A SAS macro to fit Flexible Parametric Survival Models: Applications of the Royston-Parmar models

explanation and examples

June, 2014

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Flexible parametric survival models

credit where it is due:

Royston and Parmar (2002 Stats in Medicine)

- and others

Lambert, P (2009 Stata Journal) for Stata program stpm2 and its extensions

Why parametric survival models?

- Inclusion of more prognostic factors (or continuous factors) argues against stratification
- Communication of results
- Special applications (eg. economic models)
- Some quantities that might be of interest
  - hazard rate function
  - absolute differences between groups
  - crude probability of death
  - ‘postponable’ deaths
  - cure models
  - mean survival

Flexible parametric survival models

Some advantages:

- Use of restricted cubic splines for hazard function
- Models in continuous time (no time splitting)
- Model at individual level
- Survival and hazard functions can be derived and manipulated
- Intuitive specification of non-proportional effects
- Quantify absolute effects
- Prediction at any time point, for any set of covariates

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Sas macro suite for Royston-Pamar models

- modeled on Stata programs *stpm2*, *predict* and *rcsgen*
- tested in sas 9.2 – 9.4
- Uses *nlmixed* for estimation, *iml* for post-estimation predictions
- Fits on cumulative log hazard scale
- Allows for cohort and period definitions of risk time
- Relative survival regression, competing risks
- Model fits and prediction equations are generated automatically from user specifications
- Point and interval estimates

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Analysis of a Clinical Trial*

comparing sas and stata results

	Cox	Weibull	R-P(3)
		Hazard Ratio (SE)	
Sas	0.95 (0.08)	0.93 (0.09)	0.94 (0.08)
Stata	0.95 (0.08)	0.93 (0.09)	0.94 (0.07)

	Predicted 6 month survival treatment arm vs placebo	
Sas	40.1 vs 38.4	39.6 vs 37.3
Stata	40.1 vs 38.4	39.6 vs 37.3

* 'Topical' trial: erlotinib vs placebo (Lee, et al 2012)

Application to Cancer Surveillance

Colorectal cancer patients (n = 3,800 1,200 deaths)

diagnosed in NS 2007 – 2011, follow-up to end of 2011

DCOs excluded (zero length survival causes problems)

Covariates:
  age (in years) at diagnosis
  sex
  stage (summary I – IV)

Effect of stage on hazard is time-dependent

Display hazard plots, hazard differences,
  hazard ratios

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Examples of macro calls

Model fit:

%sas_stpm2(sex stage2 stage3 stage4 age1 age2 age3 ,
scale=hazard, df=3,
tvc = stage2 stage3 stage4 , dftvc = 2) ☺

Hazard plot (for specified age and sex):

%predict(haz, hazard, at = sex:1) ☺

Hazard difference (stage II vs stage I)

%predict(hdiff, haz_diff, hdiff1 = sex:1 stage2:1 zero
hdiff2 = sex:1 zero) ☺

Hazard ratio (stage II vs stage I):

%predict(hr, hratio,
hrnum = sex:1 stage2:1 zero
hrdenom = sex:1 zero) ☺

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Effect of age on hazard

What have we learned by estimating a non-linear effect of age on survival?

Since age is NOT a time-varying component of the model, display hazard ratio with a fixed age as the reference

Example: Males CRC, Female breast cancer (similar model with age, stage) ☺

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Example 2

modeling relative survival (proceed with caution)

Net mortality (probability of death):

chances of death by year n, as if cancer were the only possible cause of death

= (1 - Relative survival)

Crude mortality:

chances of death by year n, when patient may die of non-cancer cause first

implies a competing risks framework

can be estimated from a relative survival model

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Crude probability of death

Some computational details:

underlying model for hazard:
general (all causes) mortality + excess (cancer) mortality

general mortality : population life tables
excess mortality : relative survival model

