'I'm going to live forever': the guarantee-time bias

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OK, class; let's start off with a multiple choice test. It won't take too long, because there's only 1 question: What do all of these statements have in common?

Orchestra conductors live longer than the average person.[1]

Actors who win an Oscar live longer than those who don't.[2]

Popes live longer than artists.[3]

Patients with chronic kidney disease who attended multidisciplinary care clinics had a 50% reduction in all-cause mortality compared to those who received usual care.[4]

Women with amenorrhea and estrogen receptor (ER)-negative breast cancer had improved disease-free survival and overall survival.[5] Your options are:

a. They have all have been reported in the literature.
b. They are all true.
c. They are the result of biased samples.
d. All of the above.

If you answered d, you can ask the editor for a one-year free subscription to this journal; you likely won't get it, but you can ask because you got the right answer. It's often amusing to read the "explanations" of these findings. The orchestra leaders' longevity has been attributed to a host of factors, including the cardiovascular exercise from flapping their arms around, the rejuvenating effects of good music influencing the brain's alpha rhythms, and the IQ-enhancing effects of attending to all those complex harmonies. Similarly, the Oscar winners' winnings at the survival game has been explained by the adulation they receive from adoring fans and the healthy diet they keep to remain an Oscar contender. For the kidney disease patients, their survival was naturally attributed to the multidisciplinary care (MDC); and the results in the breast cancer patients baffled the researchers, who thought that ER-negative women would have a shorter survival time.

But, as a recent article by Giobbie-Hurder and colleagues points out, these findings, and many more like them, are more probably due to a bias in terms of who is included in the studies than to the miraculous effects of occupation, winning awards, or ER status.[6] The bias has many names, including the "guarantee-time bias,"[6] the "immortal time bias,"[7] the "survivor treatment selection bias"[8] and many others. Let's take a closer look at the orchestra leaders to get an idea about what's going on. What do kids want to be when they're growing up? Maybe a cowboy or a firefighter if they are boys, or a princess or actress if they are girls (forgive the sex-role stereotyping), but we doubt whether many kids run around saying "I want to be a conductor when I grow up" (or an oncologist, for that matter). More often, conductors follow the paths of Mstislav Rostropovich or Arturo Toscanini, who had successful careers as performers (cellists, in both cases) before raising their batons.

So what does this mean? By the time that people choose to be conductors (or oncologists), they have survived all of the sometimes fatal childhood diseases, the above-average mortality rate among teenage drivers, the mortality associated with childbirth if they are women, being killed by an irate spouse, and so on; in short, they have survived until the age of 40 or 50, unlike some of their less fortunate peers. That means that they cannot be compared with the general population in terms of longevity, only to those who have survived until the age when people decide to become conductors. Another implication is that members of *any* profession that is selected after infancy will appear to live longer than the general population, and the later in life the choice is made, the greater the apparent longevity. This is very likely what is also going on with Oscar winners – they need to have survived long enough to have starred in a number of pictures, so again they are unlike the general population of actors or producers. Skewing their mean age even more are awards for "lifetime achievement," which are rarely awarded to those younger than Moses (who lived

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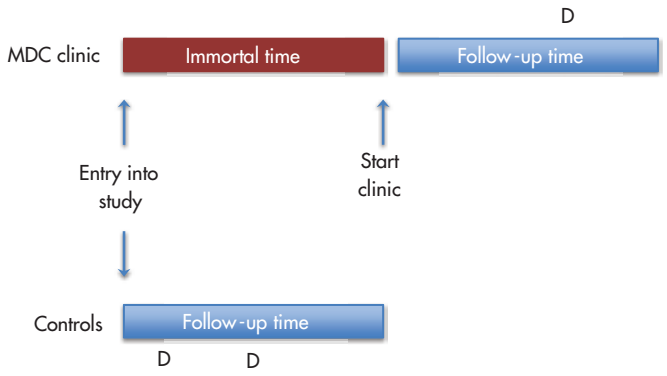

