The use of fractional polynomials to model interactions between treatment and continuous covariates in clinical trials

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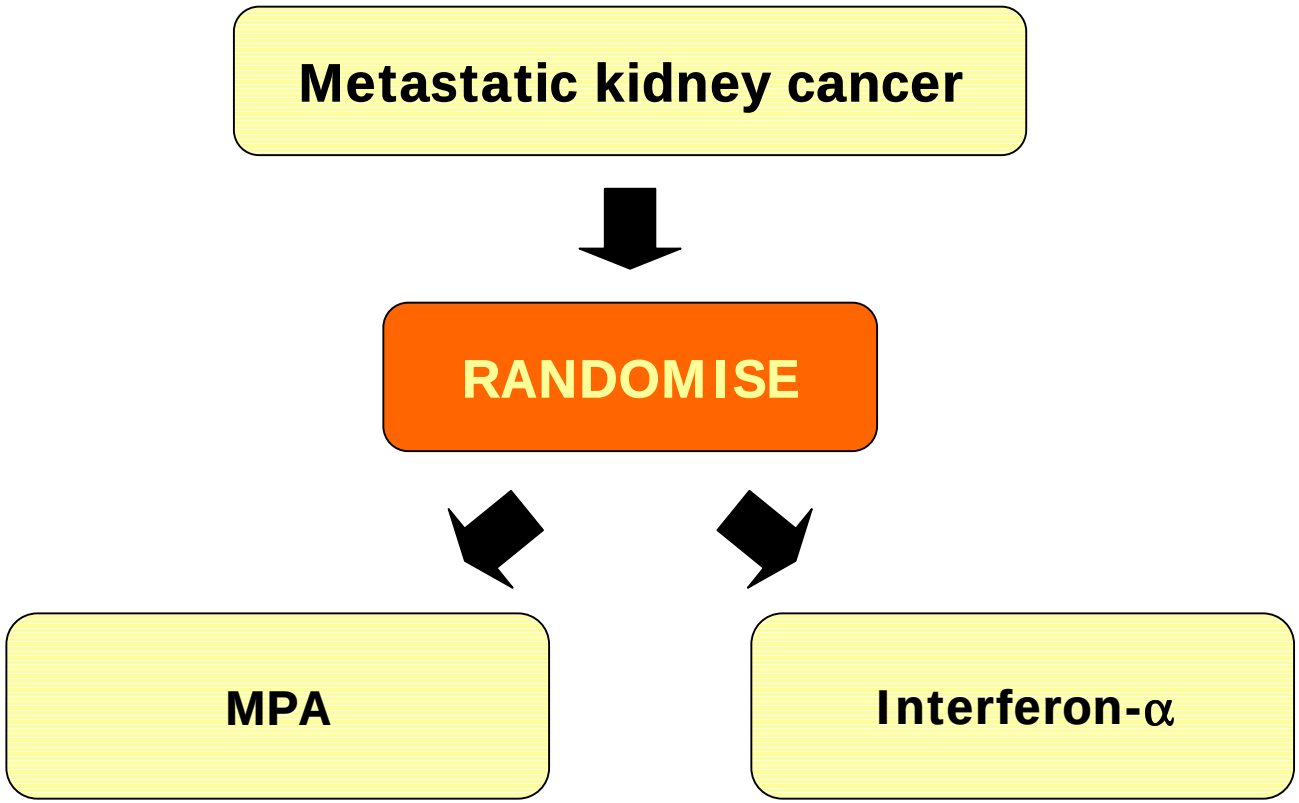
Medical Research Council RE01 trial in advanced kidney cancer



RE01 Trial design

- Eligibility
  - Renal cell cancer which had spread to other organs
  - 'Measurable' disease (to evaluate progression)
  - WHO performance status 0-2 (2 = part bedridden)
- Primary outcome - overall survival
- Group-sequential design
  - Possible early stopping if advantage/no advantage of interferon

