Chemopreventive Trials in Urologic Cancer

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Cancer prevention uses natural, synthetic, or biological chemical agents to reverse, suppress, or prevent carcinogenic progression. Chemoprevention trials are based on the hypothesis that interruption of the biological process involved in carcinogenesis will inhibit this process and, in turn, reduce cancer incidence. Bladder cancer chemoprevention trials demonstrate conflicting findings. Dietary fat, soy protein, garlic, and selenium have been reported to possess anticancer properties in the bladder, but they still remain largely unstudied in vivo. Regarding prostate cancer, vitamin D deficiency was reported to increase risk for the disease, and sunlight exposure is inversely proportional to prostate cancer mortality. The Prostate Cancer Prevention Trial reported a 24.4% prostate cancer incidence with placebo, compared with 18.4% with finasteride, and a reduction of 24.8% over 7 years. Dutasteride, a dual inhibitor of type 1 and type 2 5α-reductase, is the subject of the Reduction by Dutasteride of Prostate Cancer Events trial. Results are awaited from that study.

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Cancer prevention, as first described by Sporn in 1976,[1] uses natural, synthetic, or biological chemical agents to reverse, suppress, or prevent carcinogenic progression. It is based on the concepts of multifocal field carcinogenesis and multistep carcinogenesis. In field carcinogenesis, diffuse epithelial injury in tissues, such as those of the aerodigestive tract, results from generalized carcinogen exposure throughout the field and clonal proliferation of

mutated cells. Genetic changes exist throughout the field and increase the likelihood that premalignant or malignant cells might develop within that field. Multistep carcinogenesis describes a stepwise accumulation of alterations, both genotypic and phenotypic. Arresting one or several of those steps might impede or delay the development of cancer. Histologic assessment and intermediate markers of response are necessary to assess the validity of these therapies in a timely and cost-effective manner.

The concept of field carcinogenesis was originally described for the upper aerodigestive tract in the early 1950s.[2] The surface epithelium, or field, is chronically exposed to environmental carcinogens, predominantly tobacco smoke. Multifocal areas of cancer develop from multiple genetically distinct clones and lateral (intraepithelial) spread of genetically related preinvasive clones.[3] The hyperplastic and dysplastic changes found in areas of carcinogen-exposed epithelium adjacent to tumors are termed field carcinogenesis, and it is suggested that these multiple foci of premalignancy could progress to form multiple primary cancers (second primary tumors [SPTs]). Multifocal field carcinogenesis effects have been observed in head-and-neck, lung, esophagus, vulva, cervix, colon, breast, bladder, and skin cancers.[4-12] The pathologic observations in field carcinogenesis gave rise to the hypothesis of multistep carcinogenesis, which proposes that neoplastic changes evolve over time owing to the accumulation of somatic mutations in a single cell line, resulting in a phenotypic progression from normal to hyperplastic to dysplastic cells, and finally to fully malignant phenotypes.[12-14]

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Specific genes have been described that, when altered, might play a role in epithelial carcinogenesis. These include both tumor suppressor genes and proto-oncogenes, which encode proteins that are involved in cell-cycle control, signal transduction, and transcriptional regulation. Those alterations affect initiation, promotion, and progression of cancer. Initiation involves direct DNA binding and rapid irreversible damage by carcinogens. Promotion, which involves epigenetic mechanisms, leads to generally irreversible premalignancy. Progression, which is due to genetic mechanisms, is the period between premalignancy and manifest cancer and is generally irreversible. With rare exceptions, the stages of promotion and progression usually span decades after the initial carcinogenic exposure.

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Primary prevention strategies seek to prevent de novo malignancies in an otherwise healthy population. These individuals might have high-risk features, such as smoking history or particular genetic mutations predisposing to cancer development. Secondary prevention involves patients who have known premalignant lesions (eg, oral leucoplakia, colon adenomas) and attempts to prevent the progression of premalignant lesions into manifest cancer. Tertiary prevention focuses on the prevention of SPTs in patients cured of their initial cancer illness or individuals definitively treated for their premalignant lesions.

