Prostate Cancer Pathology, Screening, and Epidemiology

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Recent advances in the understanding of prostate cancer pathology, screening methods, and epidemiology were discussed at the 11th International Prostate Cancer Update. Regarding pathology, Dr. Gary Miller enumerated several factors that lead to the perception of prostate cancer as "unpredictable." These include the disease's multifocal nature, variable progression rates, and the uncertainty regarding the point at which carcinomas metastasize. Screening methods have been the subject of research by the Laval University Prostate Cancer Screening Program since 1988. Dr. Fernand Labrie presented the results of this 10-year study. Dr. Daisaku Hirano presented data from his studies of prostate cancer epidemiology in Japan as compared to the United States. The role of environmental factors, particularly diet, in prostate cancer pathogenesis and development is supported by the increase of the disease in Japan, concurrent with the "westernization" of diet there. Finally, useful information was presented on new computer- and Internet-based diagnostic and research tools.
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Recent advances in the understanding of prostate cancer pathology, screening methods, and epidemiology were discussed at the 11th International Prostate Cancer Update. Useful information was also presented on new computer- and Internet-based research tools.

Pathology

Gary Miller, MD, PhD presented a detailed discussion of prostate pathology. In the past decade there have been significant advances in identifying biomarkers and in our understanding of pathologic features that predict disease progression.

Prostate cancer is a disease with a variable clinical behavior, which leads clinicians to conclude that it is unpredictable. There are various factors that contribute to this perception.

First, prostate cancer is very multifocal. The average patient has at least two distinct foci of carcinoma in their prostate. The foci are anatomically distinct. The various foci can have different Gleason scores, so it is important to find as many of these as possible to eliminate sampling error. Detection of a low-grade carcinoma in a patient with an occult high-grade lesion can give the perception that a carcinoma has progressed very quickly when in fact it has not. It should also be remembered that all carcinomas, low and high grade, can invade and metastasize. This is the basis for making the diagnosis of malignancy.

Molecular "fingerprinting" studies that assay for loss of heterozygosity (LOH) across numerous chromosomal alleles confirm the distinct genetic origins of multifocal carcinomas and indicate that they are multicentric. That is, they are distinctly different and are likely to behave in independent fashions. In addition, LOH indicates that the putative precursor of prostate cancer, prostatic intraepithelial neoplasia (PIN), may have more severe genetic changes than its associated carcinoma. This casts doubt on the notion that all PIN is a precursor. Although it is likely that some PIN goes on to become cancer, some appears determined to remain in a noninvasive state, in which genetic errors continue to accumulate without malignant consequences.

Next, we must consider the fact that prostate carcinomas develop and progress over time. Changes in chromosomal composition are candidate "markers" of the time involved in this process. Dr. Miller and his associates have found that DNA aneuploidy is largely associated with high-volume disease. Furthermore, both cancers that are confined to the prostate as well as those that have perforated the capsule can be either diploid or aneuploid. Detection of ploidy abnormalities by needle biopsy is prone to sampling error because of the small amount of any given carcinoma that is represented in a needle biopsy. The same is true for standard measures of malignancy, such as Gleason scores. The ability to absolutely determine the predominant pattern is greatly influenced by sampling. Again, sampling error in assessing grade can lead to misperceptions about progression rates.

Finally, it is worth considering the point at which carcinomas begin to metastasize. Previous studies of radical prostatectomy specimens with lymphadenectomies have led some to conclude that tumors must attain a volume of 4 cc before metastasis begins. Miller has found that capsule perforation may not be a necessary event in this process. Lympho-vascular invasion can be found in carcinomas < 0.5 cc in volume. Furthermore, it is known that as many as 20% of patients with organ-confined disease can be shown to have circulating tumor cells in their marrow by reverse transcriptase polymerase chain reaction for the PSA messenger RNA. Calculation indicates that as many as 16 years may elapse between the escape of a malignant cell from the prostate and the clinical detection of a prostate cancer. Available data indicate that the beginning of the metastatic cascade may precede clinical detection by a significant period of time.

In summary, the "unpredictable" nature of prostate cancer is a complex issue that involves diagnostic underestimation, sampling error, and an as yet underdeveloped ability to assess the malignant phenotype in an objective fashion. Clearly, the solutions to these problems will come from multiple directions. Until we learn to improve our skills and combine disparate bodies of information, this disease will continue to resist our best attempts to defeat it. The promise of advanced technology is our source of hope that the end to this era is reachable.

Screening

Screening for prostate cancer remains controversial. Several clinical trials have attempted to address the value of screening by demonstrating a decrease in the mortality from the disease. Dr. Fernand Labrie reviewed his experience in this arena.

Although prostate cancer is the most frequently diagnosed cancer and the second most common cause of cancer death in men, death from this disease has decreased in the United States and in the province of Quebec by up to 22% since 1991. Because even the best treatment for advanced metastatic disease—namely combined androgen blockade—can only prolong life by a few months,[1,2] the recent decrease in death rates from prostate cancer can only be due to the treatment of early disease, which of course requires early diagnosis or screening.