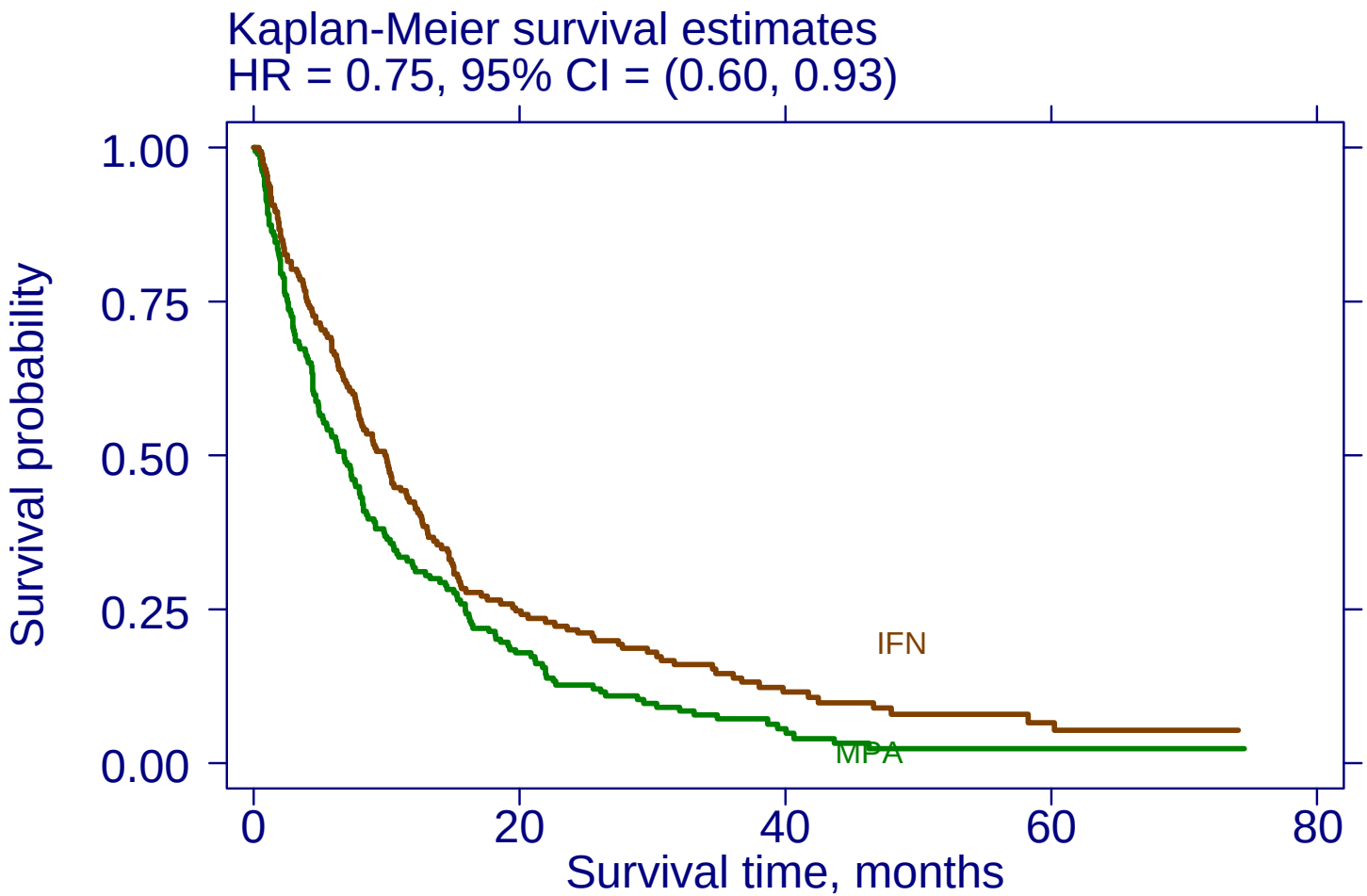
Treatment and follow up

- MPA arm:
  - Tablets 300 mg by mouth daily for 12 weeks
- Interferon-α arm:
  - Injection 3 times per week for 12 weeks
- Follow-up:
  - every 4 weeks until 12 weeks post randomisation
  - 6 months, 1 year then every 6 months to death

Results

- Trial stopped early due to advantage of IFN
- 350 patients randomised (176 MPA, 174 IFN)
  - No follow-up on 3 patients, leaving (175, 172)
- Overall mortality (updated to June 2001):
  - MPA arm: 167/175 (95%)
  - IFN arm: 155/172 (90%)
- Absolute improvement in one year survival 12% (95 percent CI 3-22%), P = 0.01

Survival curves



Continuous prognostic factors

Factor	% Complete	Median	IQR
Age at randomisation	100	60	52, 66
Months since first diagnosis of RCC	100	3	1, 19
Max. tumour diam.	59	10	7, 12
Bodyweight	77	72	64, 82
Serum calcium	88	2.43	2.33, 2.53
Haemoglobin	93	12.3	10.9, 13.7
White cell count	93	8.0	6.6, 9.9
ESR	49	43	21, 72
Viscosity	14	1.8	1.7, 2.1

Categorical prognostic factors

Factor		% Complete	%
Male sex		100	68
WHO perf. status		100	
	0		27
	1		48
	2		24
Multiple metastases		99.7	84
Had kidney out		100	57

Impute missing prognostic factors data by using probabilistic method (van Buuren et al 1999)

Prognostic modelling

- Use all reasonable data (original + imputed)
- Build a multivariable model using Cox regrn.
- Apply backward elimination to remove redundant predictors
  - Drop a variable from the model if P > 0.05
- Keep the continuous predictors continuous
  - Use fractional polynomials (FP) to model them

Fractional polynomials

- There are many problems with using cut-points to model continuous predictors such as age (particularly “optimal” cut-points)
- We want to *keep continuous predictors continuous* in the analysis
- First choice: straight lines; but, not all relationships are accurately modelled as straight lines
- Instead, can use *fractional polynomials* which are a sensible compromise between really complex curves and over-simplified straight lines