Chemoprevention trials are based on the hypothesis that interruption of the biological process involved in carcinogenesis will inhibit this process and, in turn, reduce cancer incidence. This hypothesis provides a framework for the design and evaluation of chemoprevention trials. It provides a rationale for the selection of agents that are likely to inhibit biological processes and for the development of intermediate markers associated with carcinogenesis. Intermediate markers are crucial for chemoprevention trials, and premalignant lesions are a potential source for intermediate markers. If disappearance of these lesions can be correlated with a reduction in cancer incidence, then markers of premalignancy might serve as intermediate endpoints for chemoprevention trials.

Bladder Cancer

Bladder cancer is the fourth most common cancer in the United States. In most cases, bladder cancer presents as a superficial transitional cell carcinoma that is easily resectable. However, high local recurrence rates have been observed (66% at 5 years and 88% at 15 years), and approximately 10% to 30% of cases will progress to invasive cancer.[15,16] Screening for bladder cancer requires cystoscopy and the use of urine tumor markers.[16] Risk factors for bladder cancer include cigarette smoking, low intake of vitamin A, infrequent consumption of milk and carrots, low consumption of cruciferous vegetables, low serum carotene and retinol levels, occupational exposure to aromatic amines

from rubber or paint, schistosomiasis, and chronic bladder infections. Bladder cancer might develop from a low-grade, high recurrent superficial papillary lesion or from a high-grade flat carcinoma in situ (CIS) lesion. In the initiation of low-grade tumors, abnormalities on chromosome 9 have been reported. For high-grade lesions, no gatekeeper candidate genes have been identified. The World Health Organization defined several categories for flat urinary bladder lesions: reactive atypia, atypia of unknown significance, dysplasia, and CIS. The classification is based on the growth pattern (papillary or flat) and cytologic and architectural changes. Dysplasia is considered a low-grade lesion and CIS a high-grade lesion.[17]

Various bladder cancer chemoprevention trials have focused on nutritional supplementation. (Table 1). In a primary prevention study, Shibata and colleagues[18] observed 11,580 retirement community residents who were cancer free at enrollment. At year 8 of follow-up, an inverse relationship between vitamin C supplement use and bladder cancer risk was seen. However, studies in retinoid and vitamin B6 therapy are conflicting. The National Bladder Cancer Collaborative Group A failed to prove a benefit in using 13-cis-retinoic acid (13cRA) in patients with rapid recurring bladder cancer.[19] Yet in other studies, etretinate, a synthetic retinoid, was shown to decrease recurrence rates and lengthen the mean time to tumor recurrence in superficial papillary bladder tumors.[20-22] A different study showed that N-(4-hydroxyphenyl) retinamide could reverse abnormal cytology in patients with suspicious or positive flow cytometry.[23] Vitamin B6 was reported to decrease tumor recurrence rates in patients with stage 1 bladder cancer; however, later trials did not show any benefit.[24] A combination of high doses of different vitamins was reported to have a beneficial effect on preventing superficial and low-grade bladder cancer recurrence.[25] Sixty-five patients with former bladder cancer were randomized to recommended daily allowance (RDA) multivitamins or RDA multivitamins plus 40,000 IU of vitamin A, 100 mg of vitamin B6, 2000 mg of vitamin C, 400 IU of vitamin E, and 90 mg zinc. Recurrence rates were 80% in the control arm, compared with 40% in the megavitamin arm ($P = .0011$).

An inverse relationship between vitamin C supplement use and bladder cancer risk was seen.

