

## Cox proportional hazards models

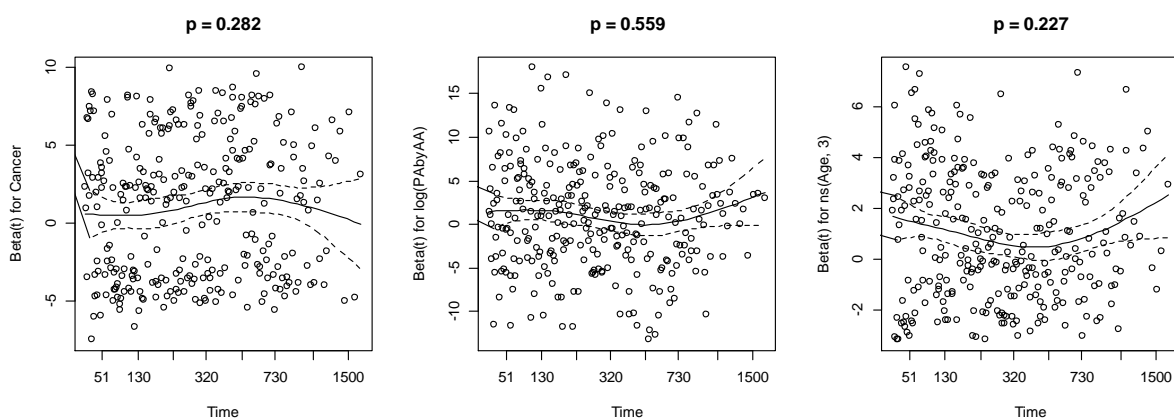
Models were fit in R (version 4.3) using the packages `survival` 3.5-5 and `splines` 4.3 using data of patients with no missing values ( $n = 969$ , number of events = 299). The effect of PA/AA is controlled for UICC stage, Sex and Age by including these variables as co-variables in the model. Age is modelled as a continuous variable and mapped by a natural spline with 3 degrees of freedom to allow for a non-linear relationship between age and the log hazard. Cancer is added as a fixed effect to estimate the hazard ratios between cancers, other categorical variables are added as strata, allowing different baseline hazards for each category.

### Model 1

This model assumes that the effect of PAbyAA is the same in all cancers. The model formula is

```
surv ~ Cancer + log(PAbyAA) + ns(Age, 3) + strata(UICC) + strata(Sex)
```

The proportional hazards assumption is checked using the `pxc.zph` function (for details see: P. Grambsch and T. Therneau (1994), Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*, 81, 515-26):



The global p-value of the score test is 0.33. There is no evidence for a violation of the proportional hazards assumption.

The summary of the fitted model is as follows:

	coef	exp(coef)	se(coef)	z	Pr(> z )	
CancerHNC	-0.3188	0.7270	0.1407	-2.266	0.02345	*
CancerUROC	0.2478	1.2812	0.1575	1.573	0.11580	
log(PAbyAA)	0.9996	2.7172	0.3493	2.862	0.00422	**
ns(Age, 3)1	0.6377	1.8922	0.3574	1.784	0.07438	.
ns(Age, 3)2	0.2849	1.3296	1.3501	0.211	0.83287	
ns(Age, 3)3	1.5107	4.5300	0.3793	3.983	6.81e-05	***

Concordance= 0.64 (se = 0.019 )  
 Likelihood ratio test= 75.1 on 6 df, p=4e-14  
 Wald test = 79.27 on 6 df, p=5e-15  
 Score (logrank) test = 83.46 on 6 df, p=7e-16

The coefficients denote the log hazard ratios. CancerHNC and CancerUROC refer to the hazard ratios to CancerGI, which is not shown here because it serves as the reference. The coefficient of log(PAbyAA) is positive (translating to an *increase* in the hazard or a decrease in survival with increasing PA/AA ratio) with a p-value of 0.004. The coefficients of Age refer to the spline basis and should not be interpreted directly. These coefficients are required by the model to correct the hazard ratios of the other variables by the impact of age.

### Model 2

This model is similar to Model 1 but uses a dichotomized variable (PAbyAA.) distinguishing  $PA/AA \leq 1$  and  $PA/AA > 1$  to estimate the hazard ratio comparing these two groups:

```
Surv ~ Cancer + PAbyAA. + ns(Age, 3) + strata(UICC) + strata(Sex)
```

	coef	exp(coef)	se(coef)	z	Pr(> z )	
CancerHNC	-0.3307	0.7184	0.1404	-2.356	0.01847	*
CancerUROC	0.2595	1.2963	0.1572	1.650	0.09885	.
PAbyAA.PA/A ratio > 1	0.4885	1.6299	0.1660	2.943	0.00325	**
ns(Age, 3)1	0.6093	1.8391	0.3563	1.710	0.08724	.
ns(Age, 3)2	0.2414	1.2731	1.3431	0.180	0.85735	
ns(Age, 3)3	1.5655	4.7852	0.3792	4.129	3.65e-05	***

### Model 3

This model tries to dissect the effects of PA/AA within the different cancers by including an interaction term of Cancer and log(PAbyAA):

```
Surv ~ Cancer + log(PAbyAA):Cancer
      + ns(Age, 3) + strata(UICC) + strata(Sex),
```

	coef	exp(coef)	se(coef)	z	Pr(> z )
CancerHNC	-0.3189	0.7270	0.2140	-1.490	0.1362
CancerUROC	0.2207	1.2469	0.2099	1.051	0.2932
ns(Age, 3)1	0.6429	1.9020	0.3581	1.795	0.0726 .
ns(Age, 3)2	0.2906	1.3372	1.3487	0.215	0.8294
ns(Age, 3)3	1.5116	4.5338	0.3798	3.980	6.89e-05 ***
CancerGIC:log(PAbyAA)	1.0502	2.8583	0.5818	1.805	0.0710 .
CancerHNC:log(PAbyAA)	1.0452	2.8439	0.5586	1.871	0.0614 .
CancerUROC:log(PAbyAA)	0.8693	2.3851	0.6622	1.313	0.1893

The last three coefficients in the table show the effects of PA/AA estimated within each cancer type. All estimates are positive and of similar size, but fail to reach statistical significance. A comparison to model 1 shows that no evidence is provided that the effect of PA/AA would differ between cancers (likelihood ratio test  $p = 0.97$ ). A comparison to model 3 excluding the interaction term demonstrates that the information of the cancers together is sufficient to conclude that the hazard ratio increases with PA/AA (likelihood ratio test,  $p = 0.043$ ), in-line with the results of model 1. The corresponding analysis based on dichotomized PA/AA values gave very similar results.