Fractional polynomial models

- *Conventional* polynomial of degree *m* with powers **p** = (1,…, *m*) is defined as

$$P(m) = \beta_1 X^1 + \beta_2 X^2 + \ldots + \beta_m X^m$$

- *Fractional* polynomial of degree *m* with powers **p** = (p_1,…, p_m) is defined as

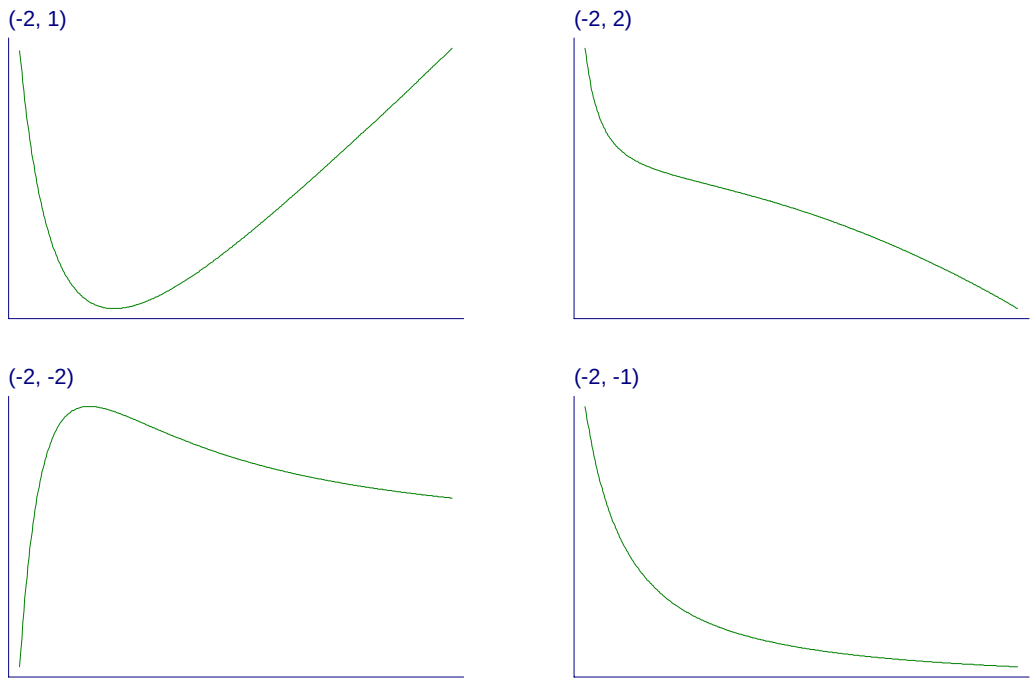
$$FP(m) = \beta_1 X^{p_1} + \beta_2 X^{p_2} + \ldots + \beta_m X^{p_m}$$

- See **`[R] fracpoly`** in Stata Manual

Choosing powers for FP

- Powers **p** are taken from a predefined set *S*
- We use $S = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$
- Power 0 means log *X* here
- *S* may be varied, e.g. could include 1/3 to give a linear measure if *X* was a volume
- Little advantage in better model fit by adding intermediate fractional powers, such as 1.5

