Commentary: Frailty and heterogeneity in epidemiological studies

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The paper by Aalen et al.1 is a timely discussion of an important topic. However, it conflates two concepts, frailty and heterogeneity, which are best kept apart. I would use the term frailty only when there is clear biological evidence that a fraction of the population is either exclusively at risk, or at vastly increased risk compared with the general population, of contracting a disease. An example of the former situation is cystic fibrosis, an autosomal recessive condition, which is caused only by inherited mutations in a single gene; an example of the latter is familial adenomatous polyposis (FAP) of the colon, a dominantly inherited condition that greatly increases the risk of colon cancer. Although there is no direct estimate of the relative hazard associated with FAP, it can be surmised to be several thousand and strongly age-dependent.2 I would reserve the term heterogeneity for inter-individual variation in susceptibility that is much more modest and arises from factors that do not clearly single out a sub-population at greatly increased risk of the disease. Heterogeneity of susceptibility may arise from biological factors, such as polymorphisms in metabolizing enzymes or inter-individual variations in efficiency of DNA repair or cell proliferation, or from purely stochastic considerations.

The role of stochasticity as a factor in heterogeneity has been under-appreciated. To their credit, Aalen et al.3 clearly recognize the importance of stochastic factors, and they correctly note that it is not easy to distinguish between stochasticity and chaotic behaviour arising from unstable dynamical systems. I prefer to work with stochastic models. Many toxicology experiments are conducted with highly inbred strains of animals kept under identical environmental conditions. Yet, despite identical ‘nature and nurture’, these animals do not succumb to disease at identical ages, and they show considerable heterogeneity in the number and size distribution of lesions. The same would presumably be true of humans subjected to similar experimental conditions. To summarize, there are three sources of inter-individual variation in susceptibility in human populations: first, at the most fundamental level, we have stochastic variations that are present even in genetically uniform populations living under similar or identical environmental conditions; second, we have inter-individual variations in the efficiency with which fundamental biological processes are carried out; and finally, large differences in susceptibility are determined by major gene defects (e.g. FAP) or by events occurring in embryonic life that alter populations of critical cells (perhaps exemplified by testicular carcinoma, as Aalen et al. note4).

Methods of analysis based on stochastic models of carcinogenesis automatically address stochastic heterogeneity if (and only if) the exact (stochastic) solutions to the models are used for data analyses. In this regard, I find the discussion of carcinogenesis models in this paper unclear. The models described in the papers by Heidenreich, Meza et al., Moolgavkar et al. and Armitage and Doll cited by Aalen et al.3 were not developed to describe hazard functions in individuals, as the authors state, but rather in populations of like individuals. If the exact (stochastic) solution of these models is used in homogeneous populations, stochastic heterogeneity is immediately introduced. Let \( X_{n-1} \) and \( X_n \) be random variables representing the number of pre-malignant and malignant cells, respectively, in a tissue at age \( t \) and let \( \mu_n \) be the last mutation rate. Then, the exact stochastic solution to a carcinogenesis model is equivalent to solving the following expression for the hazard function, \( h(t) = \frac{P'(t)}{1-P(t)} = \mu_n E[X_{n-1} | X_n = 0] \), where \( P(t) \) is the probability of a malignant cell at age \( t \) and \( E \) is the expectation. Quite often, approximate (deterministic) solutions, \( h(t) = \mu_n E[X_{n-1}] \), are used and these can yield misleading results and inferences. Thus, for example, the pioneering Armitage-Doll model is stochastically a pure birth process; the almost universally used power function approximation, which is the hazard function arising from a Weibull survival model, is only the first non-zero term in the Taylor series expansion of the exact (stochastic) solution.3 In contrast to this approximation, which is monotonically increasing without bound, the exact hazard function approaches a finite asymptote, which would be expected with a heterogeneous population. Thus, starting with a homogeneous population, the (exact) Armitage-Doll and other stochastic models introduce stochastic heterogeneity.

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Critical examination of the Armitage-Doll model shows that neither the exact nor the approximate solution describes cancer incidence data well, and that models incorporating cell proliferation kinetics do better.4 Be that as it may, for any stochastic model, stochastic heterogeneity is immediately introduced if the stochastic solution is used. Inter-individual variations in susceptibility arising from variations in the rates of critical biological processes can be modelled by assuming a distribution on the parameters of the model. Major gene defects, such as FAP, can be modelled along the lines suggested by Knudson10 for retinoblastoma by assuming that one of the mutations along the pathway to carcinogenesis has been inherited by every cell in the tissue of interest. The critical point here is that all sources of inter-individual variation in susceptibility can be modelled using specific biological considerations. It is not necessary to use the artifice of multiplying the hazard function of the Weibull model by a frailty parameter, as Aalen et al. suggest.1

I agree with the authors that ignoring heterogeneity and frailty can yield misleading inferences. That said, another equally important factor in the misinterpretation of epidemiological data is the ubiquitous and often inappropriate application of the proportional hazards model for analysis and the virtually universal use of the relative risk as a measure of effect. It is becoming increasingly clear that summary measures of exposure, such as cumulative exposure, cannot capture the impact of complex temporal patterns of exposure on disease risk,5,6 and that the relative hazard, which is the target of estimation with the proportional hazards model, has serious limitations.7,8 For cohort data, the use of parametric hazard functions derived from multistage models of carcinogenesis that explicitly incorporate patterns of exposure can simultaneously address both issues and provide insights that are difficult or impossible to obtain using the proportional hazards model.9

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References

Authors’ response: Understanding variation in disease risk

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