Beware of Registries for Their Biases

Hasan Yazici, M.D.

Abstract

Patient registries are very popular. On the other hand, scientific data collections in registries are commonly observational and retrospective and, in many instances, are prone to biases. Same thing is true of administrative databases. The selection of the control group(s) is probably the Achilles heel of scientific data collection in observational studies, and there are historical examples of how a properly chosen control group can help or its absence deceive us. Somewhat more recently recognized biases are the wandering comparisons of risk, confounding by disease severity, channeling bias, depletion of the susceptible, and the immortal time bias. The last bias can especially be deceiving and give us false hopes of new remedies. A particularly important selection bias we have come across is what we call the “mortality bias.” This is where the mortality in a mother population lessens the mortality in the registry that stems from this mother population simply because deaths in the former cannot be represented in the latter.

Patient registries are very popular. They surely tidy up patient care and are considered to be most useful in collecting observational and real life scientific data. All studies aiming at scientific data collection in medicine can be divided into 1. observational and 2. interventional studies. As implied, observational studies are those in which the observer observes, records, analyzes, and draws conclusions from what he or she observes. The interventional studies, on the other hand, are those in which the investigator, on purpose, interferes with what is observed and again observes, records, analyses, and draws conclusions, but this time before during and after his or her intervention. The latter activity can also most justifiably be called an experiment if we choose to bear the harsh remarks of our surgical colleagues as they report their experience with patients in their line of work.

Based on the time element, observational studies can further be divided into prospective, cross sectional, or retrospective studies. It is intuitively obvious that of the three kinds it is usually the last mentioned, and studies based on registries are mostly of this last kind, that is potentially the most vulnerable to problems with observation and recording if not only for the fact that this observation and recording, most of the time, has been done by somebody else other than the investigator. It is for this reason that interventional studies usually provide us with the strongest scientific evidence, while the retrospective observational studies the least.

However, high quality data can indeed be collected by retrospective observational data. In fact, in assessing drug harm, retrospective data are probably scientifically superior to randomized controlled trials, the epitome of interventional data collection, in assessing harm.

The main three advantages of observational data are summarized in Table 1. It is also to be noted that with proper statistical methodology one can also assess multiple outcomes and even causality in observational data.

Table 2 summarizes the main, this time, weaknesses.

I will now give two historical examples of how observational data can fully deceive us. Both are taken from Investigating Disease Patterns by Stolley and Lasky,1 by the way, a must to read for anybody interested in measurement in medicine.

The first story is about diethylstilbestrol (DES) use in threatened abortion, and the subsequent development of vaginal cancer in the offspring of such pregnancies. Table 3 paraphrases this extraordinary story as given in the Stolley
and Lasky book.

The most important take home message from the above story to me has been how a properly selected control group, even very small, can give us the correct answer. What is most curious, on the other hand, is how the investigators still pursue the answer in a group of patients from which by definition (note the penultimate line in Table 2) such an answer cannot be provided because of inadequate numbers.

The second story is again about the female hormone; this time estrone.

It is well known that apart from accelerated osteoporosis and related bone fractures many women get unpleasant symptoms after menopause due to lowered estrogen levels. It has also been recognized for over half a century that estrogen replacement can rather successfully prevent the osteoporosis and the unpleasant symptoms. There is, on the other hand, a trade off.

It is now well appreciated that there is an increase in frequency of cancer, especially that of the endometrium, in women who use estrogen replacement. The state of the art is to use the lowest dose of estrogen combined with progesterone for replacement. However, in the early days of estrogen use, this was not appreciated. When the hints of such an increase began to surface from observational data, the national statistics continued to show no increase in endometrial cancer since the health authorities continued to include hysterectomized women in the statistics. When the data were eventually corrected, the association became apparent.

A retrospective but a well controlled study from one center in Seattle also confirmed the association. This was a tumor registry study, and it is interesting to note how the investigators worded their conclusions. In this study, among 317 women with endometrial cancer 152 (48%) had used estrogen while the number of estrogen users was 54 (17%) among 317 women with other types of cancer from the same database. The investigators, in the abstract, concluded: “Thus, the risk of endometrial cancer was 4.5 times greater among women exposed to estrogen therapy.” This is not the best logic and should probably be reworded as: “…among women in a cancer registry.” The conclusion as it appears in the abstract is misleading for two reasons: 1. It has the implication that women who take estrogen have 4.5 times more risk of endometrial cancer as compared to women who do not. It is to be noted that there is no information in the quoted study in this direction since we have no indication about the total number of women exposed to estrogen in the first place; and 2. The study gives us an important clue that estrogen use is associated more strongly (4.5 times) with endometrial cancer as compared to the other forms of cancer, and the quoted sentence from the journal ignores this. Finally, we must also realize that this survey does not provide data on whether estrogen use is associated with increased cancer, including endometrial cancer, since the study did not report data concerning the frequency of cancer among the total users and non-users of estrogen. Note that the same data are also compatible with the assumption that estrogen therapy even decreases cancer in general, but this decrease is significantly less among the estrogen users. In brief, with the last study, we again have a registry situation at hand, and all registry data should be handled with due circumspect.