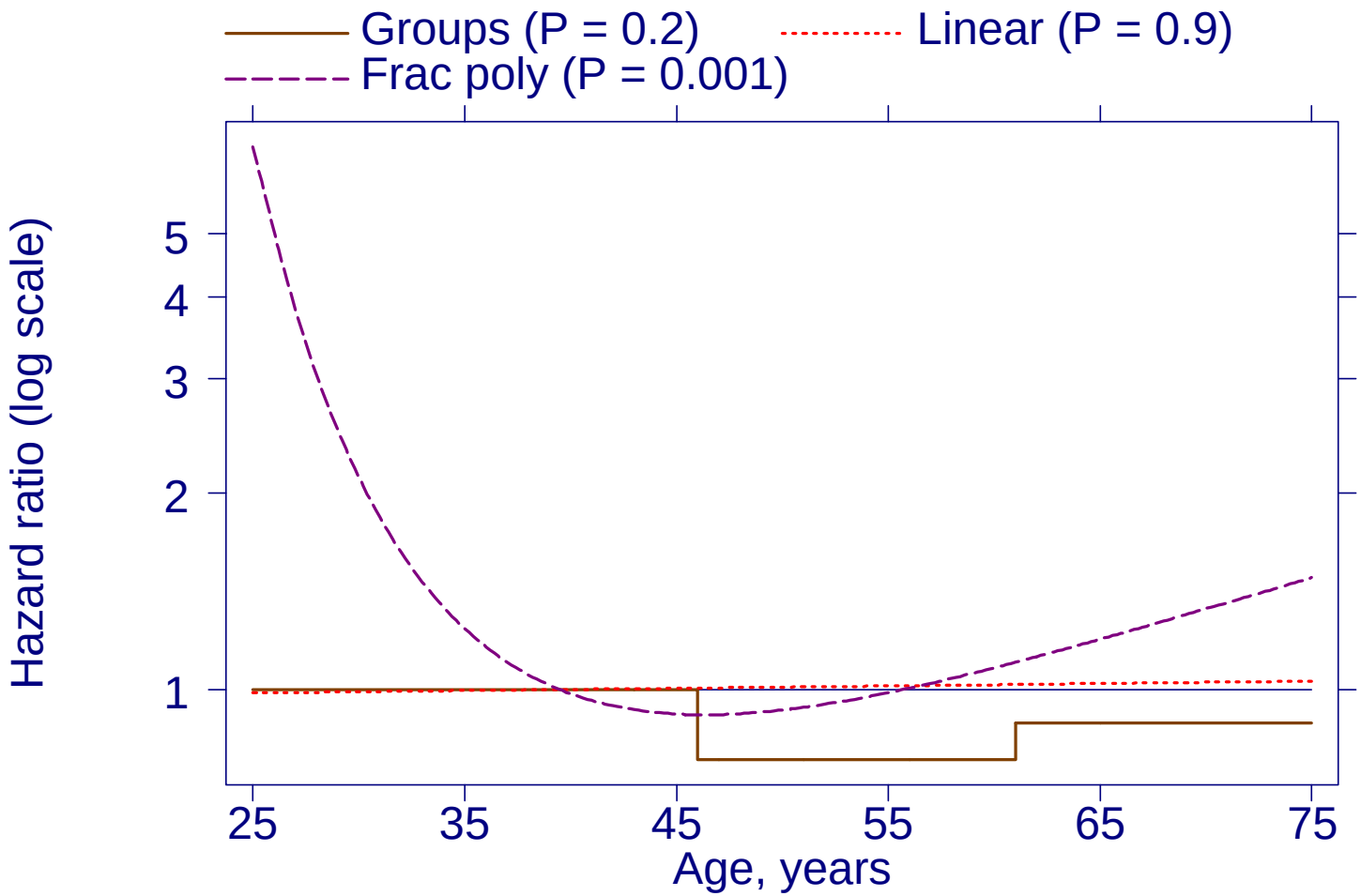
Some examples of fractional polynomial curves



Royston P, Altman DG (1994) *Applied Statistics* **43**: 429-467.

Sauerbrei W, Royston P, et al (1999) *British Journal of Cancer* **79:**1752-60.

