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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

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Section 1:   Guideline Recommendations
Section 2:   Evidentiary Base
Section 3:   EBS Development Methods and External Review Process
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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

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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.

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Risk Reduction of Prostate Cancer
with Drugs or Nutritional Supplements:
Evidentiary Base

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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.

INTRODUCTION

Prostate cancer is the most common non-dermatologic malignancy and the third leading cause of cancer death in males in Western countries. There were an estimated 24,600 new cases and 4,300 deaths due to prostate cancer in Canada in 2010 (1). Prostate cancer is associated with a long latency of disease, late-age onset, and a high incidence rate (2). Prostate cancer has a low mortality rate relative to the incidence rate. The discordance between histologic incidence and death leads to overdiagnosis and overtreatment, making disease prevention an attractive alternative (3). The prevention of prostate cancer is a recent health intervention, with studies not performed until the late 1980s. Many candidate agents were identified in hypothesis-generating studies or from secondary analyses of clinical trials in which the incidence of prostate cancer was not an a priori outcome. This systematic review gathers the evidence on the effectiveness of drugs or supplements in reducing the risk of prostate cancer by collecting randomized controlled trials (RCTs) or systematic reviews containing RCTs in which drugs or nutritional supplements are evaluated and prostate cancer is an outcome.

In considering this topic, the authors acknowledge that recommendations for preventative strategies must be based on the highest levels of evidence, taking into account the fact that large numbers of otherwise well individuals will be potentially exposed to the adverse effects of therapy. The authors also acknowledge that the question of prostate

cancer screening remains controversial, and coupled with many of the studies quoted herein, but is a topic outside the scope of this guideline.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (4). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Genitourinary Disease Site Group (GU DSG) and one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on prostate cancer prevention. The body of evidence in this review is primarily comprised of systematic reviews and mature RCTs. That evidence forms the basis of the recommendations developed by the GU DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

A literature search was performed to identify published studies specifically addressing the prevention of prostate cancer. Searches were run in MEDLINE (1950 to 17 October 2011), EMBASE (1980 to 17 October 2011), and the Cochrane Library (April 2011). Relevant abstracts were searched in the conference proceedings of the American Society of Clinical Oncology (ASCO), the American Urological Association (AUA), and the European Association of Urology for the past three years. Relevant practice guidelines, technology assessments, and systematic reviews were searched in the U.S. National Guideline Clearinghouse, the U.K. National Institute for Health and Clinical Excellence, the Canadian Partnership Against Cancer - Cancer Guidelines Resource Centre, CMA Infobase, and the U.K. National Institute for Health Research - Health Technology Assessment Programme. Reference lists of relevant articles were scanned, and experts in the field were consulted.

Study Selection Criteria

The literature searches were designed to retrieve English-language systematic reviews, meta-analyses, RCTs, and clinical practice guidelines that evaluated drugs or nutritional supplements for the prevention of prostate cancer. RCTs had to include 50 or more patients. Systematic reviews and meta-analyses had to include a detailed description of the review methods (literature search, study selection, and data extraction) in the text of the article and one or more RCTs meeting the above criteria. Studies of healthy volunteers and patients at risk for prostate cancer (e.g., patients with high-grade prostatic intraepithelial neoplasia [HGPIN]) were eligible for inclusion.

Studies and reviews were excluded if the outcome was recurrence of prostate cancer. Studies were also excluded if the intervention focused on diet modification or healthy lifestyle (e.g., consumption of foods rich in certain vitamins or minerals, exercise, other non-drug interventions) rather than on taking specific drugs or supplements.

All studies identified by the literature search were assessed against the selection criteria by three reviewers (CW, NF, and EW). Discrepancies regarding eligibility were resolved by consensus.

Quality Appraisal

The methodological quality of the eligible studies was assessed by the same three reviewers. The Assessment of Multiple Systematic Reviews (AMSTAR) tool was applied to

evaluate the systematic reviews. The RCTs were examined with respect to indicators of methodological rigour, including random allocation, allocation concealment, blinding, handling of patient withdrawals and dropouts, and intention-to-treat analysis.

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument was applied to any clinical practice guidelines that met the inclusion criteria (5). The AGREE Instrument evaluates the process of practice guideline development and the quality of reporting. The SAGE Inventory of Cancer Guidelines (http://www.cancerguidelines.ca/Guidelines/inventory/index.php) was checked because AGREE II scores are included for all guidelines in the inventory. The Inventory of Cancer Guidelines is a searchable database of over 1,100 English language cancer control guidelines and standards released since 2003, developed and maintained by the Canadian Partnership Against Cancer's Capacity Enhancement Program.

Synthesizing the Evidence

When two or more trials provided appropriate data on outcomes of interest, statistical pooling using meta-analysis was done using Review Manager software (RevMan 5.1) (6) provided by the Cochrane Collaboration. A random effects model was used for all pooling, because it provides a more conservative estimate. Pooled results are expressed as relative risks (RRs) with 95% confidence intervals (CIs). An RR of less than one favours the drug/supplement, and an RR of greater than one favours the placebo or control intervention.

RESULTS
Literature Search Results

Appendix 1 contains a summary of the search strategies conducted in MEDLINE and EMBASE, and Appendix 2 provides a flow chart of the search process. The search of literature databases, conference proceedings, and other sources yielded 91 citations that were considered relevant. After reviewing the full text of the relevant papers, 56 articles were excluded, resulting in 35 articles meeting the inclusion criteria: one practice guideline, 13 systematic reviews, and 21 RCTs (16 full publications and five abstracts).

The 13 systematic reviews encompassed 32 reports of 25 RCTs (Appendix 3). The literature search identified an additional 21 articles. From all literature sources, there were 53 reports representing 35 RCTs. When multiple reports of the same study were available, we included the most recent or most complete report.

We found the studies meeting the inclusion criteria fell into two distinct groups with respect to their objectives: studies that focused directly on the prevention of prostate cancer, and studies in which prostate cancer incidence was a secondary outcome. We also recognized that, in studies of interventions for cancer prevention in otherwise well persons, it is especially important that the adverse effects of the intervention be identified with precision. This can only be accomplished by very large randomized placebo-controlled trials in which exposure to the intervention and follow-up are prolonged. We decided that clinical recommendations should only be made on the basis of such very large trials with a primary endpoint of prostate cancer mortality or risk reduction. To define these trials, we chose >10,000 person-years of exposure to agent, crudely calculated by multiplying the median intervention exposure time by the number of patients exposed for prostate cancer prevention in otherwise healthy men; and >1,000 person-years of exposure similarly calculated for prostate cancer prevention in men with HGPIN (who are at a higher risk of developing prostate cancer). RCTs that met the above criteria are discussed in detail below. In the absence of other mitigating data, trials not meeting these criteria could only inform hypotheses for further study in larger trials, and these are described in less detail in a supplementary studies section beginning on page 19.

Study Design and Quality

The practice guideline (7) was included in the Inventory of Cancer Guidelines, and the AGREE II scores are in Appendix 4.

The quality of the 13 systematic reviews was assessed using the AMSTAR tool (8). Appendix 5 shows how each of the 13 systematic reviews and meta-analyses scored on each of the 11 AMSTAR items (9-21).

None of the systematic reviews addressed all the agents of interest, and few included studies with prostate cancer as a primary outcome. Thus, the RCTs identified are mostly discussed individually, regardless of whether they were included in a systematic review. One trial in abstract form had a discrepancy in the results and thus will not be discussed further (22).

The remaining trials were categorized based on whether prostate cancer risk reduction was a primary or non-primary study outcome. The methodological quality attributes of the 34 RCTs are in Appendices 6a and 6b.

Study Characteristics

Four RCTs met the revised criteria to inform recommendations (23-26). Of these large RCTs, two evaluated hormonal agents (5-ARIs) (23,24), and two evaluated nutritional supplements (vitamin E and/or selenium) (25,26). One clinical practice guideline (7) that was identified also evaluated hormonal agents. The study characteristics for these trials are shown in Table 1. The Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial had protocol-mandated biopsies for the detection of prostate cancer (23,24). The detection of prostate cancer in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) and Physicians' Health Study (PHS) II was based on information from medical records (25,26).

Table 1. Study characteristics of RCTs with the primary outcome of prostate cancer risk reduction.

Study (ref)	Patient characteristics	Comparison	Number of male patients	Patient age	Follow-up period	Method of detection of prostate cancer
Hormonal Agents						
PCPT (23)	Men ≥55 y with normal DRE, no significant coexisting conditions, and AUA symptom score <20	Finasteride (5 mg/d) vs. placebo	18,882	55 to 59 y: 31% 60 to 64 y: 31% ≥65 y: 38%	7 y	Clinical suspicion & end-of-study protocol-mandated biopsy
REDUCE (24)	Men >50 y, elevated PSA, & previous suspicion of prostate cancer leading to biopsy	Dutasteride (0.5 mg/d) vs. placebo	8231	Mean 63 y	4 y	Protocol-mandated biopsies after 2 and 4 y of treatment
Nutritional Supplements						
SELECT (25)	Men >50 y, PSA ≤4 ng/mL & DRE not suspicious for cancer	Selenium (200 µg/d), vitamin E (400 IU/d), placebo (factorial)	35,533	Median 63 y	Median 7 y	Self report & medical records
PHS II (26) (Vitamin E vs. placebo comparison)	7641 men from PHS I plus 7000 additional U.S. male physicians	Vitamin E (400 IU every other day), vitamin C (500 mg/d), placebo (factorial)	14,641	Mean 64 y	Median 7.6 y Mean 8.0 y 117,711 person-y of follow-up	Medical records

An additional 11 RCTs had a primary endpoint of prostate cancer risk reduction but were considered to be of insufficient sample size (27-37). In another 20 RCTs, prostate cancer risk reduction was not the primary endpoint (26,38-56). In the PHS II study, the comparison of vitamin E versus placebo had a primary outcome of prostate cancer risk reduction, while for the comparison of vitamin C versus placebo, prostate cancer was a secondary outcome (26). Thus, this trial is included in both the primary and non-primary prostate cancer outcome RCTs. In total, of these 31 RCTs (11 trials with primary outcomes but small sample size and 20 non-primary outcome trials), 11 evaluated hormonal agents (27-34,38-40), six evaluated nonhormonal agents (41-46), and 14 evaluated nutritional supplements (26,35-37,47-56). Because of their smaller size or lack of prostate cancer as the primary outcome, these 31 RCTs individually were considered to provide an insufficient basis for guideline recommendations but were considered of value for hypothesis generation and support for future confirmatory RCTs. They are reviewed, synthesized, and discussed separately from the four large, primary endpoint studies (Supplementary Studies section).

Study Outcomes
Prostate Cancer Risk Reduction
The results of the four large primary endpoint prostate cancer prevention RCTs are shown in Table 2.

Table 2. Results of RCTs with the primary outcome of prostate cancer risk reduction.

Study (ref)	Comparison: number of patients	Patient follow-up	Outcome		
Hormonal Agents					
PCPT (23)	Finasteride: 9423 Placebo: 9459	86.3%	Prevalence of prostate cancer over 7 y: Finasteride: 803/4368 (18.4%) Placebo: 1147/4692 (24.4%) RRR 24.8% (95% CI, 18.6 to 30.6), p<0.001 NNT 17 (95% CI, 13 to 23) Prostate cancer detected for cause: Finasteride: 435/1639 (26.5%) Placebo: 571/1934 (29.5%) NNT 34 (95% CI, 17 to 4202)		
REDUCE (24)	Dutasteride: 3305 Placebo: 3424	6729/8231 (82%)	Incidence of prostate cancer over 4 y: Dutasteride: 659/3305 (19.9%) Placebo: 858/3424 (25.1%) Restricted crude rate (all men with ≥1 biopsy after baseline): RRR 22.8% (95% CI, 15.2 to 29.8) NNT 20 (95% CI, 15 to 32)		
Nutritional Supplements					
SELECT (25)	Selenium + vitamin E: 8863 Selenium + placebo: 8910 Vitamin E + placebo: 8904 Placebo + placebo: 8856	30,490/35,533 (86%)	Diagnosis of prostate cancer at 7 y: Selenium + vitamin E: 555/8702 (6.4%) Selenium + placebo: 575/8752 (6.6%) Vitamin E + placebo: 620/8737 (7.1%) Placebo + placebo: 529/8696 (6.1%) Cumulative incidence		

Cumulative incidence:

Comparison	HR (99% CI)	p
Vit E vs. plac	1.17 (1.004 to 1.36)	0.008
Sel + vit E vs. plac	1.05 (0.89 to 1.22)	0.46
Sel vs. plac	1.09 (0.93 to 1.27)	0.18

Study (ref)	Comparison: number of patients	Patient follow-up	Outcome
PHS II (26)	Vitamin E + C: 3656 Vitamin E + placebo: 3659 Vitamin C + placebo: 3673 Placebo + placebo: 3653	13 983/14,641 (96%)	Vitamin E + C: 238/3497 (6.8%) Vitamin E + plac: 255/3486 (7.3%) Vitamin C + plac: 270/3509 (7.7%) Plac + plac: 245/3491 (7.0%) Vitamin E vs. placebo: 9.1 vs. 9.5 pr ca cases per 1000 person-y; HR, 0.97 (95% CI, 0.85 to 1.09); p=0.58

HR=hazard ratio; NNT=number needed to treat; PCPT=Prostate Cancer Prevention Trial; PHS=Physicians' Health Study; plac=placebo; pr ca=prostate cancer; REDUCE=Reduction by Dutasteride of Prostate Cancer Events; RRR=relative risk reduction; sel=selenium; SELECT=Selenium and Vitamin E Cancer Prevention Trial; vs.=versus; y=year.

