Practice of Epidemiology

Immortal Time Bias in Pharmacoepidemiology

Samy Suissa

From the Department of Epidemiology and Biostatistics, and Department of Medicine, McGill University, Montreal, Canada.

Immortal time is a span of cohort follow-up during which, because of exposure definition, the outcome under study could not occur. Bias from immortal time was first identified in the 1970s in epidemiology in the context of cohort studies of the survival benefit of heart transplantation. It recently resurfaced in pharmacoepidemiology, with several observational studies reporting that various medications can be extremely effective at reducing morbidity and mortality. These studies, while using different cohort designs, all involved some form of immortal time and the corresponding bias. In this paper, the author describes various cohort study designs leading to this bias, quantifies its magnitude under different survival distributions, and illustrates it by using data from a cohort of lung cancer patients. The author shows that for time-based, event-based, and exposure-based cohort definitions, the bias in the rate ratio resulting from misclassified or excluded immortal time increases proportionately to the duration of immortal time. The bias is more pronounced with a decreasing hazard function for the outcome event, as illustrated with the Weibull distribution compared with a constant hazard from the exponential distribution. In conclusion, observational studies of drug benefit in which computerized databases are used must be designed and analyzed properly to avoid immortal time bias.

bias (epidemiology); cohort studies; databases; epidemiologic methods; pharmaceutical preparations; relative biological effectiveness; statistics; treatment outcome

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; RR, rate ratio.

The randomized controlled trial design is essential to evaluate the effectiveness and safety of medications and to obtain regulatory approval for their use in clinical practice. Yet, it rarely provides information on their pragmatic benefit in terms of major disease outcomes. Nonexperimental observational studies have been conducted in pharmacoepidemiology in an attempt to fill this gap by assessing long-term effects of medications on infrequent outcomes, including mortality (1). The use of computerized health databases, constituted from routinely collected administrative or clinical data, has been encouraged, along with cautions on the methodological complexities of conducting such observational studies (2–4). This trend has led to an explosion in the last decade in the number of published observational database studies of the impact of medications.

Many of these observational studies have used a cohort approach that emulates the randomized controlled trial design. This cohort approach, however, in its attempt to simplify data analysis and presentation of results from the quasi–randomized controlled trial approach, has produced a form of bias called *immortal time bias*. This bias, first identified in epidemiology in the 1970s in the context of heart transplant research, has been recently appearing in an alarming number of pharmacoepidemiology papers. It was initially documented in studies of drug treatments for chronic obstructive pulmonary disease (COPD) and allergic rhinitis (5–7). It was shown to systematically underestimate the rate ratio, thereby creating the false illusion that a medication is effective at reducing the rate of major disease outcomes (8–11). In a previous paper, I identified 20 observational studies of the effects of commonly prescribed drugs that were subject

Correspondence to Dr. Samy Suissa, McGill Pharmacoepidemiology Research Unit, Royal Victoria Hospital, 687 Pine Avenue West, Ross 4.29, Montreal, Québec, Canada H3A 1A1 (e-mail: samy.suissa@clinepi.mcgill.ca).

to immortal time bias (12). In this paper, I review the origins of immortal time bias, describe five study designs that can lead to this bias using examples taken from published studies, quantify its magnitude under different survival distributions, and illustrate the bias using data from a cohort of patients with lung cancer.

THE BIAS IN EPIDEMIOLOGY

Immortal time refers to a span of time in the observation or follow-up period of a cohort during which the outcome under study could not have occurred (13, 14). It usually occurs with the passing of time before a subject initiates a given exposure. While a subject is not truly immortal during this time span, the subject necessarily had to remain event free until start of exposure to be classified as exposed. An incorrect consideration of this unexposed time period in the design or analysis will lead to immortal time bias.