Bladder cancer chemoprevention trials demonstrate conflicting findings. Although some trials using vitamin C in healthy patients or megavitamins

Table 1
Selected Bladder Cancer Chemoprevention Trials

Author	Year	Patients (n)	Target Group	Target	Substances	Results
Byar et al[44]	1977	121	Prior stage I bladder cancer	Bladder cancer	Pyridoxine (25 mg)	Negative
National Bladder Cancer Collaborative Group[19]	1992	20	Prior T_{a-1} superficial bladder cancer	Bladder cancer	13cRA (0.51 mg/kg)	Negative
Shibata et al[18]	1992	11,580	Healthy elderly	Bladder cancer	Vitamin C (dietary)	Positive
Lamm et al[25]	1994	65	TCC bladder cancer receiving intravesical bacillus Calmette-Guérin	Bladder cancer	Vitamin A (40,000 IU), vitamin B6 (100 mg), vitamin C (2000 mg), vitamin E (400 IU), zinc (90 mg)	Positive
EORTC Genitourinary Cooperative Group[24]	1995	291	Prior T_{a-1} superficial bladder cancer	Bladder cancer	Pyridoxine (20 mg)	Negative
Studer et al[20]	1995	90	Prior T_{a-1} superficial bladder cancer	Bladder cancer	Etretinate (25 mg)	Positive

13cRA, 13-cis-retinoic acid; TCC, transitional cell carcinoma; EORTC, European Organization for Research and Treatment of Cancer.

and etretinate in the adjuvant setting showed positive effects, further confirmation is necessary before they can be accepted in daily clinical practice.

Dietary fat, soy protein, garlic, and selenium have been reported to possess anticancer properties in the bladder, but they still remain largely unstudied in vivo. Because nutritional supplementation failed to show definitive benefit, ongoing trials using targeted agents are under way. These include nonsteroidal anti-inflammatory drugs (NSAIDs), oltipraz (4-methyl-5-[2-pyrazinyl]-1,2-dithiole-3-thione), and difluoromethylornithine (DFMO).

Prostate Cancer

Prostate cancer is the most common cancer in men. The lifetime risk of developing prostate cancer is 19% in the United States. Risk factors include older age, positive family history, race and ethnicity, and high dietary fat intake.[26] Screening methods for prostate cancer include digital rectal examination (DRE) and prostate-specific antigen (PSA) measurement.[27]

Prostatic intraepithelial neoplasia (PIN) is an intraluminal proliferation of secretory cells of the prostate duct–acinar system and is considered a premalignant lesion.[28] Various genetic alterations in PIN and prostate cancer have been identified, for instance, gain of chromosome 7, loss of 8p, gain of 8q, and loss of 10q, 16q, and 18q.[26] Whereas the predictive value of low-grade PIN for malignancy is unclear, high-grade PIN is suspected to be the precursor to prostatic carcinoma. High-grade PIN also has a high predictive value for adenocarcinoma originating from the peripheral zone of the prostate.[29] For the transition zone, atypical adenomatous hyperplasia has been considered the premalignant lesion, but it is not well defined.

Vitamin A and its derivatives have been shown to be protective against various malignant tumors, but the data regarding prostate cancer are conflicting (Table 2).[30,31] Several studies show a statistically significant trend of increased prostate cancer risk associated with decreased serum retinol levels. Another trial reports that vitamin A does not have any benefit and might be harmful.[32,33] Vitamin D deficiency was reported to increase the risk of prostate cancer, and sunlight exposure is inversely proportional to prostate cancer mortality.[15,34,35]

Preclinical, epidemiologic, and phase III data from randomized, placebo-controlled clinical trials suggest that both selenium and vitamin E might be effective in prostate cancer prevention. Low plasma levels of vitamin E were related to an increased risk of prostate cancer.[36] The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study showed that men receiving vitamin E had a 34% lower incidence of prostate cancer during a 6-year period.[37,38] The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is the second large-scale study of chemoprevention for prostate cancer, with enrollment starting in 2001 and final results expected in 2013. It is a phase III, randomized, double-blind, placebo-controlled, population-based clinical trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer. Study duration is planned for 12 years, with a mini-

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Table 2
Selected Prostate Cancer Chemoprevention Trials

Author	Year	Patients (N)	Target Group	Target	Substances	Results
Prostate Cancer Prevention Trial[30]	2003	18,882	Male	Prostate cancer	Finasteride (5 mg)	Positive
McConnell et al[31]	2003	3,047	BPH	Progression of BPH	Doxazosin (4 mg or 8 mg); Finasteride (5 mg)	Positive
SELECT						
REDUCE						

BPH, benign prostatic hyperplasia.

mum of 7 and maximum of 12 years of intervention. The primary endpoint for SELECT is the clinical incidence of prostate cancer, as determined by a recommended routine clinical diagnostic workup including yearly DRE and serum PSA assay.