Hormonal Agents

Androgens play an important role in prostate cancer. Androgens not only help to maintain the normal secretory and metabolic function of the prostate, but may also contribute to the development of prostate cancer and BPH. The enzyme 5-alpha-reductase is responsible for converting circulating testosterone to localized dihydrotestosterone (DHT), the androgen that causes prostate epithelial growth. The inhibition of 5-alpha-reductase reduces the levels of DHT in prostate tissue. Finasteride, a 5-ARI, blocks the type II isoenzyme of 5-alpha-reductase, and dutasteride blocks type I and type II receptors (57).
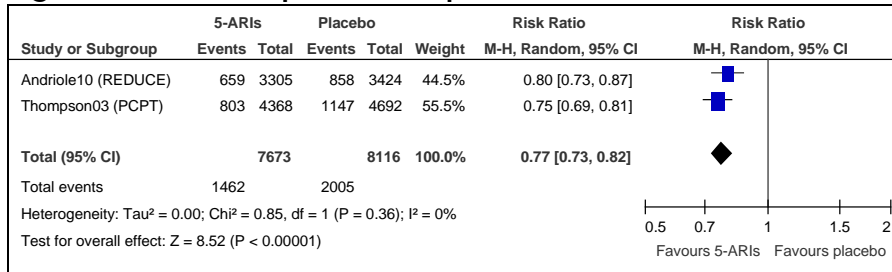
In the PCPT, 18,882 men aged 55 years or more with a normal DRE and PSA level ≤3.0 ng/mL were randomized to finasteride 5 mg/d or placebo for seven years (23). The men received annual PSA and DRE testing. A biopsy was triggered by a significant increase in PSA or an abnormal DRE result (for-cause biopsy). Prostate cancer was diagnosed by biopsy either for cause (51.6%) or at the end of the study (48.4%). The study was terminated early because the primary objective had been met. Prostate cancer was detected in 18.4% of men in the finasteride group and 24.4% of men in the placebo group (24.8% reduction in prevalence over 7 years [95% CI, 18.6 to 30.6], p<0.001). The finasteride and placebo groups did not differ for overall mortality (7.0% vs. 6.7%); five in each group died from prostate cancer.

In the REDUCE study, 6,729 men aged 50 to 75 years with a PSA level of 2.5 to 10 ng/mL and a negative prostate biopsy within six months of enrolment were randomized to dutasteride, 0.5 mg/d, or placebo for four years (24). The men were seen every six months for measurement of their PSA and International Prostate Symptom Score. All the men had biopsies after two and four years of treatment. For-cause biopsies were performed as clinically indicated by the treating physician. Prostate cancer was detected in 19.9% of men in the dutasteride group and 25.1% of men in the placebo group (22.8% reduction in prevalence over 4 years [95% CI, 15.2 to 29.8], p<0.001). The risk of prostate cancer was lower with dutasteride across all prespecified major subgroups, including age (<65 to ≥65 y), presence or absence of family history of prostate cancer, baseline PSA (<4.9, 4.9 to <6.8, ≥6.8 ng/mL), baseline prostate volume (<36.6, 36.6 to <51.8, ≥51.8 mL), baseline International Prostate Symptom Score (<8 or ≥8), and body mass index (<25.5, 25.5 to <28.4, or ≥28.4). There was no difference between the dutasteride and placebo groups for overall mortality (1.7% vs. 1.9%, p=0.65). There were no prostate cancer-related deaths.

We believed that the PCPT and REDUCE trials were similar enough in population (i.e., sufficient overlap of patient characteristics), intervention (drug class), and outcome (biopsy diagnosis of prostate cancer) to justify pooling them in a meta-analysis. The meta-analysis of these two large primary studies of prostate cancer prevention showed a 23% decrease in the risk of prostate cancer with 5-ARIs (pooled number needed to treat [NNT] 18, 95% CI, 15 to 23) (Figure 1). It is noteworthy that in the PCPT trial, the rate of biopsy performed for clinical suspicion was reduced from 24.8% to 22.5% (p<0.001) with finasteride (23). Similarly, in

REDUCE, the number of protocol-independent biopsies was reduced from 13.6% to 10.4% (p<0.001) with dutasteride (24).

Figure 1. 5-ARIs vs. placebo for prostate cancer overall.

	5-ARIs		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andriole10 (REDUCE)	659	3305	858	3424	44.5%	0.80 [0.73, 0.87]	
Thompson03 (PCPT)	803	4368	1147	4692	55.5%	0.75 [0.69, 0.81]	
Total (95% CI)		7673		8116	100.0%	0.77 [0.73, 0.82]	
Total events	1462		2005				
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%							
Test for overall effect: Z = 8.52 (P < 0.00001)							

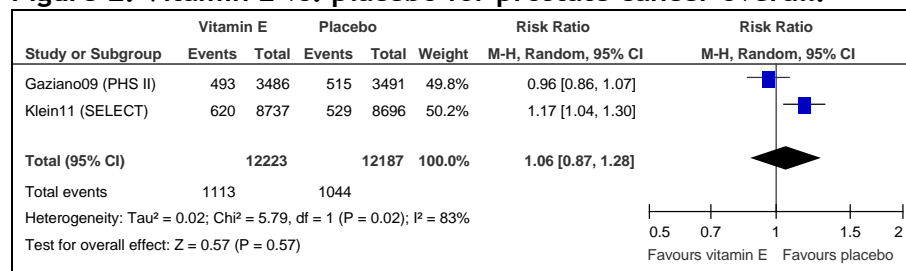Favours 5-ARIs Favours placebo

Nutritional Supplements

The SELECT study evaluated selenium and vitamin E on the risk of prostate and other cancers using a factorial design (25). The study recruited 35,533 men 55 years of age or greater (≥50 y if African-American) with no previous prostate cancer diagnosis. The SELECT trial was terminated at the second interim analysis, meeting the criteria for stopping because the expected reduction in prostate cancer was not observed. At median follow-up of 5.46 years, selenium or vitamin E, alone or in combination, did not prevent prostate cancer. The five-year rates of prostate cancer in the selenium, vitamin E, selenium plus vitamin E, and placebo groups were 4.56%, 4.93%, 4.56%, and 4.43%, respectively. Compared with placebo, the hazard ratios (HRs) for prostate cancer with selenium, vitamin E, and selenium plus vitamin E were 1.04 (95% CI, 0.90 to 1.18, p=0.62); 1.13 (95% CI, 0.99 to 1.29, p=0.06); and 1.05 (95% CI, 0.91 to 1.20, p=0.52), respectively (58). Participant follow-up continued for a median of seven years, with 54,464 additional person-years of follow-up since the 2009 report (25). This longer term follow-up showed a statistically significant increase in risk of prostate cancer with vitamin E (HR, 1.17; 95% CI, 1.004 to 1.36; p=0.008). The risk associated with selenium was slightly increased but statistically nonsignificant (HR, 1.09; 95% CI, 0.93 to 1.27; p=0.18). The risk associated with selenium and vitamin E combined was similar to the previous time frame (HR, 1.05; 95% CI, 0.89 to 1.22; p=0.46). The HRs for death with selenium, vitamin E, and selenium + vitamin E were 0.98 (99% CI, 0.84 to 1.14), 1.01 (99% CI, 0.86 to 1.17), and 0.96 (99% CI, 0.82 to 1.12), respectively.

The PHS II was a placebo-controlled factorial study evaluating vitamins E and C in the prevention of prostate and total cancer in 1,641 U.S. male physicians (26). Only vitamin E was studied with prostate cancer risk reduction as a primary endpoint. There was no effect of vitamin E on the incidence of prostate cancer (9.1 vs. 9.5 events per 1000 person-year; HR, 0.97; 95% CI, 0.85 to 1.09; p=0.58). There was no significant effect of vitamin E on total mortality (HR, 1.08; 95% CI, 0.98 to 1.19) or prostate-specific cancer mortality (HR, 1.01; 95% CI, 0.64 to 1.58).

The SELECT and PHS II studies were considered sufficiently similar in patient characteristics and intervention to combine in a meta-analysis. Meta-analysis of the primary studies evaluating vitamin E showed a statistically nonsignificant increase in the risk of prostate cancer (RR, 1.06; 95% CI, 0.87 to 1.28) (Figure 2).

Figure 2. Vitamin E vs. placebo for prostate cancer overall.

Study or Subgroup	Vitamin E Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gaziano09 (PHS II)	493	3486	515	3491	49.8%	0.96 [0.86, 1.07]
Klein11 (SELECT)	620	8737	529	8696	50.2%	1.17 [1.04, 1.30]
Total (95% CI)		12223		12187	100.0%	1.06 [0.87, 1.28]
Total events	1113		1044			

Heterogeneity: Tau² = 0.02; Chi² = 5.79, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.57 (P = 0.57)

Risk Ratio M-H, Random, 95% CI — Favours vitamin E Favours placebo (scale 0.5 0.7 1 1.5 2)

Adverse Effects

Hormonal Agents

Endocrine and Genitourinary Effects

5-ARIs have been used for many years for the treatment of benign prostatic hypertrophy (BPH), and their toxicity profile is well known and quite favourable. Nonetheless well-documented adverse effects have been noted (Table 3).

In the PCPT, men who received finasteride reported more adverse sexual functioning or endocrine effects, while adverse genitourinary effects were more common in the placebo group (23).

The REDUCE trial reported less overall serious adverse events for patients treated with dutasteride compared with placebo (18.2% vs. 20.3%, p=0.02). Dutasteride reduced the risk of acute urinary retention, the need for surgery for BPH, and urinary tract infection. Urinary symptoms were also improved. However, any drug-related adverse events were higher with dutasteride (22.0% vs. 14.6%, p<0.001) (24).

Table 3. Rates of adverse effects in the PCPT and REDUCE trials.

	PCPT (23)			REDUCE (24)		
	Finasteride	Placebo	p-value	Dutasteride	Placebo	p-value
Sexual and endocrine effects						
Erectile dysfunction	67.4%	61.5%	<0.001	9.0%	5.7%	<0.001
Loss of libido	65.4%	59.6%	<0.001	1.9%	1.3%	0.03
Reduced volume of ejaculate	60.4%	47.3%	<0.001	-	-	-
Decreased semen volume	-	-	-	1.4%	0.2%	<0.001
Gynecomastia	4.5%	2.8%	<0.001	1.9%	1.0%	0.002
Genitourinary effects						
BPH	5.2%	8.7%	<0.001	-	-	-
BPH-related surgery	-	-	-	1.4%	5.1%	<0.001
Urinary retention	4.2%	6.3%	<0.001	1.6%	6.7%	<0.001
Urinary tract infection	1.0%	1.3%	<0.001	5.3%	8.8%	<0.001

BPH=benign prostatic hyperplasia; PCPT=Prostate Cancer Prevention Trial; REDUCE=Reduction by Dutasteride of Prostate Cancer Events.

