



Kala Pohl. *The Old Tree and the Sea*. Acrylic on canvas, 24" × 30".

More effective measures to determine the actual prevalence of prostate cancer will better define the biological variability of the disease and will optimize prostate cancer management.

The Role of Prevalence in the Diagnosis of Prostate Cancer

Nicolas B. Delongchamps, MD, Amar Singh, MD, and Gabriel P. Haas, MD

Background: *The worldwide incidence of prostate cancer has been rising rapidly, likely due to intensified effort in early detection and screening. Intense effort is also directed at novel schemas of chemoprevention and therapy. Incidence data are insufficient to identify the true magnitude of prostate cancer in a given population. The true prevalence of prostate cancer must be identified.*

Methods: *We reviewed the latest worldwide epidemiologic data and clinical studies on prostate cancer studying the true prevalence of this disease.*

Results: *The incidence of prostate cancer is increasing worldwide, with strong variation among regions. Prevalence studies based on autopsy data have confirmed a high frequency of latent prostate cancer in men of all ages. More aggressive screening measures using a lower prostate-specific antigen (PSA) threshold, together with an increasing number of biopsies, have escalated the detection of these latent cancers.*

Conclusions: *Recent improvements in prostate cancer detection narrow the gap between the incidence and true prevalence of prostate cancer. This, however, raises concerns about the risk of over detection of latent cancers and thus identifying a need for improvement in screening strategies to better identify clinically significant disease.*

From the Department of Urology at State University of New York Upstate Medical University, Syracuse, New York.

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Address correspondence to Gabriel P. Haas, MD, Department of Urology, Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210. E-mail: haasg@upstate.edu

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Abbreviations used in this paper: PSA = prostate-specific antigen, DRE = digital rectal examination.

Introduction

Prostate cancer is the most common malignancy other than superficial skin cancer, and it is the second leading cause of cancer-related death in American men. The incidence of the disease is increasing in the United States where 1 in 6 American men will develop prostate cancer over his lifespan.¹ Its incidence has also been increasing worldwide with a marked peak incidence in the 1990s following the introduction of the prostate-specific antigen (PSA) test. However, there are

wide international variations in the incidence rates of prostate cancer. Although these differences have been attributed to the variations in medical care and screening policies, the importance of environmental and genetic factors may also play an important role in the natural history of the disease and may help explain these differences.

The true prevalence of prostate cancer is difficult to determine. A large number of cancers are latent and undetected by currently available screening tests. These cases are not taken into account by most epidemiologic studies. However, these data are needed for an improved understanding of prostatic carcinogenesis. Recent improvement in early detection techniques enables the diagnosis of some of these cases and has led to a downward stage migration.² Some authors have also suggested that the overdiagnosis related to systematic screening might lead to an overtreatment for a large number of patients with small and well-differentiated tumors.³

This review reports the current epidemiologic and prevalence data on prostate cancer throughout the world.

Epidemiologic Studies

Incidence and Mortality

The American Cancer Society predictions placed prostate cancer as the most common cancer in American men, with 234,460 new cases expected in 2006.⁴ This is nearly 3 times higher than the number of new cases that occurred in 1985. Mortality from prostate cancer increased by 20% between 1976 and 1994 and showed stabilization and then a downward trend since 2000.^{5,6} An estimated 27,350 deaths due to prostate cancer are expected in 2006.⁴

Many studies have shown the increased incidence of prostate cancer.^{7,8} Suggestions for possible causes include a longer life expectancy, increased disease prevalence resulting from environmental carcinogens, and the availability of novel diagnostic modalities. Furthermore, the advancement in the disease detection using PSA testing and systematic biopsy procedures may also partially explain this increase.

The reasons for the decrease in prostate cancer mortality are not clear. The relationship between the decrease in mortality and the increase in early detection has not been proven, but the impact of early detection is highly suggested by the decreasing rate of advanced prostate cancer at diagnosis.^{9,10} While increasing mortality trends are observed in some countries like Australia where PSA screening is high, mortality rates have declined in other countries like the United Kingdom where screening rates are relatively low.^{11,12} Nevertheless, there is now evidence that PSA

screening and extended biopsy sampling of the prostate has led to a downward stage migration and a decrease in postoperative PSA failure.^{13,14} Decreased mortality may also be explained by other factors such as improvement of treatment of advanced disease, standardization of radical prostatectomy technique, and improvements in radiotherapy.

