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.1 (this issue) is cancer and the various ways in which frailty (differences in cancer risk between individuals) can arise during the succession of genetic or epigenetic changes required to produce a malignant tumour.

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.2 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.1 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.3

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
much higher lifelong risk than in the contralateral breast. This hypothesis might explain the anomalous incidence patterns of familial and contralateral breast cancer and should be testable by genetic analysis of multiple tissue samples from both breasts in women with breast cancer.

v. Cancer occurs in a dominant pattern in families carrying a critical mutation in a gene such as Rb1 (the retinoblastoma gene) or p53 (the Li-Fraumeni syndrome gene) because carriers have inherited a rate-limiting step in multi-stage carcinogenesis. Many such genes have been identified in Mendelian cancer families, and the same genes are often mutated somatically in the multi-stage evolution of cancer in the general population.

vi. There is wide variation in cancer risk in the rest of the population after excluding people with mutations in such genes. First-degree relatives of cancer patients are at approximately 2-fold risk of developing the same cancer, and 10-fold or larger differences in risk must underlie this apparently moderate familial effect. The suggestion that this is the result of many genes with small effects acting in combination was subsequently confirmed by genome-wide association studies, which have identified large numbers of inherited genetic variants that contribute to this polygenic variation in susceptibility to specific cancers and to many other diseases. Such variants usually have very small effects, often accounting for less than 1% of the overall familial variation, and for most diseases the combined effect of all known variants does not account for much of the familial variation. This realization drives the continuing search for the causes of this ‘missing heritability’.

A variety of frailty models can usually be fitted, so mechanistic inferences from them are inevitably speculative. A peak in age-specific cancer incidence may reflect the elimination of a highly susceptible subgroup but could be due to age-related decline in cellular turnover, a cohort effect or underdiagnosis in old age, and it seems unlikely that only 12% of the US population is susceptible to colon cancer. Nonetheless, the recognition that there are many individuals at much higher or lower risk than the population average drives the continuing effort to identify them and hence elucidate underlying genetic and environmental mechanisms, as illustrated by these and the other examples discussed by Aalen et al.

Frailty may prove important legally as well as scientifically. A worker who develops lung cancer following exposure to an industrial carcinogen that causes a relative risk of 1.5 for lung cancer does not receive compensation under English law because on the balance of probabilities the carcinogen was not the cause. Compensation might however be awarded if it could be shown that without the exposure the cancer would have developed more slowly. The very large number of common inherited variants, each explaining a small fraction of polygenic variation in inherited cancer risk, would not be rate-limiting events if they arose as somatic mutations and would not be classified as driver mutations in a lung cancer. However, some may slightly increase the rate at which the steps in carcinogenesis occur in the affected cell. If a subset of the large number of ‘passenger’ mutations were caused by the industrial carcinogen and accelerated the lung cancer’s development by a few years, the law should change. The courts accept the concept of accelerated disease progression for chronic obstructive lung disease. The only difference is in the frailty models. At present the probability that the same individual would have developed lung cancer a few years later without the industrial exposure is meaningful but unmeasurable.

Acknowledgement

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Conflict of interest: The last paragraph outlines my (unpaid) advice to dependants of coke oven workers who developed lung cancer. The case turns on whether the majority developed cancer earlier due to the exposure.

References