When Is a Death From Prostate Cancer Not a Death From Prostate Cancer?

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Since the advent of testing for prostate-specific antigen (PSA) more than a decade ago, the number of men diagnosed with prostate cancer has increased dramatically (1). Many of these men have been subjected to treatments, such as radical prostatectomy, radiation therapy, and, more recently, radioactive seed implantation. As these men age, a substantial number of them will also receive androgen ablation therapy through either luteinizing hormone-releasing hormone analogues or bilateral orchiectomy (2). This enormous diagnostic and treatment effort has been implemented on the basis of the theory that earlier diagnosis and treatment of prostate cancer will lower mortality from this disease. Unfortunately, considerable controversy still surrounds this effort because no randomized trials have been completed that demonstrate that screening and treatment by any modality will increase life expectancy following diagnosis. Furthermore, to date, the decline in prostate cancer mortality has been very modest and can be attributed to multiple causes (3). Most information concerning the efficacy of various treatment modalities relies on data provided by large case series analyses. In an effort to highlight the impact of a particular intervention, clinicians frequently report their data utilizing a cause-specific survival analysis (4). This is a particular issue in prostate cancer because of the considerable mortality associated with competing medical hazards in an aging population. Critical to a cause-specific survival analysis is an accurate determination of cause of death. Similarly, efforts to document declines in prostate cancer mortality from data compiled by the National Center for Health Statistics, Hyattsville, MD, also rely on an accurate determination of cause of death.

In this issue of the Journal, Newschaffer et al. (5) have examined critically whether a bias in attribution of cause of death may exist for patients who have died following a diagnosis of prostate cancer at age 67 years or older. These men account for more than half of the newly diagnosed prostate cancer patients within the United States and constitute the group of men for whom diagnosis and treatment are most controversial. The article by Newschaffer et al. confirms that a majority of these men (61%) did not die of their disease but instead died of competing medical hazards. These hazards were similar to those faced by men who were not diagnosed with prostate cancer.

Their analysis yielded several expected findings. Specifically, older men at diagnosis were at a decreased risk of dying of their disease. Men with multiple comorbidities had a decreased risk of dying of prostate cancer. Men with advanced-stage disease had a relatively large increase in the probability of death attributed to prostate cancer. Their analysis, however, also yielded some unexpected findings among men diagnosed with multiple tumors. This problem is not uncommon because older men are at substantial risk of developing other cancers, such as lung and colon cancers. The authors were surprised to note that men undergoing aggressive treatment of prostate cancer had a higher odds ratio of dying of a competing cancer compared with the nonprostate cancer cohort. In addition, men who did not receive treatment of their prostate cancer had a lower odds ratio of dying of a competing cancer compared with the nonprostate cancer cohort. What could explain these differences?

Newschaffer et al. (5) propose several hypotheses. The most obvious is a problem in cause-of-death reporting within subgroups of prostate cancer patients. The authors clearly identified that subgroups defined by initial treatment differed significantly in the probability that their deaths would be classified as being from prostate cancer as opposed to the competing cancer. While this may be a statistical artifact, the authors suggest that health-care providers completing death certificates for prostate cancer patients may be influenced by the treatments that patients received. This type of systematic reporting bias can yield important distortions when reporting cancer statistics. The authors estimate that inaccurate reporting of prostate cancer deaths on death certificates may be as high as 20%.

These findings are extremely important. It is unlikely that the controversy surrounding early diagnosis and treatment will be fully resolved solely by randomized clinical trials. Additional resolution will come from an analysis of tumor registry data. For example, large decreases in mortality from cervical carcinoma confirmed the importance of Pap testing and treatment of cervical dysplasia. Similar declines in prostate cancer mortality could validate the importance of PSA testing and aggressive intervention. The accurate determination of prostate cancer deaths is, therefore, a critical component to determining accurate prostate cancer mortality statistics and cause-specific survival analyses. Recently, we examined this issue and also found that 10%–20% of deaths were misattributed. Misattributions occurred most commonly when another cancer was present or a patient died following surgery. Confounding medical conditions such as heart disease also posed difficulties (6). Newschaffer et al. have demonstrated that the proper cause of death attribution is not a trivial task and deserves increased attention by the research community. Specifically, information on death certificates needs to be validated against primary medical records. If a systematic reporting bias exists, especially one associated with initial treatment selection, it would have a major impact on our ability to validate or refute the primary hypothesis that early detection and treatment lead to decreased prostate cancer mortality. Accurate determination of the nature and magnitude of such systematic biases will be crucial to appropriate interpreta-
tion of population trends. Newschaffer et al. raise important issues that need to be pursued by the research community.

REFERENCES