The prostate arm of the Prostate, Lung, Colon and Ovary Cancer Screening Trial, together with the European Randomized Study of Screening for Prostate Cancer, is expected to establish whether screening has an effect on prostate cancer mortality.^{15,16} In this trial, 38,350 men were randomly assigned to the screening arm from November 1993 through June 2001. Diagnostic follow-up was obtained from their primary care provider. Screening was based on digital rectal examination (DRE) and serum PSA level, using a threshold of 4 ng/mL. Of the men with positive screening tests, 74.2% underwent additional diagnostic testing, and 31.5% underwent prostate biopsies within 1 year. Overall, 1.4% of the men in the screening arm were diagnosed with prostate cancer, the majority of whom had clinically localized cancer. The European Randomized Study of Screening for Prostate Cancer, a large randomized, controlled trial of screening vs control, is being conducted in eight European countries (Belgium, Finland, France, Italy, The Netherlands, Spain, Sweden, and Switzerland). Definitive endpoint-related data from these two studies are expected between 2006 and 2010 depending on the differences in prostate cancer mortality that may be shown between the screening and control arms. Whether such screening will result in a reduction of prostate cancer mortality cannot be answered until these studies have been completed and results are available for review.

Worldwide Epidemiology

Global cancer incidence rates show that prostate cancer has become the third most common cancer in men. Half a million new cases occur each year, representing almost 10% of all cancers in men (Fig 1).^{17,18} In most industrial countries, prostate cancer incidence rates are increasing, whereas mortality rates are declining. In 2004, Baade et al¹⁹ reported significant reductions in prostate cancer mortality in the United Kingdom, Austria, Canada, Italy, France, Germany, Australia, and Spain, and downward trends in The Netherlands, Ireland, and Sweden. However, the recorded incidence of prostate cancer varies enormously around the world. Obvious reasons for these disparities are access to medical care and prostate cancer screening policies. In countries where no screening is available, information is sparse regarding the incidence and management of the disease. Moreover, because of economic and social factors, some populations have limited access to health care. In China, for example, the reported incidence rate of

prostate cancer in 1991 was 26-fold lower than in the United States.²⁰ A retrospective analysis of 431 consecutive patients treated for prostate cancer at six Chinese institutions showed that median patient age at diagnosis was 72 years and the median PSA was 46.1 ng/mL.²¹ Most prostate cancer cases were symptomatic with urinary symptoms (76%) or bone pain (13%). Surgical castration was the standard treatment, and only 24 patients underwent radical prostatectomy. Among the patients treated by medical or surgical castration, nearly two thirds had experienced biological recurrence at a median follow-up of 16.8 months.²¹ Despite the relatively low incidence of prostate cancer in China, screening probably could help detect earlier-stage tumors and improve outcomes. Recently, the prostate cancer incidence has been reported to be increasing rapidly in China and other Asian countries.²² This evolution cannot simply be attributed to screening practices. Therefore, some authors have suggested that environmental and/or genetic changes also may be responsible of the increasing incidence of prostate cancer. Cook et al²³ analyzed the incidences of prostate cancer in Chinese, Japanese and Filipino immigrants and their descendants

in the United States. They found that prostate cancer incidences in the native immigrants were approximately half that of US-born Chinese, Japanese, and Filipino men. These findings corroborate results of similar studies by Shimizu et al²⁴ and Tsugane et al,²⁵ who studied prostate cancer incidence rates in Japanese men relocated to the United States or other countries. It appears that when individuals from a low-incidence region move to a high-incidence region, the disease becomes more common within their own generation. These findings highlight the significance of environmental and genetic risk factors.

Risk Factors

Many factors have been suggested to take part in the development of prostate cancer, but epidemiologic studies show that those most significantly associated with an increased incidence rate of the disease are race, age, and family history of prostate cancer.²⁶⁻²⁸

Family History: Prostate cancer has long been recognized as an important risk factor, yet the complex genetic influence on the disease has not been well characterized. Hereditary prostate cancer was initially defined as a prostate cancer diagnosed in a family that met at least one of the following three criteria: three or more relatives affected with the disease, prostate cancer in each of three successive generations, or two relatives affected with prostate cancer at 55 years of age or younger.²⁸

Although this definition has been operational and used in a large number of studies, some authors suggested that it was likely to miss some families with autosomal recessive or X-linked transmission.²⁹ The hereditary form of prostate cancer has been reported to comprise only 5% to 6% of all prostate cancer cases and usually occurs 10 years earlier than sporadic prostate cancer.²⁸ One third of prostate cancer cases diagnosed before 60 years of age are hereditary³⁰ and half of those are diagnosed before 55 years of age.²⁸ As a consequence of the earlier onset, prostate cancer is the cause of death for a greater proportion of men with hereditary than sporadic