FIGURE 1 The guarantee-time bias. D, death; MDC, multidisciplinary care

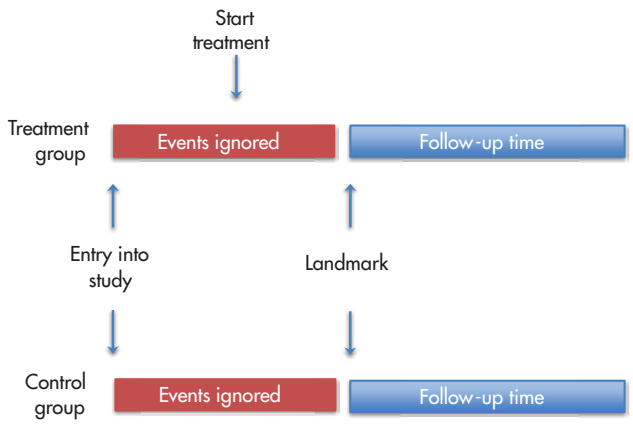

FIGURE 2 Conditional landmark analysis

until he was 120) or George Burns. Similarly, you can be young and be an artist, but who ever heard of people becoming a pope while they were still in their 20s, at least since the middle ages? (All of this is the converse of the shocking finding that the average age at death for students is much younger than the average age of death for other occupations.)

How does this explain the seemingly counter-intuitive finding about women with amenorrhea and ER-negative breast cancer? The problem was with the definition of amenorrhea, which required at least 6 months without a menstrual period during the first 24 months of follow-up. Women who had disease-free survival times of less than 6 months were therefore classified as not amenorrheic, and this applied disproportionately to the ER-negative women, who were more likely to have early relapses. Consequently, the group of ER-negative women who had amenorrhea was a biased one, because all of those who had an early relapse had been removed, just as the group of conductors eliminated all those who died before they were old enough to choose to go into that profession.

The same phenomenon likely explains the purported beneficial effects of the multidisciplinary care clinic, where the improved survival was seen long before the interventions could have exerted any influence. Those attending the clinic must have lived long enough to have been referred, for the referral to have been received and accepted, and for the patient to have started attending. No similar restrictions applied to those in the control condition and, as would be expected, some of these patients died during this interval (Figure 1). This helps explain the various names for this type of bias – the patients are guaranteed to be alive (or can be considered temporarily to be immortal) between the time they are enrolled in the study (or are born, in the cases of conductors, popes, and Oscar winners) and when the response status is recorded.

This leads to 2 questions: first, is this really a problem, or is it just an issue affecting people in unusual occupations and a few poorly designed studies? and second, if it is a problem, how can it be avoided? The answer to the first question, sad as it is, is that it's a pervasive problem in oncology. In one review,[9] the majority of articles in various cancer journals that were susceptible to this bias ignored it completely. Kinda sorta makes you wonder whether all those treatments were really as effective as the papers said they were. So how should those studies have avoided this bias; in other words, what should readers look for when they're reading about some new miracle cure?

The easiest way to avoid the guarantee-time bias is *matching*. In Figure 1, the clock started ticking for people in the control condition as soon as they entered the study. But, for those in the MDC group, it began when they enrolled in the program. A much better strategy would be to pair patients in the 2 groups; if the first patient in the intervention group has to wait 30 days until the treatment starts (that is, he has been "immortal" for this time), then he is matched with a patient in the comparison group who has survived for 30 days.

A related method is called *conditional landmark analysis*, which avoids the problem of having to match people. Rather than starting the clock when patients are enrolled, a landmark time is selected, say as soon as the patients in the experimental group have started treatment or 1 month later (Figure 2). Events such as deaths or recurrences before this time are ignored in both groups. It gets its name because the results are *conditional* on patients surviving until the landmark. There are a couple of problems with this approach (the "so what else is new" phenomenon). First, the choice of time is arbitrary, and the results can change if a different landmark is used. Second, the results don't apply to all patients with the condition, but only to those who live long

enough to reach the landmark time. Third, if a lot of people die or have events before that time, the sample size could be greatly reduced. Despite this, it gives a more accurate picture than a "naïve" analysis that ignores the guarantee-time bias.

There are also sophisticated statistical ways of dealing with the bias, such as time-varying Cox proportional hazards models and inverse probability-weighted models, but the less said about them the better (mainly because we don't understand them either). But, if papers use these approaches, you can be fairly confident in the conclusions, because at least the authors knew enough about the bias to do something about it.

The bottom line is to be very skeptical of any study in which (a) patients in the experimental group have to wait a certain length of time before their events are counted, (b) those in the control group don't have to wait, and (c) no provision was made for this in the analyses.

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