requires numerical integration of product of survival and hazard functions

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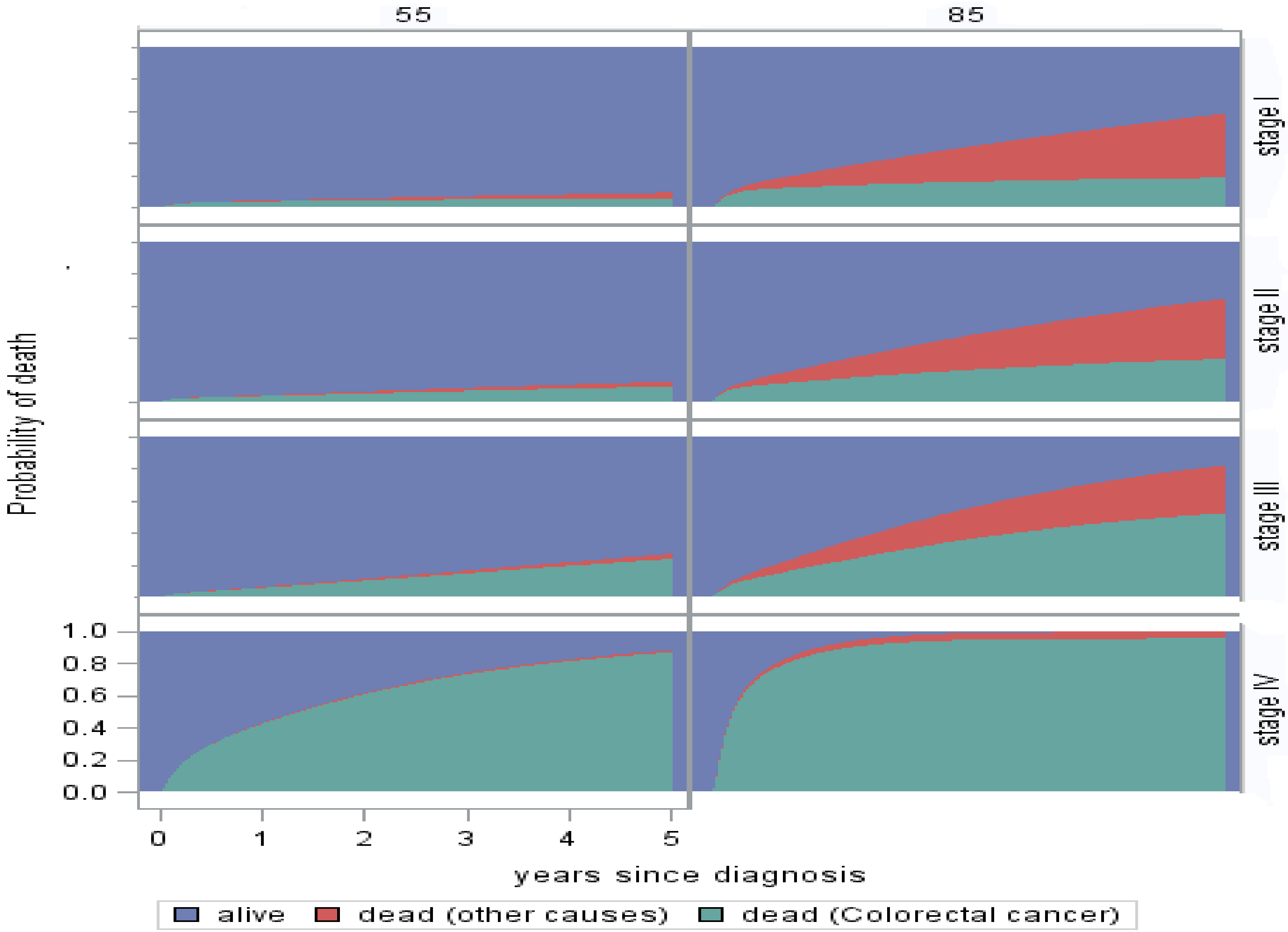
Colorectal Survival

probability of death by 5 years
men, by age at diagnosis

			Crude (%)	
	stage	Net (%)	cancer	other causes
age 55	I	6	6	3
	II	10	10	3
	III	24	24	3
	IV	88	87	1
age 85	I	21	18	40
	II	33	27	38
	III	66	52	30
	IV	100	95	4

Crude Probability of Death

Men, Colorectal Cancer



Conclusions

Flexible parametric survival modeling allows for new ways to explore the impact of patient characteristics on survival
- hazard plot
- hazard difference
- hazard ratio
- time-dependent covariate effects
- non-linear effects of covariates