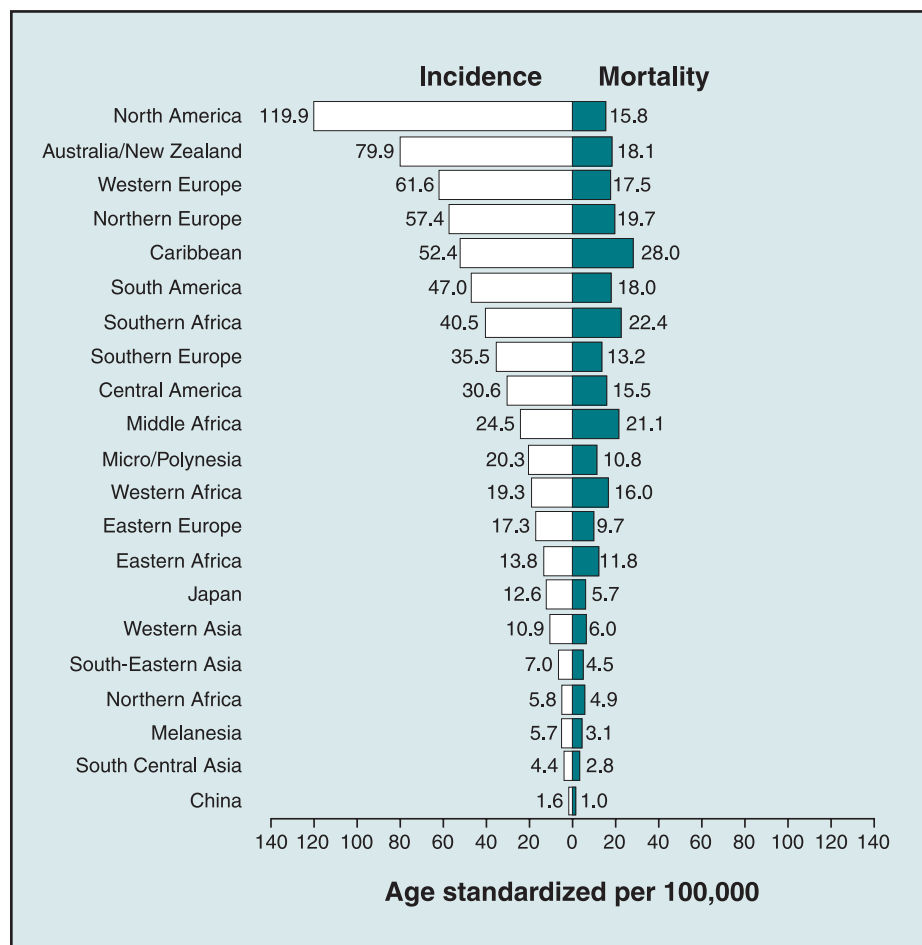


Fig 1. — Worldwide incidence and mortality of prostate cancer. From Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74-108. Reprinted with permission by Lippincott Williams & Wilkins. www.lww.com

prostate cancer. However, family history has not been reported to be a prognostic factor by itself. Gronberg et al³¹ found similar cause-specific and overall survival in patients with sporadic and familial prostate cancer. Screening of cohorts with positive family history should therefore be initiated at the age of 40 to 50 years, commencing at least 5 years earlier than the time of diagnosis for prostate cancer and at least 10 years before the age at which metastatic disease appeared in the familial cases.

There is now evidence that prostate cancer is genetically heterogeneous, with several genes having different frequencies and penetrance. Significant linkage to chromosome 1q23-25 was first reported in 1996 with the discovery of a susceptibility locus for prostate cancer on chromosome 1, called HPC1 (Human Prostate Cancer 1).³² Several candidate genes were then studied in this region, including the gene RNASEL, which appears to play a role in hereditary prostate cancer carcinogenesis.²⁹ Other chromosome regions, including chromosome X, have also been implicated in the hereditary prostate cancer. Also, environmental factors may have a role in inducing different genetic processes and molecular pathways. Heterogeneity of both environment factors and susceptibility genes could explain partially the discrepancies of prostate cancer incidence between populations and in different geographic areas. However, further research is needed in localizing and identifying the susceptibility genes.^{29,30}

Age: Prostate cancer has been known as a disease of elderly men. Diagnosis is rare before age 50, but after this age incidence increases exponentially, and the rate of increase is faster than that seen in other malignancies. The exact role of age in development of prostate cancer is controversial. As sclerotic atrophy is a characteristic age-dependent alteration in the prostate gland, it has been suggested that sclerotic atrophy could be a precancerous change.³³ However, histologic studies have subsequently provided evidence that prostate cancer arises from the active glandular epithelium rather than the atrophic glands. Additionally, Kovi et al³⁴ studied the age-related changes of vessels, glands, and stroma in 795 unselected and consecutive autopsy prostates of black men from the Washington, DC, area and from several African countries. They did not find any correlation between histologic changes related to aging and the presence of carcinoma. Other reports suggested that the role of aging was probably more to provide the time necessary for the cumulative effects of environmental insults and accumulation of the cellular events leading to neoplasia.³⁵ This hypothesis, associated with increased life expectancy, also could partially explain the increasing prostate cancer incidence.

