Nanos gigantium humeris insidentes: the awarded Cox proportional hazards model

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"Life tables are one of the oldest statistical techniques and are extensively used by medical statisticians and by actuaries […]. The present paper is largely concerned with the extension of the results of Kaplan and Meier to the comparison of life table and more generally to the incorporation of regression-like arguments into life-table analysis […]. The applications are more likely to be […] in medical statistics than in actuarial science" (1).

You have still read the *incipit* of the Sir David Cox's 1972 paper where he described the proportional hazards model that today bears his name. The Cox proportional hazards model is widely used in the analysis of survival data and enables researchers to more quickly identify the risks of specific factors for mortality or other survival outcomes among groups of patients with different characteristics. The mark on the research of David Cox is so great that this paper (1) is the second most-cited papers in statistics and ranked 24th in *Nature*'s list of the top 100 most-cited papers of all time field (2). In these days, Sir David Cox has been named the recipient of the International Prize in Statistics, the highest honour in its scientific area (3).

The Cox proportional hazards model is widely used in the analysis of survival data and enables researchers to more quickly identify the risks of specific factors for mortality or other survival outcomes among groups of patients with different characteristics. From disease risk assessment, the Cox model has been applied mainly in all fields of science, as well as in Medicine. Survival analysis involves the analysis of the time between a fixed starting point and a terminating event. The event could not necessarily have occurred in all subjects by the date of the study ends. Therefore, for these patients, full survival times are unknown. For example, in the measurement of the length of survival after the diagnosis of a lung cancer, a proportion of individuals commonly remain alive and disease-free at the end of the follow-up with a lower limit on their actual time to event (4).

The Cox proportional hazards model is also a survival analysis regression model, which describes the relation between the incidence of an event, expressed by the hazard function, and a set of covariates (1). The hazard could be the instantaneous event probability at a given time, or the probability that an individual experiences the event in a period centred on that point in time. The covariates then act multiplicatively on the hazard at any point in time, and this provides us with the fundamental assumption of the proportional hazards model: the danger of an event in a group is a constant multiple of the risk in another (4). This model is an appealing analytic method because it is both powerful and flexible. The hazard ratio, derived from the model, offers a test of treatment efficacy and an estimate of relative risk of events of interest to surgeons. However, the hazard ratio must be interpreted carefully in clinical trials where the duration of events or the disease is the main efficacy variable. The hazard ratio may be used for purposes of statistical hypothesis testing and as an indication of the amount of benefit, but other measures must also be applied to understand the full importance of the study. Time effects are sometimes wrongly inferred from the hazard ratio. Terms such as accelerated time, twice as fast, etc. in the context of the hazard ratio value suggest to readers that degrees of change (equivalent to the hazard ratio) have been effected on the time scale when only a risk has been modified (5).

As remembered by the Organize Committee of the International Prize in Statistics, the successful application of the Cox proportional hazards model has led to life-changing discoveries with far social effects, as:

- ❖ The demonstration that major reduction in smoking-related cardiac deaths could be seen within one year of smoking cessation, not more years as previously thought;
- ❖ The mortality effects of particulate air pollution: a finding that has changed both industrial practices and air quality regulations worldwide;
- ❖ The analysis of the treatments for lung cancer (3).

Cox considers himself to be a scientist who happens to specialise in the use of statistics. Statistics as a science began in the second half of the 17th century with the aim to collect data to lay down laws as a rational foundation of decision-making and to gain a better understanding of measurements. Nevertheless, it is only in the last century that few statisticians were active in developing new methods of analysis, theories, and applications of statistics (6). Thanks to Sir David Cox fundamental role, biostatistics is a growing topic of a continuous development of new techniques. And with a laptop, biostatistics could accompany the life of many thoracic surgeons, since the boundary between the essential statistics and the more advanced statistical methods has been blurred.

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Footnote

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