An important observation, based on overwhelming scientific evidence, is that prostate-specific antigen (PSA) can be efficiently used as a prescreening test for prostate cancer, thus keeping the more costly and less well tolerated digital rectal examination (DRE) and transrectal ultrasonography (TRUS) as second step procedures.[3–6] Using this approach, practically 100% of prostate cancers can be diagnosed at a clinically localized or potentially curable stage, therefore practically eliminating the diagnosis of metastatic disease.[3,4]

The Laval University Prostate Cancer Screening Program. Definitive proof of the benefits of early diagnosis, however, can only

be obtained from prospective and randomized studies comparing the incidence of death from prostate cancer in a group of men screened and treated early with a parallel group of men receiving standard medical care. Accordingly, the Laval University Prostate Cancer Screening Program (LUPCSP) was started in November 1988. In this study, men aged 45 to 80 years were randomly selected for screening tests from the electoral rolls of Quebec City and the surrounding area. The men in the control group not invited for screening were followed according to current medical practice for prostate cancer diagnosis and treatment. Deaths from prostate cancer for all invited and non-invited men were identified using the Quebec Cancer Death Registry up to December 1998.

Methods. From November 1988 to December 1998, a total of 7,195 men (>99% Caucasian) in the invited group of the electoral rolls were examined at first visit, and 30,891 follow-up visits were performed. Other men (4,616) not invited for screening as part of the LUPCSP but who had not undergone any prior screening procedure received the same screening tests at first visit, and 15,860 follow-up visits were performed in this group of non-invited men. Those men were not part of the analysis on the impact of screening on survival.[7,8]

Participants had their serum PSA measured, and all underwent DRE at first visit. The PSA and DRE tests were performed independently. Serum samples were taken before DRE for measurement of PSA by immunoradiometric assay (Tandem-R PSA, Hybritech Inc., San Diego, CA, or its equivalent). TRUS was performed only in cases with positive PSA (>3.0 ng/mL) and/or positive DRE, except for the first 1,002 men, who all had the three procedures, as previously reported.[9] At follow-up visits, TRUS was done if serum PSA already above 3.0 ng/mL had increased by more than 20% compared with the value measured 1 year earlier (the interassay coefficient of variation [c.v.] being 9.6%, Labrie and co-workers accepted 10% as a possible increase attributable to the interassay c.v., leaving a 10% increase attributable to changes in PSA secretion), or if the measured PSA was increased by more than 20% above the predicted PSA.[10,11]

Results. As shown in Figure 1, 16.6% of 11,811 men at first visit had serum PSA > 3.0 ng/mL (PSA^+), whereas in 46,751 follow-up visits PSA was abnormal in 15.6% of cases. Thus, at first (11,811) and follow-up (46,751) visits, 83.4% and 84.4% of men had serum PSA at or below 3.0 ng/mL, respectively. Serum PSA was at or below 2.0 ng/mL in 72.5% of men at first visits and 73.6% at follow-up visits.

The most significant changes observed between first and annual follow-up visits are seen in the percentage of men with serum PSA values above 20 ng/mL where a 6.3-fold reduction was seen between the first and follow-up visits (the incidence rate decreasing from 0.69% to 0.11%).

Because a major concern about screening is a potential increase in the number of clinically insignificant cancers detected, it is important to observe that only 215 cancers were found at 46,751 follow-up visits, for an incidence of 0.46%, compared to a prevalence of 2.85% (337 cancers in 11,811 men) at first visit. The percentage of men found as having prostate cancer at follow-up visits is thus 6.2 times lower compared to first visits.

A particularly important finding is that the percentage of men showing serum PSA > 3.0 ng/mL who were found as having prostate cancer decreased from 15.3% at first visits to 2.8% at follow-up visits. There was thus a 5.5-fold decrease in the incidence of diagnosed prostate cancer at follow-up compared to first visits in men having abnormal PSA. In other words, prostate cancer was found in 1 out of 6.5 men having serum PSA above 3.0 ng/mL at first visits, compared to only 1 out of 35.5 men at follow-up visits.

Table 1 describes the relative sensitivity of serum PSA and DRE to detect prostate cancer at first visits and at annual follow-up visits. Because DRE was eliminated from

Figure 1. *Distribution of serum prostate-specific antigen at first and follow-up visits in 45–80-year-old men.*