Race: African American men develop the disease 50% more frequently than their white counterparts of the same age.^{36,37} Compared with white Americans,

they are younger at the time of diagnosis and their tumors are higher in stage and grade. Furthermore, their 5-year survival rate has been reported to be less than that of their white counterparts.³⁸ Fowler et al³⁹ compared the outcomes of 396 white and 524 black American men with prostate cancer between 1982 and 1992. They reported that local-stage prostate cancer was more lethal in black men than in white men, particularly for men under 70 years old. However, there was a disproportionate incidence of high-grade localized tumors (Gleason 7 to 10) in black men, and the differences in cause-specific survival between the two groups were not significant when adjusted for Gleason score.

The reasons for the higher prostate cancer incidence in black Americans are not known and are probably multifactorial, combining environmental and genetic factors. It has been reported that black men have higher levels of androgen metabolites compared to white men.⁴⁰ Although these differences have not been proven to explain these racial discrepancies, these interesting data warrant further investigation. Vitamin D also could play a role. Compared to whites, black individuals have a reduced production of ultraviolet-induced vitamin D₃. Several studies have suggested the role of vitamin D₃ in cellular differentiation, growth, and oncogene regulation (notably *c-myc*).^{41,42} The role of nutritional factors have also been suggested since black Americans tend to have an alimentation richer in animal fat.⁴³

Similarly, several theories have been suggested to explain the low survival rate in black men with prostate cancer, particularly socioeconomic status or health care access. In a recent report, Tewari et al⁴⁴ compared the survival rates among black and white American men with prostate cancer using a multivariate model that included socioeconomic status and treatment method. They reported that socioeconomic status was related to 50% of the differences in survival rates between the two groups. The lower surgical treatment rate in African Americans explained 34% of the difference in survival.

Other Factors: There is an association between bladder and prostate cancer.⁴⁵⁻⁴⁷ According to Chun,⁴⁵ the rate of prostate cancer in patients with bladder cancer is 19-fold higher than in those without bladder cancer. They also report that the rate of bladder cancer in patients with prostate cancer is 18-fold higher than in a control population. The common association of these two malignancies may be explained by some genetic factors. Singh et al⁴⁶ reported that tumor suppressor genes such as p53 and Rb may play a major role in the development of both prostate and bladder cancers. Furthermore, the prostate stem cell antigen is often overexpressed in human transitional cell carcinomas.⁴⁷

Vasectomy may be associated with an increased risk of prostate cancer, by either increasing serum androgen level or inducing an immunologic reaction.

However, the relationship between vasectomy and prostate cancer remains unclear.⁴⁸⁻⁵⁰

Another path of investigation is the possible relationship between sexual behavior and the development of prostate cancer. Indeed, some authors suggested that prostate cancer was related to early intercourse, number of sexual partners, or venereal disease.⁵¹ However, an equal number of studies have shown conflicting results.⁵²

Finally, some studies link prostate cancer to known carcinogens in tobacco smoke, but the results of cigarette smoking on the epidemiology of prostate cancer are inconclusive and difficult to interpret.⁵³

Prevalence Statistics in Prostate Cancer

Statistics for incidence and prevalence do not provide the same information. Incidence statistics show the number of new cases diagnosed in a population during a specific period, while prevalence statistics provide information about the number or proportion of people who have that disease in a specified period. Traditional epidemiologic studies are based on diagnosed cases. However, the specificity of prostate cancer is that many cases are latent, asymptomatic, and undetected through diagnostic tests. Therefore, the true prevalence of the disease is unknown. This observation came first from autopsy studies that showed the importance of latent cancers inside the prostate gland in deceased men.^{54,55} These missing epidemiologic data could be useful to develop a better understanding of the natural history of the disease, to plan early detection studies, to organize cancer prevention trials, and therefore to improve prostate cancer management. However, constant advances in prostate cancer detection allow continually more accurate assessments of the disease's true prevalence.

Latent Prostate Cancer

Several indirect means have been used to estimate prostate cancer prevalence in a given population. In the past, unsuspected carcinoma was found in approximately 20% to 25% of specimens after transurethral surgery for what was thought to be benign prostatic hyperplasia.⁵⁶ These data have shown decline with the widespread use of PSA testing. The prevalence of prostate cancer can also be estimated by the frequency of incidental prostate cancer in cystoprostatectomy specimens.⁵⁷⁻⁵⁹ Most of the recent data, however, comes from autopsy studies from around the world.⁶⁰⁻⁶⁷

