Commentary

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Studying the Effects of Nonindicated Medications on Cancer: Etiologic versus Action-Focused Analysis of Epidemiologic Data

John W. Jackson[1,2] and Xabier García-Albéniz[3]

Abstract

The study of nonindicated medications on cancer outcomes is challenged by potential time-related biases. The literature has strongly advocated for treating the exposure as time-varying and summarizing the outcomes through a dose–response model (an etiologic-focused analysis). An alternative is to refashion the data to resemble a hypothetical randomized trial of drug use (an action-focused analysis). To our knowledge, their relative treatment of time-related bias and aspects of interpretation have not been compared. In this commentary, using the study of metformin use on colorectal cancer risk by Bradley and colleagues (2018) as motivation, we compare the etiologic versus action-focused analysis of epidemiologic data. We examine their treatment of immortal person-time, time-varying confounding, selection bias, and the biological and clinical relevance of their results. In doing so, we aim to establish areas of common ground and points of departure that can guide future observational studies of medications on cancer risk, recurrence, and survival. *Cancer Epidemiol Biomarkers Prev; 27(5); 520–4. ©2018 AACR.*

See related article by Bradley et al., p. 525

Introduction

In recent years, there has been considerable interest in repurposing commonly used drugs (e.g., oral antidiabetics, cholesterol-lowering drugs, beta-blockers) for other therapeutic and preventive uses. A prime of example of this is metformin—there are more than 100 trials examining its potential as an anticancer agent (1). The association between metformin use and decreased cancer risk was first reported in 2005 (2). Since then, observational studies published strong inverse associations between metformin and colorectal, liver, pancreatic, breast, and any cancer diagnosis (1). However, many of these studies have been criticized as vulnerable to strong forms of time-related bias (3–5). In this issue of *Cancer Epidemiology, Biomarkers & Prevention,* Bradley and colleagues (6) present an analysis of colorectal cancer risk and metformin use that overcomes immortal person-time bias and time-lag bias.

In this commentary, we consider two analytic paradigms for studying the effects of nonindicated agents on cancer risk. Although they certainly share certain aspects, they seem to take fundamentally different paths toward describing the risks and benefits of metformin use. Is one road safer to travel? Do they lead to the same destination? The answers to these questions can inform future investigations of metformin and cancer and how we interpret their results.

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. [2]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

Corresponding Author: John W. Jackson, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205. Phone: 4432875059; E-mail: john.jackson@jhu.edu

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Epidemiologic Cohort Designs

For purposes of exposition, we broadly classify cohort study designs into two paradigms: those that focus on informing etiology versus informing interventions. Fundamentally, both rest on the same foundations for causal inference. Informally, they both assume that adjustment for measured confounding can make comparisons of metformin use fair (conditional exchangeability), that comparisons are represented at all levels of confounders (positivity), and that we can use outcomes under observed metformin use to infer outcomes under assigned metformin use (consistency). Formal articulation of these assumptions can be found elsewhere (7). The paradigms diverge, though, in how they leverage these assumptions to estimate effects of metformin use. Broadly speaking, an *etiology-focused* approach tries to summarize the person-time experience with metformin use and its relationship to the outcome. An *action-focused* approach tries to mimic the design of an explicit hypothetical randomized controlled trial (a target trial). After outlining their basic elements, we examine their treatment of common biases and the type of understanding they provide. We focus our discussion on cohort designs since case–control studies can be viewed as an efficient sampling of their underlying person-time.

Etiology-focused paradigm

This paradigm arose as a strategy to learn about chronic disease etiology and estimate measures of disease occurrence in a study population (8–10). Arguably, it was explicitly developed to study the epidemiology of cancer (11) and later repurposed to study other diseases. Here, a broad population of interest is defined and followed over time. Each person's experience is carved up into units of person-time—in which the rate of cancer incidence is thought to be homogeneous—according to an underlying timescale (e.g., age). These units are classified according to metformin use and cancer occurrence. They are further classified according to fixed or time-varying characteristics. For example, a person's unit

of person-time at age 45 could be classified as currently exposed to metformin use, no diagnosis of cancer, and being male with controlled diabetes. If we are studying incidence and not survival, person-time after cancer diagnosis would be discarded. A model is then fit to the person-time data to describe the relationship between cancer occurrence and some dose–response function of metformin use over time. This model explicitly or implicitly conditions on time. For example, Poisson regression or Cox proportional hazards regression ratios might be used to compare the rates or hazards of currently taking versus not taking metformin at a given time. If there are hypotheses about an induction period, these could be incorporated by lagging exposures. The etiologic paradigm appears to be the path taken by Bradley and colleagues, who report relative estimates of cancer incidence according to various functions of metformin exposure history, including "former use," "recency of use," and "cumulative duration" (6).