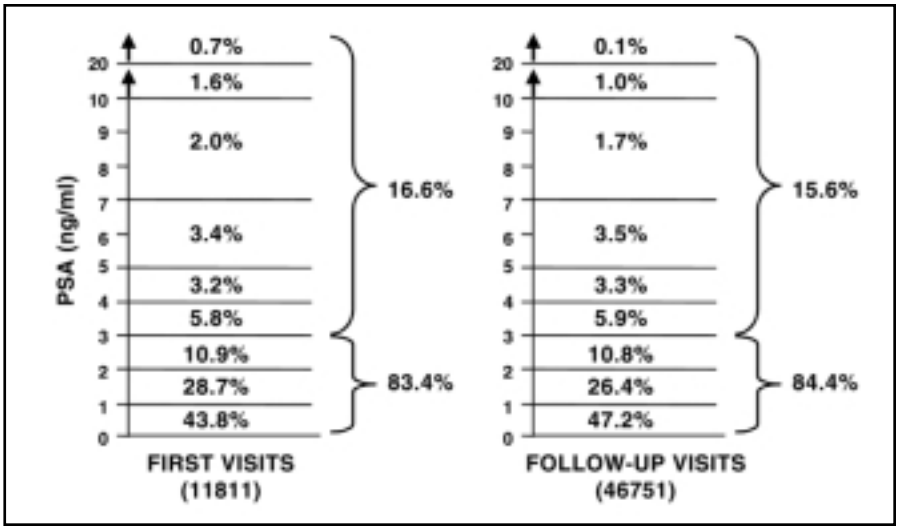


Table 1
Number of Transrectal Ultrasonography (TRUS)-Guided Biopsies and Positive Biopsies According to Serum Prostate-Specific Antigen (PSA) and Digital Rectal Examination (DRE) in Men Who Had Both Exams at All Visits at First and Follow-Up Visits

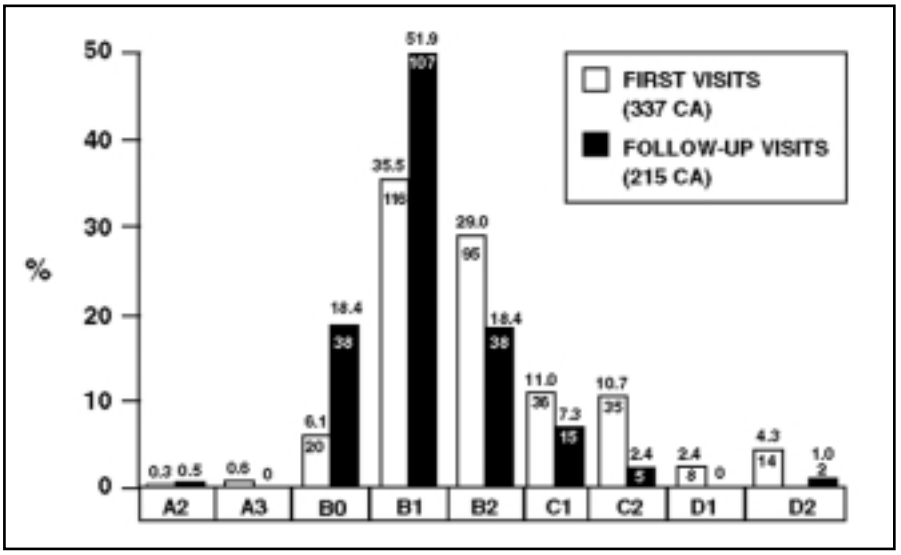
		FIRST VISIT							FOLLOW-UP VISITS						
			TRUS		Biopsies		CaP			TRUS		Biopsies		CaP	
PSA	DRE	No. Visits	No.	% Visits	No.	% TRUS	No.	% Biopsies	No. Visits	No.	% Visits	No.	% TRUS	No.	% Biopsies
–	–	7,281							7,674	45	0.6	15	33.3	1	6.7
	+	404	381	94.3	246	64.6	27	11.0	189	115	60.8	59	51.3	5	8.5
+	–	1,379	1,298	94.1	494	38.1	158	32.0	1,662	584	35.1	224	38.4	53	23.7
	+	232	220	94.8	173	76.6	97	56.1	68	43	63.2	32	74.4	15	46.9
	Total	9,296	1,899	20.4	913	48.1	282	30.9	9,593	787	8.2	330	41.9	74	22.4

follow-up visits in January 1993, the data are presented only for the visits where both PSA and DRE were performed. These data do not include the cancers found by TRUS in the presence of normal PSA and DRE in the early phase of the detection program (first 1002 men).[9] At first visits, 97 of the 282 cancers (34.4%) were both PSA^+ and DRE^+; 158 cancers (56.0%) were PSA^+ and DRE^-, whereas only 27 cancers (9.6%) were PSA^- and DRE^+. At follow-up visits, 15 of the 74 cancers (20.3%) were PSA^+ and DRE^+; 53 (71.6%) were PSA^+ and DRE^-, whereas only 5 (6.8%) were PSA^- and DRE^+. Thus, 255 of the 282 cancers (90.4%) detected at the first visits were PSA^+, whereas only 124 (44.0%) were DRE^+. At the follow-up visits, 68 of the 74 cancers (91.9%) were PSA^+, but only 20 (27.0%) were DRE^+. It is important to mention that of the 74 prostate cancers diagnosed at follow-up visits in invited men who had DRE and PSA at all visits, 68 were PSA^+, and only 6 (8.1%) were missed by PSA and found by DRE, thus demonstrating the unique efficacy of serum PSA to detect prostate cancer, especially at annual follow-up screening visits.

Discussion. The present data show that 344 DREs are required to find one case of prostate cancer at first visit and that 1,919 DREs are required at follow-up visits. On the other hand, 36 and 141 PSA measurements are required at first and follow-up visits, respectively, to diagnose one case of prostate cancer. Based on 18,889 visits where men had both PSA and DRE, the present data show that PSA is about 10 times more efficient than DRE at detecting prostate cancer at a clinically localized and potentially curable stage.