Hudson and Suissa have summarized the common pitfalls in analyzing observational drug studies in rheumatoid arthritis in a very useful editorial (Table 4). What they point out is surely applicable to such studies in other disease, as well.

A good example of a wandering comparison of risk is the wandering lymphoma rates associated with anti-TNF use reported by different geographies from the same country, Sweden, and almost within the same years. Among anti-TNF users one group reports an odds ratio of lymphoma of 0.8 when the comparison group is early RA patients or 1/1 when the comparison group is a group of inpatients. On the other hand, another group of investigators assigns an odds ratio of 4.9 to this risk when the comparators are RA patients in the community.

Confounding by disease severity is the situation where an outcome after an exposure is not the result of the exposure itself but of the disease severity. For example, anti-TNF agents are usually prescribed to more severe patients with RA.

The channeling bias is a selection bias when the effect of an exposure is studied among a group of patients who are made up of individuals heterogeneous for a previous exposure to the agent being studied or the outcome sought. The example given is the apprehension that leflunomide use in rheumatoid arthritis was associated with interstitial lung disease (ILD). If one looks at this possibility among all patients with RA, the risk ratio of leflunomide being associated with ILD is 1.9 while that of methotrexate is 1.4. Furthermore, among those patients with previous use of methotrexate or who already had ILD, one finds that leflunomide use would be associated 8 times more with ILD as compared to methotrexate. Finally, when one studies this association only among the first time users of leflunomide or methotrexate (the correct way of doing it) one sees that methotrexate is associated with ILD almost 3 times (3.9%) as compared to leflunomide (1.4%). It has been the improper channeling of the patients into the various subsets that had produced the misleading associations.

The depletion of the susceptible bias arises when, in a cohort, patients at more risk to a certain outcome (i.e., an adverse event) are excluded from the observations done on the remaining members of the cohort at later time points. This artificially dilutes the frequency of the sought after outcome in the cohort. A good example of this bias is in using the problematic patient-years unit in reporting adverse
events. If a drug causes anaphylaxis and death soon after its first use, this outcome will be observed less and less in this cohort the longer the cohort is observed. Time bias arises in a cohort study when an outcome can hinder, totally or partially, the effect of the exposure. The recently popular administrative databases, as sources of observational data on large numbers of patients, are particularly prone to this bias.

Let us assume that we have the unlikely hypothesis that topical antifungals also decrease mortality. To test this hypothesis, we resort to a prescription database. We first identify all individuals who have had a prescription for an antifungal from January 1st to March 31, 2011. We then follow-up all these people from the first day of their prescription to the last day of 2011 and tabulate those who have died. We finally compare the mortality in this group with that in the remaining population who never had a prescription for an antifungal from January 1 to the first date of prescription for the antifungal.

There are many recent examples of this bias and one should be immediately suspicious of its presence, especially in the setting of an unexpected, impressive, yet a difficult to biologically explain reported remedial new use of an established drug.

Recently, we became aware of another important selection bias related to registries. A group from Taiwan reported on the cancer frequency in a national registry of RA patients. The cancer data also came from a national registry, which probably catches all patients with cancer. It was interesting to note that at the end of the first year of follow-up the frequency of cancer was 59 times more in the RA registry as compared to what was expected in the general population. On the other hand, this frequency decreased to 0.30 of the expected at the end of 8 years of follow-up. This is biologically very difficult to explain. What is most probably happening is that those individuals who develop cancer before they develop RA in the mother population never proceeded to develop RA and have the chance to be represented in the registry.

In brief, registries are surely useful in organizing our work; registries come up with useful hypotheses to be tested and can also provide sound observational data otherwise unobtainable by controlled trials. On the other hand, we must be aware of their weaknesses, especially related to the use of inadequate and improper control groups yielding to a myriad of especially selection biases.

Disclosure Statement
The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References
5. Geborek F, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated