Survival-related biases survive well
From RODOLFO SARACCI*

Survival-related biases, potential or actual, affecting inferences on health and disease in the population of the selected survivors have a long history in epidemiology, at least since Ogle¹ noted some aspects of the ‘healthy worker effect’. They reflect either the selective admission of survivors into a study or the selective availability of information only on survivors. These biases continue to creep in, often unrecognized, not only in clinical but, more surprisingly, in epidemiological studies. Three recent cohort studies, with potential important implications at practical level, illustrate the point.

Diabetes as ‘equivalent’ to CHD
The first example² is a follow-up investigation of the relation between age and cardiovascular disease in diabetic and non-diabetic subjects. In one analysis, the authors assessed whether the rate of fatal or non-fatal coronary events and of all causes deaths in people with diabetes is ‘equivalent’ to that among people with previous myocardial infarction. The study population was composed of subjects eligible in the Ontario Health Insurance (covering practically all residents) on April 1, 1994: diabetic subjects were those registered as such at or before that date, numbering 379 003, followed-up, together with 9 018 082 non-diabetic, till March 31, 2000. Cox’s proportional hazards models were used to calculate age and sex-adjusted hazard ratios for acute myocardial infarction (AMI) and all causes deaths in subjects with diabetes but no recent AMI, relative to those with history of recent AMI but no diabetes. AMI was regarded as recent if recorded as occurring within the three years before April 1, 1994. Hazard ratios for AMI were found to be consistently (across ages and sex) <1 when comparing subjects with diabetes alone with subjects with previous AMI alone. However, ratios not significantly different from 1 were found when comparing all causes deaths in diabetic men (without AMI) aged 50 or more with men with previous AMI alone. The authors conclude that ‘we showed that in older men the presence of diabetes alone conferred a similar risk of death from any cause as did a recent history of AMI, probably because of the effect of diabetes on fatal CHD’. Because the same result was not found in younger men nor in women they add ‘…other studies lend support to the finding that diabetes is not a coronary equivalent in all circumstances’. Whether diabetes is a ‘coronary equivalent’, namely whether it entails the same rate of death (or of occurrence of some other event), cannot be found by comparing—as the authors did—event rates in subjects who, at the start of follow-up, had already survived an unspecified time since the onset of diabetes or/and variable intervals, up to 3 years, since the onset of the AMI episode. This ‘wobbly zero time’ bias is particularly serious in presence of AMI, a condition which even in recent survival observations shows a high fatality, in the range of 20–30% or more at one year.³,⁴ The issue of ‘coronary equivalence’ of diabetes, whatever its implications for pathogenesis, treatment or public health, ‘remains controversial’.³,⁴ It is bound to remain so unless it is clarified by the study of cohorts (prospective or, if suitable, historical) that allow in the first place to identify subcohorts of subjects with new (incident) diabetes or first AMI. The occurrence of subsequent deaths or other events can then be compared between these subcohorts, taking into account the competitive risk nature of the two conditions.

Mediterranean diet and survival in subjects with myocardial infarction or angina
In the second example⁶ a study group of subjects was identified with self-declared previous AMI or angina pectoris at the time of recruitment in one national cohort of the international European Prospective Investigation on Cancer and Nutrition (EPIC) prospective study. From the very detailed information in the dietary questionnaire a 10 point ‘Mediterranean diet’ score was elaborated, ranging from 0 (minimal adherence to traditional Mediterranean diet components) to 9 (maximal adherence). The study group (n=1302) was followed-up for an average of 3.8 years. Multivariate Cox’s models were run adjusting for sex, age and a number of variables as recorded at entry in the EPIC cohort (body mass index, smoking status, waist-to-hip ratio, physical activity score, total energy intake, diabetes mellitus, treatment for hypertension and hypercholesterolaemia). A higher adherence to Mediterranean diet by 2 score units was to be found associated with a 27% reduction in mortality suggesting a favourable and sizable effect of Mediterranean diet on survival after AMI or in subjects with angina pectoris. This promising suggestion, however, is softened by the fact that the study group is composed of subjects who at the time of entering the EPIC study had each already survived an unspecified and variable time after their AMI or onset of angina. Any factor associated with the degree of adherence to Mediterranean diet which could have differentially affected this survival could materially