A most important finding is that only 2 of 215 cancers (1.0%) diagnosed at 46,751 follow-up visits were metastatic, compared with 6.7% at first visit (Figure 2). It can also be seen that stage C2 prostate cancers decreased from 10.7% at first visit to only 2.4% at follow-ups. Stages T1C, on the other hand, increased from

Figure 2. *Distribution of clinical stages of 337 and 215 (327 and 206 staged) prostate cancers diagnosed at first and follow-up screening visits, respectively. Data are expressed as percentage of total number of staged cancers in each group to facilitate comparison.*



6.1% at first visit to 18.4% at follow-up visits; stage T2A disease increased from 35.5% to 51.9%, and stage T2B cancers, on the other hand, decreased from 29.1% to 18.4%.

As clearly suggested in these investigators' previous reports[3,4] (and well demonstrated by the present update and extension of the previous data), the most cost-effective strategy is measurement of serum PSA as first-line approach, as recently concluded by Schröder et al[5,6] in another large-scale screening study. Following this strategy, the costs for finding one case of prostate cancer at first visits and follow-up visit are estimated at $2,418.75 and $7,105.00, respectively.

Impact on survival (November 15, 1988 - December 31, 1998). Of the 46,480 eligible men aged 45 to 80 years included in the prospective randomized study started in 1988, 31,130 were invited by letter to be screened for prostate cancer, and 15,350 were allocated to the control unscreened group. Figure 3 shows the breakdown in terms of the number of men, man-years, and deaths from prostate cancer according to original randomization and participation to screening.[8]

Over the 10-year period, the annual cause-specific death rate incidences are 16.0 (Figure 3, Group A) and 50.5 (Figure 3, Group B) per 100,000 man-years in the invited screened and control unscreened groups, respectively ($P < .01$). The prostate cancer death incidence rate thus decreased by 68% in men of the screened group.

Conclusions. PSA used as a single test for prescreening, followed by DRE and TRUS when PSA is abnormal, is highly efficient in detecting prostate cancer at a localized (potentially curable) stage in close to 100% of cases, thus practically eliminating the diagnosis of metastatic and non-curable prostate cancer.[3,4] The approach used is highly reliable, sensitive, efficient, and acceptable by the general population.[9] With the kits available, PSA measurement is a low-cost routine procedure that requires a simple blood sampling and a minimum of expense. Only 17% of men then need to be referred to specialized prostate cancer clinics when PSA becomes abnormal (>3.0 ng/mL), thus reducing the costs and optimizing the use of specialized health care personnel and expertise. The detection of clinically nonsignificant cancer is an exception. Coupled with treatment of localized disease, the present approach demonstrates, in the first prospective and randomized study, that early diagnosis and treatment permit a dramatic decrease in death from prostate cancer. If the present trend continues, the present data suggest that among the male population in the United States, the present approach could save the lives of 2.0 million of the 3.0 million presently living in the United States and expected to die from prostate cancer if no significant change in diagnosis and/or treatment occurs.

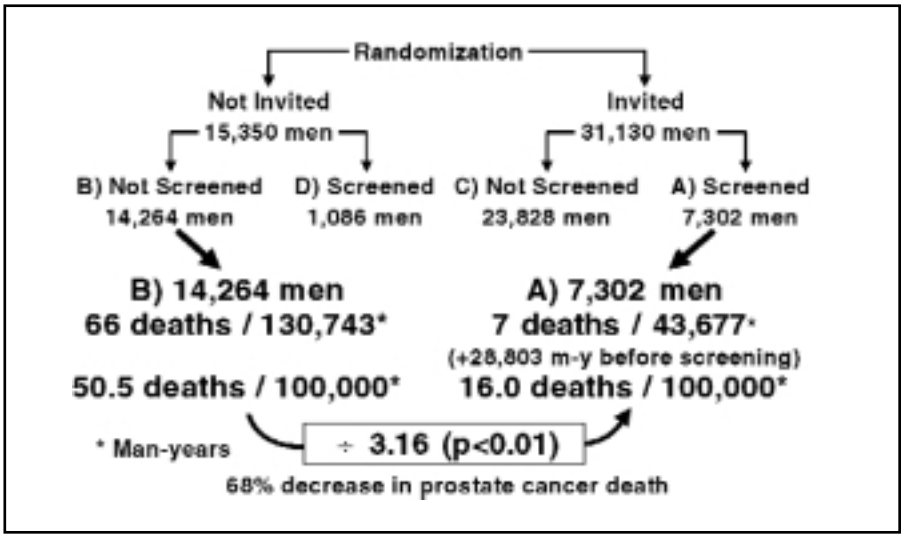


Figure 3. *Summary of data of the Laval University prostate cancer screening program (November 15, 1988 to December 31, 1998).*

Two other randomized screening trials for prostate cancer are ongoing, namely the Prostate, Lung, Colon, and Ovarian Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). Results from those trials are not expected before year 2005. Moreover, their relatively late start carries the high risk of significant contamination of the control group by screening.

