An Iatrogenic Confounding Variable

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Why do some men develop clinically significant prostate cancer whereas others do not? Epidemiologists have pondered this dilemma for decades. During this time, we have learned that many men harbor incidental prostate cancers, some even as young as 30 years, but that most men will not develop clinically significant disease (1,2). Careful examination of racial patterns of disease progression has taught us that environmental factors play a major role in the development of clinically significant disease. Prostate cancers, for example, are relatively rare among Asians living in China and Japan but are more common among Asians who have migrated to western countries or adopted western habits (3). Diet has frequently been cited as a major potential factor contributing to prostate cancer disease progression, but other environmental factors are receiving increasing scrutiny.

The role of inflammation in the development of prostate cancer has been a target of research for many years (4). Several intriguing correlations have been identified. In this issue of the Journal, Stark et al. (5) reported the role of Trichomonas vaginalis infection as a possible environmental factor that facilitates the development of clinically significant disease. Although the researchers were unable to demonstrate a statistically significant correlation between a T. vaginalis seropositive state and overall prostate cancer risk, their findings deserve serious attention.

One of the most important environmental factors affecting the incidence of prostate cancer during the past two decades has been the introduction of testing for prostate-specific antigen (PSA). Widespread testing for PSA began in the United States in the late 1980s and has dramatically changed the population of men diagnosed with prostate cancer during the follow-up period. Before the late 1980s, men with newly diagnosed prostate cancer presented with clinically significant disease often in advanced stages. Now most men are identified with localized disease usually 5–10 years earlier in the natural course of the disease (6). The study by Stark et al. is a case in point. These researchers chose a classic study design, the case–control study, to assess the potential impact of a specific variable, T. vaginalis infection, on an outcome of interest, prostate cancer. They turned to the Physician’s Health Study because of the large sample size and the availability of serum drawn at baseline that allowed researchers to assess exposure to T. vaginalis. PSA testing, however, has altered the population of men diagnosed with prostate cancer during the follow-up period. Before the late 1980s, men with newly diagnosed prostate cancer presented with clinically significant disease often in advanced stages. Now most men are identified with localized disease usually 5–10 years earlier in the natural course of the disease (8).
Furthermore, many of the cancers identified appear to have a low potential for progression and are often graded as Gleason 3+3 disease. As a consequence, researchers now have much more difficulty distinguishing clinically significant cancers from indolent disease.

Why is this relevant to the study conducted by Stark et al.? The outcome of interest, clinically significant prostate cancer, has been contaminated by large numbers of men with indolent disease. Therefore, the sample size needed to identify a statistically significant association with overall prostate cancer risk has increased dramatically. Failure of the study by Stark et al. to find a statistically significant association between the T. vaginalis seropositive status and overall prostate cancer risk may therefore be due to a type II error. The finding that the time between blood collection and the diagnosis of prostate cancer had the greatest influence on effect estimates supports this point. Men diagnosed before 1987 were much more likely to harbor clinically significant disease than men diagnosed as a result of PSA testing after this date. This finding also may explain why Stark et al. noted a statistically significant association between T. vaginalis infection and prostate cancer, whereas researchers conducting the finasteride chemoprevention trial did not (9). Finally, Stark et al. did identify a statistically significant association between T. vaginalis seropositivity and those men who clearly had evidence of clinically significant disease. Specifically, they found a much stronger statistical association between T. vaginalis seropositivity and men who suffered a prostate cancer–specific death, developed bone metastases, or had extraprostatic disease.

What are the implications for future epidemiological studies exploring potential risk factors for prostate cancer? First, researchers should not assume that the label “prostate cancer” describes the same disease in all patients. Much greater effort must be made to separate newly diagnosed prostate cancers by their potential probability of disease progression. Several classification systems have been developed; most usually rely on a combination of Gleason score, serum PSA level at diagnosis, and clinical stage (10). Second, researchers must separate screen-detected cancers from those that present clinically. Many of the former may not be clinically relevant, whereas most of the latter often are. Third, researchers must also understand that the doubling of prostate cancer incidence during the past decade has dramatically increased the sample size needed to uncover statistically meaningful associations between potential risk factors and clinically significant disease. The larger number of patients with newly diagnosed prostate cancer has actually made the epidemiologist’s job harder not easier.

Understanding the factors leading to prostate cancer progression and death continues to challenge researchers and clinicians alike. Only carefully constructed scientific studies can separate fact from opinion. Our enthusiasm to embrace scientific studies before understanding the true clinical impact of this disease has added another confounding variable to an already complex problem.

References