Risk of High-Grade Prostate Cancer

The PCPT trial showed an overall reduction in prostate cancer with finasteride, but when results were examined by Gleason score, the possibility existed of an increased risk of high-grade prostate cancer (23). Examination of the trial results by histologic grade resulted in the observation that finasteride had the greatest effect in preventing lower grade cancers (Gleason score ≤6). High-grade tumours (Gleason score 7 to 10) were more common in men who were allocated to finasteride than to placebo (6.4% vs. 5.1%; RR, 1.67; 95% CI, 1.44 to 1.93) (Table 4). This observation raised the possibility that finasteride could actually cause high-grade tumours and created concern over the use of finasteride for prostate cancer prevention.

Table 4. Rates for prostate cancer by Gleason score in the PCPT trial (23).

Gleason score	All cancers		Cancers diagnosed in for-cause biopsies		Cancers diagnosed in end-of-study biopsies	
	Finasteride (757)*	Placebo (1068)*	Finasteride (393)*	Placebo (504)*	Finasteride (364)*	Placebo (564)*
2 to 6	477 (63%)	831 (78%)	205 (52%)	356 (71%)	272 (75%)	475 (84%)
7	190 (25.1%)	184 (17.2)	118 (30.0%)	103 (20.4%)	72 (19.8%)	81 (14.4%)
7 to 10	280 (37%)	237 (22.2%)	188 (47.8%)	148 (29.4%)	92 (25.3%)	89 (15.8)
	280/4368† (6.4%)	237/4692† (5.1%)	188/1639† (11.5%)	148/1934† (7.7%)	92/3652† (2.5%)	89/3820† (2.3%)
8 to 10	90 (11.9%)	53 (5.0%)	70 (17.8%)	45 (8.9%)	20 (5.5%)	8 (1.4%)
	90/4368† (2.1%)	53/4692† (1.1%)	70/1639† (4.3%)	45/1934† (2.3%)	20/3652† (0.5%)	8/3820† (0.2%)
Not graded	46	79	42	67	4	12

*Denominator is number of graded tumours.
†Denominator is number of men in the analysis.

Histologic grade was also assessed in the REDUCE study (24). Over the four years of treatment, there were 437 tumours in the dutasteride group and 617 tumours in the placebo group, with Gleason scores of 5 to 6 (p<0.001). The number of tumours with Gleason scores of 7 to 10 did not differ between the dutasteride and placebo groups (220 vs. 233, p=0.81). There was also no difference between dutasteride and placebo at Gleason scores of 8 to 10 (29 vs. 19, p=0.15). The dutasteride and placebo groups did not differ for the number of tumours at Gleason score 8 to 10 during the first two years (17 vs. 18). However, during years 3 and 4, there were 12 such tumours in the dutasteride group compared with one in the placebo group (p=0.003). Furthermore, a post hoc U.S. Food and Drug Administration (FDA)-mandated re-analysis of the REDUCE Gleason score distribution, utilizing the modified Gleason scoring system (the system used in PCPT), revealed a statistically significant increased risk of high-grade tumours (Gleason score 8 to 10) among men randomized to dutasteride (59) (Table 5).

Table 5. Rates for prostate cancer by Gleason score in the REDUCE trial (24).

Gleason score	Years 1 to 2			Years 3 to 4			Years 1 to 4		
	Dutasteride (3239)	Placebo (3346)	p-value	Dutasteride (2247)	Placebo (2343)	p-value	Dutasteride (3299)	Placebo (3407)	p-value
5 to 6	290 (9%)	401 (12%)	<0.001	147 (6%)	216 (9.2%)	<0.001	437 (13.2%)	617 (18.1%)	<0.001
7	127 (3.9%)	157 (4.7%)		64 (2.6%)	57 (2.4%)		191 (5.8%)	214 (6.3%)	
7 to 10	144 (4.4%)	175 (5.2%)	0.15	76 (3.1%)	58 (2.5%)	0.19	220 (6.7%	233 (6.8%)	0.81
8 to 10	17 (0.5%)	18 (0.5%)	1.00	12 (0.5%)	1 (<0.1%)	0.003	29 (0.9%)	19 (0.6%)	0.15

Gleason score	Years 1 to 2			Years 3 to 4			Years 1 to 4		
All tumours	434 (13.4%)	576 (17.2%)		223 (9.1%)	274 (11.7%)		657 (19.9%)	850 (24.9%)	
8 to 10 revised*							32/3284 (1.0%)	16/3388 (0.5%)	0.02

*FDA-mandated reanalysis (59).

Meta-analysis of the PCPT and REDUCE studies using the FDA-mandated reanalysis data for REDUCE showed a significant increase in the risk of high-grade prostate cancer (pooled number needed to harm [NNH] 134, 95% CI, 77 to 293) (Figure 3). When a Gleason score of 7 was included, the difference was no longer statistically significant (Figures 4 and 5).

Figure 3. 5-ARIs vs. placebo for high-grade prostate cancer (Gleason score 8 to 10).
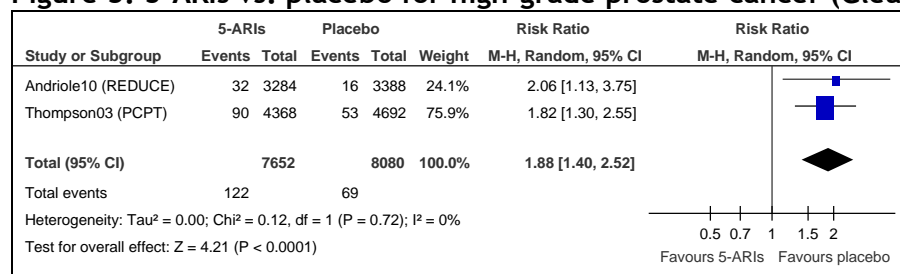
Figure 4. 5-ARIs vs. placebo for high-grade prostate cancer (Gleason score 7 to 10).
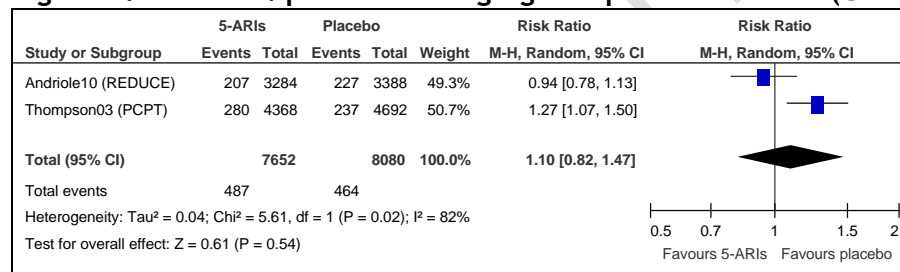
Figure 5. 5-ARIs vs. placebo for high-grade prostate cancer (Gleason score 7).
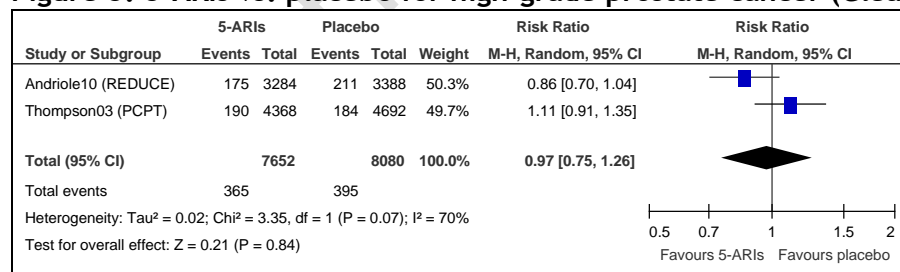
As well as reanalyzing the biopsy specimens in the REDUCE trial using the modified Gleason scores, the FDA review addressed the possibility of detection bias as a reason for the increase in high-grade prostate cancer with 5-ARIs. One explanation was that 5-ARIs reduce serum levels of PSA, thus leading to an increase in the detection of high-grade prostate cancer with 5-ARIs. However, it was observed in the FDA review that an increased risk of high-grade tumours occurred in analyses of scheduled biopsies not triggered by PSA results, arguing against a detection bias pertaining to PSA. Another explanation was that 5-ARIs reduce

prostate volume, enabling core needle biopsies to detect more high-grade cancer in smaller prostates because of increased sampling density. The FDA reanalysis adjusted for prostate volume using a modified Gleason score of 8 to 10 as the definition for high grade, using logistic regression analyses and the Peters-Belson method, and concluded that increased sampling density was not responsible for the increased incidence of high-grade tumours. Despite the post hoc exploratory logistic regression analysis bordering on statistical insignificance (odds ratio for Gleason 8-10: 1.51 [95% CI, 1.01–2.26]), the FDA concluded that finasteride and dutasteride did not have a favourable risk–benefit profile for the use of chemoprevention of prostate cancer in healthy men (60).

Nutritional Supplements

In the SELECT study, most prostate cancers diagnosed were early stage and low grade. There were no major toxicities. Mild alopecia and dermatitis, known side effects of selenium, were more commonly seen in the selenium group than in the placebo group. The RR for alopecia was 1.28 (99% CI, 1.01 to 1.62; p<0.01) and for grade 1 to 2 dermatitis was 1.17 (99% CI, 1.00 to 1.35; p<0.01) (25). A small statistically nonsignificant increase in diabetes mellitus occurred in the selenium group (RR, 1.07; 99% CI 0.94 to 1.22; p=0.16) at median of 5.5 years of follow-up (58); at seven years the relative risk was 1.04 (99% CI, 0.93 to 1.17; p=0.34) (24).

In the PHS II study, a greater number of hemorrhagic strokes occurred in patients allocated to vitamin E than to placebo (HR, 1.74; 95% CI, 1.04 to 2.91; p=0.04) (26).

DISCUSSION

Four large RCTs had prostate cancer risk reduction as the primary outcome (23-26). One study evaluating vitamin E, selenium, and vitamin E plus selenium showed a significantly increased risk of prostate cancer with vitamin E alone after a median of seven years of follow-up (25). Vitamin E may also be associated with increased risk for stroke (26). Selenium did not reduce the risk of prostate cancer (25).

With respect to 5-ARIs, it appears that both finasteride and dutasteride have a similar ability to reduce the risk of biopsy-detected prostate cancer (relative risk reduction, 23%; NNT, 18; 95% CI, 15 to 23) in men without prostate cancer (23,24). Neither trial showed differences in overall or prostate-specific mortality. Endocrine and sexual side effects were modestly increased. Urinary problems related to BPH were somewhat decreased. No treatment-related deaths were reported. Similar results were seen with these drugs in smaller RCTs studying men with BPH when combined in meta-analysis (RR, 0.71; 95% CI, 0.54 to 0.92; p=0.01) (See Supplementary Studies, Figure 6); therefore, it is quite reasonable to generalize these effects to this group of men also who are often treated with these drugs for BPH symptoms.

The practice guideline by Kramer et al (7), a collaboration of ASCO and the AUA, addressed the use of 5-ARIs for the chemoprevention of prostate cancer. The guideline was based on expert consensus supported by clinical evidence. The primary source of evidence was a Cochrane systematic review by Wilt et al on the role of 5-ARIs in the chemoprevention of prostate cancer (13). The Expert Panel reviewed all the data from the primary studies identified in the systematic review and the results of the meta-analyses contained in the systematic review. A meta-analysis of the trials that contributed data to the evaluation of for-cause prostate cancer showed a 26% relative risk reduction with 5-ARIs and a similar reduction for prostate cancer detected overall. The meta-analysis combined smaller or non-primary endpoint studies with the larger primary endpoint study (23,27-29,38-40).

With respect to the question of whether men should routinely be offered a 5-ARI for the chemoprevention of prostate cancer, the ASCO/AUA practice guideline advised that "asymptomatic men with a PSA ≤3.0 who are regularly screened with PSA or are anticipating

undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of the benefits of 5-ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer) to be able to make a better-informed decision" (7). Since the publication of the ASCO/AUA guideline, the REDUCE trial (24) has been published and reports results with dutasteride in men with elevated PSA levels (5 to 10 ng/mL) and negative prostate biopsies that are consistent with the results of the PCPT.

The evidence from large RCTs supports the use of 5-ARIs to reduce the risk of biopsy-detected prostate cancer (Gleason score ≤6). The PCPT trial supports this approach for men 55 years of age or older with a normal PSA level (23). The REDUCE trial shows similar results for men 50 years of age or older with a PSA elevation of ≤10 ng/mL and a negative prostate biopsy (24).