As strong support for the crucial role of early diagnosis and treatment, this first prospective and randomized prostate cancer screening study shows that early diagnosis combined with treatment of localized disease decreased death from prostate cancer by 68%. The present data are also in agreement with the 42% decrease observed in 1998 in the prostate cancer death rate in the Tyrol area, where PSA screening was made available as of 1993, compared to the rest of Austria where PSA screening was not offered.[12] Because about two thirds of men were screened in Tyrol during that period, the 42% decreased death rate observed is comparable to the 68% value measured in the LUPCSP study among the men who were screened.

Epidemiology

Trends of Prostate Cancer Incidence in Japan. The International Prostate Cancer meeting was fortunate to have several presentations from our

esteemed colleague from Japan, Daisaku Hirano, MD. In his first presentation, he reviewed the increasing incidence of the disease in Japan. This increase incidence is likely due to dietary changes, along with increased public awareness and early detection efforts.

In the United States prostate cancer has become the most common type of cancer among men, and the second leading cause of male cancer death. Prostate cancer incidence had been increasing for some time; however, from 1989 to 1992, it increased, on average, 20% per year and then swung dramatically downward at a rate of 10.8% per year.[13] In contrast, prostate cancer was rare in Japan. The age-adjusted prostate cancer incidence rate in Japan in 1990 was approximately 1/11 of that in the United States. Based on the trends in prostate cancer incidence in Japan, the age-adjusted prostate cancer incidence rate was 8.5 per 100,000 in 1990; it had increased approximately two-fold, to 16.1 per 100,000 in 1995.[14] Precise epidemiological data from all parts of the country in Japan regarding prostate cancer after 1995 have not been available. However, based on some reports[15] regarding a limited area in Japan and the Nihon University Department of Urology survey, incidence rates of prostate cancer have been also gradually increasing since 1995. Figure 4 shows the trend of new patients with prostate cancer treated in three Nihon University Hospitals and eight affiliated hospitals in Tokyo areas between 1995 and 1999. With respect to incidence rates by stage, based on mass screening using PSA in Gunma Prefecture, Japan, the percentage of early stage cancer increased.[16] The Nihon University survey indicates that the incidence of early stage, likewise, has increased; stage T1c, particularly, has drastically increased among patients who received radical prostatectomy in the Nihon University, Itabashi hospital since 1996 (Figure 5).

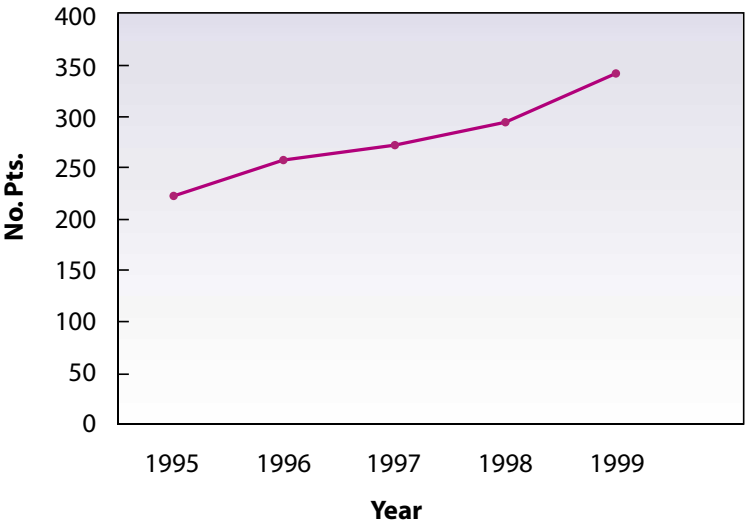


Figure 4. *The trend of new patients with prostate cancer treated in the Nihon University Hospitals and affiliated hospitals between 1995 and 1999.*

Environmental factors play an important role in the pathogenesis and development of prostate cancer. This assertion is supported by the autopsy studies that showed that there was no difference in the prevalence of small latent cancer between Japanese and Western men,[17] and the observation that the incidence rate of prostate cancer among Japanese immigrants living in Los Angeles and Hawaii is far higher than that among Japanese men living in Japan. During the period of 1983 to 1987, the average annual age-adjusted prostate cancer incidence rates for Japanese men in Los Angeles and Hawaii were 47.2 and 51.0 per 100,000, respectively. These rates are roughly four times higher than the average 12.1 per 100,000 of age-adjusted incidence rates from six regions in Japan during the same time period.[18] The higher rates of prostate cancer in Japanese-American men than in native Japanese men have prompted the hypothesis that lifestyle characteristics play a major role in prostate carcinogenesis.

It is generally known that factors contributing to prostate cancer prevention are lower serum androgen levels, a low-fat and high-fiber diet,[19] high intake of vitamin A from plant sources,[20] and high intake of soy products, including high intake of isoflavonoids.[21] Japanese men had traditionally consumed these prostate cancer–preventive diets, rather than the prostate cancer–promoting products such as animal fat, animal protein, meat, and milk, which are consumed by Western men. However, in recent years, the Japanese diet has been become westernized. The incidence of prostate cancer has been increasing. Improved diagnostic techniques, such as the use of PSA testing and systematic sextant or more biopsies guided TRUS for the detection of prostate cancer, and increased awareness among the general public regarding prostate cancer may also be factors contributing to the increased incident rate of prostate cancer in Japan.