Action-focused paradigm

This paradigm also has a long history (12, 13). In the early literature, it was often used as a strategy to evaluate nonrandomized intervention programs (14). Later, epidemiologists realized that a prescribing decision can represent a nonrandomized intervention arm (a treatment strategy) and adapted the paradigm to evaluate the risks and benefits of alternative treatment strategies (15, 16). This paradigm has three components (17). The first is that, as in an actual randomized controlled trial, eligibility, comparison group membership, and the start of follow-up are aligned at an index date. Thus, unlike the etiologic-focused approach, the underlying time-scale is time-on-study. Second, action-based strategies are prespecified as comparison groups, and patients are classified according to the strategy they are following at the index date. For example, suppose "start taking metformin" is the strategy of interest. This analysis can be implemented by classifying patients according to whether they initiate metformin at baseline, which approximates an "intent-to-treat" strategy. We may be interested in more clinically relevant strategies like "start taking metformin, stop if your HbA1c goes below certain threshold, restart when it goes above the threshold." A per-protocol analysis of such strategies can be implemented by censoring patient follow-up if/when they stop taking metformin as the protocol directs (18, 19). Usually, a strategy specifies how long it is to be followed as well. The third component is the construction of comparison groups that have similar distributions of measured confounders at baseline (e.g., through propensity score matching, subclassification, and inverse probability weighting; refs. 20, 21). This is meant to emulate randomization, which separates the control for baseline confounding from the estimation of the treatment effect through design. There are different but compatible algorithms for emulating a trial (22), and it is possible to evaluate stopping or switching strategies (23, 24). But to be clear: an emulated trial is an observational study and, as such, relies on the assumption that unmeasured confounding, measurement error, and model misspecification are absent. As in a real trial, though, the estimation of relative or absolute effect measures—including survival curves—is straightforward.

Dealing with Threats to Validity

Immortal person-time

Early studies of the association between metformin and cancer use classified exposure status according to a person's entire person-time experience in that study (1, 4). For example, a person who initiated metformin 2 years after cohort entry, and then discontinued later, would have been described as an "ever user" and also a "former user" for their entire follow-up. Part of their person-time experience is misclassified because the definition depends on future metformin use. As a result, only those cases who are alive and do not develop cancer before they initiate metformin could be an "ever user" at baseline. Similarly, only those cases who are alive and do not develop cancer until after they discontinue metformin could be a "former user" at baseline. The amount of time before metformin use for these ever users (and discontinuation for the former users) is "immortal," and it leads to an underestimation of incidence rates.

With an eye toward the etiology-focused paradigm, epidemiologists proposed to rectify this bias by treating metformin use as time-varying (4, 10). The basic principle is that the exposure definition does not depend on the future, but rather on use at the current or prior times. For example, in a patient with no prior use at baseline, their person-time would be classified as "non-user" before initiation, but "ever user" after initiation. After that point, their person-time could also be classified as "current user" while taking metformin, but "former user" after they discontinue. Thus, comparisons are made of people as they are classified at a certain point in follow-up. This approach, used in the Bradley and colleagues' study (6), is essentially the Mantel–Byar method (25) for avoiding immortal person-time (26).

In the action-focused paradigm, person-time is never immortal as long as eligibility criteria, strategy membership, and the start of follow-up are synced (27). This follows because membership in the treatment strategy comparison group depends on present or past metformin use. Thus, a person's strategy classification cannot depend on being alive or not developing cancer up through a later point during follow-up. For example, suppose we had a person who initiated metformin at baseline and then discontinued 2 years later. If we were studying an "intent-to-treat" strategy, each unit of person-time would be classified according to their initial use. If instead we were studying a per-protocol strategy that specified adherence to metformin, their person-time would be classified to this strategy at the index date and during follow-up. As soon as they stop following the strategy, they are censored. Again, this immunity only holds when eligibility, strategy membership, and the start of follow-up are aligned.

