Advances in prostate cancer
Charles J. Ryan and Eric J. Small

Purpose of review
The purpose of this review is to highlight the most important developments in the diagnosis, prevention, and management of prostate cancer reported in the past year that have been published in the medical literature.

Recent findings
Recent research has yielded important insights into the effects of lowering the serum prostate-specific antigen threshold for prostate biopsy on the incidence of prostate cancer and suggests that a cutoff value of 2.5 ng/mL would double the rate of diagnosis of the disease in young men. Other developments demonstrate that oral finasteride reduces the incidence of the disease but increases the proportion of high-grade tumors. The incidence of mutations of the androgen receptor gene has been shown to be lower than was previously thought. New randomized data suggest that for patients with high-risk localized prostate cancer treated with radiation, 4 months of androgen deprivation in combination with whole pelvis radiotherapy confers a clinical benefit. The clinical benefits associated with chemotherapy and supportive care therapies such as the bone targeting bisphosphonates continue to be refined.

Summary
The data reported in the past year have widespread implications for all clinicians involved in the management of prostate cancer, ranging from primary care physicians who screen for and diagnose the disease to those who manage localized as well as systemic disease. Several of the year’s findings will result in significant changes in the manner in which the disease is treated.

Keywords
prostate cancer, chemoprevention, hormonal therapy, secondary hormonal therapy, antiandrogens, antiandrogen withdrawal, corticosteroids, chemotherapy

Introduction
Prostate cancer continues to be a major health problem in the developed world. A significant amount of new data has been reported within the past year that has important implications for the prevention, diagnosis, and management of this disease. The purpose of this review is to acquaint the reader with the major findings in the field of prostate cancer research reported in the past year and to give perspective on the impact these findings may have on the care of prostate cancer patients in the future.

Screening and diagnosis
Prostate-specific antigen (PSA) screening continues to be a controversial issue in general medical practice. Current standards use a value of 4.0 ng/mL as the upper limit of normal. Estimates of the sensitivity of PSA screening are biased in part by the fact that not all men with an abnormal PSA level (e.g., >4.0 ng/dL) will have biopsy-confirmed disease. Likewise, biopsy-confirmed disease can be detected in a proportion of men with “normal” PSA values. Overestimation of test sensitivity occurs because of verification bias, the fact that a lower fraction of subjects with a negative test result (e.g., ≤4.0 ng/dL) undergo biopsy than those with a “positive” test result (e.g., >4.0 ng/dL). To determine the extent of this bias on the diagnosis of prostate cancer, Punglia et al. [1 •] conducted a study of 6691 men enrolled in a screening study in which the threshold for prostate biopsy was a PSA level of ≥2.5 ng/mL (or an abnormality on digital rectal exam). The authors estimated that reducing the threshold for prostate biopsy to >2.5 ng/mL would double the rate of prostate cancer detection in men under the age of 60, from 18% to 36%. This would be accompanied by a minimal decrease in the specificity of the test from 0.98 to 0.94. These findings suggest that many early prostate cancers in young men are associated with a PSA in what is considered the “normal” range and that, as a consequence, current screening strategies fail to detect a substantial number of cases. The implications of using a lower threshold on disease-related outcomes, survival, and health-related quality of life (HRQOL) is not known.
Chemoprevention of prostate cancer

The sensitivity of prostate cancer to hormonal ablation, the availability of well-tolerated inhibitors of 5 alpha-reductase (the enzyme that converts testosterone to the more active dihydrotestosterone) coupled with the proven efficacy of tamoxifen in the prevention of breast cancer, raised optimism that prostate cancer is amenable to chemoprevention. The first large-scale prostate cancer prevention trial was recently reported. The Prostate Cancer Prevention Trial randomized 18,882 men with a normal digital rectal examination result and a PSA of 3.0 ng/mL or lower to receive either finasteride (5 mg/day) or placebo for 7 years [2••]. The final report from this study demonstrated a reduction in the total number of cases of prostate cancer diagnosed in the finasteride group (18.4% vs 24.4%, P < 0.001). Despite the positive results, enthusiasm for this approach has been dampened by (1) the fact that the absolute risk reduction was only 6%, (2) the observation that toxicity is associated with this therapy, including sexual dysfunction, and (3) the observation that in the finasteride group there was a statistically significant increase in the proportion of tumors with a Gleason pathologic grade of 7 or greater (37% of the cancers in the finasteride group vs 22.2% of those in the placebo group (P < 0.001). Therefore, although the chemoprevention of well-differentiated tumors may have occurred, it is possible that changes in the hormonal milieu induced by finasteride may have altered differentiation leading to the development of higher-grade, and therefore more aggressive, prostate cancers.