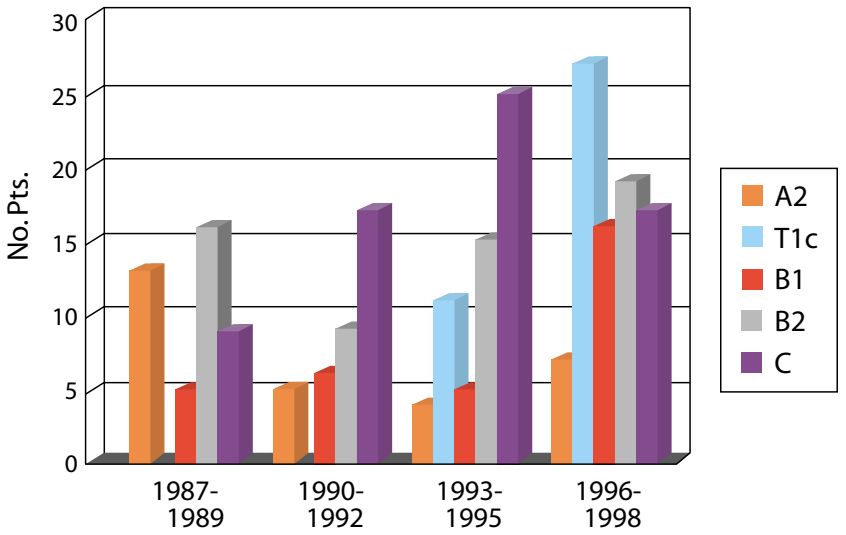


Figure 5. *The trend of clinical stages every 3 years in patients who received radical prostatectomy in the Nihon University, Itabashi Hospital between 1987 and 1998.*

In summary, although the prostate cancer incident rate in the United States has decreased since 1992, the rate in Japan has been continually increasing. A major contributing factor may be dietary changes. Another factor may be increased screening, with widespread use of PSA testing, thanks to growing public knowledge regarding prostate cancer.

Computer-based research. Joseph Batuello, MD, JD, presented an outstanding overview of the use of artificial neural networks (ANNs) in prostate cancer research. ANNs are computer applications that can be used to model complex relationships that exist in large arrays of data. Like logistic regression and other classical modeling techniques, most ANNs used in medical applications are regression models. Because they do not rely on explicit assumptions about the distributions of the underlying data, they can detect hidden and unsuspected relationships contained within those data. ANNs have been explored for a number of applications in clinical urology, including cancer detection, staging, prognosis, and survival prediction. Because ANNs are largely independent of assumptions regarding the statistical distributions contained in the data, they are more reliant on large quantities of data. This limitation has restricted the widespread use of ANNs in clinical practice.

Clinical diagnosis and treatment planning incorporates multiple clinical data to arrive at appropriate patient management decisions. These decisions depend on an individual clinician's experience and the relevant literature regarding the significance of individual clinical variables. Furthermore, the clinician may reference statistical models that allow clinical predictions to be derived from data stored in large institutional databases.

These models have long been derived using established statistical methods, such as logistic regression, and this methodology has been validated in clinical practice. However, the task of deriving valid models becomes more complex as the number of included variables increases and more powerful methods of modeling are being sought. One such method is broadly referred to as artificial neural network (ANN) modeling. The Artificial Neural Networks in Carcinoma of the Prostate (ANNs in CAP) project was undertaken through the Institute for Clinical Research in Washington, D.C. to investigate the capabilities and limitations of ANNs in the management of prostate cancer. This group has completed a number of different projects evaluating the utility of ANNs. They have implemented the first web-based neural networks for prostate cancer, and these are available on the website, www.annsincap.org. Both physicians and patients can utilize this website to predict outcomes of treatment. By the end of the year, approximately five neural networks will be available for use.

Prostate cancer on the Internet. The final discussion of this session was by Dr Michael Glodé, who discussed the Internet as a medium for the patient and clinician.

The amount of information for cancer patients, including those with prostate cancer is overwhelming. Although there are no specific studies for prostate cancer, many of the common search engines, such as Yahoo, Excite, and Google, will retrieve more than 100,000 pages contained on thousands of websites when asked to search on "prostate cancer."

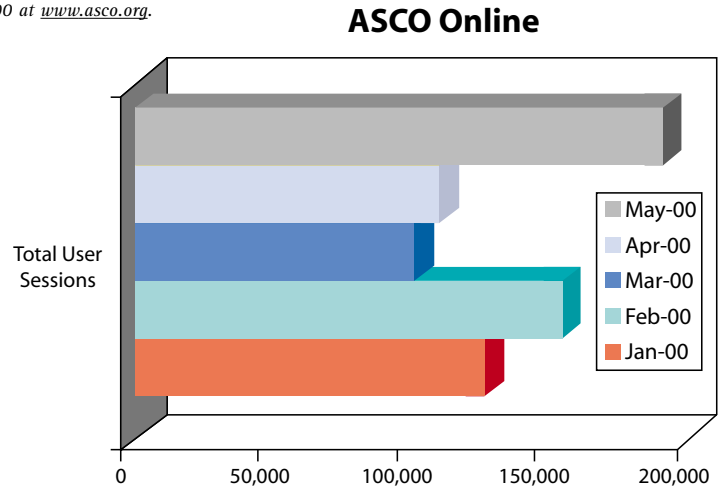
Cyber Dialog Inc. and Deloitte Research recently released the results of a comprehensive survey of 1200 physicians scientifically chosen to represent a cross-section of practicing U.S. generalists and subspecialists.[22] The study accurately reflects the attitudes and practices in June–July 2000 of practicing U.S. physicians with an error of ± 2.8% at the 95% confidence interval. The study found that 90% of physicians had accessed the Web at some time in the previous 12 months, 82% went online weekly,