An increased risk of high-grade prostate cancer was observed in both the PCPT and the REDUCE trials, but considerable debate exists regarding the significance of this observation. It may relate to true biologic change or to systematic bias and may be harmful or possibly beneficial. Benefit is certainly possible as 5-ARIs may contribute to the earlier detection of a pre-existing occult high-grade cancer by reducing the normal prostate volume and consequently improving the reliability of PSA monitoring and/or increasing the diagnostic accuracy of prostate biopsy (61,62). In the PCPT trial, 6.4% of men in the finasteride group and 5.1% of men in the placebo group had a tumour with a Gleason score of 7, 8, 9, or 10 (NNH=77). In the REDUCE trial, using the reassessed tumour grade data, 6.3% of men in the dutasteride group and 6.7% of men in the placebo group had a tumour with a Gleason score of 7, 8, 9, or 10 (NNT=250).

As most of the biopsies in these RCTs were protocol driven and not done for clinical reasons, it is also likely that the underestimation of the NNT could occur when generalizing to usual practice. Furthermore, most of the prostate cancers prevented were low grade.

The absolute increase in patient-reported sexual dysfunction rates with 5-ARIs was small in comparison with placebo and similar with both drugs. However, it is possible that the perceived rates of sexual dysfunction may be higher in clinical practice. In real-world clinical practice, however, these adverse effects are reversible; thus patients who experience them would not continue on active treatment.

As no differences were seen in prostate cancer death rates, it is unclear whether chemoprevention using 5-ARIs is superior to a strategy of early detection using PSA screening alone for preventing prostate cancer death. In fact, since there is controversy over the benefits of population-wide screening by monitoring PSA, it is unclear whether 5-ARIs are superior to no intervention at all for mortality. However, in the present practice environment, prostate cancer biology cannot be easily predicted, and clinically diagnosed prostate cancer is frequently (over)treated with aggressive management options. Therefore, a strategy of chemoprevention that reduces unnecessary cancer treatment (i.e., surgery and radiotherapy) for biologically indolent prostate cancers may lead to a reduction in the overtreatment of clinically insignificant prostate cancers. Future research that explicitly examines such outcomes would contribute much to the literature and would provide clinicians and their patients with the ability to make better-informed decisions about using 5-ARIs for the prevention of prostate cancer. In the interim, we believe that patients who have made an informed decision to screen and who are committed to active monitoring for the development of cancer would benefit from a shared decision-making process with their provider to weigh the potential risks and benefits. Formal decision aids have been shown to help patients and providers in making shared, informed decisions (63). A decision aid is available from ASCO (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);

providers and patients may benefit from using this until a revised version is developed that includes all data synthesized in this review.

SUPPLEMENTARY STUDIES

As noted above, a set of post hoc criteria were developed to differentiate between studies with greater and lesser reliability with respect to determining the effect of the intervention on the prevention of prostate cancer. Studies that met these criteria are described in detail above. In this section, the studies that did not meet these criteria (e.g., they did not have prostate cancer as a primary endpoint, their sample size was lower than the criteria stipulated) are described in less detail.
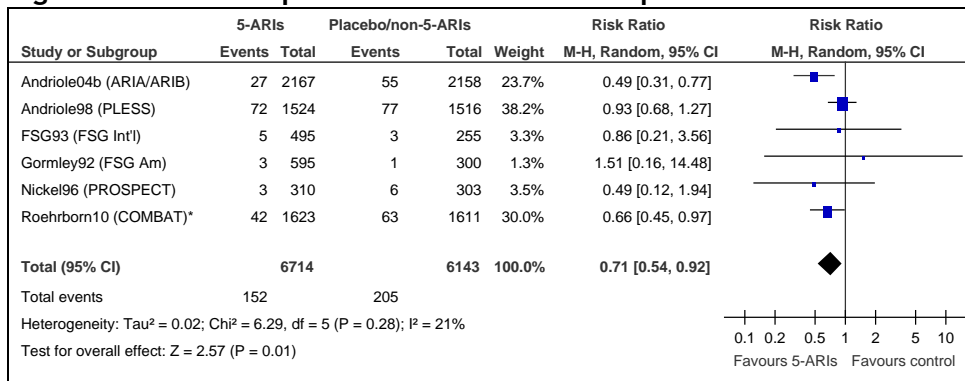
A total of 31 RCTs studied prostate cancer risk as a non-primary endpoint (20 trials) or were considered to have insufficient sample size (11 trials). Eleven RCTs studied hormonal agents, six studied nonhormonal agents, and 14 studied nutritional supplements. Appendix 7 details the study characteristics for these trials. Eleven of these studies had protocol-mandated biopsies for the detection of prostate cancer (27,28,30-32,34-37,40).

Hormonal Agents

Of 11 RCTs evaluating hormonal agents, seven RCTs studied 5-ARIs (27-29,33,38-40), and six of these included men with BPH only (27,29,33,38-40). BPH is a common prostatic condition that increases with age. It is identified on DRE and characterized by an enlarged prostate with or without associated bothersome lower urinary tract symptoms. Of two studies that evaluated the effectiveness of dutasteride, one showed a significant reduction compared with placebo at 27 months (1.2% vs. 2.5%, p=0.002) (29), and one showed a reduction compared with tamsulosin at four years (2.6% vs. 3.9%, p=0.021) (33). Two trials from the Finasteride Study Group assessed the effect of finasteride at two different dosages on men with BPH. The rates of prostate cancer at one year in both studies were low: in the American study of 895 men, there were four cases of prostate cancer (two in the 1 mg group, one in the 5 mg group, and one in the placebo group) (38), and in the international study of 750 men, there were eight cases of prostate cancer (one in the 1 mg group, four in the 5 mg group, and three in the placebo group) (39). The PROscar Safety Plus Efficacy Canadian Two-year study compared finasteride with placebo for two years in 613 men with BPH. Prostate cancer was diagnosed in three of 310 men in the finasteride group and six of 303 men in the placebo group (40). The Proscar Long-Term Efficacy and Safety Study (PLESS) randomized 3,040 men with BPH to finasteride or placebo and showed no difference in the detection of prostate cancer at four years (4.7% vs. 5.1%, p=0.7) (27). A small study comparing finasteride and placebo in 58 men with elevated PSA showed an increase in prostate cancer at 12 months with finasteride (30% vs. 4%, p=0.025) (28).

The meta-analysis of these six trials showed a reduction in the risk of prostate cancer (RR, 0.71; 95% CI, 0.54 to 0.92) (Figure 6). Although prostate cancer incidence is a secondary endpoint in these BPH studies, this result is consistent with the results of the PCPT (23) and REDUCE (24) trials in men without BPH. Therefore, it seems reasonable to generalize the results of these larger trials to patients with BPH.
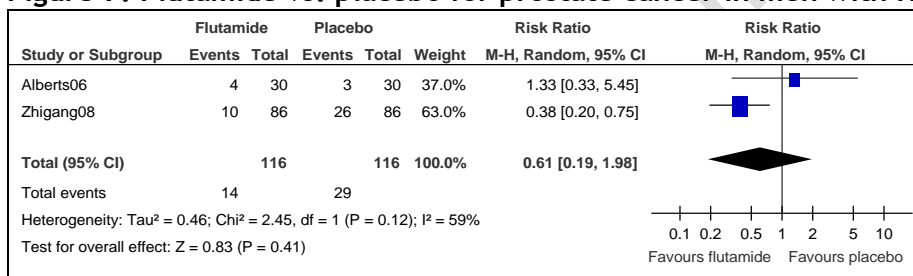
Figure 6. 5-ARIs vs. placebo or non-5-ARIs for prostate cancer in men with BPH.

Study or Subgroup	5-ARIs Events	Total	Placebo/non-5-ARIs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Andriole04b (ARIA/ARIB)	27	2167	55	2158	23.7%	0.49 [0.31, 0.77]	
Andriole98 (PLESS)	72	1524	77	1516	38.2%	0.93 [0.68, 1.27]	
FSG93 (FSG Int'l)	5	495	3	255	3.3%	0.86 [0.21, 3.56]	
Gormley92 (FSG Am)	3	595	1	300	1.3%	1.51 [0.16, 14.48]	
Nickel96 (PROSPECT)	3	310	6	303	3.5%	0.49 [0.12, 1.94]	
Roehrborn10 (COMBAT)*	42	1623	63	1611	30.0%	0.66 [0.45, 0.97]	
Total (95% CI)		6714		6143	100.0%	0.71 [0.54, 0.92]	
Total events	152		205				
Heterogeneity: Tau² = 0.02; Chi² = 6.29, df = 5 (P = 0.28); I² = 21%							
Test for overall effect: Z = 2.57 (P = 0.01)							

0.1 0.2 0.5 1 2 5 10
Favours 5-ARIs   Favours control

*The control group in COMBAT received tamsulosin. All other studies were placebo-controlled.

Two small RCTs studied flutamide in men with HGPIN (31,32). HGPIN is a premalignant lesion, and patients with HGPIN have an increased risk of prostate cancer. Alberts et al showed no difference between flutamide and placebo in progression to prostate cancer at one year (14% vs. 10%, p=0.71) (31). Zhigang et al showed a significant reduction in prostate cancer with flutamide compared with placebo at five years (11.6% vs. 30.2%, p=0.0027) (32). The meta-analysis of these two studies showed a nonsignificant reduction of prostate cancer (RR, 0.61; 95% CI, 0.19 to 1.98) (Figure 7).

Figure 7. Flutamide vs. placebo for prostate cancer in men with HGPIN.

Study or Subgroup	Flutamide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Alberts06	4	30	3	30	37.0%	1.33 [0.33, 5.45]	
Zhigang08	10	86	26	86	63.0%	0.38 [0.20, 0.75]	
Total (95% CI)		116		116	100.0%	0.61 [0.19, 1.98]	
Total events	14		29				
Heterogeneity: Tau² = 0.46; Chi² = 2.45, df = 1 (P = 0.12); I² = 59%							
Test for overall effect: Z = 0.83 (P = 0.41)							

0.1 0.2 0.5 1 2 5 10
Favours flutamide   Favours placebo

One dose-finding RCT compared three doses of toremifene with placebo in men with HGPIN (30). The 12-month incidence of prostate cancer was lowest in men receiving 20 mg of toremifene compared with placebo (9.1% versus [vs.] 17.4%, p=0.045). The 40 mg and 60 mg doses were also associated with lower incidences of prostate cancer, but the differences were not statistically significant (14.3% and 13.0%, respectively, vs. 17.4%). The definitive phase III trial in 1,590 men showed no benefit in terms of prostate cancer-free survival (p=0.385) (34).

Adverse Effects of Hormonal Agents

Two trials reported higher rates of ejaculatory disorders with finasteride than with placebo (38,40), and three reported higher rates of impotence (38-40). One trial reported higher rates of gynecomastia and diarrhea with flutamide (31).

Four trials reported results broken down by Gleason score. No significant differences were observed for proportions of patients with a Gleason score ≥7 receiving dutasteride versus tamsulosin (33), dutasteride versus placebo (29), or toremifene versus placebo (30). The PLESS trial stated that the distributions of Gleason scores in the finasteride and placebo groups were similar to each other (27).

Nonhormonal Agents

The six non-hormonal trials evaluated statins compared with placebo and were contained in a systematic review (14). The trials addressed the cholesterol-lowering effects of statins, but site-specific cancers including prostate cancer were among the secondary outcomes in all six RCTs. None of the trials used a protocol-driven biopsy to determine prostate cancer. One trial evaluated lovastatin (41), one trial evaluated fluvastatin (43), two trials evaluated pravastatin (42,46), and two trials evaluated simvastatin (44,45). Meta-analysis of the six RCTs showed a nonsignificant increase in the incidence of prostate cancer with the use of statins (RR, 1.06; 95% CI, 0.93 to 1.20).

Nutritional Supplements

14 RCTs studied nutritional supplements (26,35-37,47-56).

Selenium

Two RCTs compared selenium with placebo (36,50). The Nutritional Prevention of Cancer trial randomized 1,312 adults with a history of basal cell or squamous cell carcinoma of the skin to selenium or to placebo. Duffield-Lillico et al reported on the secondary outcome of prostate cancer at a mean follow-up of 7.5 years and showed a protective effect of selenium supplementation on the risk of prostate cancer (HR, 0.48; 95% CI, 0.28 to 0.80; p=0.005) (50). Marshall et al randomized 423 men with HGPIN to selenium or placebo for three years and showed no difference between groups (35.6% vs. 36.6%; p=0.73) (36). In view of the results of the SELECT trial (25), these studies are not considered further.

