Prostate-Specific Antigen

A Clinical and Mathematical Conundrum

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Prostate cancer is a highly prevalent disease that is characterized by a wide range of aggressiveness, ranging from the clinically irrelevant to the rapidly progressive, lethally metastatic. Since its introduction as a serum test in the late 1980s, prostate-specific antigen (PSA) has been increasingly promulgated as an important biomarker for prostate cancer, both for screening and as a monitoring tool for posttreatment recurrence of tumor. Yet, a variety of questions remain concerning these uses of serum PSA. Many of these questions relate to specificity for cancers that will cause clinical disease if not treated and the consequent "overdiagnosis" of possibly large numbers of patients. Numerous studies have attempted to answer these elusive questions, often with contradictory results.[1,2]

In this issue of the *Journal*, Vollmer[3] tackles a question regarding the clinical use of serum PSA: if a patient enters the clinic with a serum PSA of x, what is the probability that he has prostate cancer? Following the traditional frequentist statistical approach, most studies have focused on quantifying the sensitivity and specificity of serum PSA as a biomarker of prostate cancer being present. However, few studies have approached the more clinically relevant question of determining the positive predictive value (PPV) in a cohort of patients in whom disease prevalence (in this case, prostate cancer) is already known. Vollmer attempts to improve the value of PSA screening by basing his analysis on large-scale databases and incorporating factors that include the underlying probability of the disease being present in the study population and false-positive rates.

Bayesian vs Frequentist Statistics: The Battle Line

For the statistically challenged among us, it may not be clear what the big deal is about using Bayesian statistics.[4] Most medical statistics has been grounded for decades in a frequentist approach in which the focus is on the probability that a given outcome of a study or trial will occur, assuming that a particular hypothesis is true. For example, the well-known *P* value describes the probability of observing results as or more extreme than those observed, assuming that the null hypothesis is true. On the other hand, Bayesian statistics, which has it roots in Bayes rule, puts frequentist statistics on its head and focuses on the probability that a hypothesis is true given the available preexisting evidence.[5] Hence, we can regard Bayesian statistics as being more evidence-based (assuming that the already available or "prior" evidence is correct). Of note, the fact that Bayesian analysis is based on prior knowledge has been a source of criticism, since the assumption that the prior knowledge is accurate may not be true. Basically, the former ("frequentist" or *P* value) approach is based on deductive reasoning and the latter (Bayesian) on inductive reasoning. In the recent trend towards evidence-based medicine, under the discomfort or protest of frequentist fans, Bayesian approaches have become more common.[5]

In his study, Vollmer[3] reintroduces us in anatomic pathology to Bayesian statistics and the value of using the prior probability of an event occurring (namely, prostate cancer being diagnosed in a needle biopsy) as a basis for determining what value a new test (in this case the serum PSA of a certain range of values for specified ranges of patient ages) adds to that probability. Vollmer has already provided readers of the *Journal* the opportunity to incorporate Bayesian approaches in his study of Spitz nevi.[6]

Figure 1 of Vollmer's article illustrates that at low PSA cut points younger men (50-59) have a lower Bayesian PPV value, while the trend inverses as the PSA cut point increases.

This finding is based on the fact that older men are more likely to have prostate cancer.

Assessing Clinical Relevance of Serum PSA

A study done by Punglia et al[7] assessed the PSA screening test after correcting for verification bias. In this case, verification bias occurs when disease status (biopsy-confirmed or refuted prostate cancer) is not determined in all patients who are tested and the probability of verification is dependent on the test result, clinical variables, or both. Their study utilized a frequentist approach to evaluate the PSA test and came to the conclusion that the threshold of PSA for recommending biopsy should be lowered, particularly in the case of younger men.

However, Vollmer's data supports the opposite expectation by showing that for a given PPV the serum PSA cut point increases with age (see Vollmer's Figure 1).[3] Using the Bayes rule, Vollmer suggests that in the case of younger men the PSA threshold level should in fact be increased if the goal is to attain the same PPV in all age groups. The disparity between the frequentist and Bayesian approach comes to a head here, each statistical method coming to a different conclusion. By using Bayesian statistics, Vollmer's evaluation incorporates background knowledge, such as underlying probabilities, false positive probabilities, and sensitivity. The study of Punglia et al[7] only attempts to improve the current PSA screening by correcting for verification bias. While Vollmer's expansion on PSA guidelines appears to incorporate more evidential data, it cannot be taken as the gold standard in clinical assessment of prostate cancer. That said, we should remember that in this study Vollmer is only concerned with developing a strategy that uses serum PSA to efficiently find as many of the cancers as possible, not to find those cancers in which clinical action is important. And that brings us to a broader set of questions.