and 55% daily. Within the group were 24% of physicians who, although they might not go online daily, were characterized as "professional users" in that at least 75% of the time spent online was activity related to their practice of medicine.

Among the important findings of this study were the specific activities of these users related to medicine. Approximately 75% of the physicians searched literature databases, ~60% accessed professional journals or websites describing medical devices or therapies, and a similar number used the Web to communicate with colleagues. Less than half accessed clinical trials information or took CME courses on the Web. Although the study noted that patients and physicians both have great interest in e-mail contact, only one fourth of the doctors currently use e-mail to communicate with their patients. These activities were most frequently discussions of symptoms or treatment options or notification of test results.

When looking to the future, in spite of predictions that electronic medical records (EMR) will replace current paper systems, fewer than 10% of physicians in this survey were currently using EMR technology. Reasons cited for this lack of adoption were most frequently privacy/security concerns, the inability to easily enter historical data, and lack of standards for online records. The central conclusion of the Deloitte-Cyber Dialog study was that "most doctors simply do not see the value proposition (time, money and quality impact) to justify using the Web or online applications in their practices...." Other studies continue to find that health care management organizations as well as patients predict that within 10 years, EMR will increasingly become the norm, and virtually all surveys of Internet use document the continued intense interest of consumers in finding health information, especially for cancer.

Figure 6. *User sessions in the first half of 2000 at www.asco.org.*



The American Society of Clinical Oncology website is an example of a website offering both professionals and persons living with cancer high-quality, vetted information.[23] The continued growth in users is reflected in Figure 6.

Information functions available to visitors to ASCO OnLine include all meeting abstracts dating to 1997, slide–audio lectures from the 1999 and 2000 annual and fall educational meetings, CME courses, practice guidelines, patient information brochures, and the membership database, along with a patient-friendly description of the role of medical oncologists in cancer care. In May 2000, corresponding with the Society's annual meeting, more than 1.6 million page views were served to visitors.

Clinical trials management has been an area of rapid development in Web-based applications. Numerous websites allow physicians and patients alike to search for available studies often involving the latest techniques or pharmaceuticals. Prominent among these is the National Cancer Institute webpage, "CancerTrials."[24] Here, using logical search screens in the Physicians Data Query (PDQ) section, a physician or patient can designate a stage of disease, treatment desired, and location in the country and receive a hypertext-linked list of available protocols. Data monitoring at the National Cancer Institute is also rapidly evolving through the use of standardized automated systems, which use common toxicity criteria and common data element dictionaries.

The future evolution of Internet technology in medicine will almost certainly involve the Human Genome. Currently all DNA sequences from every known species including plants, flies, worms, rodents, and primates including man are being catalogued and linked by the National Center for Biotechnology Information (NCBI).[25] One of the most widely used systems, PubMed, contains most of the peer-reviewed medical literature, and rapid growth is occurring in the area called OMIM, the Online Mendelian Inheritance in Man. There are now more than 12,000 conditions listed in this database, including many cancer genes and/or cancer genetic syndromes, which have comprehensive, frequently updated articles that link the conditions to specific genes. These genes are in turn mapped to chromo-

somes and lower organisms via a complex set of data links that are easily navigated, even by inexperienced users.

In conclusion, the Internet remains an evolving tool in cancer medicine. Although current usage in practice is relatively unsophisticated and does not meet the needs of most practicing physicians, it appears likely that electronic medical records and e-communication among physicians and patients will continue to grow. "Second-wave" applications, which attack problems ranging from billing to genetic testing using gene arrays on tumor specimens are likely to become integrated into most clinical practices. ■

