1
Defining the Problem: From Subclinical Disease to Clinically Insignificant Prostate Cancer

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Abstract

The widespread use of prostate-specific antigen testing and the increasing rate of prostate needle biopsies with recent refinement of sampling approaches have led to a dramatic increase in the diagnoses of small-volume, early-stage prostate cancer and premalignant lesions (prostatic intraepithelial neoplasia). The Wayne State autopsy study has shown the prevalence of subclinical prostate cancer and prostatic intraepithelial neoplasia to be much higher than previously reported, with a steady increase with advancing age. The findings of this and other studies raise challenges regarding the potential relationship of subclinical cancer to minute cancer foci detected in biopsies. The clinical management of patients diagnosed with such cancers is becoming more controversial because the progression potential of clinically detected small cancer foci is difficult to predict.

Keywords: “subclinical prostate cancer,” autopsy, prevalence, screening

Compared with other solid tumors, prostate cancer is rather unique in its epidemiologic characteristics and the marked variations in the progression potential for patients clinically diagnosed with the disease. Over the last decade, the debate regarding this cancer focused mainly on aspects of screening/early detection approaches in terms of defining serum prostate-specific antigen (PSA) values that are “abnormal” to trigger a biopsy, and more recently, on the number and location(s) of needle biopsies deemed adequate to establish a pathologic diagnosis of cancer. An equally important issue in this debate is the controversy regarding the “clinical significance” of at least a proportion of the cancers discovered through

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screening/early detection efforts and, finally, the impact of these efforts on disease-specific mortality.

This introductory chapter offers an overview of the epidemiology/prevalence of early neoplastic transformation of prostatic epithelium resulting in carcinoma and/or prostatic intraepithelial neoplasia (PIN). It also attempts to relate the concept of “latent/subclinical disease” to that of clinically diagnosed cancer by focusing on questions such as the following:

Is subclinical disease the precursor for what is to become clinically evident cancer? If so, why does the latter show more than 30-fold differences in incidence among different geographic populations and ethnicities whereas the prevalence of the undetected disease is reported to be remarkably less variable?

What about the potential precursor role for recently defined epithelial alterations such as PIN?

How long is the “latency” period, and what determines the progression subsets of subclinical tumors to manifest clinically?

From a practical standpoint, does the growing category of men who have small-volume, often low-grade cancers in radical prostatectomy specimens suggest that our detection methods have started to tap into the huge pool of prostate cancer historically kept “undisturbed”?

The preference to use the term “subclinical” cancer (rather than latent, incidental, or histologic) to characterize prostate cancer discovered in post-mortem settings, reflects a conceptual approach to a “biologic continuum” of what is largely a slow progressing disease that encompasses a relatively small subset with a more aggressive course. These views offered are influenced by the trends in prostate cancer demographics during the last two decades and by observations gathered from a rather unique autopsy study the author has been involved with. The intent is to try to reconcile observations from these two phases of the disease to better understand the natural history of prostate cancer and hopefully to offer insight into reasonable management approaches.

How Prevalent Is “Subclinical” Prostate Cancer?

Although the incidence of clinically diagnosed prostate cancer has increased markedly since the introduction of PSA testing and, subsequently, the evolving biopsy approaches, the prevalence of the subclinical form of the disease discovered in prostates of autopsied men remains by far remarkably higher. The microscopic changes required to fulfill the criteria needed to characterize a prostatic epithelial lesion as carcinoma are exceedingly prevalent. Historically, this form of prostate cancer, often referred to as “latent” cancer, has been reported to be present in approximately 30% of men older than 50 years of age upon postmortem examination. More recently,