Montironi et al⁵⁹ reviewed the pathologic findings of incidentally detected prostate cancer in cystoprostatectomy specimens from patients treated for bladder cancer and compared those findings with radical prostatectomy specimens from patients treated for prostate cancer. They found that incidentally detected cancer was less aggressive than clinically detected can-

cer. These incidentally detected cancers are likely to be similar to latent cancers diagnosed on autopsy specimens. The term *latent cancer* is used in the pathology literature to characterize malignancies that are discovered only on postmortem examination. Although the term may imply low virulence, the malignant potential for individual cancers discovered after death cannot be ascertained. The length of time from the first histologically recognizable form of prostate cancer to clinically evident cancer is not known and probably varies widely. For the small subset of all histologic cancers that come to clinical discovery during the lifetime of the individual, studies⁶⁸ of tumor doubling time indicate that this process may take more than 10 to 15 years. In addition, the initiating events leading to clinically relevant prostate cancers likely occur at a remarkably young age. Indeed, histologic cancers are surprisingly common in young men (Fig 2).⁵⁴ In an autopsy study of 249 prostates from men 20 to 69 years of age, Sakr et al⁵⁴ encountered latent prostate cancer in 2% and 29% of men in the third and the fourth decades, respectively. The latent tumors are usually classified as either non-infiltrative (LNT) or infiltrative (LIT).⁶⁰ LNT is approximately equivalent to well-differentiated adenocarcinoma (Gleason grade 1 or 2), and LIT is equivalent to moderately to poorly differentiated adenocarcinoma (Gleason grade 3 to 5). It is assumed that LNT and LIT are two different steps in the evolution of latent carcinoma before being detected clinically.^{60,66} These hypotheses are interesting when comparing the characteristics of latent carcinomas in different autopsy series and at different periods of the 1980s, when the prostate cancer incidence rate was increasing. In Japan, Yatani et al⁶⁶ compared two sets of autopsy prostates analyzed in two different periods: 1965 to 1979 and 1982 to 1986. They

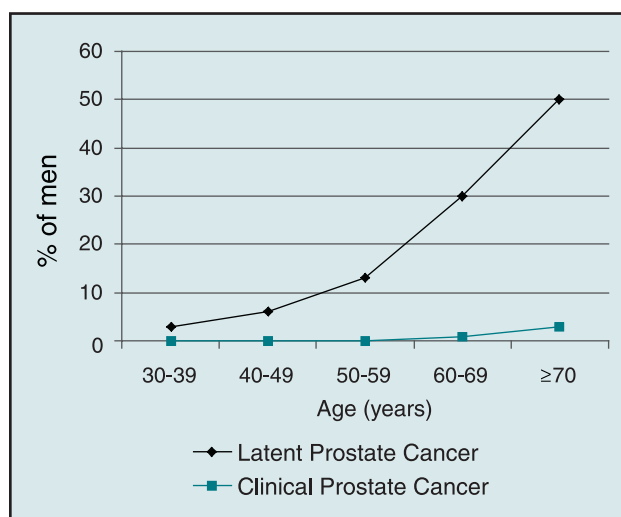


Fig 2. — Prevalence of prostate cancer with age: comparison of clinically detected cases with cases diagnosed at autopsy. Data from Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *In Vivo*. 1994;8:439-444.

found that the frequency of latent prostate carcinoma had increased from 1965 to 1986. Moreover, the ratio of LITs to LNTs had increased, which was consistent with the trends of the disease in Japanese population. Surprisingly, the specimens collected in 1982 to 1986 contained smaller tumors than did those of the 1965 to 1979 series. However, this decline in average volume of LITs was not due to reduction in the size of individual tumors but rather was due to the relative increase in the number of smaller carcinomas. Therefore, the authors suggested that progression from LNT to LIT was ongoing when the tumors were still small. The same authors compared the prevalence of latent prostate cancer in autopsy series from indigenous Japanese and Japanese migrants in Hawaii.⁶⁹ Given the higher incidence of prostate cancer among Japanese migrants compared with indigenous Japanese, a higher rate of latent carcinomas would have been expected in the migrant population; however, the rates were similar. The authors concluded that differences in the frequency of clinical prostate cancer are probably the result of genetic or environment factors that promote progression from its latent form.

More autopsy data are now available from around the world (Table).^{53,60,63-65,70} Comparisons of Western and Oriental prevalence studies showed a similar prevalence of prostate cancer.^{55,66} However, other autopsy studies carried out in non-Japanese populations in Southeast Asia showed significantly lower prostate cancer prevalence rates in China, Hong-Kong, and Singapore.^{62,63} A report was recently published on the prevalence of prostate cancer in an autopsy study from Hungary, where prostate cancer is the third most common cause of cancer-related death in men.⁶⁵ In this autopsy series illustrating a central European Caucasian population, the rate of prostate cancer was as high as 39%. Data are also available in the Greek male population, where the rate of latent carcinoma is lower (19%) but similar to the Spanish population.^{61,64} These findings raised the discussion that Mediterranean Caucasians, regardless of the geographic locations, were likely to have a lower risk of prostate cancer than other European white populations, including Hungarians. Some authors have suggested that the traditional Mediterranean dietary habits in Spain and Greece could be factors that lower the prostate cancer risk. However, it is difficult to compare detection rates of autopsy studies because the detection of small tumors is strongly correlated to the pathologic processing method, particularly the thickness of the whole-mount step sections analyzed.