The Prostate Cancer Prevention Trial (PCPT) used finasteride, a type-2-specific 5α-reductase inhibitor. This trial randomized 18,882 men 55 years of age and older with normal DRE results and a PSA level of less than 3 ng/mL to finasteride and placebo for 7 years.[30,39,40] This trial reported a 24.4% prostate cancer incidence in the placebo arm, compared with 18.4% in the finasteride arm, and a reduction of 24.8% over 7 years ($P < .001$). In the finasteride-supplemented group, the detected prostate cancer lesions showed more aggressive Gleason grades (> 7). Moreover, more adverse sexual side effects were reported. Most evidence points to a histologic artifact, because it is known that finasteride induces histologic changes in the prostate.[41] The Gleason prostate cancer grading system is not considered valid after any hormonal treatment, including finasteride, because it seems to overestimate the assessment of high-grade cancer.[42] Therefore, finasteride intervention should be cautiously considered for primary prevention.

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial is assessing dutasteride, a dual inhibitor of type 1 and type 2 5α-reductase. Evidence suggests that there might be increased expression of the type 1 5α-reductase in prostate cancer versus benign prostatic tissue, making dutasteride an interesting agent to study. This 4-year, international, multicenter, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of daily oral dutasteride (0.5 mg) in men at increased risk of developing prostate cancer. The target enrollment is 8000 men, who will be randomized 1:1 to receive dutasteride or placebo for 4 years. Whereas the PCPT criteria included men older than 55 years, REDUCE includes men older than 50 years. For men aged less than 60 years, the PSA level required for enrollment in the study has been lowered to 2.5 ng/mL for REDUCE, compared with 3.0 ng/mL in PCPT. Results remain to be determined.[43]

Conclusion

The future of cancer chemoprevention depends on innovative trials. In addition, there is a specific need for emphasizing cancer prevention in public health policy. The continued study of tumor biology and natural history in controlled trials, focusing not only on efficacy endpoints but also on biologic markers in tissue and serum, will help to develop detailed risk models. Chemopreventive agents seem to be effective in several tumors, and they might play an important role in the future treatment and prevention of cancer in high-risk individuals. Moreover, chemopreventive agents might help to prevent SPTs. Further studies will be performed to define their role in preventing SPTs.

The future of cancer chemoprevention depends on innovative trials.

The aims of chemoprevention trials are to devise tumor-specific risk models for identifying high-risk patient groups, increase preclinical drug testing

Main Points

- Chemoprevention trials are based on the hypothesis that interruption of the biological process involved in carcinogenesis will inhibit this process and, in turn, reduce cancer incidence.
- Bladder cancer chemoprevention trials demonstrate conflicting findings; some trials using vitamin C in healthy patients or megavitamins and etretinate in the adjuvant setting showed positive effects, but further confirmation is necessary before they can be accepted in daily clinical practice.
- Dietary fat, soy protein, garlic, and selenium have been reported to possess anticancer properties in the bladder, but they still remain largely unstudied in vivo.
- Vitamin A and its derivatives have been shown to be protective against various malignant tumors, but the data regarding prostate cancer are conflicting; vitamin D deficiency was reported to increase the risk of prostate cancer, and sunlight exposure is inversely proportional to prostate cancer mortality.
- Preclinical, epidemiologic, and phase III data from randomized, placebo-controlled clinical trials suggest that both selenium and vitamin E might be effective in prostate cancer prevention.
- Finasteride intervention should be cautiously considered for primary prevention of prostate cancer.

models, develop translational mechanistic studies to produce novel chemopreventive agents, identify molecular alterations that can serve as surrogate endpoints, locate promising new targets of drug activity, and extend the study of already-existing candidate surrogate endpoint markers. The results of those trials will help physicians to have a meaningful impact on the survival of high-risk patients. ■