Sas macros facilitate fitting and display

Work in progress:
- 'cure' models
- 'avoidable' deaths
- mean survival

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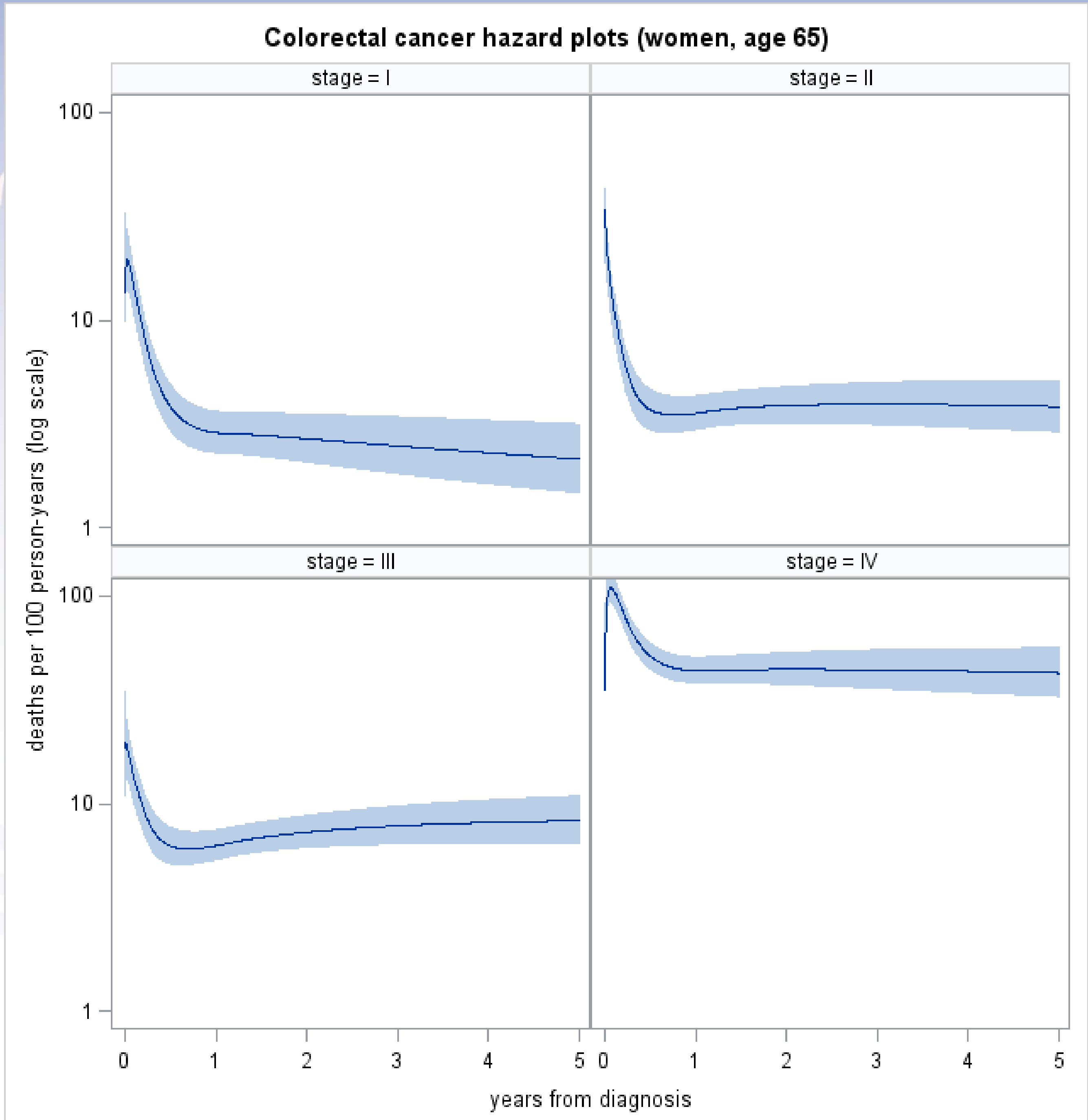
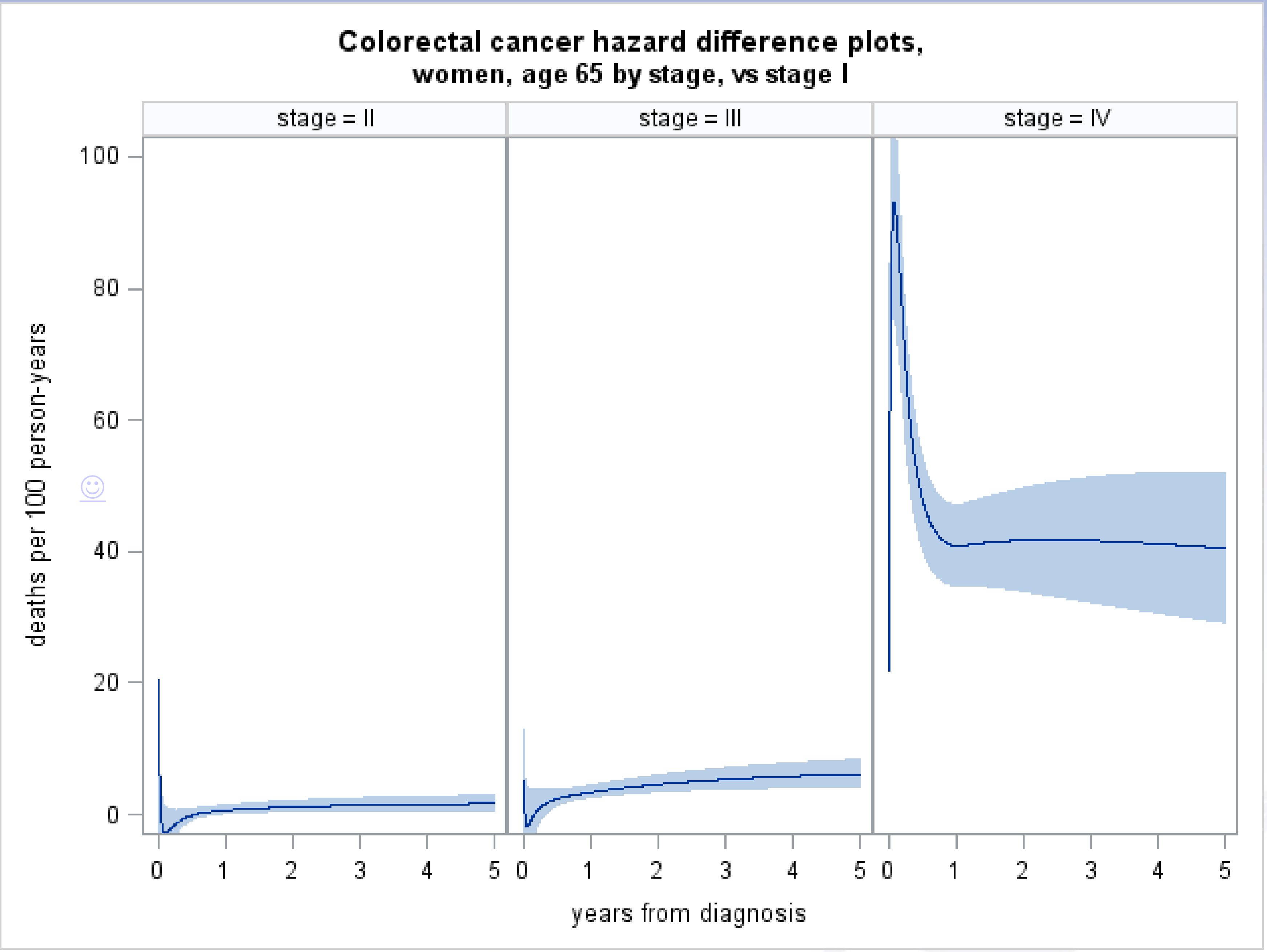
