Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 3-3

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Risk Reduction of Prostate Cancer with Drugs or Nutritional Supplements

N. Fleshner, N. Ivers, H. Lukka, B. Shayegan, C. Walker-Dilks, E. Winquist, and Members of the Genitourinary Cancer Disease Site Group

Report Date: May 17, 2012

An assessment conducted in November 2015 deferred the review of Evidence-based Series (EBS) 3-3, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-Based Series (EBS) 3-3 consists of 3 sections:
Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

EBS 3-3 is available on the CCO website (http://www.cancercare.on.ca)
PEBC Genitourinary Cancer Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-ebs/.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Citation (Vancouver Style): Fleshner N, Ivers N, Lukka H, Shayegan B, Walker-Dilks C, Winquist E, et al. Risk reduction of prostate cancer with drugs or nutritional supplements. Toronto (ON): Cancer Care Ontario; 2012 May 17. Program in Evidence-based Care Evidence-Based Series No.: 3-3.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 3-3: Section 1

Risk Reduction of Prostate Cancer with Drugs or Nutritional Supplements: Guideline Recommendations

N. Fleshner, N. Ivers, H. Lukka, B. Shayegan, C. Walker-Dilks, E. Winquist, and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 17, 2012

QUESTION

In patients without a diagnosis of prostate cancer, how effective are drugs or nutritional supplements in reducing the risk of prostate cancer and prostate cancer-related death? Lifestyle modification and population screening strategies were not reviewed.

TARGET POPULATION

Men older than or equal to 18 years of age who are being assessed and monitored for prostate cancer.

INTENDED USERS

Urologists, oncologists specializing in genitourinary cancers, primary care practitioners, and the general public.

RECOMMENDATION 1

In men who are being assessed and monitored for prostate cancer, it is reasonable to offer 5-alpha-reducatase inhibitor (5-ARI) therapy if:

1. They are ≥50 years of age with a normal prostate-specific antigen (PSA) level or,
2. They have an elevated PSA level (2.5 to 10 ng/mL) and a negative result on prostate biopsy or,
3. They have moderately symptomatic benign prostatic hyperplasia (BPH),

in order to reduce the risk of needing definitive treatment for prostate cancer.

Men who meet these criteria should discuss the pros and cons of this option with their physician. 5-ARI therapy is not being recommended on a population-wide scale.

Qualifying Statements

- It is important for the user to recognize that the recommendation simply urges that it is worth a conversation about the use of 5-ARI therapy between a man (who meets the above criteria) and his physician.
- It is important to acknowledge that the recommendations received mixed reviews from clinicians who participated in the external review of this document (see Section 3).
- The user must consider their view of what constitutes "worthwhile" cancer risk reduction when reading this recommendation. Ideally, drugs effective for prostate cancer risk reduction would be offered only to individuals at high risk for fatal forms of the disease. Currently, such knowledge is lacking, and so different perspectives on the value and application of imperfect drugs such as 5-ARIs is expected. Three perspectives are of specific relevance. First, as none of the randomized controlled trials (RCTs) of 5-ARI therapy reported any reduction in overall or prostate cancer-specific mortality, 5-ARI therapy must be considered an unproven intervention from this perspective. Second, as two large RCTs of 5-ARI therapy both reported a small but real increase in higher grade prostate cancers, 5-ARI therapy could be considered ineffective from the perspective of the "first do no harm" principle. A third perspective argues that the observation of more high-grade cancers is due to detection artefacts not 5-ARI therapy. This guideline recommendation offers an alternative perspective that the value of drug therapy for prostate cancer risk reduction should consider the contemporary clinical context. 5-ARI therapy may be worthwhile to reduce prostate cancer risk in a clinical context where case finding is routine due to screening; aggressive anticancer treatment (with uncertain benefits and certain risks) is routinely pursued by and offered to patients; and uncertainties regarding the safety and efficacy of more conservative approaches such as surveillance remain. From this perspective, the recommendation considers the current risk of being "overtreated" for prostate cancer as easily exceeding the small risk associated with developing a high-grade (and still potentially curable) cancer due to 5-ARI therapy.
- The Genitourinary Disease Site Group (GU DSG) recognizes the challenge of weighing this complex set of benefits and risks for each patient. Formal decision aids would be useful to help patients and providers make shared, informed decisions on the use of 5-ARIs for the reduction of prostate cancer. A decision aid on the use of finasteride is available from the American Society for Clinical Oncology: providers and patients may benefit from using this until a revised version is developed that includes all the data synthesized in this review (http://www.asco.org/ASCO/Downloads/Cancer%20Policy%20and%20Clinical%20Affairs/Clinical%20Affairs%20(derivative%20products)/5%20ARI/5ARI%20discussion%20guide%2012.3.08.pdf)
- 5-ARI therapy has been shown to reduce the risk of less aggressive prostate cancer (pooled number needed to treat [NNT] for detection of one less prostate cancer during the period of the studies=18), but not to reduce prostate cancer mortality or overall mortality. Currently, many men with slower progressing prostate cancer are treated with surgery or radiotherapy even though such treatment may not be necessary. The GU DSG highly values reducing the number of men treated in this aggressive manner and, therefore, considers the above recommendation reasonable. If the ability and willingness to precisely identify and observe men with biologically indolent prostate cancers emerges in the future, these recommendations would need to be re-evaluated.
- 5-ARI chemoprevention for men without benign prostatic hyperplasia (BPH) should only be considered for those who have initially decided to pursue regular monitoring for prostate cancer development, with the PSA test based on an informed choice regarding risks and