Confounding and selection bias

The eligibility criteria do more than just define target populations. They are often critical for reducing confounding at baseline. Bradley and colleagues (6) restrict their cohort to those who were naïve to metformin, thereby avoiding confounding by past treatment history. This principle is staunchly advocated for in the trial emulation literature as well (28–30). However, the eligibility criteria in the action-based paradigm can be leveraged further. If there are people who would never (or always) initiate metformin given certain HbA1c levels, we would have intractable confounding. Removing these people not only eliminates this bias, it places our focus on those that must choose between metformin and an alternative (31, 32). In the action-focused paradigm, restriction can further be used to eliminate off-label uses that involve unmeasured confounding (33). For example, if we were studying survival, we might want to exclude uses alongside antipsychotics to offset their risk of induced weight-gain. If we did not, our metformin users might include those with serious mental illness,

who have a much shorter life expectancy than the general population (34). Another subtle form of confounding in this context is that severity of diabetes, metformin's indication, increases colorectal cancer risk (35). In either paradigm, one can use exclusion criteria to restrict to new cases of diabetes or adjust for duration of diabetes at baseline as Bradley and colleagues (6) were able to. Either form of adjustment avoids residual confounding by disease duration (time-lag bias).

Now, if metformin use is fixed from the start of follow-up in the etiologic-focused paradigm, or the "intent-to-treat" strategy is compared in the action-focused paradigm, then adjustment only has to be made at baseline. In the action paradigm, this is achieved by creating groups with similar confounder distributions at baseline, typically through matching or weighting. In all other scenarios, both paradigms are vulnerable to time-related bias involving dynamic factors. That is, we must account for the fact that some risk factors for the outcome may also be related to the decision to persist with or discontinue metformin. Poorly controlled diabetes can result in a switch to a second-line agent (e.g., sulfonylureas). This is a classic example of time-varying confounding in which there is treatment-confounder feedback (35).

In the etiology-focused design, it is possible to adjust for diabetes control if the time-varying exposure is not a function of treatment history. For "current use," one can simply adjust for prior metformin use and confounders as covariates (36, 37). Though, in the presence of treatment-confounder feedback, this strategy will lead to bias for any definition of time-varying exposure that depends on prior exposure (38). This includes time-varying definitions of "ever," "former," and "recent" use, among others. The action-focused approach avoids time-varying exposures altogether, as the strategy is defined at the start of follow-up and enforced through censoring. However, this censoring merely trades time-varying confounding for selection bias. Patients may depart from a treatment regime when their diabetes becomes poorly controlled, which is informative of colorectal cancer risk.

In both paradigms, the most commonly used appropriate adjustment method is the same: fit a model for metformin use given prior use and confounders and estimate inverse probability of treatment (or censoring) weights (39). In the weighted data, there is no time-varying confounding (or selection bias) for changes in metformin therapy. The weights, if estimated well, would address (measured) time-varying confounding/selection bias by balancing measures of diabetes control across levels of the time-varying exposure conditional on exposure history (etiology-focused paradigm) or across levels of departure from the initiated strategy (action-focused paradigm). Thus, in both paradigms, the performance of the weights can be checked empirically (40).

To obtain measures of treatment effect in the etiology-focused approach, the weights are used to fit a marginal structural model by regressing the outcome on the time-varying exposure in the weighted data (41). This model is especially necessary for cumulative exposures which must be summarized with a dose–response function. With the action-focused approach, one can regress the outcome on the treatment strategy indicators in the weighted data. When control for baseline confounding is achieved entirely through weighting or matching, this model perfectly describes the pattern of average outcomes in the data (e.g., it is saturated). With a saturated model, it is straightforward to obtain effect estimates on the difference scale for measures of public health benefit. Adjusted survival curves can also be easily obtained (7, 42). These presentations can easily detect early elevations in risk that might signal unmeasured bias (35).

Just as both designs can suffer bias when those who discontinue metformin are at higher (or lower) risk of colorectal cancer than those who remain on metformin, bias can ensue when those who are lost to follow-up are at higher (or lower) risk than those retained. A selection bias can arise, even when attrition rates are similar with respect to metformin use (43). Removing the selection bias requires adjusting for determinants of selection that also cause the outcome (or their proxies). These factors may occur at baseline or during follow-up. If they are not affected by metformin use, or an unmeasured cause of metformin use, they could be adjusted for in an outcome regression model. However, if there is feedback, selection bias should be removed through the use of inverse probability of censoring weights (17).

