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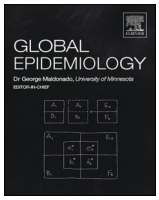

Commentary

Commentary: On measurement error, PSA doubling time, and prostate cancer

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ABSTRACT

Exposure measurement error is a pervasive problem for epidemiology research projects designed to provide valid and precise statistical evidence supporting postulated exposure-disease relationships of interest. The purpose of this commentary is to highlight an important real-life example of this exposure measurement error problem and to provide a simple and useful diagnostic tool for physicians and their patients that corrects for the exposure measurement error. More specifically, prostate-specific antigen doubling time (PSADT) is a widely used measure for guiding future treatment options for patients with biochemically recurrent prostate cancer. Numerous papers have been published claiming that a low calculated PSADT value (denoted $\widehat{\text{PSADT}}$) is predictive of metastasis and premature death from prostate cancer. Unfortunately, none of these papers have adjusted for the measurement error in $\widehat{\text{PSADT}}$, an estimator that is typically computed using the popular Memorial Sloan Kettering website very often visited by both physicians and their patients. For this website, the estimator $\widehat{\text{PSADT}}$ of the true (but unknown) PSADT for a patient (denoted PSADT*) is computed as the natural log of 2 (i.e., 0.6931) divided by the estimated slope of the straight-line regression of the natural log of PSA (in ng/mL) on time. We utilize $\widehat{\text{PSADT}}$ to derive an expression for the probability that the unknown PSADT* for a patient is below a specified value C (> 0) of concern to both the physician and the patient. This probability is easy to interpret and takes into account the fact that $\widehat{\text{PSADT}}$ is a statistical estimator with variability. This variability introduces measurement error, namely, the difference between a computed value $\widehat{\text{PSADT}}$ and the true, but unknown, value PSADT*. We have developed an Excel calculator that, once the [time, ln(PSA)] values are entered, outputs both the value of $\widehat{\text{PSADT}}$ and the desired probability. In addition, we discuss problematic statistical issues attendant with PSADT* estimation typically based on at most three or four PSA values. We strongly recommend the use of this probability when physicians are discussing $\widehat{\text{PSADT}}$ values and associated treatment options with their patients. And, we stress that future epidemiology research projects involving PSA doubling time should take into account the measurement error problem highlighted in this Commentary.

Introduction

It is generally well-known that epidemiology research studies very often suffer from the harmful consequences of exposure measurement error [1]; these harmful consequences include statistical bias and loss of power. As a very important practical example, prostate-specific antigen doubling time (PSADT) has received considerable attention with regard to the treatment of prostate cancer. An an example, three successful clinical trials (SPARTAN, PROSPER, and ARAMIS) only enrolled patients with observed PSADT values that were less than 10 months [2]. Several published papers [3–11] describe the use of multivariable modeling (e.g., multiple linear regression, logistic regression, Cox regression) for data analyses using a statistical estimator $\widehat{\text{PSADT}}$ as the key exposure variable, the goal being to provide valid and precise statistical evidence that a short $\widehat{\text{PSADT}}$ is predictive of adverse health outcomes like metastasis and premature death from prostate cancer [12]. Unfortunately, no consideration in these articles has been given to

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the measurement error in $\widehat{\text{PSADT}}$. There are numerous published articles [13–19] that could have been used to correct for this measurement error, but none were used. Despite this problem, we do feel that there is sufficient evidence, although somewhat imperfect, that a short $\widehat{\text{PSADT}}$ is potentially problematic. Given this motivation, we have developed an expression for the probability that the unknown PSADT* for such a patient is below a specified value C ($\rangle 0$) of concern (e.g., 0.50 years), an expression that appropriately accounts for the measurement error in $\widehat{\text{PSADT}}$. This probability expression is derived in the next section.

Methods

For a patient with biochemically recurrent prostate cancer, we assume an exponential rise in PSA levels [4,5] and a lognormal distribution for PSA levels [20,21]. We also assume that the PSA measurements for such a patient are gathered sufficiently far apart in time so as to be mutually uncorrelated; we will illustrate how to assess the validity of this assumption in the Examples section.

Suppose that a patient provides a PSA_i measurement (in ng/mL) at time $t_i, i = 1, 2, \ldots, n$. Let $\widehat{\beta}_1$ (assumed to be positive in value since only trends upward are relevant) be the point estimator of the slope $\beta_1 (\rangle 0)$ for the straight-line model $ln(\text{PSA}_i) = \beta_0 + \beta_1 t_i + \varepsilon_i, i = 1, 2, \ldots, n$, where ε_i has a normal distribution with mean 0 and variance σ^2.

With $\text{SE}(\widehat{\beta}_1)$ denoting the estimated standard error of $\widehat{\beta}_1$, it follows, given the stated assumptions, that the statistic $T_{n-2} = (\widehat{\beta}_1 - \beta_1)/\text{SE}(\widehat{\beta}_1)$ has a Student's T-distribution with $(n-2)$ degrees of freedom [22], $n \geq 3$.