Although it is a step closer, the Bayesian PPV (or, the probability that a patient of age y with serum PSA of x will have prostate cancer in a needle biopsy specimen) is still not the most clinically relevant question. A more clinically relevant question is: if a patient with a serum PSA of x has prostate cancer, what is the chance that the disease will be aggressive enough to affect his life expectancy? The wide range of biologic behavior of prostate cancers in patients with the same serum PSA[8] means that there are a significant number of patients for whom their disease is clinically irrelevant. Hence, there are an unknown, but probably high, number of prostate cancer patients who are treated with radical therapy (contributing to significant morbidity and mortality) for a disease that may well be irrelevant on the timescale of their expected life spans.

Vollmer's Bayesian PPV approach must then be evaluated on the integration of aggressiveness in the PPV assessment. Is the reason that the PSA threshold drops due to the fact that the PSA levels that once fell in this category were not aggressive enough to be considered? If this is true, Vollmer's approach agrees with the idea that clinically significant (aggressive) prostate cancer should be the gold standard, not prostate biopsy as suggested by Punglia et al.[7] Lowering the serum PSA threshold for biopsy across the board, as concluded by Punglia et al, suggests that the aggressiveness of the tumor may not be under consideration, and using these guidelines may lead to an increase in the overdiagnosis and overtreatment in younger men.[7]

To help answer this question, an outcome analysis is necessary. In a study by Concato et al[9] no significant survival benefit was found among patients screened for prostate cancer using serum PSA as the screening assay. This suggests that serum PSA testing has increased the detection of prostate cancer in general but not necessarily of aggressive, clinically relevant prostate cancer in particular.

In 2001, Swanson et al[8] developed a mathematical model for the dynamics of serum levels of PSA as a function of tumor volume. The model showed that with a slow-growing prostate cancer (as a xenograft) serum PSA levels increase at a similar rate as the tumor volume. However, the model suggests that rapidly growing tumors have a tumor volume that increases at a significantly higher rate than the associated serum PSA does. Swanson et al went on to demonstrate that for any given tumor volume, a wide range of serum PSA levels can be observed depending on the tumor growth rate. This study was discrepant with the general clinical impression that an enlarged prostate is always associated with an increased serum PSA level and that serum PSA is a quantitative assay for prostate cancer volume. Both in mice with prostate cancer xenografts[8] and in patients with disseminated prostate cancer an elevated PSA serum level does not necessarily result from a large tumor volume. The results of this study agreed with experimental observations and suggest that although serum PSA may be a useful marker of tumor growth, care must be taken in interpreting single serum PSA values.

The discrepancy between preclinical prostate cancer and clinically relevant disease is a distinction that becomes very significant in the overdiagnosis and overtreatment of men. A study by Sakr et al[10] on 249 autopsy cases revealed that 55% of men in their 50s and 64% of men in their 70s were found to have invasive prostate carcinoma at the end of their life. This resonates with the findings of Swanson et al[8] that not all elevated PSA levels are associated with clinically significant and/or high volume prostate cancer. Analysis of serum PSA levels needs to be interpreted with the knowledge of the values of potentially compounding factors, as was done by Vollmer.[3]

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The use of serum PSA to screen for patients whose quality and quantity of life will, hopefully, be improved by curative therapy of their prostate cancer is presumably temporary. We have already discussed the importance of focusing our screening efforts on identifying aggressive prostate cancers. Tissue biomarkers promise to provide additional tools. Serum assays using ever more sensitive and specific proteomics methods promise to further improve our ability to obtain progressively better PPVs from our assays. As molecules that play crucial mechanistic roles in prostate cancer biology are identified, molecular pathways and points of therapeutic intervention will also be elucidated. Since these days have not arrived, Vollmer's study[3] helps us refine the use of that assay (namely serum PSA) that has been so valuable in identifying large numbers of patients who can be treated for their prostate cancers.

We appreciate Dr Vollmer's introducing us to statistical concepts that are not widely used in medicine but that have the prospect of improving both the applicability of our clinicopathologic studies and our ability to better stratify patients for prognosis based on laboratory assays. Articles that we have found useful in learning the power of Bayesian analysis are back-to-back articles by Goodman[4,11] and a commentary on the use of Bayesian statistics by Malakoff.[12]

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