Autopsy Prevalence Rates of Prostate Cancer Worldwide (%)

Age (Yrs)	US White ^{53,69}	US Black ^{53,69}	Spain ⁶⁰	Japan ⁶⁵	Greece ⁶³	Hungary ⁶⁴
21-30	8	8	4	0	0	0
31-40	31	31	9	20	0	27
41-50	37	43	14	13	2.6	20
51-60	44	46	24	22	5.2	28
61-70	65	70	32	35	13.8	44
71-80	83	81	33	41	30.9	58
81-90	0	0	0	48	40	73
Total	34.6	36.9	18.5	20.5	18.8	38.8

The “end of study” biopsies of the Prostate Cancer Prevention Trial (PCPT) recently provided the first clinical confirmation of the high rate of prostate cancer detected in men with a normal PSA and DRE. The trial suggested that many of the “prevalent” cancers would be diagnosed if biopsies were performed for “no cause.” However, it also suggested that cancer detection is reduced at lower PSA levels.⁷¹ Gosselaar et al⁷² compared prostate autopsy and cystoprostatectomy findings with those of the PCPT. The prevalence of prostate cancer in cystoprostatectomy series (23% to 46%) and autopsy series (18.5% to 38.8%) was higher than in the PCPT (15.2%). This can be explained by the underdetection rate of biopsies compared with whole-mount prostate analysis. Moreover, the authors reported similar tumor features between autopsy and cystoprostatectomy series compared to men with low PSA values from the PCPT, even if comparison was difficult due to variability in execution of studies. They concluded that prostate cancer in men with low PSA levels (<3 ng/mL) was comparable to latent autopsy cancer.

Improvements in prostate cancer detection have led to a downward stage migration of diagnosed cancers.^{13,14} The hypothesis emerged that a substantial amount of autopsy-diagnosed latent cancers were currently detected clinically through screening. Konety et al⁷³ reported a decreasing prevalence of latent prostate cancer in their autopsy series, and they interpreted that as a result of screening. These findings, if they are confirmed by further studies, could explain the increasing incidence of prostate cancer while mortality remains unaffected. The concern, however, is to identify specifically those latent cancers among all prostate cancers diagnosed. Stamey et al⁷⁴ proposed a pathologic definition of clinically diagnosed latent cancers, defined as clinically insignificant. Although not decisive in discriminating the malignant potential of a tumor, pathologic features such as volume and grade indicate which carcinomas are likely to be aggressive.

Improvements in Prostate Cancer Detection

As described previously, the introduction of PSA as a screening test has been followed by a strong increase in

prostate cancer incidence rates. Although screening alone does not explain this increase, measured prevalence in the population is probably closer now to the true prevalence than it was before. Since the introduction of PSA in current practice, many efforts have focused on improving its accuracy as a screening test, and similar improvements were achieved for diagnostic tests.

PSA: PSA was isolated in 1970 and was characterized 9 years later as a serine protease involved in seminal liquid synthesis. Detected in 1980 in serum, the conviction of its clinical usefulness as a screening test took 10 years. However, PSA is not a specific marker of prostate cancer since its serum level increases with prostatic hyperplasia and is affected by many factors such as medication (finasteride), urologic manipulations, inflammation, or even ejaculation.^{75,76}

The first evaluations of PSA as a screening test concluded that the cutoff of 4 ng/mL had the best predictive value.⁷⁷ This cutoff was supposed to allow the best detection rate for curable prostate cancers while reducing the number of unnecessary biopsies in patients without cancer. This cutoff benchmark has been recently reconsidered. Smith et al⁷⁸ showed that among 10,248 patients, 48% of those with an initial PSA level of <4 ng/mL were upgraded to a PSA level >4 ng/mL within 4 years and that 13% had cancer detected during this interval. Another report noted that the positive predictive value of sextant biopsy for a PSA level between 2.6 and 4 ng/mL was 26%.⁷⁹ They also studied 94 radical prostatectomy specimens to compare the pathologic characteristics of tumors detected with a PSA level between 2.6 and 4 ng/mL with those detected with a PSA level between 4.1 and 10 ng/mL. The tumors detected with a PSA level <4 ng/mL were smaller and more often localized to the gland (88% vs 63%).⁷⁹ Additionally, the "end of study" biopsies of the PCPT, as explained earlier, provided some data from 2,950 men having a PSA level <4 ng/mL and normal DRE (control group). Prostate cancer was diagnosed in 449 (15.2%) of the 2,950 men. At the time of diagnosis, these 449 patients had a PSA between 0.6 and 1 ng/mL in 10.1% of cases, between 1.1 and 2 ng/mL in 17% of cases, between 2.1 and 3 ng/mL in 23.9% of cases, and between 3.1 and 4 ng/mL in 23.9% of cases.⁷¹ These findings question the traditional diagnostic approach of prostate cancer, and the very notion of PSA cutoff is debatable. Thus, several authors recommend prostate biopsy at a PSA cutoff of 2.6 ng/mL.⁷⁸