The first recorded instance of bias from immortal time in epidemiology was in the early 1970s in the context of two cohort studies from Texas and Stanford University (Palo Alto, California) of the benefit of heart transplantation (15, 16). In the Texas Heart Institute study, the survival time of 15 patients who received a heart transplant (mean 111 days, including the waiting time from acceptance for a transplant until transplantation) was found to be longer than the survival of 42 potential recipients who were accepted for a transplant but did not receive one (mean 74 days) (15). In the Stanford Heart Transplant study, the survival of 20 patients who received a heart transplant (mean 200 days after transplantation) was found to be longer than the survival of 14 potential recipients who did not receive a transplant (mean 34 days) (16).

Gail (17) identified a source of bias in these two studies stemming from a relevant portion of follow-up time—namely, the waiting time of all patients who survived to make it to the transplant—that was not properly accounted for in the data analysis. Indeed, because this portion of the follow-up time was classified as exposed to transplantation instead of unexposed, it offered a guaranteed survival time to the transplanted group. As a result, by not being correctly classified, this immortal time produced an artificial increase in the mortality rate of the reference group, thus suggesting a benefit of heart transplant surgery. In a reanalysis of the Stanford Heart Transplant data, Mantel and Byar (18) found that the apparent major survival advantage of the transplanted group disappears when the immortal time is properly accounted for by a time-dependent analysis (hazard ratio (HR) = 0.93, $p = 0.9$).

This bias has appeared in several areas of epidemiology. An environmental cohort study suggesting that increasing duration of vinyl chloride exposure was associated with decreasing mortality was corrected with a proper analysis that showed otherwise (19, 20). It was also uncovered in a study suggesting no association between increasing exposure to asbestos and lung cancer mortality (21, 22). This bias, under the name survivor treatment selection bias, appeared in the context of treatment for human immunodeficiency virus (23). More recently, immortal time bias was shown to elu-

cidate a prior study that suggested the surprising proposition that movie Oscar winners live longer (24, 25).

THE BIAS IN PHARMACOEPIDEMIOLOGY

Lately, this bias has been appearing in several observational studies of the effects of medications that used computerized health care databases as their source of data (12). These studies used different approaches to form the cohort, leading to variations in the resulting immortal time bias. These design variations in cohort definition are described below.

Time-based cohorts

Time-based cohorts are characterized by having cohort entry defined by a time point, usually a calendar date, with subjects followed up from this date until the occurrence of the outcome event under study or another calendar time point. An example is the cohort study of 16,941 asthma patients identified by using data from a health maintenance organization in eastern Massachusetts, with cohort entry defined as October 1, 1991, and follow-up until the first hospitalization for asthma or September 30, 1994 (26). In this study, exposure was measured by the mean number of prescriptions for inhaled corticosteroids dispensed during follow-up. This approach resulted in the implausible finding that the use of less than one canister of inhaled corticosteroids per year was associated with a significant reduction of 60 percent in the risk of hospitalization for asthma.

In studies using this design, the analysis has been based on exposure defined by a prescription or the mean number of prescriptions during follow-up (7, 26, 27). Clearly, the time between cohort entry and the first prescription is "immortal" for the exposed subjects; to have received the treatment implies that the subject "survived" until the first prescription. According to this phenomenon, the subjects classified as exposed will have a guaranteed survival advantage over the unexposed subjects: they will be artificially "protected" during the immortal period until they become exposed (11). The solution is simply to classify as unexposed this immortal person-time prior to the first prescription and the subsequent person-time as exposed, using either a Poisson model approach if the hazards are constant or, alternatively, a Cox proportional hazards model with a time-dependent definition for the drug exposure.

Event-based cohorts

Event-based cohorts are characterized by cohort entry defined on the basis of a clinical event, such as the first diagnosis or hospitalization for a given condition, with subjects followed up until the occurrence of the outcome event under study. To emulate a randomized trial, exposure to treatment is defined by a prescription within a certain period *after* cohort entry. This exposure time can vary from short periods such as the first 90 days in a 1-year follow-up study to the entire follow-up period. An example is the study in which the Ontario, Canada, health insurance databases were used to identify a cohort of 13,623 elderly patients

discharged from a hospital with a diagnosis of acute myocardial infarction between 1993 and 1995 and followed for up to 1 year after discharge or until death (28). The treated group was formed from all subjects who received two or more prescriptions for a beta-blocker during follow-up, while all others formed the untreated group. The study reported that the patients given beta-blockers, including with the lowest doses, at least twice during follow-up had significantly lower rates of death (HR = 0.40, 95 percent confidence interval (CI): 0.34, 0.47).