References

1. Labrie F. Screening and early hormonal treatment of prostate cancer are accumulating strong evidence and support. *Prostate*. 2000;43:215–222.
2. Prostate Cancer Triallists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet*. 2000;355:1491–1498.
3. Labrie F, Candas B, Cusan L, et al. Diagnosis of advanced or noncurable prostate cancer can be practically eliminated by prostate-specific antigen. *Urology*. 1996;47:212–217.
4. Candas B, Cusan L, Gomez J-L, et al. Evaluation of prostatic specific antigen and digital rectal examination as screening tests for prostate cancer. *Prostate*. 2000;45:19–35.
5. Schröder FH, van der Maas P, Beemsterboer P, et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. *J Natl Cancer Inst*. 1998;90:1817–1823.
6. Schröder FH, Roobol-Bouts M, Vis AN, et al. Prostate-specific antigen-based early detection of prostate cancer-validation of screening without rectal examination. *Urology*. 2001;57:83–90.
7. Labrie F, Candas B, Dupont A, et al. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate*. 1999;38:83–91.
8. Labrie F, Candas B, Cusan L, et al. Decrease of prostate cancer death by screening: update of the Quebec prospective randomized controlled trial at 10 years of follow-up. Abstract presented at the 36th Annual Meeting ASCO; May 20-23, 2000; New Orleans, LA. Page 337a, Abstract 1326.
9. Labrie F, Dupont A, Suburu R, et al. Serum prostate specific antigen (PSA) as prescreening test for prostate cancer. *J Urol*. 1992;147:846–852.
10. Lee F, Littrup PJ, Loft-Christensen L, et al. Predicted prostate specific antigen results using transrectal ultrasound gland volume. Differentiation of benign prostatic hyperplasia and prostate cancer. *Cancer*. 1992;70(Suppl):211–220.
11. Myschetzky PS, Suburu RE, Kelly BS Jr, et al. Determination of prostate gland volume by transrectal ultrasound: correlation with radical prostatectomy specimens. *Scand J Urol Nephrol Suppl*. 1991;137:107–111.
12. Bartsch G, Horninger W, Klocker H, et al. Decrease in prostate cancer mortality following introduction of prostate specific antigen (PSA) screening in the federal state of Tyrol, Austria. *J Urol*. 2000. Page 88, Abst.: 387.
13. Gloeckler-Ries LA, Kosary CL, Hankey BF, et al, eds. *SEER Cancer Statistics Review 1973–1994*. Bethesda, MD: US Dept. of Health and Human Services, National Cancer Institute, 1997. NIH Publication No. 97-2789.
14. Kuroishi T. International comparisons of prostate cancer incidence and mortality. *Jpn Nihon Rinsho*. 2000;58(Suppl):12–21.
15. Fujii A, Natumoto H, Hashimura T, et al. The epidemiology of prostate cancer in Himeji area. *Jpn J Urol*. 2001;92(suppl II):337.
16. Kubota Y, Imai K, Yamanaka H. The correlation of stage and pathology of prostate cancer in Japan. *Int J Urol*. 2000;7:139–144.
17. Akazaki K, Stemmermann GN. Comparative study of latent carcinoma of the prostate among Japanese in Japan and Hawaii. *J Natl Cancer Inst*. 1973;50:1137–1144.
18. Parkin DM. *Cancer Incidence in Five Counties, Volume VI*. Lyon (France): International Agency for Research on Cancer; 1992.
19. Pusateri DJ, Roth WT, Ross JK, et al. Dietary and hormonal evaluation of men at different risks for prostate cancer: plasma and fecal hormone-nutrient interrelationships. *Am J Clin Nutr*. 1990;51:371–377.
20. Kolonel LN. Nutrition and prostate cancer. *Cancer Causes Control*. 1996;7:83–94.
21. Evans BA, Griffiths K, Morton MS. Inhibition of 5-alpha-reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids. *J Endocrinol*. 1995;147:295–302.
22. Deloitte Research-Health Care Institute. *Taking the Pulse – Executive Summary*. Available at: http://dccps.nci.nih.gov/eocc/jan_01/Taking_the_Pulse_Exec_Sum_Final.pdf (contact Scott Haiges, 212-651-7032).
23. ASCO OnLine; available at: http://www.asco.org.
24. CancerTrials, A Service of the National Cancer Institute. Available at: http://cancertrials.nci.nih.gov/.
25. National Center for Biotechnology Information. Available at: http://www.ncbi.nih.gov.

Main Points

- Prostate cancer is very multifocal. The average patient has at least two distinct foci of carcinoma in their prostate. The foci are anatomically distinct and can have different Gleason scores, so it is important to find as many of these as possible to eliminate sampling error.
- Previous studies of radical prostatectomy specimens with lymphadenectomies have led some to conclude that tumors must attain a volume of 4 cc before metastasis begins, but lympho-vascular invasion can be found in carcinomas <0.5 cc in volume.
- Data from the Laval University Prostate Cancer Screening Program show that PSA is about 10 times more efficient than DRE at detecting prostate cancer at a clinically localized and potentially curable stage.
- The role of environmental factors, particularly diet, in prostate cancer pathogenesis and development is supported by the increase of the disease in Japan, concurrent with the "westernization" of diet there.
- Artificial Neural Networks are computer applications that can be used to model complex relationships that exist in large arrays of data. The ANNs in CAP project (http://www.annsincap.org) was undertaken through the Institute for Clinical Research in Washington, D.C. to investigate the capabilities and limitations of ANNs in the management of prostate cancer.
- In spite of predictions that electronic medical records (EMR) will replace current paper systems, fewer than 10% of 1200 physicians in a recent survey were currently using EMR technology. However, other studies find that health care management organizations as well as patients predict that within 10 years, EMR will increasingly become the norm.
- Numerous websites allow physicians and patients alike to search for available studies often involving the latest techniques or pharmaceuticals. Prominent among these is the National Cancer Institute webpage, "CancerTrials" (http://cancertrials.nci.nih.gov/), where a physician or patient can designate a stage of disease, treatment desired, and location in the country and receive a hypertext-linked list of available protocols.