Since serum PSA values increase with prostate volume and age, the specificity and sensitivity of PSA in screening is lower for older and younger men, respectively. Therefore, some advocate age-adjusted PSA cutoffs in screening practices. Using age-ponderation tables, Partin et al⁸⁰ detected significantly more cancers in men less than 60 years of age. However, controver-

sies remain on the use of these tables in black men because the prostate volume does not progress the same way in all ethnic populations.⁸¹

Another way to improve the accuracy of PSA screening is to compare different PSA measurements at different periods. It appeared clearly that the kinetic of PSA level was more informative than an isolated measurement. Moreover, the elevation kinetic of PSA level is faster in cancer than in benign hyperplasia. This notion was introduced in 1992 by Carter et al.⁸² They showed that a PSA velocity of more than 0.75 ng/mL per year was strongly correlated with cancer (sensitivity 72%, specificity 95%). This method presents some practical inconvenience as a minimum of three PSA level measurements in a 2-year period are required to calculate an accurate PSA velocity. In addition, all the measurements have to be done with the same test for reproducibility reasons. Nevertheless, PSA velocity is useful in making the decision to perform a biopsy on patients with low PSA levels or on those with persistent elevation of PSA following an initial negative biopsy.

Also in 1992, Benson et al⁸³ suggested that PSA level would be more informative if prostate volume was taken into account. The PSA density, calculated by dividing PSA level by the ultrasound measurement of prostate volume, would better distinguish benign hyperplasia from cancer in men with intermediate PSA values (4 to 10 ng/mL) and normal DRE. However, Catalona et al⁸⁴ reported subsequently that the use of a biopsy cutoff of 0.15 ng/mL/cm³ in men with a PSA level of 4.1 to 9.9 ng/mL and normal DRE findings was likely to miss prostate cancer in half of patients. Other authors⁸⁵ proposed to sharpen PSA density to transition zone (TZ) and showed that TZ-PSA density enhanced the specificity of serum PSA for prostate cancer detection in patients with a PSA of 4 to 10 ng/mL.

In blood circulation, the majority of PSA is bound to protease inhibitors. Only a low fraction of PSA remains free. This free fraction of PSA (fPSA) is lower in patients with cancer and is less affected by benign hyperplasia than is total PSA. For patients with intermediate PSA values (4 to 10 ng/mL), fPSA increases screening specificity and thus decreases the number of unnecessary biopsies.⁸⁶ The risk of cancer is high for those who have a free/total PSA (f/tPSA) of less than 15%, whereas benign hyperplasia is more likely when f/tPSA is more than 25%.⁸⁷ However, for most patients, f/tPSA falls between these two values. For patients with intermediate PSA values, f/tPSA is mainly used to evaluate the need for repeat biopsies when negative. Since almost 20% of patients with low PSA values (2.6 to 4 ng/mL) will be diagnosed with prostate cancer within next 5 years, f/tPSA would identify those patients earlier and would avoid unnecessary biopsies for the others.⁸⁶

Other studies evaluating different forms of PSA (combined PSA, pro-PSA) or new biological markers (human glandular kallikrein, prostate-specific membrane antigen [PSMA]) are ongoing to improve PSA accuracy by detecting prostate cancer earlier and more efficiently.

Transrectal Ultrasound-Guided Biopsy (TRUS): Ultrasound images of prostate cancer are not specific; only 40% of hypoechoic images correspond to a prostate cancer.⁸⁸ Furthermore, 20% of normal glands on ultrasound images are positive for cancer on biopsies.⁸⁹ The value of ultrasound is in guiding systematic biopsies. The systematic sextant biopsy technique as described by Hodge et al⁹⁰ has been the gold standard for many years. However, the false-negative rate of standard sextant biopsy has been reported to be as high as 15% to 31%,⁹¹ and several studies have shown that additional biopsy cores, particularly in the far lateral zone, would increase the detection rate by 30% to 35%.^{92,93} Bauer et al⁹⁴ recently reported that among patients diagnosed with prostate cancer, 54% were diagnosed by the sextant biopsy only. The 10-core pattern resulted in an additional 46% being diagnosed solely with the laterally placed biopsies. Others showed that the initial use of a biopsy protocol of 10 cores (including the far lateral zone) was likely to detect more tumors than in repeated sextant biopsies when negative.⁹⁵ Additional transition zone biopsies were also evaluated. In a recent study,⁹⁶ 493 consecutive men with elevated serum PSA levels and/or abnormal DRE underwent TRUS with a 12-core protocol. In addition to sextant biopsies, six further biopsies were obtained, two from the transition zone (mid-gland) and four from the lateral peripheral zone (base and mid-gland). Prostate cancer was diagnosed in one third of the patients. Nearly 20% of the prostate cancers were missed by the first 6 cores. The lateral peripheral-zone biopsy cores alone detected one third of the prostate cancers missed by sextant biopsies, and the transition-zone biopsy cores alone detected more than the half of them. The authors concluded that this 12-core biopsy protocol markedly improved the detection rate for prostate cancer when compared with the standard sextant biopsy protocol alone.⁹⁶ However, it is difficult to evaluate the number of prostate cancers that are missed by additional biopsies since patients with additional negative biopsies do not undergo surgery. Another methodology was used to evaluate the number of missed tumors in prostates showing 1 or more positive biopsy cores. In their study, Bak et al⁹⁷ reviewed 71 radical prostatectomy specimens and located every tumor foci. They compared on each specimen the tumors location with the location of the positive biopsy cores. They found additional lesions missed by sextant biopsy in 54% of cases. The majority of them were located in the peripheral zone. However, two thirds of them were well differentiated (Gleason score <7) and