The time between cohort entry and the second prescription for a beta-blocker is clearly "immortal" since the exposed subjects must survive this period to receive their two prescriptions. Thus, classifying this immortal period from hospital discharge until the second prescription as exposed when computing the mean survival time of the group exposed to the beta-blocker provides this "treated" group with an artificial survival advantage over the unexposed subjects. Here again, a solution is to classify as unexposed the immortal person-time prior to the second prescription using either a Poisson model approach or a Cox proportional hazards model with time-dependent drug exposure. Alternatively, redefining time zero as the day after the selected exposure time period (for example, 90 days in Sin and Tu (5)) removes the source of immortal time bias and has the advantage of using a Cox model analysis without time-dependent exposures (29).

Exposure-based cohorts

Some studies define cohort entry hierarchically on the basis of exposure, such as the first prescription for the drug under study. Thus, first, subjects who receive the treatment under study are considered "exposed" and enter the cohort at the time they start exposure. Second, all other subjects are then considered unexposed, and their cohort entry is defined arbitrarily by a comparison treatment or a diagnosis.

An example is the General Practice Research Database study of the effect of inhaled corticosteroids and long-acting beta-agonists on mortality in patients with COPD (6). First, all 1,045 COPD patients who received prescriptions for both an inhaled corticosteroid and a long-acting beta-agonist during 1990–1999 were identified and formed the exposed cohort, with follow-up starting at the time of their first combined prescription. They were compared with 3,620 COPD patients who used other treatments (bronchodilators) but not inhaled corticosteroids or long-acting beta-agonists during the observation period, with follow-up starting at the time of their first prescription for a bronchodilator. In a 3-year follow-up, the rate of death was lower with combination therapy compared with bronchodilators (HR = 0.48, 95 percent CI: 0.31, 0.73).

Because of the hierarchic definition of exposure, the exposed subjects may also have been exposed to the comparison treatment or have had the diagnosis used to define the unexposed group prior to their exposure-defined cohort entry date. Indeed, table 1 of that study (6) confirms that the majority of exposed subjects used bronchodilators prior to starting combination therapy. Thus, these exposed subjects were in fact also exposed to the comparison medication for some time before reaching this combination exposure status. This preexposure time period is immortal since the subjects who reach the combination treatment status will necessarily do so alive. Had they died before receiving this therapy, they would, by definition, have belonged to the bronchodilator cohort. Thus, immortal time bias occurs because valid bronchodilator person-time of follow-up with no deaths is not accounted for in the reference rate of death, resulting in an artificial increase in the rate of death in the reference group, leading to a spurious appearance of effectiveness (10). The solution is to include in the reference rate calculation this immortal person-time prior to exposure from the combination therapy that was excluded by design. This can also be achieved by using a Cox proportional hazards model in which time zero is taken as the first occurrence of the exposure or reference definition and a time-dependent factor for the drug exposure.

Multiple-event-based cohorts

Some studies define cohorts by requiring several events over time, such as the number of times a diagnosis was made or a drug was prescribed. Immortal time can be introduced when follow-up starts at the first of the events. In this case, the time between the first and last events is immortal. An example is a cohort study of the cardiac risks of cyclooxygenase-2 inhibitors in which subjects were required to have at least two prescriptions of a given cyclooxygenase-2 inhibitor (rofecoxib or celecoxib) to be considered exposed (30). The 15,271 subjects in the celecoxib cohort and the 12,156 subjects in the rofecoxib cohort were followed from their first prescription for up to 1 year until death or hospitalization for acute myocardial infarction. On the other hand, the 100,000 nonusers of these drugs were followed from a date selected randomly from the observation period. In the 1-year follow-up, the study reported that the rate of acute myocardial infarction in subjects was similar with rofecoxib (HR = 1.0, 95 percent CI: 0.8, 1.4) or celecoxib (HR = 0.9, 95 percent CI: 0.7, 1.2) compared with that for the unexposed subjects.