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bias the comparison between subjects with different degrees of adherence to Mediterranean diet. For instance subjects with a high degree of adherence may have been those who also received the best medical treatment (e.g. revascularization and stent) in the acute phase of AMI, putting them on a more favourable survival track. Or a diverse scenario might hold in which the survival curve has in fact no relation to the adherence of Mediterranean diet but people living in rural areas and with, say, a high degree of adherence to Mediterranean diet have also less frequent contact with the health services, so that on an average they would have been recruited into the study after a longer interval from the AMI than people living in urban areas. What one would observe in this case would be the same survival curve but within different windows of observation, an earlier one, when fatality rates are higher, for people with low adherence to Mediterranean diet and a later one, when fatality rates are lower for people with high adherence to Mediterranean diet. Fortunately the prospective context of the EPIC study should allow to test in future the article’s findings by prospectively relating the degree of adherence to Mediterranean diet to the entire fatality experience of new cases of AMI.

Mortality and childhood vaccinations in low-income countries

The third example has been the object of some debate even in this journal. The key issue at stake is whether in low income countries with poor environmental and nutritional conditions and a still high childhood mortality some vaccines, namely DPT (but not BCG) may non-specifically increase mortality, possibly via immune status modifications affecting general body defences. An observational cohort study in Guinea-Bissau showing a 84% increase in total mortality in children vaccinated with DPT in respect to the non-vaccinated raised this issue of major public health relevance. Other studies in low-income countries produced the opposite result of a reduced total mortality in children exposed to DPT, fuelling the controversy. An inherent problem in the Guinea-Bissau study, probably present to an unknown extent also in the other studies, is that information on vaccination tends to become available conditional to a vaccinated child having survived till the first post-vaccination home-visit of the research team. This happens because often vaccination cards are missing if the child dies so that the vaccination status remains unknown and the child is assigned to the unvaccinated group. This survivor effect has a double consequence: (i) it spurious increases the mortality rate in the unvaccinated group and (ii) it spurious dilutes, by overestimating person-years at risk, the mortality in the vaccinated group to the extent that person-years for this group are calculated from the date of vaccination recorded in the card: the period between such date and the first post-vaccination visit of the research team is in fact an ‘immortal person-time’ as the child must be alive for the date to become known. When the data from the Guinea-Bissau study were re-analysed in this probably biased way the 84% increase in mortality of the DPT vs the unvaccinated group shown by the original analysis was reversed into a 32% reduction (the original analysis had been carried out taking conservatively as date of vaccination the date of the first visit after it). This confusing and important issue could only be solved by observational studies (or even randomized trials testing, for instance, different time schedules of DPT administration) with full information on the vaccination status in time for close to 100% of the study population.

A key screening question: is it an inception or a survivor cohort?

These three recent examples demonstrate two different types of survival-related biases capable of distorting comparisons in cohort studies. In the first two examples, selection of subjects into the study is at stake, while selective availability of exposure information only for the survivors is a main issue in the third example.

A modest suggestion to protect against overlooking survival-related biases is to look at a study design as actually implemented in the light of the distinction, made particularly in occupational epidemiology but of general import, between ‘inception cohort’ and ‘survivor cohort’. In an ‘inception cohort’ the unfolding of risk from a workplace exposure is observed from the start of the exposure while in a ‘survivor cohort’ the risk is observed in subjects present at the workplace at a given point of time, hence implying that the relevant exposure started for them (and for their unobserved dead fellows) some time in the past. Only the inception cohort can provide results free of the survivor-related biases here discussed. The distinction and the two terms ‘inception’ and ‘survivor’ neatly translate the simple principle that to measure and compare risks as materializing after different exposures every study subject should be actually observed and information on exposures and events recorded since the beginning of exposure.