Quality of life for prostate cancer patients

As outcomes for patients with clinically localized prostate cancer improve, the HRQOL after treatment becomes an important area of consideration in clinical decision making. Given that many patients and clinicians must choose between radiotherapy and radical prostatectomy, several studies have addressed the extent to which these modalities affect HRQOL. A previous nonrandomized study of 258 patients in The Netherlands suggested that HRQOL was slightly higher after radical prostatectomy, making. Given that many patients and clinicians must choose between radiotherapy and radical prostatectomy, primary hormonal therapy, and watchful waiting. After correcting for potential confounding variables such as baseline urinary, bowel, and sexual function, the investigators found that the type of primary treatment was not associated with changes in general HRQOL at the 2-year time point. These data suggest that previous assumptions that radiation had a more dramatic (negative) impact on HRQOL than surgery may not be correct.

The quality of life changes associated with androgen deprivation (AD) are well known. Segal et al. [5•] reported the results of a study in which men treated with AD underwent resistance exercise training three times per week. When compared with control participants, the patients who exercised experienced significantly less fatigue (P = 0.002) and an overall improvement in quality of life (P = 0.001).

Treatment of localized disease

Surgery

Many studies have demonstrated that AD before radical prostatectomy is associated with a reduction in positive surgical margins but has no effect on PSA progression-free or overall survival. Furthermore, complete eradication of tumors with androgen ablation alone is a rare event. Kollermann et al. [6] reported the long-term outcome in a cohort of individuals who were treated with prolonged AD before prostatectomy and were found to have stage pT0 disease at the time of surgery. From a total of 227 patients treated with this prolonged therapy, 38 patients (16.7%) had a pT0 tumor, slightly higher than previously reported. Whereas most patients with pT0 tumors appeared likely to have prolonged disease-free intervals, 3 went on to experience relapse (2 locally, 1 systemically).

Radiotherapy

Previous studies reported by Bolla [6a] and Pilepich [6b] have demonstrated a therapeutic advantage to the use of adjunctive AD along with prostatic irradiation in patients with high-risk prostate cancer. However, for these high-risk patients (defined by high Gleason grade, PSA, or T stage), it was not clear whether the benefit observed was simply the added effect of long-term AD or whether there was an interaction between radiation and AD. In addition, the benefit of pelvic nodal irradiation in the patients with a high risk of pelvic lymph node involvement was not known.

The Radiation Therapy Oncology Group 9413 trial addressed this question by randomizing 1323 patients in a 2 × 2 fashion to pelvis and prostate radiation versus prostate-only radiation and AD before and during radiation (2 months neoadjuvant, 2 months concurrent) versus the same duration of AD administered completely adjuvantly (after the completion of radiation). With a median follow-up time of 59 months, there was a statistically significant progression-free survival advantage in favor of the combination of neoadjuvant and concurrent (NC) androgen ablation together with pelvic and prostate radiotherapy. The direct comparison of patients treated...
with whole pelvic radiation to those treated with prostate-only radiation revealed a progression-free survival rate of 54.2% versus 47%, respectively \((P = 0.022)\). The time to PSA failure also differed significantly among the four treatment arms, with whole pelvic radiation + neoadjuvant/concurrent hormonal therapy yielding the most favorable results \((P = .008)\) \([7••]\). The direct comparison of those treated with neoadjuvant versus concurrent hormonal ablation yielded nonsignificant results with respect to progression-free survival rate: 52% versus 49% \((P = 0.56)\).

The results of this study should change clinical practice. It defines pelvic radiation therapy as a standard of care in patients with a high risk of loco-regional nodal invasion, and it confirms laboratory data that suggested true synergy between concurrent AD and radiation therapy. Unfortunately, this study does not define the optimal duration of AD. Although it is tempting to extrapolate from these data and provide this therapy to all prostate cancer patients undergoing radiation therapy, it is applicable only to high-risk patients undergoing standard-dose therapy. Nevertheless, it establishes the precedent that loco-regional nodal irradiation in prostate cancer, as is the case with many other malignancies, provides therapeutic benefit.