small (<0.5 cc). These findings highlight the major concern that increasing sampling may increase the detection rate of insignificant tumors.

Staging Improvement

Since the beginning of the PSA era, an increasing number of cases of prostate cancer have been diagnosed solely on the basis of elevated PSA level (T1c disease). Moreover, most screening protocols have decreased their PSA cutoff. Clinicians therefore feared that widespread PSA screening was leading to the detection of an unreasonable number of so-called clinically insignificant tumors and, in turn, to a marked increase in potentially unnecessary treatment.^{3,98} Indeed, among T1c diseases, low-grade (Gleason grade <7) and small, confined tumors are considered either as "clinically insignificant" (volume <0.2 cm³), or "clinically unimportant" (volume <0.5 cm³). In the latest series of patients with T1c prostate cancers, 11.5% to 12% of the tumors were insignificant and 24% to 27% were clinically unimportant.^{79,91} These findings are raising the concern of over-treatment for those patients.

Adverse pathologic features on biopsy, such as high Gleason grade, multiple positive cores, or high percentage of prostate cancer on biopsy, predict advanced disease in the corresponding prostate.^{99,100} However, difficulties arise when using prostate biopsy to predict limited adenocarcinoma at radical prostatectomy.¹⁰¹ In 1994, the term *microfocal prostate cancer* was introduced by Epstein et al¹⁰² when they developed PSA- and needle biopsy-related criteria to predict tumor significance on prostate specimen. These criteria were defined by a PSA density <0.15 ng/mL/cm³ and the presence of low-grade prostate cancer on sextant biopsy (no Gleason grade 4 or 5) in fewer than 3 cores and of no more than 50% prostate cancer involvement in any of these cores. These criteria were subsequently evaluated prospectively in 240 men with T1c prostate cancer who underwent radical prostatectomy. Correlation analysis showed poor predictive values (positive and negative predictive value of 75%).¹⁰⁰ In another study, Allan et al¹⁰¹ used more restrictive criteria to predict insignificant tumor. Among a retrospective series of patients with prostate cancer, they selected only those who had a single microfocal prostate cancer on sextant biopsy, defined as a single focus less than or equal to a 40× microscopic field. They found that one third of them had clinically significant tumors on radical prostatectomy specimen. Finally, other authors reported that only 18% of patients with microfocal prostate cancer on biopsies presented insignificant prostate cancer on radical prostatectomy specimens.¹⁰³

The variability of the results reported in literature may be partially due to the different biopsy protocols

used, and especially to the low number of biopsy cores taken. Prostate cancer is known to be multifocal; one single microfocal cancer detected in 6 to 10 cores does not exclude other overlooked contiguous or distant tumors that would be detected by a more extensive biopsy protocol.¹⁰⁴

Conclusions

Prostate cancer incidence rates are increasing all around the world. This increase in incidence affects all age groups and is more pronounced in younger men. Based on the additional effect of increased life expectancy, epidemiologic estimates show that prostate cancer is on the verge of becoming one of the world's leading health issues. This trend has generated worldwide epidemiologic studies, providing important data and contributing to the better understanding of prostate cancer natural history.

Recent advances in detection efficiency in prostate cancer are narrowing the gap between the measured incidence of prostate cancer and its true prevalence. The endpoint is to better define the biological significances of newly diagnosed prostate cancer and therefore optimize prostate cancer management.

Many studies, including the prostate arm of the Prostate, Lung, Colon and Ovary Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer, will soon provide information about the effect of prostate cancer screening on mortality. Ongoing studies are comparing different sets of biopsy protocols with disparate methodologies including human autopsy studies. Additionally, saturation prostate biopsy techniques as staging procedures or as repeat biopsy regimens for prior negative biopsies are being evaluated.^{105,106} New prostate cancer markers are also being developed with the goal of improving screening and staging of prostate cancer. Last, but not least, as prevalence data for particular cohorts of men become available (focusing on age, race, geographic location), specific detection scenarios will be developed to identify cancer.

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