Vitamin E

Two RCTs compared vitamin E (alpha-tocopherol) with placebo (49,53). The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) study was a factorial trial evaluating the effect of alpha-tocopherol and beta–carotene supplementation on the incidence of lung cancer and other cancers in men 50 to 69 years of age who smoked (49). At a six-year post-intervention follow-up assessment of cancer incidence, the risk of prostate cancer did not differ between men receiving alpha–tocopherol compared with nonrecipients (RR, 0.88; 95% CI, 0.76 to 1.03). The Heart Outcomes Prevention Evaluation (HOPE) trial and HOPE-The Ongoing Outcomes extension trial evaluated whether long-term vitamin E supplementation decreased the risk of cancer, cancer death, and cardiovascular events in men and women with vascular disease or diabetes mellitus (53). At a median follow-up of 7.2 years in the extension trial, there was no effect of vitamin E on prostate cancer (RR, 0.90; 95% CI, 0.68 to 1.19; p=0.46). As with selenium, these studies are superseded by the SELECT trial (25) and the PHS II vitamin E versus placebo comparison (26).

Vitamin C

The PHS II studied vitamin C with prostate cancer as a secondary outcome and showed no effect on prostate cancer risk reduction (HR, 1.02; 95% CI, 0.90 to 1.15; p=0.80) (26).

Beta–Carotene

Two RCTs compared beta-carotene with placebo (47,49). In the ATBC trial, the risk of prostate cancer did not differ between men receiving beta–carotene compared with nonrecipients (RR, 1.06; 95% CI, 0.91 to 1.23) (49). In the PHS I trial, beta-carotene had no effect on the risk of prostate cancer (RR, 1.0; 95% CI, 0.9 to 1.1; p=0.62) (47). Meta-analysis was not done due to the unavailability of raw data.

Calcium

Calcium supplementation was studied in one RCT. The Calcium Polyp Prevention Study evaluated the effect of calcium supplementation on the risk of recurrent colorectal adenomas. In a post-treatment follow-up, the secondary outcome of prostate cancer was assessed and showed a nonsignificant reduction in prostate cancer risk with calcium over the 10-year study period (rate ratio, 0.83; 95% CI, 0.52 to 1.32) (52).

Folic Acid

The Aspirin/Folate Polyp Prevention study evaluated folic acid supplementation with or without aspirin on the risk of recurrent colorectal adenomas. Prostate cancer was assessed as a secondary outcome (54). The probability of being diagnosed with prostate cancer over a 10-year period was substantially higher in the folic acid group than in the placebo group (9.7% vs. 3.3%; HR, 2.63; 95% CI, 1.23 to 5.65; p=0.01).

Green Tea

In a proof-of-principle study, Bettuzzi et al evaluated the effectiveness of green tea catechins in reducing the risk for prostate cancer among 60 men with HGPIN (35). At one year, one man was diagnosed with prostate cancer in the green tea group compared with nine men in the placebo group (3.3% vs. 30%; RR, 0.11; 95% CI, 0.02 to 0.61; p<0.01).

Ginkgo Biloba

The Ginkgo Evaluation of Memory study assessed the effectiveness of Ginkgo biloba in the prevention of dementia in men and women 78 years of age or over. A secondary analysis reported the rates of hospitalizations for cancer (56). Twenty-seven men who received Ginkgo biloba were hospitalized for prostate cancer compared with 36 men who received placebo (HR, 0.71; 95% CI, 0.43 to 1.17; p=0.18).

Combination

Combinations of nutritional supplements were compared with placebo in four RCTs (37,48,51,55). Fleshner et al randomized 303 men with HGPIN to a combination of soy protein, vitamin E, and selenium, or placebo for three years. There was no difference between groups for the primary endpoint of development of invasive prostate cancer (HR, 1.03; 95% CI, 0.67 to 1.60; p=0.88) (37). The Carotene and Retinol Efficacy Trial found no association of the combination of retinyl palmitate (vitamin A) and beta–carotene (plus at least one other self-reported dietary supplement) and the risk of prostate cancer during an 11-year intervention period (RR, 1.26; 95% CI, 0.96 to 1.64) or an additional nine-year active follow-up period (RR, 0.89; 95% CI, 0.71 to 1.11) (55). An adjunct study to the Supplémentation en Vitamines et Minéraux Antioxydants primary prevention trial reported whether supplementation with nutritional doses of antioxidant vitamins and minerals could reduce the incidence of prostate cancer (51). A nonsignificant reduction in prostate cancer was observed in men allocated to a supplement containing vitamin C, alpha-tocopherol, beta-carotene, selenium, and zinc compared with placebo at a median of nine years (HR, 0.88; 95% CI, 0.60 to 1.29). The Medical Research Council/British Heart Foundation Heart Protection Study compared a combination of vitamin E, vitamin C, and beta–carotene with placebo in 20,536 persons with high risk for death from heart disease (48). The groups did not differ for the secondary outcome of prostate cancer (1.8% vs. 2.0%; p=0.4).

Adverse Effects of Nutritional Supplements

Three trials evaluating nutritional supplements included data on Gleason score (36,37,52). None of the trials showed a difference between treatment and placebo groups by Gleason score.

Discussion

We found several studies meeting minimal inclusion criteria for this systematic review in terms of evaluating drugs or supplements with prostate cancer as an outcome that were deemed unsuitable to inform practice recommendations, because they had insufficient sample size (11 RCTs) or because they were hypothesis-generating studies in which prostate cancer was not a primary outcome (20 RCTs).

Among trials of hormonal agents, six trials that evaluated 5-ARIs in men with BPH had results similar to those of the PCPT and REDUCE studies, supporting a biologically and clinically consistent treatment effect. Among nonhormonal agents, only six trials of statins were identified, and these were included in a meta-analysis that showed no effect on the incidence of prostate cancer. Various nutritional supplements have been studied, alone and in combination, with prostate cancer as an outcome. Most showed no benefit in the reduction of prostate cancer, and some showed potential harm.

ONGOING TRIALS

The clinical trials registry of the US National Institutes of Health (http://clinicaltrials.gov) was searched on November 2, 2011 to identify ongoing trials on the prevention of prostate cancer.

Investigator	Title	Identifier	Status
Ahmann FR, University of Arizona	Selenium in preventing prostate cancer: The Negative Biopsy Study	NCT00978718	Unknown
Marshall J, Roswell Park Cancer Institute	Selenium in preventing cancer in patients with neoplasia of the prostate	NCT00030901	Ongoing but not recruiting
Melbourne University	Chemoprevention trial of selenium in familial prostate cancer: Australian Prostate Cancer Prevention Trial Using Selenium (APPOSE)	No registration information	
Milonas D, Kaunas University of Medicine, Lithuania	Prevention of prostate cancer with dutasteride in case of high grade PIN neoplasia	NCT00780754	Unknown
Kumar N, H Lee Moffitt Cancer Center, Tampa	Study of polyphenon E in men with high-grade prostatic intraepithelial neoplasia	NCT00596011	Recruiting
Alberts SR, Mayo Clinic	Flutamide In the prevention of prostate cancer in patients with neoplasia of the prostate	NCT00006214	Completed
DiPaola RS, Cancer Institute of New Jersey	Calcitriol in preventing prostate cancer in patients with prostatic intraepithelial neoplasia	NCT00118066	Ongoing but not recruiting
Shannon J, OHSU Knight Cancer Institute	Fish Oil and Green Tea Extract in Preventing Prostate Cancer in Patients Who Are at Risk for Developing Prostate Cancer	NCT00253643	Ongoing but not recruiting
GTx	A Chemoprevention Study of an Investigational Drug in Men With High Grade Prostate Intraepithelial Neoplasia (PIN)	NCT00028353	Completed

CONCLUSIONS

Ideally, interventions that reduce the risk of cancer should have no detrimental side effects or risks and should reduce the risk of the cancer targeted, including its most serious forms. Considering that well persons would be potentially exposed to these interventions, certainty of benefit must be definite and determination of risks precise. Most of the trials identified by this systematic review did not meet these criteria and could not be used to inform recommendations. A clinically significant reduction in the risk of less aggressive prostate cancers with 5-ARIs was identified. This was associated with a reduced risk of urinary tract symptoms and less frequent biopsy, but also a higher frequency of mild endocrine and sexual side effects and a slight increase in the detection of more aggressive cancers. In view of this, it might appear that the 5-ARI drugs are not particularly effective for prostate cancer risk reduction. However, the results must be considered and contextualized to the current medical environment. Currently, a diagnosis of less aggressive prostate cancer invariably leads to definitive treatment, even though the benefits in these patients are recognized as uncertain and the potential for lifelong effects on quality of life absolute. In such an environment, it is arguable that preventing a less aggressive prostate cancer is of value, as it prevents exposure to potentially unnecessary and toxic definitive cancer treatment. Regarding the small increased risk of more aggressive cancers, a strong case can be made that this observation is due to detection bias, because, due to reduced prostate mass, the test characteristics of PSA and prostate biopsy are improved in men receiving 5-ARIs. 5-ARI therapy could conceivably also benefit men by leading to the earlier detection of more biologically aggressive cancers for which the benefits of definitive cancer treatment are far more certain. Currently, 5-ARI therapy for prostate cancer risk reduction can be viewed as a reasonable option for men who wish to reduce their risk of exposure to definitive prostate cancer treatment. If the ability and willingness to precisely identify and observe men with biologically indolent prostate cancers emerges in the future, then this strategy would need to be re-evaluated. This systematic review also identified that vitamin E is associated with an increased risk of prostate cancer and selenium appears to be ineffective for prostate cancer risk reduction. Supplemental calcium (risk reduction) and folic acid (risk increase) are of interest for further study. In men with HGPIN, further studies with nonsteroidal antiandrogens and green tea catechins may also be of interest.

CONFLICT OF INTEREST

The conflict of interest details are shown at the end of Section 3.

Neil Fleshner
- Grant/support as principal or co-investigator: Unrestricted educational grant from GSK
- Principal investigator for a clinical trial involving the topic: GSK supported clinical trials – REDEEM and REDUCE
- Published on the topic: GU ASCO Meeting Feb 2011:Abstract Submission ID: 72231 Abstract Title: Effect of dustasteride on prostate cancer progression and cancer diagnosis on rebiopsy in the REDEEM active surveillance study;
  Fleshner NE, Kapusta L, Donnelly B, Tanguay S, Chin J, Hersey K, Farley A, Jansz K, Siemens DR, Trpkov K, Lacombe L, Gleave M, Tu D, Parulekar WR. Progression from high-grade prostatic intraepithelial neoplasia to cancer: a randomized trial of combination vitamin-e, soy, and selenium. J Clin Oncol. 2011 Jun 10;29(17):2386-90.

Jack Barkin
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All other Working Group members and GU DSG members declared no conflict of interest.

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Appendix 1. Literature search summary.

Methods terms
Publication types, MeSH terms, text words for meta-analyses, systematic reviews, practice guidelines, and RCTs

AND
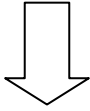
Terms for prostate cancer
Prostatic neoplasms or prostate carcinoma or prostate cancer
Prostat:.tw. and (cancer or carcinoma or adenocarcinoma or neoplas:.tw.)

AND
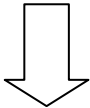
Terms for drug/supplement interventions
Chemoprevention or chemoprophylaxis or dietary supplements
Chemoprevent:.tw.
(diet: or nutrition:).tw. and (supplement: or agent:).tw.
Prostate cancer/pc

AND
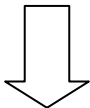
1950 to 2011
English and humans only

Appendix 2. Flow diagram of results from literature search strategies.

Literature Databases MEDLINE EMBASE Cochrane Library	Conference Proceedings ASCO AUA	Other Reference checking, hand searching, experts' suggestions
↓	↓	↓
86 relevant citations	4 relevant citations	1 relevant citation

91 citations examined full text

Excluded: 57
(RCTs with <50 participants, non-systematic reviews, systematic reviews with no RCTs, duplicate reports, secondary analyses)

Retained: 34
(1 practice guideline, 13 systematic reviews, 20 individual RCT reports)

In total: 52 unique reports representing 34 RCTs

Appendix 3. RCTs covered by systematic reviews.