**Serologic relapse**

The clinical outcomes in patients with a rising PSA after local therapy are highly heterogeneous but correlate significantly with factors such as the Gleason grade of the primary tumor, the time to development of the rising PSA after primary therapy, and the rate of rise of PSA, most commonly measured in the form of the PSA doubling time. Because therapeutic options outside of AD are limited, significant interest exists in the development of nontoxic nonhormonal agents that may have biologic activity. Among the approaches studied are tumor vaccines, oral targeted therapies, and immunostimulatory cytokines. A study of this latter approach was recently reported in a cohort of men with rising PSA treated with the cytokine granulocyte-macrophage colony stimulating factor injected subcutaneously for 14 days of a 28-day cycle \([7a]\). Although only 3 of 30 patients (10%) experienced a greater than 50% decline in PSA level, the median PSA doubling time increased from the pretherapy baseline of 8.4 months to 15 months \((P = 0.001)\). On the basis of this endpoint, the authors concluded that granulocyte-macrophage colony stimulating factor has biologic effects against prostate cancer and suggest that further work is needed in the development of novel meaningful study endpoints in patients with a rising PSA.

**Hormone-sensitive prostate cancer**

Research efforts in the treatment of patients undergoing initial AD now focus on delaying the emergence of androgen independence as improving the quality of life of patients receiving hormone therapy. Saad *et al.* \([8]\) have demonstrated the impact of the addition of the bisphosphonate zoledronic acid on reducing skeletal-related events and improving quality of life in patients with hormone-refractory prostate cancer (HRPC). Given these results, subsequent work seeks to determine whether the use of these agents in hormone-sensitive disease delays, or prevents altogether, bony metastases and clinically meaningful skeletal-related events.

A study from the Medical Research Council in Canada demonstrated an improvement with regard to the preservation of performance status in patients treated with clodronate. In addition to this endpoint, however, this study addressed the question of whether clodronate therapy had an impact on bone progression-free survival and on overall survival \([9]\). The hazard ratio in the clodronate group for bone progression-free survival was 0.79 and did not reach statistical significance \((P = 0.066)\). Although the hazard ratio for survival \((0.80)\) did not reach statistical significance \((P = 0.082)\), this study is provocative and raises questions as to whether a more potent bisphosphonate such as zoledronic acid might have a more dramatic effect when administered earlier in the clinical course of disease. Building on this, the Cancer and Leukemia Group B is conducting a phase III trial that randomizes patients to receive zoledronic acid or placebo in conjunction with initial AD.

**Androgen-independent prostate cancer**

**Biology**

The changes in signaling through the androgen receptor (AR) that develop as clinically androgen-independent (hormone-resistant) disease develops are not fully understood, although both up-regulation of the AR, as well as mutations in the AR, frequently in the androgen binding domain, have been previously described. Edwards *et al.* \([10]\) evaluated the proportion of hormone-sensitive tumors that demonstrated amplification of the AR gene \((2\%) \text{ versus} \) the proportion of samples from the same patients after the development of hormone resistance \((20\%) \ (P = 0.0085)\). Analysis of AR protein expression by immunohistochemistry revealed that expression was significantly higher in hormone-refractory tumors but did not significantly correlate with gene amplification. These observations are important because they demonstrate that AR gene amplification can increase over time as clinical androgen independence develops. However, the fact that only 10% of 49 hormone-refractory tumors demonstrated AR gene amplification suggest that although AR gene amplification is undoubtedly of clinical importance, it likely represents only one of multiple mechanisms by which prostate cancer becomes hormone refractory.

An alternative mode of aberrant AR signaling has been attributed to mutations in the AR gene, and previous studies have suggested that as many as 50% of hormone-refractory tumors exhibited mutations of the AR. Hara *et al.*
al. [11] demonstrated that in vitro exposure to bicalutamide is associated with mutations of the ligand binding domain of LNCaP tissue culture cells, a study that for the first time described mutations in the exact site on the receptor that is bound by bicalutamide. Taplin et al. [11a] published the results of a study in which 184 bone marrow biopsies were systematically performed in men with androgen-independent prostate cancer who were enrolled in a phase III clinical trial that randomized patients to antiandrogen withdrawal (AAWD) alone or AAWD with the addition of ketoconazole. Metastatic prostate cancer was detectable by immunohistochemistry in 48 of the 184 bone marrow samples, and the AR was sequenced in 45 cases. Five of the 45 (10%) demonstrated mutations of the AR, and there was no correlation between the detection of these AR mutations and AAWD response.

Taken together, these studies suggest that androgen-independent prostate cancer is caused by multiple mechanisms and that phenotypic and genomic alterations of the AR do contribute, albeit in a relatively low percentage of cases. These findings highlight the importance of research endeavors that seek to identify and target the alternative mechanisms associated with androgen-independent signaling of the AR.