References

1. Sporn MB. Approaches to prevention of epithelial cancer during the preneoplastic period. *Cancer Res*. 1976;36:2699-2702.
2. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamos epithelium: Clinical implications of multicentric origin. *Cancer*. 1953;6:963-968.
3. Lippman SM, Hong WK. Molecular markers of the risk of oral cancer. *N Engl J Med*. 2001;344: 1323-1326.
4. Prevo LJ, Sanchez CA, Galipeau PC, Reid BJ. p53-mutant clones and field effects in Barrett's esophagus. *Cancer Res*. 1999;59:4784-4787.
5. Copper MP, Braakhuis BJ, De Vries N, et al. A panel of biomarkers of carcinogenesis of the upper aerodigestive tract as potential intermediate endpoints in chemoprevention trial. *Cancer*. 1993;71:825-830.
6. Franklin WA, Gazdar AF, Haney J, et al. Widely dispersed p53 mutation in respiratory epithelium. A novel mechanism of field carcinogenesis. *J Clin Invest*. 1997;100:2133-2137.
7. Chu TY, Shen CY, Lee HS, Liu HS. Monoclonality and surface lesion specific microsatellite alterations in premalignant and malignant neoplasia of uterine cervix: A local field effect of genomic instability and clonal evolution. *Genes Chromosomes Cancer*. 1999;24:127-134.
8. Jothy S, Slesak B, Harlozinska A, et al. Field effect of human colon carcinoma on normal mucosa: Relevance of carcinoembrionic antigen expression. *Tumour Biol*. 1996;17:58-64.
9. Fersti A, Louhelainen J, Soderberg M, et al. Loss of heterozygosity in tumour-adjacent normal tissue of breast and bladder cancer. *Eur J Cancer*. 2001;37:1372-1380.
10. Takahashi T, Habuchi T, Kakehi Y, et al. Clonal and chronological genetic analysis of multifocal cancers of the bladder and upper urinary tract. *Cancer Res*. 1998;58:5835-5841.
11. Stem RS, Bolshakov S, Nataraj AJ, Anastaswamy HN. p53 mutation in non-melanoma skin cancers occuring in psoralen ultraviolet-treated patients: Evidence for heterogeneity and field cancerization. *J Invest Dermatol*. 2002;119:522-526.
12. Braakhuis BJ, Tabor MP, Kummer JA, et al. A genetic explanation of Slaughter's concept of field cancerization: Evidence and clinical implications. *Cancer Res*. 2003;63:1727-1730.
13. Califano J, Leong PL, Koch WM, et al. Second esophageal tumors in patients with head and neck squamos cell carcinoma: An assessment of conal relationships. *Clin Cancer Res*. 199;5: 1862-1867.
14. Potter JD. Colorectal cancer: Molecules and populations. *J Natl Cancer Inst*. 1999;91:916-932.
15. Kamar AM, Lamm DL. Chemoprevention of urologic cancer. *J Urol*. 1999;161:1748-1760.
16. Sotan Y, Roehrborn CG. Sensitivity and specifity of commonly available bladder tumor markers versus cytology: Results of a comprehensive literature review and meta-analysis. *Urology*. 2003;81:109-118; discussion 118.
17. Amin MB, McKeney JK. An approach to the diagnosis of flat intraepithelial lesions of the urinary bladder using the World Health Organization/International Society of Urological Pathology concensus classification system. *Adv Anat Pathol*. 2002;9:222-232.
18. Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: A prospective study. *Br J Cancer*. 1992;66:673-679.
19. Prout GR Jr, Barton BA. 13-cis-retinoic acid in chemoprevention of superficial bladder cancer. The National Bladder Cancer Group. *J Cell Biochem Suppl*. 1992;16I:148-152.
20. Studer UE, Jenzer S, Biedermann C, et al. Adjuvant treatment with a vitamin A analogue (etretinate) after transurethral resection of superficial bladder tumors. Final analysis of a prospective, randomized multicenter trial in Switzerland. *Eur Urol*. 1995;28:284-290.