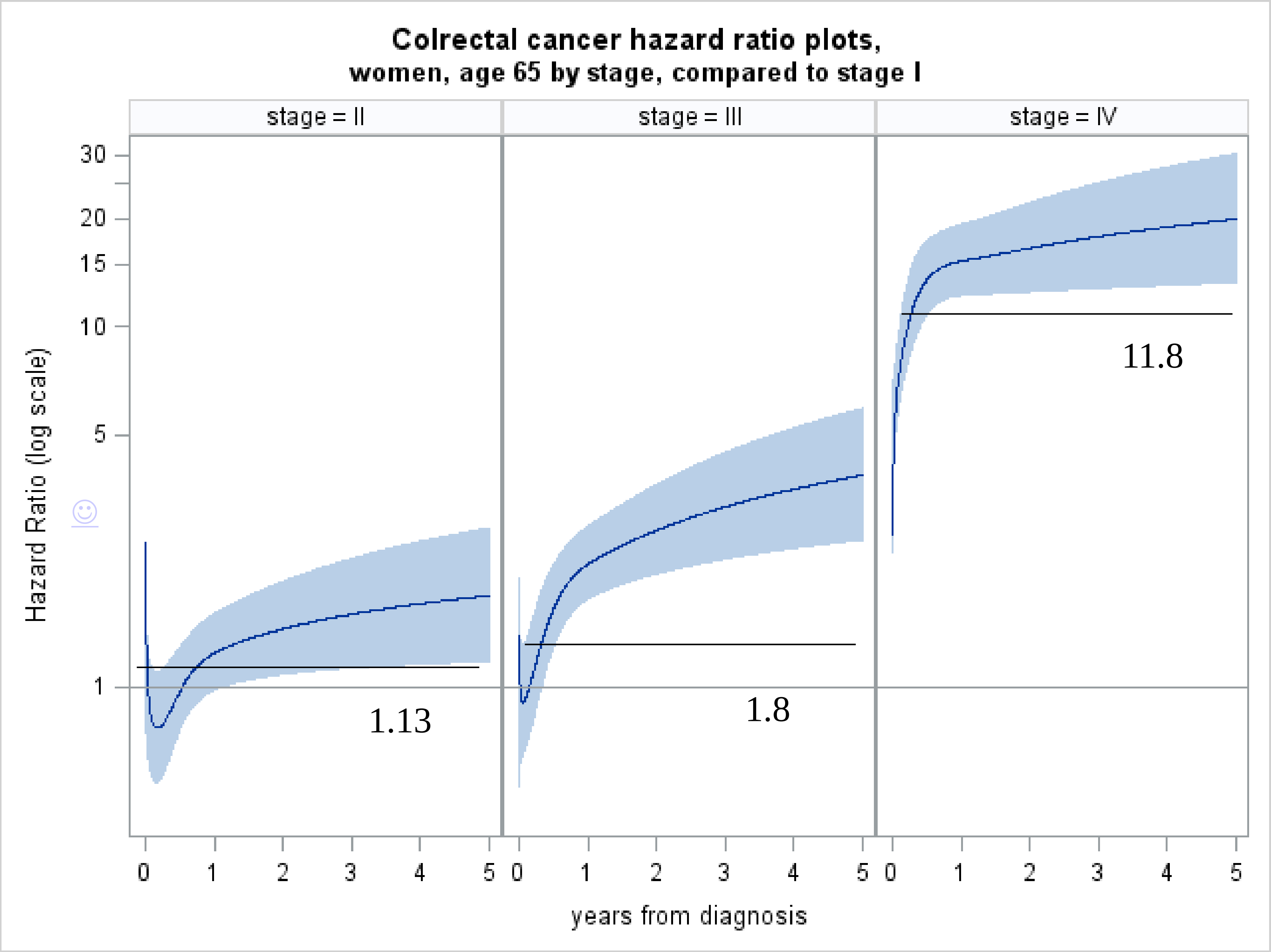
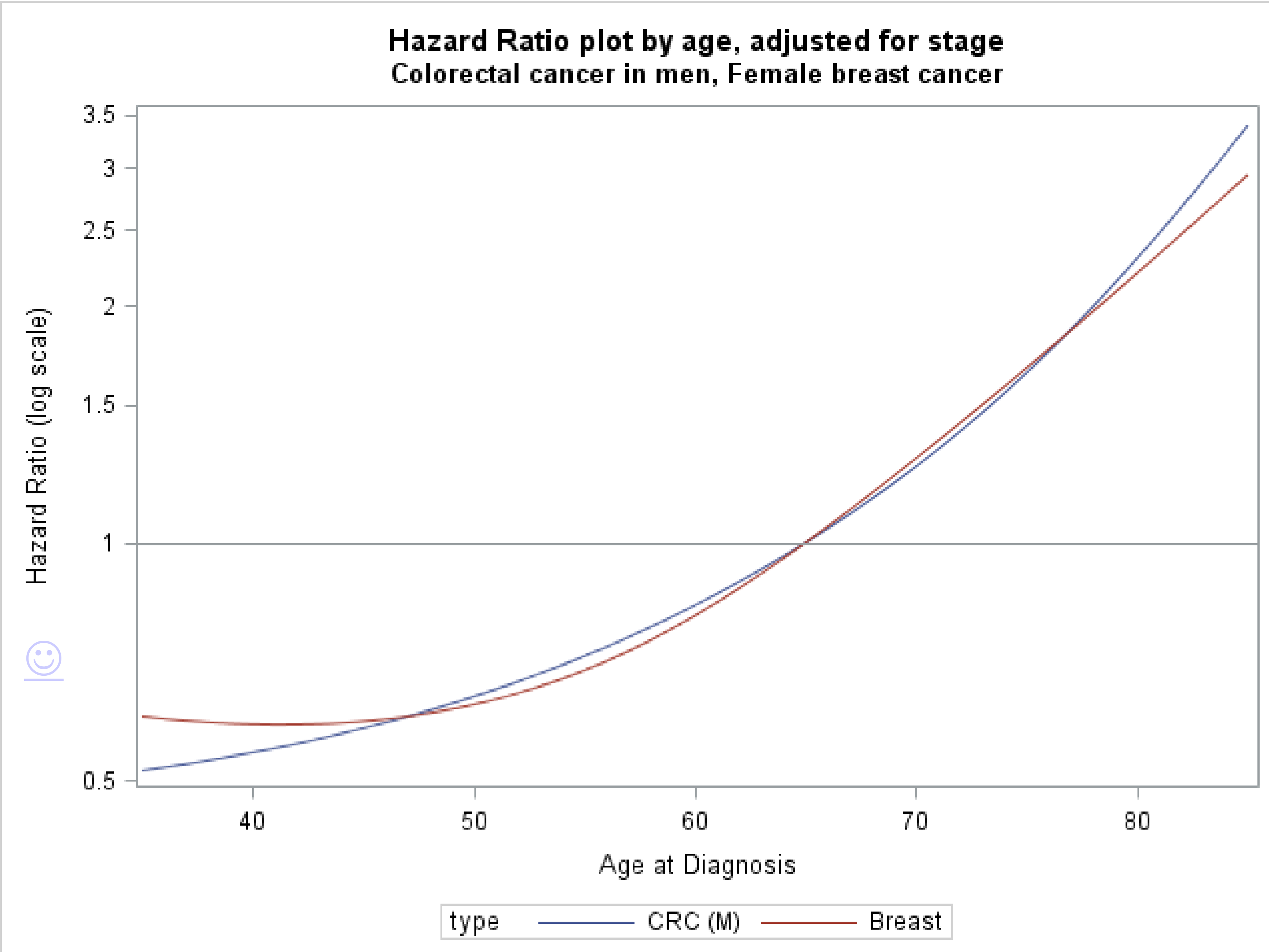
Parameter estimates (partial) log hazard ratio, SE