**Therapy**

Various therapeutic approaches have been explored in patients with progressive disease despite AD, including second-line hormonal manipulations, chemotherapy, and novel agents. Second-line hormonal manipulations have included the use of different antiandrogens after AAWD. Kassouf et al. [12•] reported sustained PSA declines of ≥50% in 29% of patients who received second-line therapy with the antiandrogen nilutamide. Interestingly, all five (100%) of the patients who had previous AAWD responses also experienced significant responses to the nilutamide, in contrast to only 18% (3 of 17) of the patients who did not have previous AAWD responses. These data suggest that secondary hormonal maneuvers are certainly warranted, particularly in patients with known sensitivity to hormonal manipulations like AAWD.

Cytotoxic chemotherapy in HRPC has gained widespread acceptance. Oh et al. [13•] reported survey data from a cohort of 232 practicing physicians (medical oncologists and urologists and radiation oncologists) and revealed that the vast majority of them (87%) used or recommended chemotherapy for their patients with hormone-refractory disease. Mitoxantrone and prednisone remains the only chemotherapy regimen that is approved by the FDA for use in HRPC. Despite this, taxane-based therapy remains the de facto standard of care for patients, and the results of completed phase III trials comparing these two types of regimens are eagerly anticipated. Whereas a substantial amount of nonrandomized data supports the use of the combination of docetaxel and estramustine, the toxicity of this latter agent is significant and includes nausea and vomiting as well as thrombosis. Because of this, many current research efforts seek to test whether regimens without estramustine are effective. One such combination that was reported involves weekly high-dose calcitriol with docetaxel. Beer et al. [14] reported 50% or greater declines in PSA in 81% of patients without a significant increase in toxicity compared with that expected with docetaxel alone. Future clinical trial data will serve to further clarify the extent to which estramustine is needed in the management of HRPC.

Several studies continue to define the activity of mitoxantrone-based regimens. The results of a randomized phase III clinical trial of mitoxantrone plus prednisone versus prednisone alone was reported by Berry et al. [15]. Although there was no difference in median survival in favor of mitoxantrone (23 and 19 months, respectively) there was a significant difference with respect to time to progression in favor of the mitoxantrone arm (8.1 vs 4.1 months, \( P = 0.018 \)) and a higher proportion of patients achieved a >50% decrease in PSA in the combination arm than in the prednisone-alone arm (48% vs 24%, \( P = 0.007 \)). These results support previous findings from the Cancer and Leukemia Group B [15a] and Tannock et al. [15b] in Canada.

The use of bisphosphonates for bone protection in patients with advanced prostate cancer has become a standard of care. Saad et al. [8] established the importance of zoledronic acid in reducing skeletal events, including pathologic fractures and palliation of pain. The efficacy of other less potent bisphosphonates such as coldronate, and pamidronate, as described by Small et al. [16], has also been reported and suggests that zoledronic acid is the superior bisphosphonate. This year, a group of centers in Canada reported the results of a study that randomized patients with HRPC to receive mitoxantrone and prednisone plus either placebo or the bisphosphonate clodronate every 3 weeks at a dose of 1500 mg [17]. Using a prostate cancer–specific quality of life instrument and a primary endpoint of palliative response, 46% of the patients in the combination group met the criteria for palliative response, and only 39% of those in the placebo group did. These results were not statistically significant, and the authors concluded that the addition of clodronate to mitoxantrone and prednisone does not improve the palliative benefit from this therapy. In another report, the pooled analysis of two placebo-controlled trials testing the palliative efficacy of pamidronate disodium also failed to show significant improvements in a variety of pain indices [16]. On the basis of these negative data, and data presented in the past 2 years, zoledronic acid should be considered the...
most potent bisphosphonate in the treatment of patients with blastic skeletal metastases from prostate cancer [8].

Conclusion

Research efforts in the past year have helped to answer preliminary questions regarding the potential for prostate cancer chemoprevention and have demonstrated the shortcomings of present screening strategies. Large-scale clinical trials have clarified the importance of early AD in patients treated with radiation therapy as well as the extent and field of radiation therapy that is optimal. Novel approaches to the management of relapsed disease continue to be tested, and the role of chemotherapy continues to evolve. Studies of the biology of the disease have given insight into some of the mechanisms of androgen independence and underscore the challenges that lie ahead in conquering the disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- Of special interest
- Of outstanding interest

1 Punglia RS, D’Amico AV, Catalona WJ, et al.: Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. N Engl J Med 2003, 349:335–342.