With this design, the time span between the two prescriptions defining the exposed subjects is necessarily "immortal." Indeed, subjects who died after their first prescription for one of these two cyclooxygenase-2 inhibitors were not included in these exposed groups. On the other hand, the unexposed subjects could have died anytime during follow-up. Such a cohort definition will necessarily provide an artificial survival advantage to the exposed group, with the resulting bias producing an underestimate of the true rate ratio. The solution here is to define cohort entry by the second prescription and to include all person-time after the first prescription as unexposed, using a Cox proportional hazards model with a time-dependent definition for the drug exposure.

Event-exposure-based cohorts

These cohorts are defined by identifying all subjects with a given diagnosis, whereas exposure is defined by a prescription for the drug of interest on the same day as the diagnosis

(31). An example is the study that used the General Practice Research Database to identify a cohort of 4,398 patients hospitalized for COPD, 1,091 of whom received a prescription for an inhaled corticosteroid on the same day as discharge to form the exposed group. Of the remaining 3,307 subjects, however, only those 538 subjects who did not receive a prescription for an inhaled corticosteroid during the entire year after discharge formed the unexposed group. In the 1-year follow-up, the rate of death was lower in the inhaled corticosteroid exposed group compared with those unexposed (HR = 0.69, 95 percent CI: 0.52, 0.93).

In this study, the 2,769 subjects who received an inhaled corticosteroid prescription during the 1-year follow-up and who were thus excluded from the study cohort all had immortal time. Indeed, to determine that a subject received an inhaled corticosteroid prescription during the follow-up implies that the subject must have been alive at that time. Moreover, these subjects were all unexposed during this immortal time and could die only after exposure. Thus, excluding these subjects with their immortal unexposed person-time from the reference group and mortal exposed person-time from the treated group will lead to a spurious appearance of effectiveness (32). Here again, the solution is to include all subjects and to classify as unexposed the immortal person-time prior to the first prescription and the subsequent person-time as exposed.

QUANTIFICATION OF THE BIAS

Consider a cohort in which the subjects are divided into exposed and unexposed according to the time-based, event-based, and exposure-based approaches described previously. Let $i = 0$ denote the group of unexposed subjects and $i = 1$ the group of "exposed" subjects. Note that the "exposed" subjects are considered exposed but are in fact also unexposed for a portion of their follow-up, as explained above, or prior to their start of exposure. Furthermore, denote for $i = 0, 1$:

T_i = Total person-time for the group of subjects i,

C_i = Number of subjects with an outcome event in group i,

k = Ratio of person-time T_0/T_1, and

p = Proportion of T_1 that is in fact unexposed (immortal time).

To quantify the magnitude of the bias, consider two distributions for the occurrence of the outcome event over time, namely, the exponential distribution with its constant hazard function and the Weibull distribution with a decreasing hazard function.

Constant hazard: exponential distribution

By assuming that the rate of outcome is constant over time and classifying exposure properly, the unbiased rate ratio RR_u is estimated by

$$RR_u = (C_1/C_0)((T_0 + pT_1)/((1 - p)T_1))$$
$$= (C_1/C_0)((k + p)/(1 - p)).$$

For time-based and event-based cohorts, the unexposed immortal person-time from cohort entry that preceded the actual start of exposure in the "exposed" group is misclassified as exposed. The corresponding biased rate ratio RR_b is then given by

$$RR_b = (C_1/C_0)(T_0/T_1)$$
$$= (C_1/C_0)\,k.$$

Using the ratio of the biased to the unbiased rate ratios as a measure of the magnitude of the bias, we find that

$$\text{Bias} = RR_b/RR_u$$
$$= k(1 - p)/(k + p).$$

Figure 1 displays this bias as a function of p for three values of k, namely, 0.1, 1, and 10, representing a wide range in the ratio of the sizes of the two groups. Note that the bias is rapidly very large when the size of the unexposed group is one tenth that of the "exposed" group, for practically any value of p. When $k = 10$, the bias appears to be linearly related to p. In this case, the bias tends to $1 - p$ as k tends to infinity.