So far, the two paradigms sound like parallel routes to the same destination. We can obtain internally valid effect estimates in both setups. The etiologic- and action-focused paradigms can both avoid immortal person-time and respond to time-varying confounding and selection bias. Aside from the benefit of reducing potential bias through restriction, what is to be gained from pursuing the action-focused approach?

Interpretation for Etiology, Treatment, and Prevention

> *"It is important, furthermore, that however the excess risk is modelled, the results of the analysis respond to the basic aims of the study. The aims are essentially of two types—first, to provide a scientific basis for public health and, second, to contribute to the understanding of the biology of human disease. The former requires accurate assessment and prediction of risk, the latter requires an understanding of the role in the disease process played out by different exposures over time."*
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> [Breslow & Day (1987); ref. 44]

In a seminal text that shaped modern epidemiologic analysis, Breslow and Day distinguished two types of studies—one that seeks to inform public health action and the other to inform biological understanding (44). They then went on to lay the groundwork for the etiologic paradigm. They established the dose–response function as a key tool for relating incidence patterns to biological models. Through case study, they considered how the risk evolved during and after exposure and whether these patterns matched expected rates under early- versus late-stage models of carcinogenesis. They examined time since first exposure versus age as a time scale, comparative trends across age of first exposure, and whether risk increased or remained constant after exposure ended.

Much of this thinking has been preserved in the etiologic paradigm. Its goal is to characterize the dose–response function to provide clues about periods when exposure is most beneficial (or harmful), and whether any effect conferred appears to be short- versus long-lasting. The difficulty is, however, that the true dose–response function is multidimensional and unknown. Any model builds in assumptions about when effects are expected to be seen (by incorporating or omitting lags; refs. 8, 9). The dose–response function could be expressed in terms of frequency, duration, intensity of exposure, or all three at once. Coarsened summaries of exposure such as time-varying "ever use," "current

use," "former use," etc. are at best rough probes of the true dose–response form. To the degree that they mischaracterize the curve, effects of metformin may be missed. For example, an effect of former use may vary with age at first exposure or time since last exposure, but this could be obscured if such effect modification were not explicitly modeled. Perhaps it is most meaningful to answer specific questions about the dose–response function as well as possible with separate models.

The action paradigm resigns the task of mapping the entire curve. Instead, it focuses on aspects after patients initiate or change their metformin exposure status. It does not aim to relate incidence to biological models or identify sensitive periods of risk. Rather, it aims to inform decision-making by accurately estimating risks under different courses of action that are of interest to patients, providers, and policy makers. In terms of external validity, it is easy to inspect the eligibility criteria's correspondence to a provider's or health system's patient profile. The ability to ask fine-grained questions for certain types of patients can inform prevention efforts, clinical guidelines, and regulatory labeling. To be sure, no single study in the action-focused paradigm will fully describe the risks and benefits of metformin for all uses and all populations. They may differ depending on the nature of the strategy, the patients' characteristics, and the context in which it is implemented. It is a strength of the action-focused paradigm that these distinctions become apparent. Last, the action-focused paradigm can easily accommodate survival curves and absolute measures of effect to provide information on public health benefit.

It is worth emphasizing that both paradigms are limited by the data. We can only describe the dose–response curve for patterns of exposure that people tend to follow. Likewise, we can only estimate risks and benefits for strategies used in the real world. Without strong modeling assumptions, some questions about the effect of metformin on cancer may remain unanswered. We must either wait until new patterns of metformin use emerge, or intervene to conduct a randomized controlled trial. The latter option may not always be possible given funding priorities and ethical concerns.

Conclusion

Epidemiologic data are becoming more abundant and diverse thanks to sources like claims, electronic medical records, e-health, and their linkage to traditional cohort studies. This precious resource has the potential to shed light on the role of nonindicated medications on cancer outcomes. Our review of the etiology-focused and action-focused paradigms suggests that they are both robust analytic approaches that can avoid immortal person-time, time-varying confounding, and selection bias. They can both be travelled safely to understand benefits and risks for metformin. However, we would agree with Breslow and Day that they have different motivations and seek different forms of knowledge. Viewing epidemiology as an arc from biological understanding to translation, we need both paradigms to inform our science and public health efforts.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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