RCT		Systematic Review												
Author, yr (ref)	Study group	Stratton 2011 (21)	Druesne-Pecollo 2010 (17)	Myung 2010 (18)	Jiang 2010 (20)	Wilt 2010 (19)	Boehm 2009 (15)	Bonovas 2008 (14)	Chan 2009 (16)	Wilt 2008 (13)	Alkhenizan 2007 (12)	Coulter 2006 (11)	Browning 2006 (10)	Ritenbaugh 2003 (9)
Virtamo, 2003 (49)	ATBC		•	•					•					
Omenn, 1996*a	CARET		•	•					•					
Meyer, 2005 (51)	SU.VI.MAX	•	•	•	•									
Cook, 2000 (47)	PHS I		•	•					•					
HPS Collaborative Group, 2002 (48)	MRC/BHF HPS		•									•		
ATBC Cancer Prevention Study Group, 1994*b	ATBC			•								•		•
Clark, 1996*c	NPC			•										
Clark, 1998*d	NPC			•										
Heinonen, 1998*e	ATBC	•		•	•				•		•	•		•
Duffield-Lillico, 2002*f	NPC			•										
Duffield-Lillico, 2003 (50)	NPC				•									
Bettuzzi, 2006 (35)							•							
Downs, 1998 (41)	AFCAPS/TexCAPS							•					•	
LIPID Study Group, 2002 (42)	LIPID							•					•	
Serruys, 2002 (43)	LIPS							•					•	
Strandberg, 2004 (44)	4S							•					•	
HPS Collaborative Group, 2005 (44 45)	Heart Protection Study							•						
Ford, 2007 (45 46)	WOSCOPS							•						
Andriole, 2004 (29)						•				•				
Thompson, 2003 (23)	PCPT					•				•				
Cote, 1998 (28)						•				•				
Gormley, 1992 (38)	FSG American					•				•				
FSG, 1993 (39)	FSG International					•				•				
Andriole, 1998 (27)	PLESS					•				•				
Nickel, 1996 (40)	PROSPECT					•				•				
Albanes, 1995*g	ATBC													•
Hennekens, 1996*h	PHS I				•									•
Lonn, 2005 (53)	HOPE/HOPE-TOO			•	•									
Lippman, 2009 (58)	SELECT	•		•										
Gaziano, 2009 (25 26)	PHS II	•		•										
Andriole, 2010 (24)	REDUCE					•								
Roehrborn, 2010 (33)	CombAT					•								

4S=Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ATBC=Alpha-Tocopherol Beta-Carotene Cancer Prevention; CARET=Carotene and Retinol Efficacy Trial; CombAT=Combination of Avodart and Tamsulosin; FSG=Finasteride Study Group; HOPE/HOPE-TOO=Heart Outcomes Prevention Evaluation/HOPE-The Ongoing Outcomes; HPS=Heart Protection Study; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; LIPS=Lescol Intervention Prevention Study; MRC/BHF=Medical Research Council/British Heart Foundation; NPC=Nutritional Prevention of Cancer; PCPT=Prostate Cancer Prevention Trial; PHS=Physicians'

Health Study; PLESS=Proscar Long-Term Efficacy and Safety Study; PROSPECT=PROscar Safety Plus Efficacy Canadian Two-year study; REDUCE=Reduction by Dutasteride of Prostate Cancer Events; SELECT=Selenium and Vitamin E Cancer Prevention Trial; SUVIMAX=Supplémentation en Vitamines et Minéraux Antioxydants; WOSCOPS=West of Scotland Coronary Prevention Study

*These studies are not discussed in the text because they were superseded by newer more complete reports.

[a]Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst. 1996 Nov 6;88(21):1550-9.

[b]The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med. 1994 Apr 14;330(15):1029-35.

[c]Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA. 1996 Dec 25;276(24):1957-63.

[d]Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol. 1998 May;81(5):730-4.

[e]Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM,et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst. 1998 Mar 18;90(6):440-6.

[f]Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr, Slate EH, Fischbach LA, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev. 2002 Jul;11(7):630-9.

[g]Albanes D, Heinonen OP, Huttunen JK, Taylor PR, Virtamo J, Edwards BK,et al. Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. Am J Clin Nutr. 1995 Dec;62(6 Suppl):1427S-1430S.

[h]Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996 May 2;334(18):1145-9.

Appendix 4. AGREE II scores for the clinical practice guideline (7).

Number of reviewers: 1

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
83.3%	72.2%	77.1%	88.9%	41.7%	75.0%

Appendix 5. AMSTAR ratings for included systematic reviews.

AMSTAR items	Stratton (21)	Druesne-Pecollo (17)	Myung (18)	Wilt (19)	Jiang (20)	Boehm (15)	Bonovas (14)	Chan (16)	Wilt (13)	Alkhenizan (12)	Coulter (11)	Browning (10)	Ritenbaugh (9)
1. Was an 'a priori' design provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was there duplicate study selection & data extraction?	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
3. Was a comprehensive literature search performed?	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	No	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No
5. Was a list of studies (included & excluded) provided?	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
7. Was the scientific quality of the included studies assessed & documented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes
10. Was the likelihood of publication bias assessed?	No	No	Yes	No	No	No	Yes	No	No	No	No	Yes	No
11. Was the conflict of interest stated?	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Total AMSTAR points	8	6	8	8	7	9	7	6	8	8	8	7	9

NA=not applicable.

Appendix 6a. Methodological quality characteristics of RCTs with prostate cancer reduction as a primary outcome.

Trial (ref)	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Hormonal agents										
PCPT (23)	NR	NR	Yes	Yes	NR	In part	We calculated that with a two-sided α of 0.05, a power of 0.92, and a three-year accrual period, we needed a sample size of 18,000.	7.7%	NR	Yes
REDUCE (24)	NR	NR	Yes	NR	Yes	Yes	We estimated that with 8000 subjects, the study would have approximately 90% power to show a 20% reduction with dutasteride in the incidence of prostate cancer detected on biopsy (i.e., an estimated rate of 19.0% in the placebo group and 15.2% in the dutasteride group), at a two-sided alpha level of 0.01.	NR	NR	No
Nutritional supplements										
SELECT (25)	NR	NR	Yes	Yes	Yes	In part	With a sample size of 32,400 men, using a 1-sided α=0.005 level (equivalent to a 2-sided α=0.01 level), there was 96% power to detect a 25% reduction in prostate cancer for either of the single agents (vs. placebo),89% power to detect a 25% reduction for selenium + vitamin E (vs. an active single agent) and more than 99% power to detect a 44% reduction of selenium + vitamin E (vs. placebo).	5.1%	Yes	Yes
PHS II (26)*	Yes	NR	Yes	Yes	Yes	In part	The PHS II was designed to have greater-than-80% power to detect a 13% reduction in the hazard of total cancer and a 19% reduction in the hazard of prostate cancer.	Morbidity and mortality follow-up as a percentage of person-time each exceeded 99.9%, with only 1055 and 289 person-years of potential morbidity and mortality follow-up lost through August 31, 2007.	Yes	No

ITT=intention to treat; NA=not applicable; NR=not reported; PCPT=Prostate Cancer Prevention Trial; PHS=Physicians' Health Study; REDUCE=Reduction by Dutasteride of Prostate Cancer Events; SELECT=Selenium and Vitamin E Cancer Prevention Trial

*This study is also among the non-primary outcome trials because the reduction of prostate cancer is a secondary outcome for the comparison of vitamin C vs. placebo.

Appendix 6b. Methodological quality characteristics of RCTs with prostate cancer reduction as a primary outcome but insufficient sample size, or non-primary outcome trials.

Trial (ref)	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Hormonal agents										
PLESS (27)	Yes	NR	Yes	Yes	Yes	Yes	NR	5.3%	Yes	No
Cote (28)	Yes	NR	Yes	NR	Yes	No	NR	10.3%	NR	No
Andriole (29)	NR	NR	Yes	NR	NR	Yes	NR	NR	Yes	No
Price (30)	NR	NR	Yes	NR	Yes	Yes	NR	1.4%	Yes	No
Alberts (31)	NR	NR	Yes	NR	Yes	No	NR	NR	Yes	No
Zhigang (32)	Yes	NR	Yes	NR	No withdrawals	NR	Assuming a 2-sided significance test with significance level α=0.05 for the current study, with our sample size of 172, the estimated power to detect the 50% target difference observed was 90%.	0%	Yes	No
CombAT (33)	Yes	NR	Yes	Yes	NR	Yes	NR	44%	Yes	No
Taneja (34)	NR	NR	NR	Yes	NR	Yes	NR	NR	NR	No
FSG Am (38)	NR	NR	Yes	Yes	Yes	Yes	NR	1.0%	The 3 groups were similar except that the total voided volume was lower (p<0.05) and the obstructive-symptom scores higher (p<0.05) in men who received 1 mg finasteride than in men who received placebo.	No
FSG International (39)	NR	NR	Yes	NR	NR	Yes	With the study sample size, the detectable between-group difference with 90% power and 5% Type I error rate was 10% for prostate volume, 1.37 mL/sec for maximum urinary flow rate, and 1.78 for total symptom score.	5.6%	NR	No
PROSPECT (40)	Yes	NR	Yes	Yes	Yes	Yes	NR	2.8%	Yes	No
Non-hormonal agents										
AFCAPS/TexCAPS (41)	NR	NR	Yes	Yes	Yes	Yes	NA	NR	Yes	Yes
LIPID (42)	NR	NR	Yes	Yes	Yes	Yes	NA	2 patients	Yes except for baseline triglyceride level (p=0.023)	No
LIPS (43)	NR	NR	Yes	Yes	Yes	Yes	NA	17 pts (1%)	Yes except for incidence of diabetes mellitus	No
4S (44)	NR	NR	Yes	Yes	No withdrawals	Yes	NR	0	Yes	No
HPS (45)	NR	NR	Yes	Yes	NR	Yes	NR	NR	Yes	No
WOSCOPS (46)	NR	NR	Yes	NR	NR	Yes	NR	NR	Yes	No

Trial (ref)	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Nutritional supplements										
PHS I (47)	NR	NR	Yes	Yes	NR	No	NR	NR	Yes	No
MRC/BHF HPS (48)	Yes	Yes	Yes	Yes	NR	In part	Based on previous studies in similar populations, it was estimated that there would be about 3000 major coronary events and 5000 major vascular events among 20,000 such high-risk patients followed for an average of 5 years. If so, and if the antioxidant vitamins reduced these event rates by at least 10%, then the study had an excellent chance of demonstrating such effects at convincing levels of statistical significance. There were also expected to be more than 1000 deaths from causes other than coronary disease and more than 1000 new cancers during the scheduled follow-up. Such numbers would allow reasonably reliable assessment of the 5-year effects of the vitamin supplementation not just on all-cause mortality but also on the main non-coronary causes of death and on the main types of cancer.	0.33%	Yes	No
ATBC (49)	NR	NR	Yes	Yes	NR	Yes	NR	NR	Yes	No
NPC (50)	NR	Yes	Yes	Yes	Yes	No	The trial had 80% power to detect a 25% change in the incidence of SCC and a 19% change in the incidence of BCC at a significance level of 0.05.	0%	Yes	No
SU.VI.MAX (51)	NR	NR	Yes	Yes	NR	No	NR	NR	Yes	No
Baron (52)	NR	NR	Yes	Yes	NR	Yes	NR	1.9%	Yes	No

Trial (ref)	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
HOPE/HOPE-TOO (53)	Yes	Yes	Yes	Yes	Yes	Yes	The duration of the HOPE-TOO trial was calculated to allow for an average follow-up of 7 years, considering the fixed number of possible participants, and to allow the detection of a 15% to 20% reduction in incident cancers with vitamin E with more than 80% power, assuming a 1.5% to 2% yearly placebo incident cancer rate (2-sided α=0.05; this calculation was made after identifying the number of study participants willing to participate in the trial extension).	0.1%	Yes	No
Bettuzzi (35)	NR	NR	Yes	NR	NR	In part	NR	NR	Yes	No
Aspirin/Folate Polyp Prevention Study (54)	Yes	Yes	Yes	Yes	Yes	No	A sample size of 1000 participants was selected to provide power of at least 80% to detect a risk reduction with aspirin (25% reduction with low-dose and 55% reduction with high-dose) or folic acid (40% reduction) using a 2-sided statistical significance level of p<0.05. This assumed a 35% adenoma occurrence rate in the placebo group and a follow-up rate of 80%. The power to detect a 40% decrease in risk with folic acid supplementation was 94%.	NR	Yes	No
CARET (55)	NR	NR	Yes	Yes	NR	No	Based on a two-sided test for the primary analysis, CARET had 80% power if carried to completion to detect a 22% observed reduction or 24% observed increase in lung cancer incidence.	NR	Yes	Yes
PHS II (26)*	NR	NR	Yes	Yes	Yes	In part	The PHS II was designed to have greater-than-80% power to detect a 13% reduction in the hazard of total cancer and a 19% reduction in the hazard of prostate cancer	Morbidity and mortality follow-up as a percentage of person-time each exceeded 99.9%, with only 1055 and 289 person-years of potential morbidity and mortality follow-up lost through August 31, 2007.	Yes	No