For exposure-based cohorts, the unexposed person-time that preceded exposure in the "exposed" group is generally overlooked and unaccounted for. In this case, the corresponding biased rate ratio RR_b is given by

$$RR_b = (C_1/C_0)(T_0/(1 - p)T_1)$$
$$= (C_1/C_0)(k/(1 - p)).$$

The magnitude of the bias is given by

$$\text{Bias} = RR_b/RR_u$$
$$= k/(k + p).$$

Figure 2 displays this bias also as a function of p for the same three values of $k = 0.1, 1,$ and 10. Note that the bias is large when the unexposed group is much smaller than the "exposed" group ($k = 0.1$). On the other hand, the bias appears to fade away when $k = 10$. Indeed, in this case, the ratio measure of the bias tends to 1 as k tends to infinity.

Decreasing hazard: Weibull distribution

Assuming that the rate of outcome is decreasing over time by using a Weibull distribution with scale parameter $\alpha < 1$ and classifying exposure properly, the unbiased rate ratio RR_u is estimated by

$$RR_u = (C_1/C_0)^\alpha((T_0 + pT_1)/((1 - p)T_1))^\alpha$$
$$= (C_1/C_0)^\alpha((k + p)/(1 - p))^\alpha.$$

Similarly as above, the biased rate ratio RR_b is given by

$$RR_b = (C_1/C_0)^\alpha(T_0/T_1)^\alpha$$
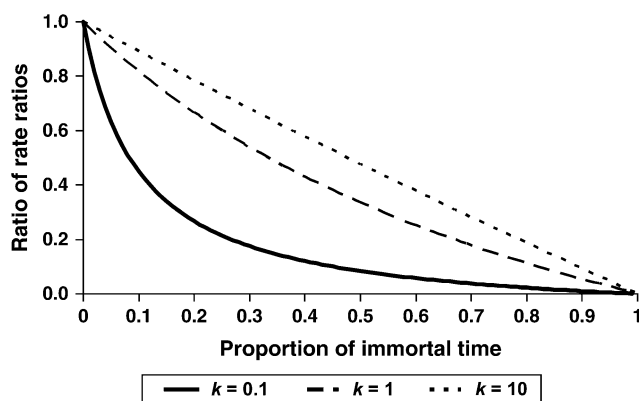$$= (C_1/C_0)^\alpha k^\alpha$$

and

FIGURE 1. For time-based and event-based cohorts, the plots show the ratio of the biased to the unbiased rate ratios, representing the magnitude of the bias, as a function of the proportion of misclassified immortal time p for three values of k, the ratio of unexposed to exposed person-time, namely, $k = 0.1$, 1, and 10.
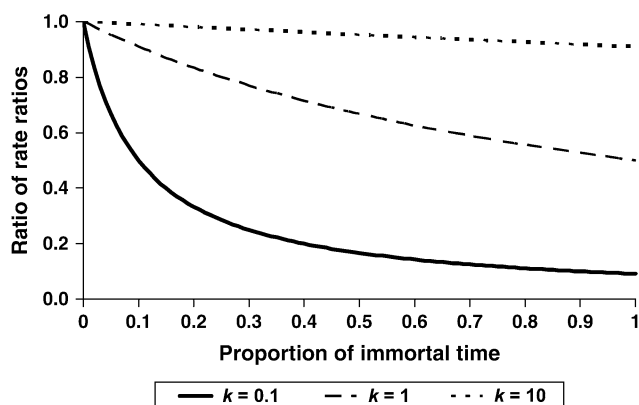

FIGURE 2. For exposure-based cohorts, the plots show the ratio of the biased to the unbiased rate ratios, representing the magnitude of the bias, as a function of the proportion of excluded immortal time p for three values of k, the ratio of unexposed to exposed person-time, namely, $k = 0.1$, 1, and 10.

