Commentary: Age and frailty—not quite the same thing

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In this special issue on epigenetics, Aalen and colleagues¹ discuss the ‘elusive concept’ of frailty which ‘can lead to surprising artefacts in statistical estimation that are important to examine’. They define frailty variation as ‘differences in risk between individuals which go beyond known or measured risk factors’. Use of the term frailty to describe all unexplained heterogeneity in longitudinal or age-related data is based on the historic statistical literature, and should not be confused with the common English usage of the term to describe the particular vulnerability of people in their declining years.

We agree that the study of age-related changes in disease risk and survival is of central importance in epidemiology. The challenge is to model heterogeneity to explain why disease risk changes with age, rather than to simply waste that information by adjusting away any age-related effects, as has often been standard practice.

Aalen and colleagues remind us that variation in risk could be due to genetic or environmental causes or random effects (though the latter would be regarded as unexplained environmental causes, given that the impact of all germline genetic effects can be determined from the disease concordance of monozygotic twin pairs). Yet this aetiological framework is incomplete unless attempts are made to measure genetic and environmental interactions and shared environmental effects (e.g. within families), and to partition random effects into those due to age-related developmental changes (which can be epigenetic in origin) and those that are truly stochastic (i.e. due to somatic genetic effects (mutations) or unexplained epigenetic effects that are not developmentally programmed). In this regard, twin and family studies are obviously important tools that can now be used more widely through a newly constructed international network.²
As epidemiologists, we view epigenetic effects as mechanisms that influence the way that genes work. For the most part, epigenetic variation is ‘environmental’ or ‘random’ in the sense that, as the small average correlation of methylation markers in monozygotic twin pairs shows, the vast majority of epigenetic differences between individuals are not (yet) explained by inherited differences in germ-line genes. Aalen and colleagues point out that small differences, initially random, could be amplified over time into major effects. Nevertheless, it seems likely that many of the developmentally programmed changes in gene expression, mediated by gene methylation or other epigenetic mechanisms, are initiated by specific germ-line genes that vary little from individual to individual, although modulated by environmental influences such as nutrition.

Variation in outcomes between individuals cannot be discussed without being explicit about the mean. Most often, epidemiologists adjust for the effects of age on the mean, either by design or in the analysis, and do not ask why the mean might change with age, or why the age at which an outcome occurs might vary between individuals. A great deal of epigenetic variation occurs at different ages—so variation due to epigenetics across different ages is quite different from variation across people of the same age.

There is no doubt that for many diseases and health-related traits, individuals of the same age differ markedly in their underlying risk (i.e. frailty), if only because having a family history of that disease is a risk factor. Probably not as well recognized as it should be, even modest increases in risk associated with having an affected relative imply large gradients in underlying ‘familial risk profile’, as pointed out more than 20 years ago by Aalen and others.

Familial risk is often greater for younger ages of the at-risk person, and for younger ages at onset of the affected relative(s). For colorectal cancer (CRC), this variation in risk with age is quite pronounced, and is in part due to the fact that people with mutations in DNA mismatch repair genes are at substantial increased risk of CRC particularly before the age of 50 years. At older ages, familial risk is less, presumably because the most susceptible individuals (i.e. those with the most potent combinations of genetic and environmental effects) have been selected out at earlier ages. Moreover, the familial modifiers of risk for mutation carriers appear to be important and distinct from the modifiers of risk for non-carriers.

But there is another important source of ‘heterogeneity in risk’ for cancers and for other age-related diseases. It has long been thought that the age-related increase in cancer risk is due to a lifetime increase in genetic errors due to somatic mutations in stem cells. Most recently, it has been shown that variation in cancer risk from organ to organ is proportional to the life-time number of stem-cell divisions in the organs concerned, showing that genetic damage leading to cancer is more likely to occur and be propagated at cell division. Cancer risk is also increased by ionizing and UV radiation and by other carcinogens. Radiation and some carcinogens appear to act by increasing the rate of somatic mutation per cell division, whereas some other carcinogens (e.g. asbestos or hepatitis B virus) might act by increasing the rates of cell division. Cancer risks following low-dose radiation from CT scans now appear to be greater than previously estimated.

There are also age-related effects for most other chronic diseases through non-malignant (degenerative) changes in cells and tissues. Such degenerative changes might arise from an age-related loss of regenerative capacity due to loss of stem cells through apoptosis or genetic damage induced by mutagens or by other environmental noxae. For example, age-related degeneration of the immune system contributes to increasing incidences of pneumonia and other diseases for older people.

How might we summarize the role of epigenetic effects over the life span? The simple answer could be that they are most important in regulating expression of genes to drive differentiation, growth and development in the embryo, fetus and in postnatal life. As individuals age, epigenetic effects may become less important than effects that are due to the loss of stem-cell and regenerative capacity. It is highly unlikely that any amount of genetic regulation can ever make up for age-related deterioration in the genes that are to be regulated.

The article by Aalen and colleagues is important in drawing attention to variation that has often been neglected by epidemiologists; we recommend it. However, we question their claim that ‘statistical selection’ explanations are separate from ‘biological explanations’. There must be a real prior (biological) explanation, even if stochastic, for the variation that is subject to statistical selection. They also suggest that ‘frailty’ and biological mechanisms are competing. A more nuanced argument would emphasize that frailty must always have a biological explanation, even if we are still struggling to understand what it is.

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References

Commentary: Frailty and cancer

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Frailty is the statistical term for variation in risk due to factors that cannot be measured in individuals, including: inherited differences; environmental influences in utero, in childhood or in later life; and purely random somatic genetic or epigenetic events. In a hypothetical population where each individual has a constant risk of dying but people have different death-rates, the most susceptible will die younger and the average death rate of survivors will fall progressively. A conventional survival analysis shows the declining average death rate in the whole population, but an appropriate frailty model in which individuals have constant but different death rates fits the data equally well and estimates the range of variation in individual risk. Frailty retreats as biology advances, because by definition it involves unknown mechanisms and individual characteristics that are not yet measurable.

A major focus of the review on frailty by Aalen et al. results from an initiating mutation that occurs in a developing organ during embryogenesis. The individual is born with a large number of cells containing the first of the mutations required for cancer and is therefore at greatly increased lifelong risk. This happens in non-familial childhood retinoblastoma and perhaps in a substantial proportion of all types of cancer.

i. Among genetically identical individuals with the same environmental exposures, those who happen to develop precursor lesions such as colonic polyps or cervical carcinoma-in-situ are at greatly increased subsequent cancer risk. This is ‘stochastic frailty’.

ii. Somatic mutations in cancer have been shown to include about three to eight ‘driver’ mutations, consistent with the number of rate-limiting steps in the classical multi-stage model of carcinogenesis, and a much larger number of ‘passenger’ mutations that are thought to be incidental effects of the cancer’s proliferation and genetic instability. Driver mutations in apparently benign lesions, or even in apparently normal tissue biopsies, could in the future enable molecular pathologists to predict an individual’s cancer risk with increasing precision.

iii. A particularly interesting example of stochastic frailty mentioned by Aalen et al. results from an initiating mutation that occurs in a developing organ during embryogenesis. The individual is born with a large number of cells containing the first of the mutations required for cancer and is therefore at greatly increased lifelong risk. This happens in non-familial childhood retinoblastoma and perhaps in a substantial proportion of all types of cancer.

iv. The population of stem cells expands independently in each breast at puberty, so such an initiating mutation in one breast during pubertal growth would cause a