This paper suggests that lowering the threshold of a normal PSA to ≥2.5 ng/mL will double the detection rate of disease for men under 60.

2 Thompson I, Goodman PM, Tangen CM, et al.: The influence of finasteride on the development of prostate cancer. N Engl J Med 2003, 349:215–224.

This paper showed a decreased incidence of prostate cancer in men treated with finasteride; however, a higher risk of high-grade tumors in the finasteride-treated patients tempers enthusiasm for this approach.

3 Madalinska JB, Essink-Bot ML, de Koning HJ, et al.: Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. J Clin Oncol 2001, 19:1619–1628.

4 Pensom DF, Feng Z, Kuniyuki A, et al.: General quality of life 2 years following treatment for prostate cancer: what influences outcomes? Results from the prostate cancer outcomes study. J Clin Oncol 2003, 21:1147–1154.

5 Segal RJ, Reid RD, Courneya KS, et al.: Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 2003, 21:1653–1659.

This paper reports that weight training decreases fatigue and increases quality of life in men treated with androgen deprivation.

6 Kollermann J, Caprano J, Budde A, et al.: Follow-up of nondetectable prostate carcinoma (pT0) after prolonged PSA-monitored neoadjuvant hormonal therapy followed by radical prostatectomy. Urology 2003, 62:476–480.

6a Bolla M, Gonzalez D, Warde P, et al.: Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997, 295–300.

6b Pilepich MV, Caplan R, Byhardt RW, et al.: Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. J Clin Oncol 1997, 15:1013–1021.

7 Roach M 3rd, DeSilvio M, Lawton C, et al.: Phase III trial comparing whole-pelvis versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression; Radiation Therapy Oncology Group 9413. J Clin Oncol 2003, 21:1904–1911.

This paper establishes neoadjuvant androgen deprivation in conjunction with whole pelvis and prostate radiation as a standard of care for patients with high-risk localized disease.

7a Rini BW, Bok R, Small EJ: Prostate-specific antigen kinetics as a measure of the biologic effect of granulocyte-macrophage colony-stimulating factor in patients with serologic progression of prostate cancer. J Clin Oncol 2003, 21:99–105.

8 Saad F, Gleason DM, Murray R, et al.: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002, 94:1458–1468.

9 Deanaley DP, Sydes MR, Mason MD, et al.: A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PRO5 Trial). J Natl Cancer Inst 2003, 95:1300–1311.

10 Edwards J, Krishna NS, Grigor KM, et al.: Androgen receptor gene amplification and protein expression in hormone refractory prostate cancer. Br J Cancer 2003, 89:552–556.

11 Hara T, Miyazaki J, Araki H, et al.: Novel mutations of androgen receptor: a possible mechanism of bicalutamide withdrawal syndrome. Cancer Res 2003, 63:149–153.

11a Taplin M, Rajeshkumar B, Halabi S, et al.: Androgen receptor mutations in androgen-independent prostate cancer: cancer and leukemia group B study 9663. J Clin Oncol 2003, 21:2673–2678.

12 Kassouf W, Tanguay S, Aprikian A: Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. J Urol 2003, 169:1742–1744.

This paper demonstrates that a previous antiandrogen withdrawal response increases the likelihood for a response to nilutamide.

13 Oh WK, Tully P, Kantoff PW, et al.: Physician attitudes toward cytotoxic chemotherapy in patients with advanced prostate carcinoma. Cancer 2003, 97:2171–2179.

This paper reports survey data indicating the widespread acceptance of chemotherapy in patients with HRPC.

14 Beer TM, Eilers KM, Garzotto M, et al.: Weekly high-dose calcitriol and docetaxel in metastatic androgen-independent prostate cancer. J Clin Oncol 2003, 21:123–128.

15 Berry W, Dahlil S, Modiano M, et al.: Phase III study of mitoxantrone plus low-dose prednisone versus low dose prednisone alone in patients with symptomatic hormoneresistant prostate cancer. J Urol 2002, 168:2439–2443.

15a Small EJ, Meyer M, Marshall ME, et al.: Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. J Clin Oncol 2000, 18:1440–1450.

15b Tannock IF, Osoha D, Stockler MR, et al.: Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996, 14:1756–1764.

16 Small E, Smith MR, Seaman JJ, et al.: Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol 2003, 21:4277–4284.

17 Ernst DS, Tannock IF, Winqist EW, et al.: Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. J Clin Oncol 2003, 21:3335–3342.