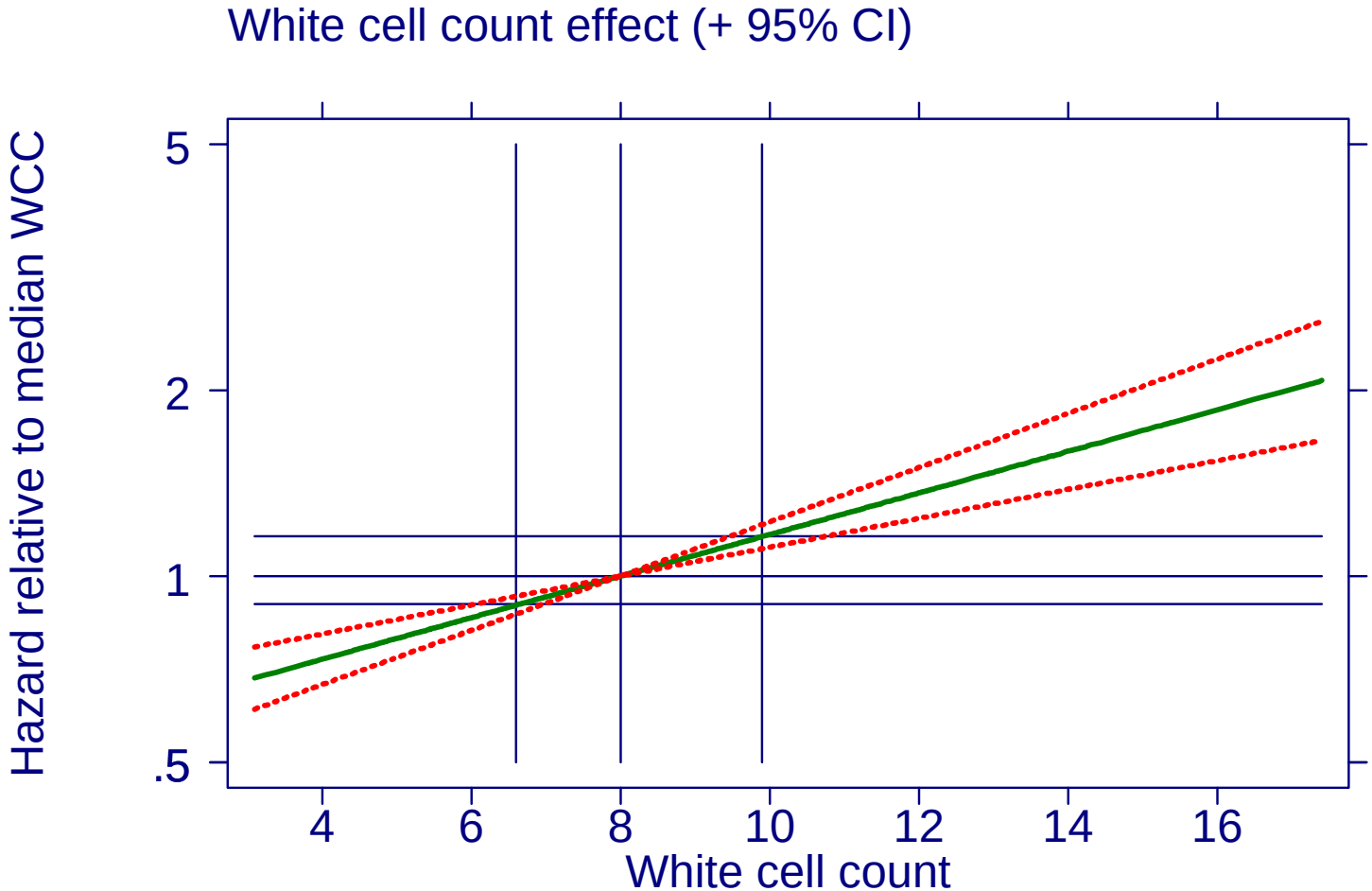
Example: age in N+ breast cancer



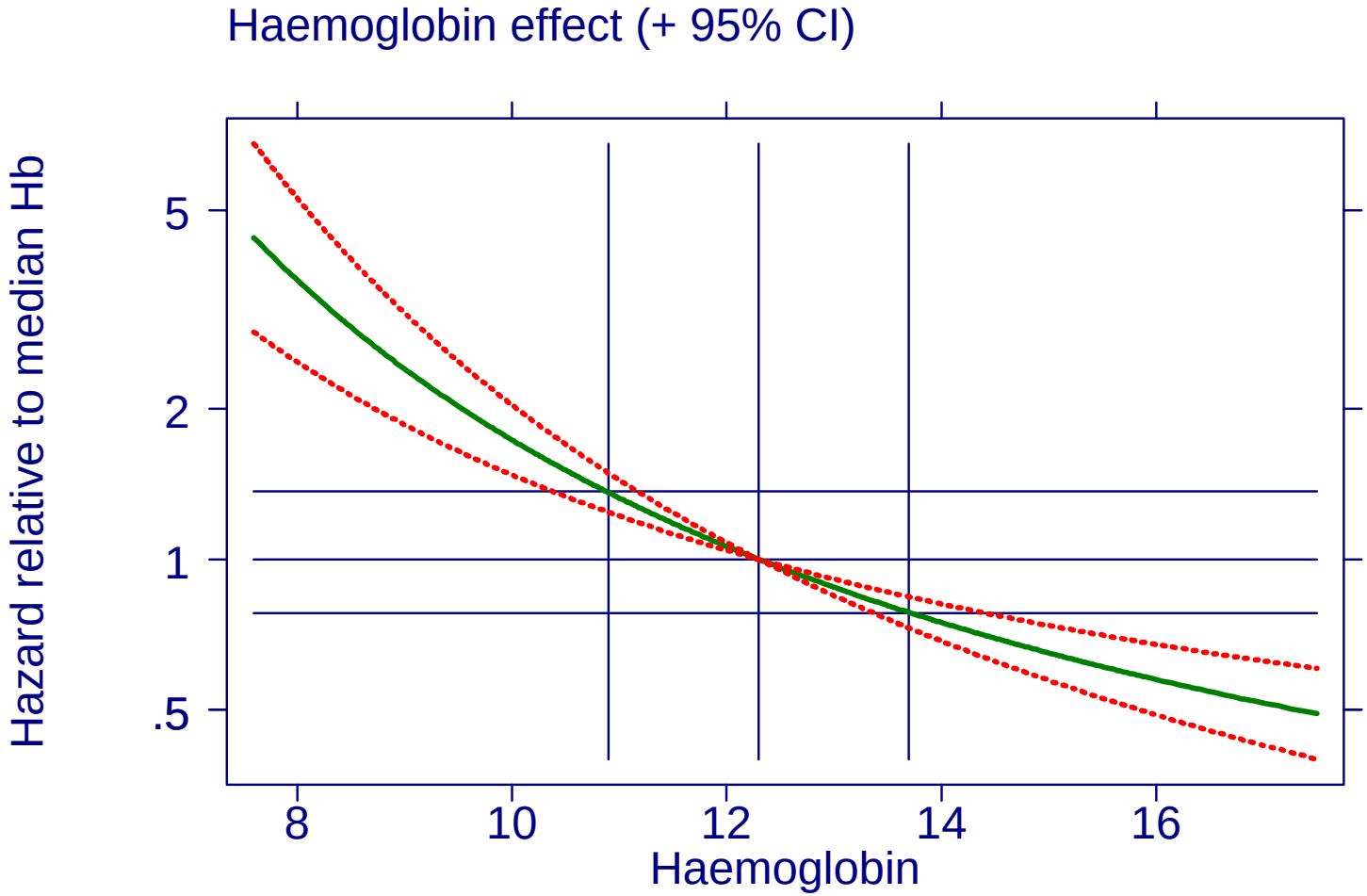
Prognostic modelling: Results for RE01

Factor	In/Out	P-value	FP	HR
Age at randomisation	out	0.8		
Months since first diagnosis of RCC	out	0.2		
Bodyweight	out	0.6		
Serum calcium	out	0.9		
Haemoglobin	in	< 0.001	–1	
White cell count	in	< 0.001	1	
Male sex	out	0.4		
WHO PS 0		–		1
WHO PS 1	in	0.02		1.37
WHO PS 2	in	< 0.001		2.35
Multiple metastases	out	0.7		
Nephrectomy	out	0.9		

