and the registries need to cooperate very closely and it is therefore not useful to separate them. Several attempts are ongoing to improve this model, but the progress achievable is highly dependent on the cooperation between the data-protection authorities, which varies from region to region.

This model cannot be recommended. It was chosen as the only way to overcome the barriers established mainly by the data protection authorities in Germany. Meanwhile, awareness that cancer registration is a very important task in healthcare to protect the population against unknown cancer risks is increasing. This task is far more important than the concern about misuse of cancer registration data. Misuse of such data has not occurred once in over five decades of cancer registration – but we know several situations where cancer risks have not been detected on time, causing many unnecessary malignant diseases.

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1 Informed consent for cancer registry data collection. *Lancet Oncol* 2000; **1:** 197.

The dangers of subgroup analysis


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Within a phase II study or a single arm of a randomised phase III trial, statisticians are often asked to compare the survival of those patients who respond against those who do not, or treatment compliers against the non-compliers, in an attempt to understand whether persisting with a sometimes difficult treatment is worthwhile. It is well known that such comparisons are clearly biased as responders/compliers have to survive long enough to respond/comply, and all the early deaths/dropouts will fall into the non-responder/non-complier group.[1]

Table 1. Survival by subgroup

	No. events/no. entered			
	A	B	O–E	Variance
No treatment	14/19	38/48	4.50	7.56
1–5 cycles	10/11	29/36	3.51	5.26
6 cycles	82/100	37/45	4.23	26.49
Total	106/130	104/129	12.24	39.30

O, observed; E, expected.

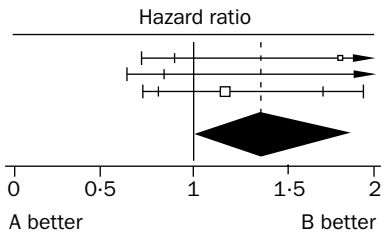

Figure 1. Hazard ratio plot

However, in a randomised phase III trial, comparing the responders in one arm against the responders in another seems on the face of it to be a less biased comparison. Unfortunately these are equally dangerous and murky waters. In a yet unpublished Medical Research Council cancer trial comparing two chemotherapy regimens there was no overall between-treatment survival difference (hazard ratio 0.97, 95% CI 0.73 – 1.29, p=0.82). The data were then re-analysed according to whether patients in each group received no treatment, 1 – 5 cycles, or all six cycles of chemotherapy. The hazard ratio plot emerged, as shown in Table 1 and Figure 1.

This indicates hazard ratios of 1.81, 1.95 and 1.17 for the three subgroups, and a combined hazard ratio, stratified for amount of chemotherapy received, of 1.37 (95% CI 1.00 – 1.87, p=0.051), all in favour of treatment B. How can this be? The result echoes the famous statement attributed to Will Rogers: "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states".[2] When subgroups are chosen, not on the basis of balanced randomised pre-treatment characteristics, but on variables that are inherently connected with survival, unexpected findings may result.

As a clarifying example, take 20 patients, 10 of whom have treatment X, and the rest have treatment Y. Survival in each arm is exactly the same – in each group one patient survives for 1 month, one for 2 months, one for 3 months, etc up to 10 months. Let us further assume that, say, three patients on treatment X and seven patients on treatment Y respond, and that not illogically the patients who respond are those who are more likely to survive longer. The possible result is shown in Table 2.

Table 2. Misleading subgroup analysis

	N	Survival time (mo)	Median survival (mo)
Responders			
Treatment X	3	8, 9, 10	9
Treatment Y	7	4, 5, 6, 7, 8, 9, 10	7
Non-responders			
Treatment X	7	1, 2, 3, 4, 5, 6, 7	4
Treatment Y	3	1, 2, 3	2

Thus in both responders and non-responders treatment X appears to result in a better survival, which considering there is no overall difference is clearly incorrect.

Perhaps the next time you see a plot showing the survival of a subgroup of patients who have responded or have received all their treatment, a vision of Will Rogers will come to mind.

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1 Weiss GB, Bunce H, Hokanson JA. Comparing survival of responders and nonresponders after treatment: a potential source of confusion in interpreting cancer clinical trials. *Controlled Clin Trials* 1983; **4:** 43–52.
2 Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312:** 1604–1608.