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References

Early references to the mutational origin of cancer
From VOLKER WUNDERLICH*

Recently in this journal, Edler and Kopp-Schneider1 reviewed the origins of the mutational theory of cancer focusing mainly on the influential book by Karl Heinrich Bauer2 published in 1928. However, like Bauer, the authors failed to mention some previous papers in which scientists had suggested a possible role of somatic mutations in carcinogenesis. In fact, it was the pathologist Ernest E Tyzzer3 (1875–1965) who in 1916 first used the term ‘somatic mutation’ with respect to a tumour. His observations on tumour immunity led him to conclude:

‘From the evidence in the biological character of tumors of a permanent modification of somatic tissue, it appears logical to regard a tumor as a manifestation of somatic mutation. As a basis for this, there may be modification of the relative value either by loss or addition, or in the nature of factors, any of which, if continuously transmitted thereafter in successive cell generations will constitute a type of mutation. […] The tumor […] may be regarded as a modification of the somatic tissue which may be termed somatic mutation’ (Italics in the original) pp. 147–51.1

In 1919, two papers published by geneticists further expanded the view of somatic mutations in cancer. Whitman4 considered tumour cells displaying anaplasia as mutated cells; yet, anaplasia was earlier discovered as a hallmark of cancer by David Hansemann.5

Whitman states:

‘Anaplasia produces a cell different from any cell at any time normally present in the body. […] This cell, the cancer cell, is thus a “new kind of cell”. In modern terminology it is, strictly and literally, a mutated cell. Since the process is, or at least may be, repeated itself from time to time, and here and there, in a tumor, it follows that the tumor cells themselves are by no means all alike in their biologic properties; that, on the contrary, an ever recurring process of mutation is taking place, with a tendency, however, to deviate more and more from the normal type. This explains why metastatic tumors, for example, are often more, but never less, malignant than the primary tumor, as well as other related phenomena of tumor growth’ (Whitman, 1919, p. 185).

Inspired by, and with reference to, Theodor Boveri,6,7 Thomas H Morgan (1866–1945) and Calvin B Bridges (1889–1938)8 remarkably contributed to the discussion as follows (since the source is not available everywhere, the text is given in full).

‘Is cancer a somatic mosaic?’

Into the difficult and obscure question as to the cause of cancer it is not our business to enter, but a suggestion made by Boveri (in 1902 and 1914) calls for a brief notice, since he appealed to a process akin to chromosome elimination as a possible explanation of the phenomenon. Boveri suggested that an imperfect or irregular division of the chromosomal complex might in certain cases produce combinations through loss of specific chromosomes that caused the different cells to run wild, so to speak, in the sense that factors that normally inhibit the rate of growth or the suppression of growth in relation to the cell environment are lost. In support of such a view he appealed to occupational cancer-growth, where cancer develops in parts of the body most subject to mechanical injury or pressure. It is known to students of embryology that compression of a dividing cell may interfere with the normal distribution of the chromosomes to the daughter cells. At present, however, reference to such possible sources is too uncertain to be of great value, for there are no instances where irregularities of this kind are known to give rise to prolific growth processes. The cancer-like or tumor-like growth shown by a mutant race of Drosophila, discovered by Bridges and described fully by Stark,9 has not been shown to be associated with abnormal distribution of the chromosomes, although this point has not been sufficiently studied to exclude such a process. On the other hand, it has been shown that the growth in question is caused by a sex-linked Mendelian gene that is inherited strictly, as are all Mendelian sex-linked genes. This mutant lethal race of Drosophila arose as a mutation, presumably in the same way as other mutations. If it is not admissible at present to draw any analogy between this case and that of mammalian cancer, it is conceivable at least that mammalian cancer may be due to recurrent somatic mutation of some gene. Such a conclusion would, however, not invalidate the

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