So, with $\widehat{\text{PSADT}} = 0.6931/\widehat{\beta}_1$ denoting the estimated value of PSADT*, we have

$$\theta_{n-2} = \text{pr}[\text{PSADT}^* < \text{C}] = \text{pr}\left[\frac{0.6931}{\beta_1} < \text{C}\right]$$

$$= \text{pr}\left[\frac{0.6931/\text{C} - \widehat{\beta}_1}{\text{SE}(\widehat{\beta}_1)} < \frac{\beta_1 - \widehat{\beta}_1}{\text{SE}(\widehat{\beta}_1)}\right]$$

$$= \text{pr}\left[T_{n-2} < \frac{\text{C} - \widehat{\text{PSADT}}}{(1.4428\text{C})(\widehat{\text{PSADT}})\text{SE}(\widehat{\beta}_1)}\right].$$

So, if $\widehat{\text{PSADT}} < \text{C}$, then $\theta_{n-2} > 0.50$. In other words, if a patient's estimated PSA doubling time $\widehat{\text{PSADT}}$ is less than a specified value C of concern, the chance is better than 50% that this patient's true (but unknown) PSADT* is less than C. And, the actual probability could be much higher than 0.50, as we will illustrate numerically in the EXAMPLES section.

Examples

Consider the following four pairs $[t_i^* = (t_i - t_1), ln(\text{PSA}_i)], i = 1, 2, 3, 4$, of data that were collected in six month intervals over a year and a half: (0, 0.20), (0.50, 0.80), (1.00, 1.50), and (1.50, 2.50). We developed an Excel calculator (attached) to obtain $\widehat{\text{PSADT}}$=0.6931/1.520 = 0.46 years. And, for C = 0.50, we have $\theta_2 = 0.79$.

So, for this patient, the chance is about 80% that his true (but unknown) PSADT* value is below 0.50, even though his computed $\widehat{\text{PSADT}}$ value of 0.46 is barely below 0.50 in value. The reason for this interesting result is that the fit of the straight line model to these four data points is quite excellent (r^2=0.99). In general, the fit of the straight line model will not be this good for typical data sets. But, as stated earlier, if $\widehat{\text{PSADT}} <$C, the probability that PSADT* is less than C is some value greater than 0.50.

The Durbin-Watson statistic [23], d, which is used to check for the presence of autocorrelation among the residuals in a regression analysis, equals 2.07 for this very small data set. We could not find critical values of the Durbin-Watson statistic for sample sizes less than six, but a simple linear extrapolation of tabulated critical values indicates absolutely no evidence of first-order autocorrelation among the four residuals produced via this simple linear regression analysis. Also, it is generally accepted that d values between 1.50 and 2.50 provide no strong evidence of first-order autocorrelation, with values close to 2.00 being the most desirable. So, we are confident that our assumption of zero correlation among the four PSA values is a reasonable one. In general, this lack of autocorrelation should be expected for PSA values gathered a few months apart from each other.

When $\widehat{\text{PSADT}} >$C, then $\theta_{n-2} <$0.50. Now, consider the following two sets of data: [(0, 0.60), (0.50, 0.50), (1.00, 1.10), (1.50, 2.50)] and [(0, 0.30), (0.50, 0.80), (1.00, 1.40), (1.50, 2.20)]. For the first data set with C = 0.50, it can be shown that $\widehat{\text{PSADT}} = 0.55$, that $\theta_2 = 0.41$, and that d = 2.00. For the second data set with C = 0.50, it can be shown that $\widehat{\text{PSADT}}$ also equals 0.55, that $\theta_2 = 0.16$, and that d = 2.03. So, when the $\widehat{\text{PSADT}}$ value is greater than 0.50, the chance that the true (but unknown) PSADT* value is below 0.50 could be either fairly high or fairly low.

Discussion

When discussing $\widehat{\text{PSADT}}$ findings, both physicians and their patients want to be confident that treatment recommendations are based on reliable information, especially since a short $\widehat{\text{PSADT}}$ has been shown to be a cause for concern. For the standard method of computing a $\widehat{\text{PSADT}}$, we have developed a probability expression that allows a physician and the patient to assess how likely it is that the patient's true (but unknown) PSADT* value is below a certain concerning value C. In particular, if the $\widehat{\text{PSADT}}$ value is below C, we have shown that the probability that the true (but unknown) PSADT* value is also below C is greater than 0.50; and, as our first numerical example illustrates, this probability could be much higher than 0.50. In addition, if the $\widehat{\text{PSADT}}$ value is greater than C, we have used numerical examples to show that the probability that the true (but unknown) PSADT* value is actually below C could be somewhat high or somewhat low in value.

It is very important to emphasize that our use of parametric statistical methods (e.g., T-distribution and attendant assumptions) is mandated by the fact that only the most recent three or four PSA measurements for a particular patient are typically considered by prostate cancer physicians. The main reason for this very small sample size is that a *recently increasing trend* in PSA values has been shown to be a very important predictor of an adverse health outcome.

In addition, as mentioned in the Abstract, many physicians and patients often utilize the Memorial Sloan Kettering Cancer Center PSA doubling time calculator at https://nomograms.mskcc.org/prostate/psadoublingtime.aspx. This is a very popular and useful tool, but it does not take into account the measurement error in the $\widehat{\text{PSADT}}$ values that are produced. It would be an easy upgrade to incorporate our Excel calculator into this popular nomogram, and we recommend that such an upgrade be made.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gloepi.2023.100129.

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