$$\text{Bias} = [k(1-p)/(k+p)]^{\alpha}.$$

When cohort entry is defined by exposure, the biased rate ratio RR_b is given by

$$\text{RR}_b = (C_1/C_0)^{\alpha}(T_0/(1-p)T_1)^{\alpha}$$
$$= (C_1/C_0)^{\alpha}(k^{\alpha}/(1-p)^{\alpha})$$

and the magnitude of the bias is given by

$$\text{Bias} = k^{\alpha}/(k+p)^{\alpha}.$$

Figures of the magnitude of the bias for this Weibull distribution with decreasing hazard for the outcome event (not shown) show effects similar in trend but more pronounced than those in figures 1 and 2 for the constant hazard.

ILLUSTRATION

The bias from the five cohort definitions can be illustrated by using data from the United Kingdom's General Practice Research Database, a primary care database that contains diagnostic and prescribing records for approximately 3.5 million patients from more than 300 general practices (33). The five cohorts were selected from the population of all patients with a first diagnosis of lung cancer between 1995 and 2005, for which all prescriptions for warfarin or clopidogrel, two antithrombotic drugs, were identified.

The time-based cohort had entry defined by January 1, 2003, and exit by December 31, 2003, with exposure defined as an antithrombotic drug prescription any time during the 2003 1-year period. The event-based cohort was defined by the day of lung cancer diagnosis as cohort entry and follow-up for 1 year, with exposure defined as an antithrombotic drug prescription during the first 90 days of follow-up. The exposure-based cohort had entry defined by the first antithrombotic drug prescription after the lung cancer diagnosis

for the exposed or the date of the lung cancer diagnosis for the unexposed (random sample of 500), with 1-year follow-up for both. The multiple-event-based cohort had cohort entry defined by the first of two antithrombotic drug prescriptions within a year after the lung cancer diagnosis for the exposed or a random date after the lung cancer diagnosis date for the unexposed (random sample of 500), with 1-year follow-up for both. Finally, the event-exposure-based cohort had entry defined 30 days after the lung cancer diagnosis date, with the exposed defined by an antithrombotic drug prescription on the same day or in the previous month (to increase the numbers) and the unexposed by subjects with no antithrombotic drug prescription during the 1-year follow-up.

For all five cohorts, the outcome was death from any cause during the 1-year follow-up from the respective cohort entry dates. The hazard ratios of death associated with antithrombotic drug exposure were estimated for each cohort by using a Cox proportional hazards model. For the biased approaches, exposure was defined as described above, namely, without any consideration for the timing of the exposure during follow-up. The corrected analysis defined exposure by using a time-dependent variable, with the subject unexposed until exposure and exposed thereafter. The only exception was the event-based cohort, for which the approach simply involved exclusion of the first 90 days of follow-up used to define exposure.

The base cohort included 8,176 subjects with a lung cancer diagnosis after January 1, 1995. Table 1 shows that, for all cohort definitions, an important portion of follow-up time is misclassified or excluded by the crude analysis that does not account for the immortal person-time. These resulting crude analyses lead to hazard ratios all below 1 for the effect of the use of antithrombotic drugs on mortality, suggesting an important benefit of these drugs. The corrected analyses that properly classify the exposure over time lead to higher hazard ratios.

TABLE 1.   Hazard ratios of death associated with antithrombotic drugs using the five different cohort definitions applied to patients with a lung cancer diagnosis, estimated by the Cox proportional haxards model using the biased and correctly classified approaches