Trial (ref)	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
GEM (56)	Yes	Yes	Yes	Yes	Yes	No	Not applicable	6.3%	Yes	No
SWOG 9917 (36)	NR	NR	NR	NR	Yes	No	Assumed 80% of men will have a 3-y prostate cancer endpoint: either an interim cancer or a 3-y end-of-study biopsy. 90% statistical power. Assumed: 1/3 reduction in risk for prostate cancer with selenium.	5.3%	NR	No
Fleshner (37)	Yes	Yes	Yes	Yes	Yes	No	The original calculation of sample size was based on data from observational studies among men with HGPIN that suggested that 65% to 70% of men with HGPIN would progress in 2 years without treatment and the assumption that nutritional supplementation would lead to a 15% increase in 2-year DFS from 30% for participants receiving placebo (corresponding to a hazard ratio of 0.66). Enrolment of 264 participants was required to detect this difference with β at .2, two-sided α at .048, and 10% lost to follow-up. To gauge the prognosis of subjects entered on the study and its potential impact on the accuracy of the sample size calculation, a blinded review of the event rate was performed on 228 subjects accrued up to May 2003. This review, in addition to consideration of previously published data, led to an increase of the sample size to 306 participants based on an assumption of 2-year DFS of 60% among the placebo participants and detection of the same hazard ratio at the same α and β levels.	0%	Yes	No

4S=Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ATBC=Alpha-Tocopherol Beta-Carotene Cancer Prevention; CARET=Carotene and Retinol Efficacy Trial; CombAT=Combination of Avodart and Tamsulosin; FSG=Finasteride Study Group; GEM=Ginkgo Evaluation of Memory; HOPE/HOPE-TOO=Heart Outcomes Prevention Evaluation/HOPE-The Ongoing Outcomes; HPS=Heart Protection Study; ITT=intention to treat; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; LIPS=Lescol Intervention Prevention Study; MRC/BHF=Medical Research Council/British Heart Foundation; NA=not applicable; NPC=Nutritional Prevention of Cancer; NR=not reported; PHS=Physicians' Health Study; PLESS=Proscar Long-Term Efficacy and Safety Study; PROSPECT=PROscar Safety Plus Efficacy Canadian Two-year study; SUVIMAX=Supplémentation en Vitamines et Minéraux Antioxydants; SWOG=Southwest Oncology Group; WOSCOPS=West of Scotland Coronary Prevention Study

Appendix 7. Study characteristics of RCTs with prostate cancer reduction as a primary outcome but insufficient sample size, or non-primary outcome trials.

Study (ref)	Patient characteristics	Comparison	Number of male patients	Patient age (mean)	Follow-up period	Method of detection of prostate cancer
Hormonal Agents						
FSG Am (38)	Men with BPH	Finasteride (1 or 5 mg/d) vs. placebo	895	64	1 y	NR
FSG International (39)	Men with BPH	Finasteride (1 or 5 mg/d) vs. placebo	750	65	1 y	NR
PROSPECT (40)	Men with BPH	Finasteride (5 mg/d) vs. placebo	613	63	2 y	Protocol-mandated biopsy
PLESS (27)	Men with enlarged prostates, BPH, & decreased urinary flow rates	Finasteride (5 mg/d) vs. placebo	3040	64	4 y	Protocol-mandated biopsy
Cote (28)	Men with PSA >4.0 ng/mL	Finasteride (5 mg/d) vs. observation	58	68	1 y	Protocol-mandated biopsy
Andriole (29)	Men with BPH & PSA ≥1.5 ng/mL	Dutasteride (0.5 mg/d) vs. placebo	4325	66	27 mo	Self-report & medical records
Price (30)	Men with HGPIN	Toremifene (20, 40, or 60 mg/d) vs. placebo	514	65	1 y	Protocol-mandated biopsy
Alberts (31)	Men with HGPIN	Flutamide (250 mg/d) vs. placebo	60	Median 66	Median 23 mo	Protocol-mandated biopsy
Zhigang (32)	Men with HGPIN	Flutamide (250 mg/d) vs. placebo	172	Median Flutamide: 64 Placebo: 62	5 y	Protocol-mandated biopsy
CombAT (33)	Men ≥50 y with BPH, IPSS ≥12, prostate volume ≥30 mL, & PSA 1.5 to 10 mg/mL	Dutasteride (0.5 mg/d) vs. tamulosin (0.4 mg/d) & Dutasteride (0.5 mg/d) + tamulosin (0.4 mg/d) vs. tamulosin (0.4 mg/d)	4844	Median 66	4 y	Clinical suspicion
Taneja (34)	Men with HGPIN	Toremifene (20 mg/d) vs. placebo	1590	NR	3 y	Protocol-mandated biopsy
Nonhormonal Agents						
AFCAPS/TexCAPS (41)	Men & women 45 to 73 y with average total and LDL cholesterol & below average HDL	Lovastatin (20 to 40 mg/d) vs. placebo	5608	58	Mean 5.2 y	NR
LIPID (42)	Men & women with previous MI or unstable angina & total cholesterol 4 to 7 mmol/L	Pravastatin (40 mg/d) vs. placebo	6361	Median 62	Mean 8 y	NR
LIPS (43)	Men & women 18 to 80 y with first percutaneous coronary intervention of ≥1 lesion in native coronary arteries &	Fluvastatin (40 mg 2x/d) vs. placebo	1406	60	Median 3.9 y	NR

Study (ref)	Patient characteristics	Comparison	Number of male patients	Patient age (mean)	Follow-up period	Method of detection of prostate cancer
	total cholesterol 3.5 to 7 mmol/L					
4S (44)	Men & women 35 to 70 y with previous MI or angina pectoris & total cholesterol 5.5 to 8 mmol/L	Simvastatin (20 to 40 mg/d) vs. placebo	3617	NR	Median 10.4 y	National registries & database linkage
HPS (45)	Men & women 40 to 80 y with total cholesterol ≥3.5 mmol/L & history of occlusive arterial disease, diabetes, or hypertension	Simvastatin (40 mg/d) vs. placebo	15,454	64	Mean 5 y Simvastatin: 51,121 p-y of follow-up Placebo: 50,664 p-y of follow-up	National registries
WOSCOPS (46)	Men with no previous MI & LDL cholesterol ≥4.0 mmol/L	Pravastatin (40 mg/d) vs. placebo	6595	55	Mean 13.2 y	National registries & database linkage
Nutritional Supplements						
PHS I (47)	U.S. male physicians with no history of cancer, heart disease, or stroke	Beta-carotene (50 mg on alternate days) vs. placebo	22,071	53	Mean 12.9 y 275,498 p-y of follow-up	Self-report & medical records
MRC/BHF HPS (48)	Men & women 40 to 80 y at substantial 5-y risk for death from heart disease	Beta-carotene (20 mg/d) + alpha-tocopherol (600 mg/d) + vitamin C (250 mg/d) vs. placebo	15,454	NR	Mean 5 y Vitamins: 50,837 Placebo: 50,948 p-y of follow-up	Self-report, family physicians, & national registries
ATBC (49)	Men 50 to 69 y who smoked ≥5 cigarettes/d free of cancer or serious disease	Beta-carotene (20 mg/d), alpha-tocopherol (50 mg/d), placebo (factorial)	29,133	64	6.1 y 350 000 p-y of follow-up	National registries & medical records
NPC (50)	Men & women with history of basal or squamous cell carcinoma of the skin & no internal malignancy in the past 5 y	Selenium (200 µg/d) vs. placebo	927	64	Selenium: mean 7.6 y Placebo: mean 7.3 y 7263 p-y of follow-up	Medical records
SU.VI.MAX (51)	Men & women 35 to 60 y free of severe health problems	Vitamin C (120 mg/d) + alpha-tocopherol (30 mg/d) + beta-carotene (6 mg/d) + selenium (100 µg/d) + zinc (20 mg/d) vs. placebo	5141	51	Median 8.8 to 9 y	Clinical suspicion
Calcium Polyp Prev (52)	Men & women with history of colorectal	Calcium (1200 mg/d) vs. placebo	672	62	Mean 10.3 y	Self-report, death certificates, & medical

Study (ref)	Patient characteristics	Comparison	Number of male patients	Patient age (mean)	Follow-up period	Method of detection of prostate cancer
	adenomas					records
HOPE/HOPE-TOO (53)	Men & women ≥55 y at high risk for cardiovascular events	HOPE: Vitamin E (400 IU/d), ramipril (10 mg/d), placebo (factorial) HOPE-TOO: Vitamin E (400 IU/d) vs. placebo	HOPE: 6996 HOPE-TOO: 5207	66	Median 7.2 y	Medical records
Bettuzzi (35)	Men with HGPIN	Green tea catechins (600 mg/d) vs. placebo	60	65	1 y	Protocol-mandated biopsy
Aspirin/Folate Polyp Prevention (54)	Men & women 21 to 80 y with history of colorectal adenomas	Folic acid (1 mg/d) +/- aspirin (81 or 325 mg/d) vs. placebo	651	57	Median 7 y	Self-report & medical records
CARET (55)	Heavy smokers (men & women) and asbestos-exposed workers (men)	Beta-carotene (30 mg/d) + vitamin A (25,000 IU/d) vs. placebo	12,000	58	Mean 11 y	Medical records & SEER registry
PHS II (26) (Vitamin C vs. placebo comparison)	7641 men from Phys Hlth Study I plus 7000 additional US male physicians	Vitamin E (400 IU every other day), vitamin C (500 mg/d), placebo (factorial)	14,641	64	Median 7.6 y 117,711 p-y of follow-up	Medical records
GEM (56)	Men & women ≥75 y	Ginkgo biloba extract (120 mg 2x/d) vs. placebo	1651	79	Median 6.1 y	Self-report & medical records
SWOG (36)	Men with HGPIN	Selenium (200 µg/d) vs. placebo	424	>40 y	3 y	Protocol-mandated biopsy
Fleshner (37)	Men with HGPIN	Vitamin E (800 IU/d) + selenium (200 µg/d) + soy protein (40 g/d) vs. placebo	303	Median 63	3 y	Protocol-mandated biopsy

4S=Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ATBC=Alpha-Tocopherol Beta-Carotene Cancer Prevention; CARET=Carotene and Retinol Efficacy Trial; CombAT=Combination of Avodart and Tamsulosin; d=day; FSG=Finasteride Study Group; GEM=Ginkgo Evaluation of Memory; HOPE/HOPE-TOO=Heart Outcomes Prevention Evaluation/HOPE-The Ongoing Outcomes; HPS=Heart Protection Study; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; LIPS=Lescol Intervention Prevention Study; mo=month; MRC/BHF=Medical Research Council/British Heart Foundation; NPC=Nutritional Prevention of Cancer; NR=not reported; p-y=person-years; PHS=Physicians' Health Study; PLESS=Proscar Long-Term Efficacy and Safety Study; PROSPECT=PROscar Safety Plus Efficacy Canadian Two-year study; SUVIMAX=Supplémentation en Vitamines et Minéraux Antioxydants; SWOG=Southwest Oncology Group; WOSCOPS=West of Scotland Coronary Prevention Study; vs.=versus; y=year(s)

Appendix 8. Members of the Working Group

Neil Fleshner	Division of Urology, University Health Network, Princess Margaret Hospital, Toronto, Ontario
Noah Ivers	Family Medicine, Women's College Hospital, Toronto, Ontario
Himu Lukka	Division of Radiation Oncology, Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, Ontario
Bobby Shayegan	Institute of Urology, St. Joseph's Healthcare, Hamilton, Ontario
Cindy Walker-Dilks	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario
Eric Winquist	Medical Oncology, London Regional Cancer Centre, London, Ontario

Appendix 9. Members of the Cancer Care Ontario Genitourinary Cancer Disease Site Group

Andrew Loblaw – Chair	Sunnybrook Health Sciences Centre, Toronto, Ontario
Sebastian Hotte – Chair	Hamilton Health Sciences, Hamilton, Ontario
Neil Fleshner – Chair	Princess Margaret Hospital, Toronto, Ontario
Jack Barkin	Humber River Regional Hospital, Toronto, Ontario
Glenn Bauman	London Health Sciences Centre, London, Ontario
Michael Brundage	Cancer Centre of Southeastern Ontario, Kingston General Hospital
Christina Canil	The Ottawa Hospital Cancer Centre, Ottawa, Ontario
Charles Catton	Princess Margaret Hospital, Toronto, Ontario
Joseph Chin	London Health Sciences Centre, London, Ontario
Urban Emmenegger	Sunnybrook Health Sciences Centre, Toronto, Ontario
Anthony Finelli	Princess Margaret Hospital, Toronto, Ontario
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Himu Lukka	Hamilton Health Sciences, Hamilton, Ontario
Scott Morgan	The Ottawa Hospital Cancer Centre, Ottawa, Ontario
George Rodrigues	London Health Sciences Centre, London, Ontario
Roanne Segal	The Ottawa Hospital Cancer Centre, Ottawa, Ontario
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Draft Evidence-Based Series 3-3: Section 3

Risk Reduction of Prostate Cancer with Drugs or Nutritional Supplements: EBS Development Methods and External Review Process

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

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:
- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its

interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the EBS development process and the results of the formal external review of the draft version of <u>Section 1: Guideline Recommendations</u> and <u>Section 2: Evidentiary Base</u>.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review

This EBS was developed by the Genitourinary Cancer Disease Site Group (GU DSG) of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on reduction of prostate cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GU DSG is comprised of medical and radiation oncologists, urologists, and pathologists with expertise in GU cancer, plus a lay representative and a methodologist. Review of the document by members of the DSG was generally positive. There were some requests for clearer wording in the first recommendation.