Continuous factors: White cell count



Continuous factors: Haemoglobin



Prognostic strength of haemoglobin and white cell count factors

- Effect of white cell count modelled as linear
- Effect of haemoglobin modelled as a curve
- Need a way to summarise the risks
- One possibility—a simple table:

Factor	Centiles			Hazard Ratio	
	25	50	75	75:50	25:50
Haemoglobin	10.9	12.3	13.7	0.78	1.37
White cell count	6.6	8.0	9.9	1.16	0.90

Prognostic and predictive factors

- Prognostic factors predict overall outcome
- Predictive factors predict response to treatment
- In statistical terms:
  - prognostic factors are influential covariates
  - predictive factors exhibit treatment/covariate interaction

Detecting predictive factors

- Investigate effects in separate subgroups—**wrong!**
- Investigation of treatment/covariate interaction requires statistical tests
  - Nevertheless, care is needed to avoid over-interpretation
  - If possible, state hypothesis in advance of study (at most, about 3 questions)
  - Searching among many subgroup effects is useful only for hypothesis generation
  - See Assmann et al (2000) Lancet for review

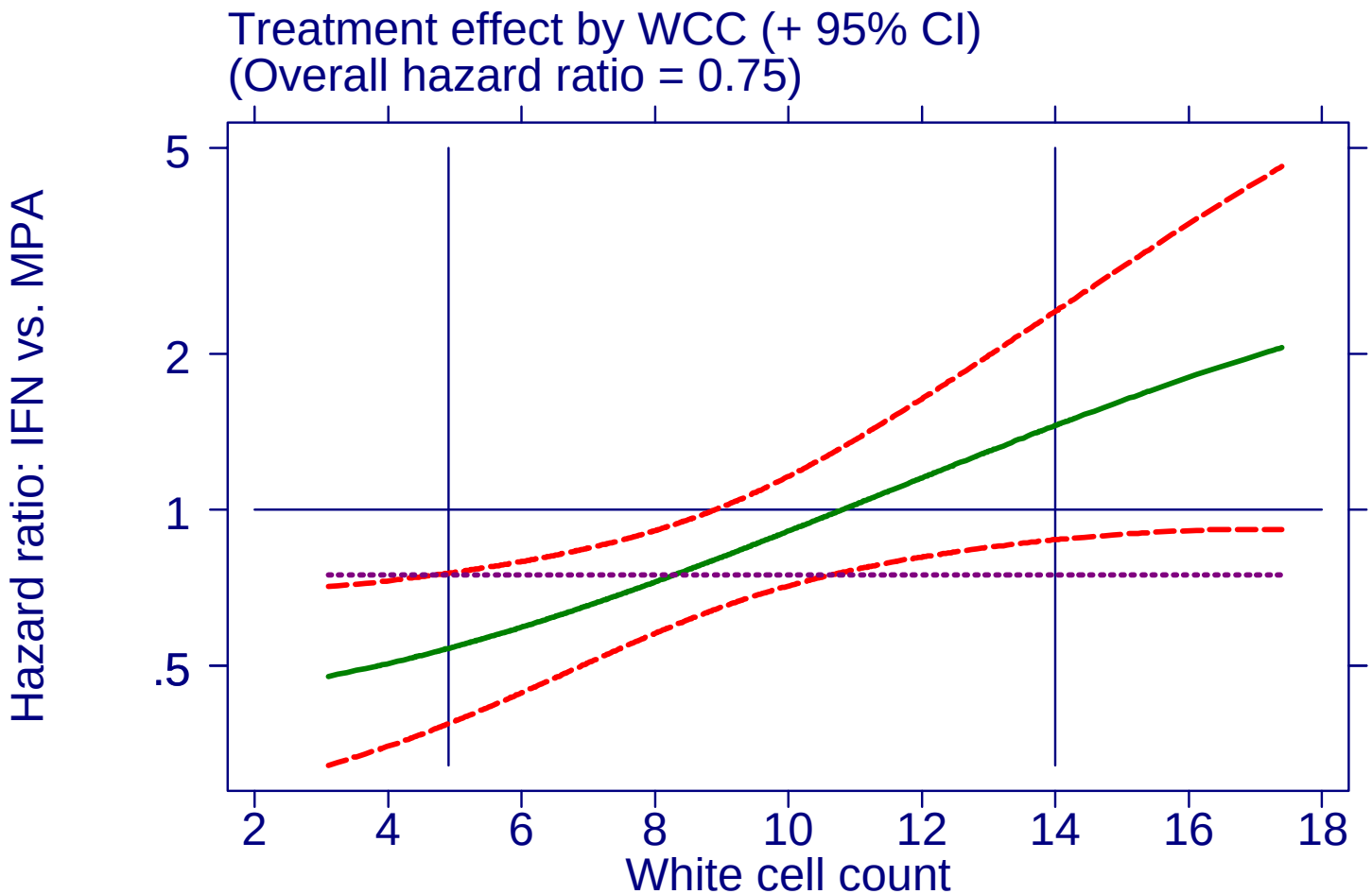
Modelling predictive factors using fractional polynomials