Parameter	Estimate	SE	t-value	Prob t
sex	-0.1704	0.05904	-2.89	0.0039
stage2	-1.1815	0.5186	-2.28	0.0228
stage3	-0.8290	0.5672	-1.46	0.1439
stage4	2.3917	0.4759	5.03	<.0001
age1	1.2696	0.7418	1.71	0.0871
age2	-0.4028	0.1241	-3.25	0.0012
age3	-0.03837	0.03716	-1.03	0.3019
rcs1	0.7911	0.05978	13.23	<.0001
rcs2	2.3442	0.4854	4.83	<.0001
rcs3	-0.1399	0.02335	-5.99	<.0001
…				


Colorectal cancer hazard plots (women, age 65)
stage = I
stage = II
stage = III
stage = IV
deaths per 100 person-years (log scale)
100
10
1
0
1
2
3
4
5
years from diagnosis


Colorectal cancer hazard difference plots,
women, age 65 by stage, vs stage I
stage = II
stage = III
stage = IV
deaths per 100 person-years
100
80
60
40
20
0
0
1
2
3
4
5
years from diagnosis


Colrectal cancer hazard ratio plots,
women, age 65 by stage, compared to stage I
stage = II
stage = III
stage = IV
Hazard Ratio (log scale)
30
20
15
10
5
1
1.13
1.8
11.8
0 1 2 3 4 5
years from diagnosis


Hazard Ratio plot by age, adjusted for stage
Colorectal cancer in men, Female breast cancer
Hazard Ratio (log scale)
3.5
3
2.5
2
1.5
1
0.5
40
50
60
70
80
Age at Diagnosis
type
CRC (M)
Breast