benefits, and for those who are committed to ongoing monitoring. The NNT to prevent detection of one case of prostate cancer was higher in this group (NNT=94). Although the optimal monitoring schedule for men receiving 5-ARI therapy to reduce their risk of prostate cancer is uncertain, evidence from the Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trials suggests that they should visit their clinic every six to 12 months for PSA and digital rectal examination (DRE) testing and assessment of medical symptoms and side effects. A low threshold for prostate biopsy in the presence of rising PSA, abnormal DRE, or clinical concerns of the treating physician is appropriate.

- The optimal 5-ARI regimen and duration of therapy are uncertain. In the primary RCTs considered, finasteride 5.0 mg orally (po) daily was given for a planned seven years and dutasteride 0.5 mg po was given daily for four years.
- The expected NNT in clinical practice will likely be much higher, as the diagnosis of prostate cancer in men without BPH was usually made by protocol-mandated prostate biopsy and not for suspicion of prostate cancer.
- Potential recipients of 5-ARI therapy should be well informed about the potential risks. There may be a small increased risk of high-grade prostate cancer with 5-ARI therapy. The pooled number needed to harm for high-grade (Gleason score 8 to 10) prostate cancer for the two RCTs was 134 (95% confidence interval [CI], 77 to 293). Alternatively, this could represent a detection bias related to a more effective detection of these cancers in men on 5-ARIs. Nevertheless, the magnitude of this risk, if real, is likely outweighed by the benefits of avoiding overtreatment for biologically insignificant prostate cancer, especially given that these men should be closely monitored.
- As the risk of sexual dysfunction increases with age as well as with 5-ARI therapy, sexual dysfunction rates may be perceived to be higher in clinical practice than when reported in the RCTs. Men should be explicitly asked about such side effects and the risk-benefit ratio of 5-ARI therapy reconsidered if sexual dysfunction is concerning to the patient.
- 5-ARI chemoprevention is inappropriate in men with limited life expectancy and/or substantial comorbid conditions for whom definitive treatment of prostate cancer would not be pursued.

Key Evidence

- Two RCTs (44,000 person years of exposure) with a pooled relative risk reduction for local, biopsy-confirmed prostate cancer of 23% (95% CI, 18 to 27) and NNT of 18 (95% CI, 15 to 23) (1,2).
  - One RCT comparing finasteride, 5 mg/day (d), with placebo (n=18,882) showed a relative risk reduction of 25% (95% CI, 19 to 31) in the period prevalence of prostate cancer over seven years, with an NNT of 17 (95% CI, 13 to 23). Removing those diagnosed by protocol-mandated biopsy from analysis resulted in a relative risk reduction of 10% (95% CI, 0.09 to 19) and an NNT of 34 (95% CI, 17 to 4,202). (1).
  - One RCT comparing dutasteride, 0.5 mg/d with placebo (n=8,231) showed a relative risk reduction of 23% (95% CI, 15 to 30) in the incidence of prostate cancer over four years, with an NNT of 20 (95% CI, 15 to 32) (2).
- Meta-analysis of six trials (n=12,857) comparing 5-ARIs with placebo/non-5-ARIs in men with BPH showed a relative risk reduction of 29% (95% CI, 8 to 46) in the period prevalence of prostate cancer, with an NNT of 104 (95% CI, 66 to 375) (3-8).