	No. of subjects	No. of deaths	No. of person-years (immortal time*)	Biased HR†	95% CI†	Corrected HR	95% CI
Time-based cohort							
No ATD† during a 1-year period	1,749	659	1,411.2	1	Reference	1	Reference
ATD during a 1-year period	146	50	128.3 (34.4)	0.83	0.63, 1.11	1.13	0.84, 1.50
Event-based cohort							
No ATD during a 90-day period	7,896	5,402	4,068.3	1	Reference	1	Reference
ATD during a 90-day period	280	162	189.5 (23.7)	0.66	0.56, 0.77	1.02	0.85, 1.22
Exposure-based cohort							
No ATD	500	352	248.6	1	Reference	1	Reference
ATD exposure	476	260	308.1 (316.5)	0.73	0.63, 0.85	1.05	0.87, 1.28
Multiple-event-based cohort							
No ATD	500	357	242.5	1	Reference	1	Reference
ATD exposure	388	188	276.3 (291.1)	0.48	0.40, 0.57	0.91	0.76, 1.10
Event-exposure-based cohort							
No ATD	6,392	4,131	3,545.0	1	Reference	1	Reference
ATD exposure on the same day	174	101	109.1	0.80	0.66, 0.98	0.95	0.83, 1.09
ATD exposure in the follow-up year	232	122	172.7 (61.0)				

* Immortal time either misclassified in the analysis or excluded by design and unaccounted for.

† HR, hazard ratio; CI, confidence interval; ATD, antithrombotic drugs.

DISCUSSION

This paper showed that immortal time bias can occur in observational studies of medication effects under a variety of cohort designs. This bias systematically overestimates the outcome rate in the unexposed group and at times also underestimates the rate in the group exposed to the medication. As a result, the rate ratio of exposure is underestimated, creating the illusion that the drug is effective in preventing the outcome under study. This paper also showed that the magnitude of this bias on the estimated rate ratio can be large.

This bias has been known to clinical epidemiology since the early 1970s, when it was identified in two clinical studies evaluating heart transplant survival (15, 16). Gail (17) explained that the waiting time of all patients who survived to make it to the transplant (immortal time period) had to be classified as unexposed to transplantation. Because of incorrect classification of this immortal time as exposed to transplantation, the transplanted group had been conferred an artificial survival advantage while the nontransplanted group had an artificial increase in the mortality rate, thus suggesting a benefit of heart transplant surgery. The current reappearance of this phenomenon is not exclusive to pharmacoepidemiology. Recently, the study that suggested that movie Oscar winners live longer was found to be subject to immortal time bias (24, 25).

Immortal time bias has been referred to in different ways, including survivor treatment selection bias or simply survival bias (23, 29). These terms may have introduced some confusion since immortal time bias is not a form of selection bias, but rather information bias, whereas survival bias refers to studies that use prevalent rather than incident cases (34, 35).

The appropriate approach for the studies using these designs requires that all immortal time be fully accounted for. First, at the design stage, the cohorts have to include all follow-up time, including that before the start of exposure. For example, the exposure-based cohort studies define cohort entry by the first drug exposure for the exposed and a first diagnosis for the unexposed. By doing so, the time from the first diagnosis to the first drug exposure for all exposed subjects is immortal and must be included in the analysis as unexposed. For multiple-event cohorts, cohort entry must simply be defined as the *n*th event for all subjects to avoid the immortal time generated by the time one must survive to get from the first to the *n*th event. This proper definition was used in several pharmacoepidemiology studies using multiple prescriptions to define the cohort (36–38). Second, at the analysis stage, the proper approach requires that the immortal time be correctly classified in terms of exposure. This is achieved by a time-dependent analysis such as that used by Mantel and Byar (18) in their reanalysis of the heart transplant data. Simple person-time methods or more sophisticated techniques, such the Cox proportional hazards model with time-dependent exposures, which classify the patients as unexposed until they become exposed and exposed thereafter, will provide proper estimates. However, these techniques assume that initiation and interruption of treatment are subject to random censoring, in the absence of which approaches such as inverse probability of censoring weighting can be considered (39).

The number of observational pharmacoepidemiology studies conducted has grown substantially during the last decade. The public health and policy impact of this research on the risks and benefits of medications is important. In the

United States alone, there were 545 million physicians visits involving medication therapy in the year 2000, with 2.3 medications prescribed per visit (40). Consequently, greater vigilance will be needed to recognize and avoid this bias that is becoming more prevalent with the increasing number of available computerized health databases used to conduct these observational studies of drug effects.

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