Hazard modelled, semi-parametrically, as

$$h_x(t) = [\exp(\beta x)]\lambda_0(t),$$

- $T = t$: a point in prognostic time,
- β : vector of parameters with unknown values;
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  $\widehat{CI}_{0-10} = 15\%$ *if* $Tx = 0; 10\%$ *if* $Tx = 1$, more helpful.
- Not specific to this particular type of patient, if grade & stage {of Pr Ca} or age/race/sex/SPB {SHEP Study} not near the typical of those in trial.
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How large should b be on relation to c?

Mantel (1973)... [our notation, and slight change of wording]

> *By the reasoning that* $cb/(c+b)$ $[= (1/c + 1/b)^{-1}]$ *measures the relative information in a comparison of two averages based on sample sizes of c and b respectively, we might expect by analogy, which would of course not be exact in the present case, that this approach would result in only a moderate loss of information. (The practicing statistician is generally aware of this kind of thing. There is little to be gained by letting the size of one series, b, become arbitrarily large if the size of the other series, c, must remain fixed.)*

- With 2008 computing, we can use a b/c ratio as high as 100.
- $b/c = 100 \rightarrow Var[\hat{\beta}]_{b/c=100} = 1.01 \times Var[\hat{\beta}]_{b/c=\infty}$, i.e. 1% $\uparrow$
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How large should b be on relation to c?

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> *By the reasoning that* $cb/(c+b)$ $[= (1/c + 1/b)^{-1}]$ *measures the relative information in a comparison of two averages based on sample sizes of c and b respectively, we might expect by analogy, which would of course not be exact in the present case, that this approach would result in only a moderate loss of information. (The practicing statistician is generally aware of this kind of thing. There is little to be gained by letting the size of one series, b, become arbitrarily large if the size of the other series, c, must remain fixed.)*

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