RECOMMENDATION 2
Vitamin E and selenium should not be used to reduce prostate cancer risk.

Key Evidence

- One RCT (n=35,533) showed an increased risk of prostate cancer with vitamin E alone at a median of seven years of follow-up (hazard ratio [HR], 1.17; 99% CI, 1.004 to 1.36) (9).
- A statistically nonsignificant increase in the risk of prostate cancer was seen with selenium alone (HR, 1.09; 99% CI, 0.93 to 1.27) and vitamin E plus selenium (HR, 1.05; 99% CI, 0.89 to 1.22) (9).
    - One RCT (n=14,641) showed no benefit from vitamin E in reducing prostate cancer risk (HR, 0.97; 95% CI, 0.85 to 1.09) and an increased risk of stroke (HR, 1.74; 95% CI, 1.04 to 2.91) (10).

FUTURE RESEARCH

This review identified supplemental calcium, nonsteroidal antiandrogens and green tea catechins to be of potential interest for further study in prostate cancer risk reduction.

PLAIN LANGUAGE SUMMARY

After skin cancer, prostate cancer is the most common cancer in men. It is a leading cause of death in men in Western countries. There were an estimated 24,600 new cases and 4300 deaths due to prostate cancer in Canada in 2010. Approximately 60% of men over 60 years of age will have prostate cancer to some extent. It is very difficult to predict accurately, but the vast majority of men who are diagnosed with prostate cancer will never have symptoms. Many men will die of other causes even if they have prostate cancer. With increased awareness and the use of screening for early detection, more men are being treated for early-stage prostate cancer. Such treatment may involve radiation and/or surgery for removal of the prostate. This often causes unwanted urinary incontinence and sexual side effects.

Because of this, reducing the risk of prostate cancer has become of interest. Scientific studies ranging from the use of oral drugs to engaging in healthy lifestyles have been conducted. The GU DSG looked at the highest scientific evidence available worldwide on the subject of prevention of prostate cancer through the use of drugs or nutritional supplements. We have concluded from numerous clinical trials that the use of certain drugs may slightly reduce the risk of prostate cancer, whereas nutritional supplements provide no benefit. We suggest therefore, that men interested in reducing their risk of prostate cancer and willing to adhere to active monitoring may consider the use of drugs called 5-ARIs (e.g., finasteride, dutasteride) taken for four to seven years. The risks and benefits of longer term treatment with these drugs are unclear.

GLOSSARY OF TERMS (definitions from MedlinePlus)

5-alpha-reductase inhibitor (5-ARI)	5-alpha-reductase is the enzyme responsible for conversion of circulating testosterone to dihydrotestosterone (DHT), which causes prostate epithelial proliferation. Inhibition of 5-alpha-reductase decreases the amount of DHT in prostate cancer tissue, thereby lowering androgenic stimulation to the prostate.
Alpha-tocopherol (Vitamin E)	Vitamin E is an antioxidant that helps protect the body from the effects of free radicals. Free radicals are substances that can damage the body's cells. Free radicals may increase the risk for heart disease and cancer.
Benign prostatic hyperplasia (BPH)	Enlarged prostate. It is common for the prostate gland to become enlarged as a man ages. Doctors call this condition benign prostatic hyperplasia (BPH), or benign prostatic hypertrophy. The enlarged prostate places pressure on the urethra. The bladder starts to contract even when it contains small amounts of urine, causing more frequent urination. Other symptoms include the sensation that the bladder is not empty, urgency to urinate, having to strain to start urination, or the need to stop and start urinating several times.
Beta-carotene	Beta-carotene is one of a group of red, orange, and yellow pigments called carotenoids. Beta-carotene and other carotenoids provide approximately 50% of the dietary vitamin A needed.
Dutasteride	Dutasteride belongs to a class of medications called 5-ARIs. It works by blocking the production of a natural substance that enlarges the prostate. This shrinks the prostate, relieves symptoms of BPH, such as frequent and difficult urination, and decreases the chance that surgery will be needed to treat this condition.
Finasteride	Finasteride belongs to a class of medications called 5-ARIs. Finasteride treats BPH by blocking the body's production of a male hormone that causes the prostate to enlarge.
Flutamide	Flutamide is in a class of medications called nonsteroidal antiandrogens. It works by blocking the effects of androgen (a male hormone) to stop the growth and spread of cancer cells.
Gleason score	The Gleason grade indicates how aggressive the prostate cancer might be. It grades tumours on a scale of 1 to 5, based on how different from normal tissue the cells are. Often, more than one Gleason grade is present within the same tissue sample. The Gleason grade is used, therefore, to create a Gleason score by adding the two most predominant grades together (a scale of 2 to 10). The higher the Gleason score, the