- Have several continuous and categoric factors
- Have a single (binary) treatment
- Use all factors to create an *adjustment model*
  - Model continuous factors by FP
- For continuous factor *X* of interest:
  - Include factors from the adjustment model
  - Find best FP-2 transformation of *X* in each treatment group
  - Use the same powers for *X* in each group
  - Test against main effects model with same FP applied to *X*
  - This gives a P-value for interaction based on χ^2 on 2 df

Predictive factors in RE01

Factor	Interaction P-value
Age at randomisation	1.0
Months since first diagnosis of RCC	0.6
Bodyweight	0.5
Serum calcium	0.8
Haemoglobin	0.9
White cell count	< 0.0001
Male sex	0.6
WHO PS	0.5
Multiple metastases	1.0
Nephrectomy	0.9

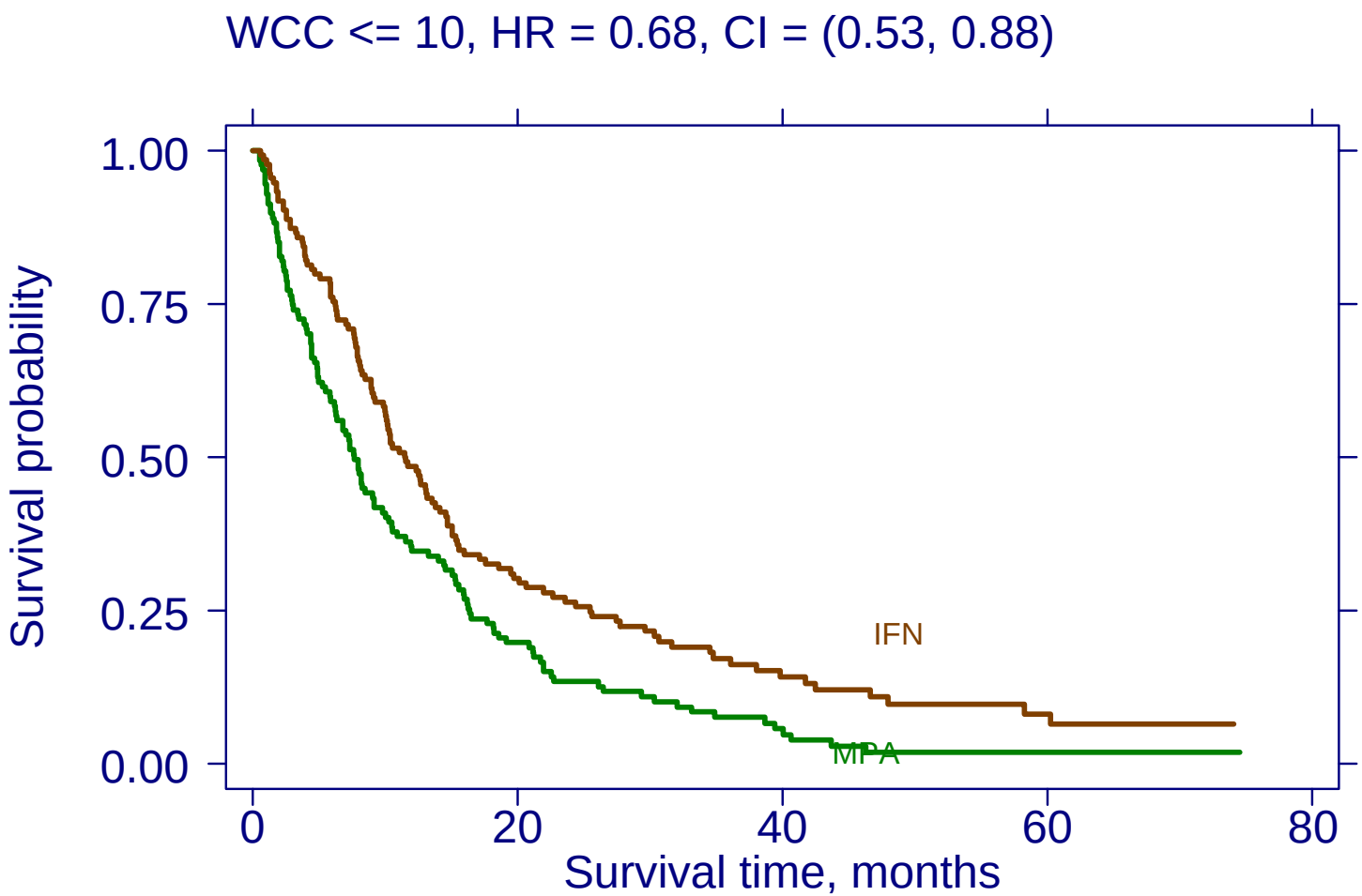
Treatment effect varies with WCC



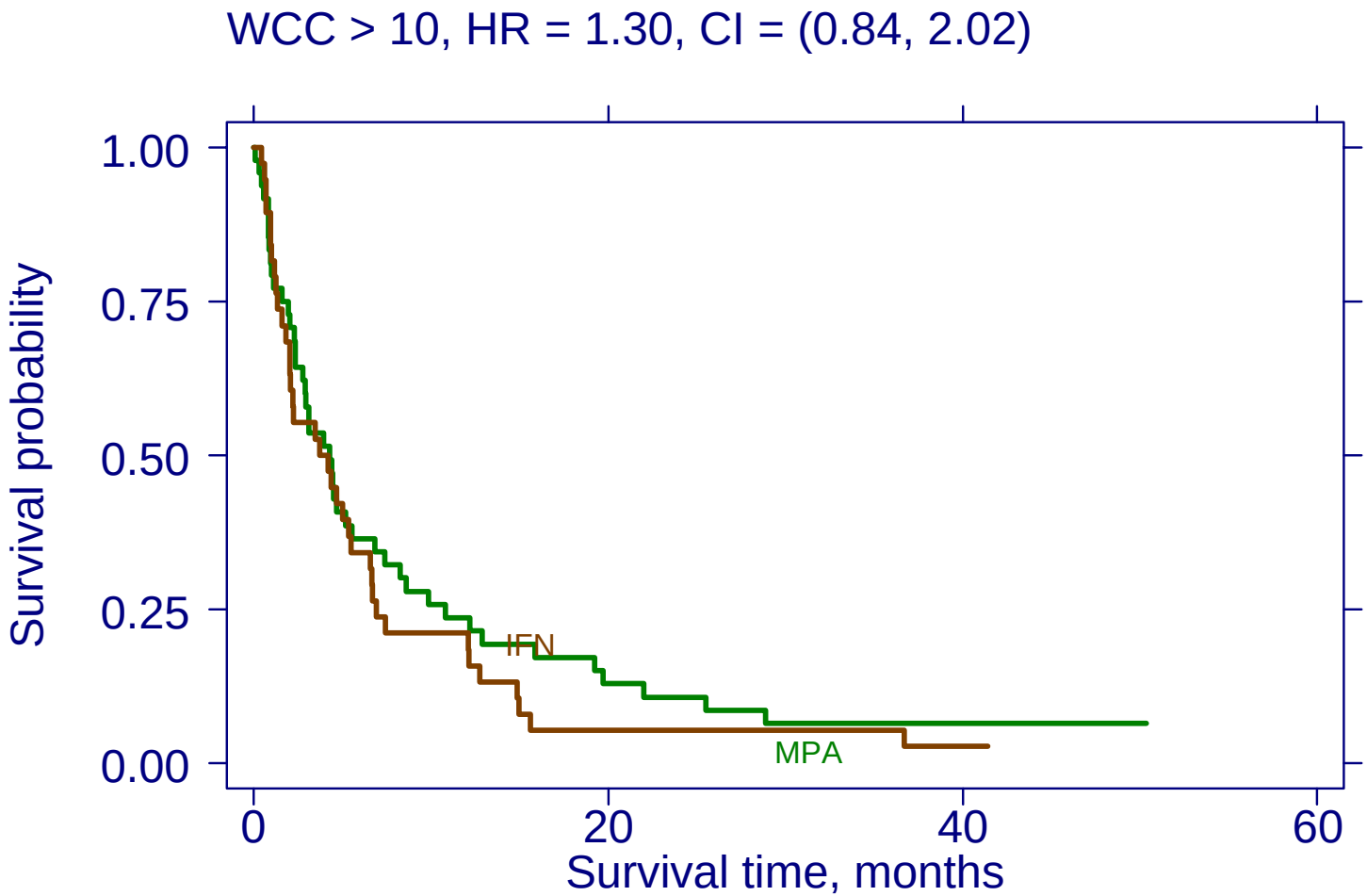
Comments on analysis of white cell count

- Sicker patients lose benefit of IFN treatment
  - Interferon could even be harmful in these patients
- $P < 0.0001$ is small enough to survive adjustment for multiple comparison
- Predictive effect seems to be real
  - but, needs to be validated in independent data
- For *presentation*, may create subgroups by cutting WCC at suitable point, e.g. at 10

Treatment effect: low WCC group



Treatment effect: high WCC group



Conclusions

- Analyses are required in which continuous predictors are kept continuous—FPs are one possibility
- Such analyses may detect important predictive effects which may be missed by standard methodology
- One strong predictive factor is present in the MRC RE01 trial: white cell count
- Despite $P < 0.0001$ this factor was not recognised as predictive in original report in the medical literature