21. Yoshida O, Miyakawa M, Watanabe H, et al. Prophylactic effect of etretinate on the recurrence of superficial bladder tumors—results of a randomized controlled study [Japanese]. *Hinyokika Kiyo*. 1986;32:1349-1358.
22. Alfthan O, Tarkkanen J, Grohn P, et al. Tigason (etretinate) in prevention of recurrence of superficial bladder tumors. A double-blind clinical trial. *Eur Urol*. 1983;9:6-9.
23. Decensi A, Bruno S, Giaretti W, et al. Activity of 4-HPR in superficial bladder cancer using DANN flow cytometry as an intermediate endpoint. *J Cell Biochem Suppl*. 1992;161:139-147.
24. Newling DW, Robinson MR, Smith PH, et al. Tryptophan metabolites, pyridoxine (vitamin B6) and their influence on the recurrence rate of superficial bladder cancer. Results of a prospective, randomised phase III study performed by the EORTC GU Group. EORTC Genito-Urinary Tract Cancer Cooperative Group. *Eur Urol*. 1995;27: 110-116.
25. Lamm DL, Riggs DR, Shriver JS, et al. Megadose vitamins in bladder cancer: A double-blind clinical trial. *J Urol*. 1994;151:21-26.
26. Nelson WG, De Marzo AM, Isaaks WB. Prostate cancer. *N Engl J Med*. 2003;349:366-381.
27. Barry MJ. Clinical practice. Prostate specific antigen testing for early diagnosis of prostate cancer. *N Engl J Med*. 2001;344:1373-1377.
28. Montironi R, Mazzucchelli R, Algaba F, Lopez-Beltran A. Morphological identification of the patterns of prostatic intraepithelial neoplasia and their importance. *J Clin Pathol*. 2000;53: 655-665.
29. Davidson D, Bostwick DG, Qian J, et al. Prostatic intraepithelial neoplasia is a risk factor for adenocarcinoma: Predictive accuracy and needle biopsies. *J Urol*. 1995;154:1295-1299.
30. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349: 215-224.
31. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349:2387-2398.
32. Hayes RB, Bogdanovicz JF, Schroeder FH, et al. Serum retinol and prostate cancer. *Cancer*. 1988;62:2021-2026.
33. Hsing AW, McLaughlin JK, Schuman LM, et al. Diet, tobacco use and fatal prostate cancer: Results from the Lutheran Brotherhood Cohort Study. *Cancer Res*. 1990;50:6836-6840.
34. Polek TC, Weigel NL. Vitamin D and prostate cancer. *J Androl*. 2002;23:9-17.
35. Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Res*. 1990;10:1307-1311.
36. Eichholcer M, Stahelin HB, Gey KF, et al. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. *Int J Cancer*. 1996;66: 145-150.
37. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin B and beta-carotene on the incidence of lung cancer and other cancers of male smokers. *N Engl J Med*. 1996;330:1029-1035.
38. Albanes D, Heinonen OP, Huttunen JK, et al. Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Prevention Study. *Am J Clin Nutr*. 1995;62(6 suppl):14278-14308.
39. Thompson IM Jr, Kouril M, Klein EA, et al. The Prostate Cancer Prevention Trial: Current status and lessons learned. *Urology*. 2001;57(4 suppl): 230-234.
40. Coltman CA Jr, Thompson IM Jr, Feigl P. Prostate Cancer Prevention Trial (PCPT) update. *Eur Urol*. 1999;35:544-547.
41. Civantos F, Watson RB, Pinto JE. Finasteride effect on prostatic hyperplasia and prostatic cancer. *J Urol Pathol*. 1997;6:1-14.
42. Bostwick DG, Qian J, Civantos F, et al. Does finasteride alter the pathology of the prostate and cancer grading? *Clin Prostate Cancer*. 2004; 2:228-235.
43. Gomella LG. Chemoprevention using dutasteride: the REDUCE trial. *Curr Opin Urol*. 2005; 15:29-32.
44. Byar D, Blackard C. Comparisons of placebo, pyridoxine, and topical thiotepa in preventing recurrence of stage I bladder cancer. *Urology*. 1977;10:556-561.