STATISTICS IN HEALTH SCIENCES AT THE SCHOOLS OF MEDICINE OF BARCELONA

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The Units of Biostatistics of the schools of medicine of Barcelona have diverse fields of interest that include epidemiology of different diseases, clinical pharmacology and drug development and public health information systems. The most interesting areas of the activity of these groups will be summarized here.

Design and analysis of clinical trials: An important area of work is methodological support for clinical trials, most of them carried out by the pharmaceutical industry. There is a need to keep high standards in the statistical analyses used, since regulatory authorities are severe in these aspects. Factorial designs (Roca-Cusachs *et al.*, 2001) have been applied to optimal dose finding for drug combinations. Many of the trials carried out nowadays have the aim to prove bioequivalence of generic drugs. Methods that account for measurement error such as structural regression models have been applied to the design and analysis of these trials which focus on «proving the null hypothesis» (Carrasco and Jover, 2001, 2002). In this area, two measures of agreement, intraclass correlation coefficient and Lin's concordance correlation, were compared and their potential usefulness was assessed for bioequivalence studies (Carrasco and Jover, 2001). Replicated designs that improve efficiency have been studied and applied to compare the bioavailability of different formulations of a drug (Calvo *et al.*, 1999).

Another area of interest is the application of sequential methods to the design and analysis of clinical trials. The methods based on continuous boundaries such as the double truncated sequential probability ratio test have been applied to a large trial on the efficacy of antiplatellet drugs to prevent mortality after a myocardial infarction (Cruz-Fernandez *et al.*, 2000). For a simple review of sequential methods in clinical trials see Moreno (1995). Similar sequential methods have been compared with inverse sampling in another context. Here the interest was to efficiently design a study to compare the proportion of chromosomal abnormalities estimated from laboratory assays in a sample of individuals with a known reference population proportion. In this study the required sample size of a classical design was compared with that of a modified inverse sampling scheme and a formal sequential method based on triangular continuous boundaries (Moreno *et al.*, 2002).

Another area which involves interesting statistical methods is meta-analysis of published clinical trials. Dose-response models to estimate the effect of morphine in drug addicts based on logistic regression with random effects were applied in Llamas *et al.*,

1994. More recently, generalized linear mixed models have also been applied to study the relative efficacy of different drugs used for detoxification of morphine drug addicts (Farré *et al.*, 2002).

Epidemiology: In the field of epidemiology, methods to estimate risk from the combined or pooled analysis of several cases-control studies have been developed for the situation where one wishes to combine studies with matched and unmatched designs (Moreno *et al.*, 1996). These methods were applied to the study of progression factors of cervical cancer (Moreno *et al.*, 1995). More recently, efforts have been devoted to develop methods to study gene-environment interactions. In a classical case-control study to estimate risk of colorectal cancer related to diet, tumors of the cases were studied to detect mutations in the K-ras oncogene. Models based on polytomous logistic regression were used to simultaneously estimate the risk for mutated and wild-type tumors compared to the same group of general population healthy controls (Bautista *et al.*, 1997).

Much work has also been done in the field of descriptive epidemiology. Analysis of temporal trends of cancer incidence has been studied in detail for cervical cancer using age-period-cohort models (Vizcaino *et al.*, 1998; 2000). A recent review of these methods has been published (González *et al.*, 2002). Models with joinpoint regression have been used to show the recent decline in trends for cancer mortality in Catalonia (Fernández *et al.*, 2001). Life time cumulative risk of cancer incidence and mortality has been estimated (Moreno *et al.*, 1998). Also extrapolation of cancer incidence to the complete Spanish territory from areas with cancer registries has been done using generalized linear mixed models to account for spatial heterogeneity. In these models the log-ratio of cancer incidence to mortality was modelled as a linear function of age (using smoothing splines), period and province of residence. Bayesian methods of estimation were used (Moreno *et al.*, 2001). A related subject of interest is the use of geostatistics to study spatial distribution of disease. In this area much research is ongoing using kriging methods involved in generalized linear mixed models with spatial correlation. These methods are being applied to model the distribution of respiratory diseases (Ascaso and Abellana, 2001*a*), malaria (Ascaso and Abellana, 2001*b*) and cancer incidence around a chemical factory (González *et al.*, 2001). Recurrent events have been studied with generalized linear models using the negative binomial distribution to account for the overdispersion observed in the distribution of events (Navarro *et al.*, 2001).

Clinical epidemiology: This is a heterogeneous area that covers clinical research using epidemiological methods. Multivariate models for prediction of prognosis after cardiac surgery have been developed using stepwise strategies to select the best subset of covariates. Models were validated with the subsample method and compared to other published models regarding calibration and predictive ability (Pons *et al.*, 1997). In the field of diagnosis, a predictive model was developed to diagnose organic dyspepsia using clinical symptoms. Bootstrap validation methods were used in this case (Barenys *et al.*,

2000). Two techniques of computer tomography scans were compared with respect to their ability to diagnose liver metastasis. Comparison of ROC curves was done with jackknife methods (Valls *et al.*, 1998).

Design and analysis of laboratory assays: Experiments in the laboratory often use complex designs that require advanced statistical methods for proper analysis. Generalized linear mixed models have been applied to compare the evolution in time of tumor markers in relation to treatments (Martín-Henao *et al.*, 2000). For the diagnosis of microsatellite instability in tumors, models with a mixture of two or three binomial distributions with covariates were used (González-García *et al.*, 2000).

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