	more likely the cancer is to have spread beyond the prostate gland: Scores 2 - 4: Low-grade cancer Scores 5 - 7: Intermediate- (or in the middle-) grade cancer. Most prostate cancers fall into this category. Scores 8 - 10: High-grade cancer (poorly differentiated cells).
High-grade intraepithelial neoplasia (HGPIN)	A prostatic pre-malignancy; a common precursor to prostate cancer. The incidence, extent, and volume of HGPIN increase with patient age. HGPIN is detected by biopsy.
Prostate specific antigen (PSA)	Prostate-specific antigen (PSA) is a protein produced by cells of the prostate gland. The PSA test measures the level of PSA in the blood. The PSA test is done to help diagnose and follow prostate cancer in men. There is no specific normal or abnormal PSA level. In addition, various factors, such as inflammation (e.g., prostatitis), can cause a man's PSA level to fluctuate. It is also common for PSA values to vary somewhat from laboratory to laboratory. Consequently, one abnormal PSA test result does not necessarily indicate the need for a prostate biopsy. In general, however, the higher a man's PSA level, the more likely it is that cancer is present.
Selenium	Selenium is an essential trace mineral. Small amounts of selenium are good for health. It helps make special proteins, called antioxidant enzymes, that play a role in preventing cell damage.
Toremifene	A first-generation selective estrogen-receptor modulator (SERM). Like tamoxifen, it is an estrogen agonist for bone tissue and cholesterol metabolism but is antagonistic on mammary and uterine tissue. In the prostate, toremifene blocks estrogen receptors.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Contact Information

For further information about this report, please contact:
Dr. Neil Fleshner, Head, Division of Urology
University Health Network and Princess Margaret Hospital
Phone: 416-946-2899 Fax: 416-946-6590 E-mail: neil.fleshner@utoronto.ca

For information about the PEBC and the most current version of all reports, please visit:
the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003 Jul 17;349(3):215-24.
2. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al; REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 2010 Apr 1;362(13):1192-202.
3. Andriole GL, Roehrborn C, Schulman C, Slawin KM, Somerville M, Rittmaster RS. Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia. Urology. 2004 Sep;64(3):537-43.
4. Andriole GL, Guess HA, Epstein JI, Wise H, Kadmon D, Crawford ED, et al. Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: results of a randomized, double-blind, placebo-controlled clinical trial. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Urology. 1998 Aug;52(2):195-202.
5. Gormley GJ, Stoner E, Bruskewitz RC, Imperato-McGinley J, Walsh PC, McConnell JD, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. N Engl J Med. 1992 Oct 22;327(17):1185-91.
6. Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. The Finasteride Study Group. Prostate. 1993;22(4):291-9.
7. Nickel JC, Fradet Y, Boake RC, Pommerville PJ, Perreault JP, Afridi SK, et al. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. CMAJ. 1996 Nov 1;155(9):1251-9.
8. Roehrborn CG, Andriole GL, Wilson TH, Castro R, Rittmaster RS. Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostates in the combination of avodart and tamsulosin trial. Eur Urol. 2011 Feb;59(2):244-9.
9. Klein EA, Thompson IM, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011 Oct 12;306(14):1549-56.
10. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2009 Jan 7;301(1):52-62.