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel included the following:

1) The backgrounds of individuals on the guideline development group should be noted. It would have been desirable to see participation from medical oncologists or clinical epidemiologists.
2) A request for fuller discussion of the harms associated with using 5-ARIs. An explanation of the frequency and severity of the side effects of these drugs is important when considering placing an individual on medication for up to seven years.
3) Make the first recommendation more explicit: include the lack of difference in prostate cancer death rates if 5-ARIs are used, the potential harms, and the need for informed discussion between physician and patient.
4) Clarify the context of the recommendation.
5) The presentation of materials is very specialist oriented and may not be very useful to the primary care provider.
6) Include advice on how the recommendations can be put into practice. Given the concern about the risk of higher grade prostate cancer, the development a decision aid would be helpful.
7) Clarify the evidence selection section, particularly the justification for the post hoc division of primary and secondary studies to ensure it was not influenced by the results of the studies.
8) Define the various risk categories (i.e., BPH, HGPIN).
9) Instead of doing separate meta-analyses of the hormonal intervention studies, combine and do a sensitivity analysis to exclude the smaller, weaker studies.
10) Describe how the hormonal agents exert their effect.

Modifications/Actions

The following modifications and responses were made to address key issues made by

the Report Approval Panel:

1) An appendix was added detailing the specialties of the working group members. Of note, one member is a medical oncologist and one is a primary care physician with expertise in knowledge translation.
2) The potential risks and the need for physician-patient discussion are outlined in the qualifying statements. A statement has been added about the discontinuation of 5-ARI therapy due to adverse effects.
3) The link between treatment with 5-ARIs and reduction in the need for more definitive treatment for prostate cancer has been made more explicit in Recommendation 1.
4) Recommendation 1 has been revised to better explain the medical context and indicate that 5-ARI does not reduce prostate cancer mortality.
5) We hope that the subject matter would be of interest to both specialists and primary care providers. Furthermore, the inclusion of a lay summary and glossary should make it more useful to nonclinicians.
6) Recommendation 1 had been revised to be more explicit regarding under what circumstances it is reasonable to offer 5-ARI therapy. The Working Group is reluctant to be more prescriptive.
7) The evidence selection section and division of studies into more and less influential has been made more explicit, and the calculation method has been added.
8) Definitions for BPH and HGPIN have been added in the supplementary studies section where those studies are described.
9) Six of the supplementary studies evaluating hormonal agents were solely in men with BPH. Two others were in men with HGPIN. The authors maintain that these studies should not be combined with the primary studies in a meta-analysis as neither primary study provided results for these subgroups of patients.
10) A description of the basic mechanism of 5-ARIs was added.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the GU DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GU DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review November 3, 2011)
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?

TARGET POPULATION

Men greater than or equal to 18 years of age.

INTENDED USERS

Urologists, oncologists specializing in genitourinary cancers, primary care

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practitioners, and the general public.

RECOMMENDATION 1
In men who are undergoing monitoring for prostate cancer and are ≥50 years of age with a normal prostate specific antigen (PSA), who have an elevated PSA (2.5 to 10 ng/mL) and a negative result on prostate biopsy, or who have moderately symptomatic benign prostatic hypertrophy (BPH), it is reasonable to offer 5-alpha reductase inhibitor (5-ARI) therapy to reduce the risk of needing definitive treatment for prostate cancer.

Qualifying Statements
- 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 Genitourinary Cancer Disease Site Group (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, then these recommendations would need to be re-evaluated.
- The optimal 5-ARI regimen and duration of therapy are uncertain. In the primary randomized controlled trials (RCTs) considered, finasteride, 5.0 mg orally (po) daily was given for a planned seven years and dutasteride, 0.5 mg po daily for four years.
- The expected NNT in clinical practice will likely be much higher, as the diagnosis of prostate cancer in men without benign prostatic hyperplasia (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 of 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, may be outweighed by the benefits of avoiding overtreatment for biologically insignificant prostate cancer.
- 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 for men without 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.

- 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.
- The 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).

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 of 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).

Methods
Targeted Peer Review: During the guideline development process, nine targeted peer reviewers from Ontario and the United States who were considered to be clinical and/or methodological experts on the topic were identified by the GU DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via

email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out November 3, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Urologists, oncologists specializing in genitourinary cancers, and primary care providers in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on November 4, 2011. The consultation period ended on December 15, 2011. The Working Group reviewed the results of the survey.

Results
Targeted Peer Review: Responses were received from three reviewers. Key results of the feedback survey are summarized in Table 6.

Table 6. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (n=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.		1	1		1
2. Rate the guideline presentation.		1		1	1
3. Rate the guideline recommendations.	1	1			1
4. Rate the completeness of reporting.		1	1		1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	1	1			1
6. Rate the overall quality of the guideline report.		2			1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	2				1
8. I would recommend this guideline for use in practice.	2				1

9. What are the barriers or enablers to the implementation of this guideline report?
- The potential for increased risk of high-grade prostate cancer and the lack of definitive criteria for selecting patients with low-grade disease for surveillance.
- The lack of survival benefit.

- Insufficient information regarding toxicities of hormones.
- Insufficient information regarding cost-effectiveness.
- The dense, user-unfriendly presentation of the information.

Summary of Written Comments

The main points contained in the written comments were:

1. The concern with a recommendation for a drug intervention that does not demonstrate a survival benefit and has significant toxicity issues. It will increase the costs of health care without benefit and increase the medicalization of society.
2. The recommendations are medically based, not based upon public health or cost-effectiveness considerations.
3. No other approach than chemoprevention, comprising hormonal agents and dietary supplements, is being considered. Chemoprevention is a small and largely unimportant component of prevention. More useful would be recommendations designed to reduce the extent of PSA screening, improve the general nutritional status of men, reduce obesity, and promote physical activity.
4. Restrict recommendation to men known to have a PSA level of ≥3 ng/mL and already in clinical care.
5. Expand table 2 to include all data on prostate cancer mortality, all-cause mortality, and advanced prostate cancer.
6. Question whether the REDUCE trial should be included in an assemblage of data intended to guide the question of using chemoprevention in healthy men since the men in REDUCE were already under suspicion of having prostate cancer, and many had an elevated PSA, so dutasteride was almost being used adjuvant therapy, not chemoprevention.
7. Concern about the validity of meta-analysis with only two studies.

Professional Consultation: 137 responses were received. Key results of the feedback survey are summarized in Table 7.

Table 7. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	3%	6%	21%	54%	16%
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	7%	13%	22%	33%	25%
3. I would recommend this guideline for use in practice.	7%	16%	19%	37%	21%

4. **What are the barriers or enablers to the implementation of this guideline report?**
   The main barriers expressed by the professional consultation respondents were:

- The potential for increased risk of high-grade prostate cancer with 5-ARIs.
- The wording of the first recommendation is confusing.
- The complex nature of the subject matter and the time required to adequately explain the information to patients.
- Concern about offering medication to essentially asymptomatic men 50 years of age.
- The lack of clear benefits of 5-ARIs.
- The requirement for additional PSA monitoring and the cost associated with it, as well as the cost of the 5-ARIs.
- Concern about the side-effects associated with 5-ARIs.

Enablers expressed were:
- Family physicians will be able to implement the recommendations.
- The guidelines are timely.
- The anxiety of the patient may be reduced.

Summary of Written Comments

The main points contained in the written comments were:
- Difficulty in accepting a recommendation for monitoring and prophylactic 5-ARI treatment in men over 50 years.
- The concern about the risk of increased high-grade prostate cancer.
- The cost of medication and screening.
- The difficulty in explaining the risks and benefits to patients and the time required to implement.
- The information is complex and is not clear enough to use in primary care without urology, but the principles of less surgery and more chemoprevention are sound.
- The long-term effects of these drugs remain unknown.
- The recommendation with respect to vitamin E and selenium is acceptable, but the recommendation for 5-ARIs is not.
- Clear, timely, and a good summary of a large, complex pool of data.
- A very reasonable option in the right patient.
- Evidence-based recommendations regarding treatment, particularly diet supplements, are very welcome.

Modifications/Actions
- The external review of this document elicited pronounced reactions to the recommendation for the use of 5-ARIs. Three main perspectives were observed:
  o 1. 5-ARIs provide no benefit. None of the randomized controlled trials (RCTs) of 5-ARI therapy reported any reduction in overall or prostate cancer-specific mortality therefore 5-ARI therapy must be considered an unproven intervention from this perspective.
  o 2. The harms of 5-ARIs outweigh the benefits. 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.
  o 3. The benefits of 5-ARIs outweigh the harms. This perspective argues that the observation of more high-grade cancers is due to detection artefacts and not to 5-ARI therapy.
- Recommendation 1 has been revised to be less confusing.

- The title and question have been modified to reflect that the scope of the guideline is on evaluating drugs and nutritional supplements for prostate cancer reduction and does not address prostate cancer screening, or dietary interventions.
- The qualifying statements have been rearranged and emphasize that 5-ARI therapy is not being recommended on a population-wide scale but offered for consideration as an option based on one's values in the current clinical environment of prostate cancer treatment.
- An observation was made in external review that the meta-analysis performed on two separate groups of studies of 5-ARIs was not appropriate. We had made the decision to separate the studies based on whether they focused directly on the prevention of prostate cancer as the primary outcome and whether they were sufficiently large and long enough to support recommendation for an intervention in otherwise well people. In response to this comment we have pooled all eight studies of 5-ARIs: the two primary studies, and the six secondary studies. This produced a relative risk of 0.77 (95% CI 0.79 to 0.82), almost identical to that of the meta-analysis of the two primary studies (RR 0.77; 95% CI 0.73 to 0.82).

5-ARIs vs placebo or non-5-ARIs – all studies

Study or Subgroup	5-ARIs Events	5-ARIs Total	Placebo/non-5-ARIs Events	Placebo/non-5-ARIs Total	Weight	Risk Ratio M-H, Random, 95% CI
Andriole04b (ARIA/ARIB)	27	2167	55	2158	2.1%	0.49 [0.31, 0.77]
Andriole10 (REDUCE)	659	3305	858	3424	41.4%	0.80 [0.73, 0.87]
Andriole98 (PLESS)	72	1524	77	1516	4.3%	0.93 [0.68, 1.27]
FSG93 (FSG Int'l)	5	495	3	255	0.2%	0.86 [0.21, 3.56]
Gormley92 (FSG Am)	3	595	1	300	0.1%	1.51 [0.16, 14.48]
Nickel96 (PROSPECT)	3	310	6	303	0.2%	0.49 [0.12, 1.94]
Roehrborn10 (COMBAT)*	42	1623	63	1611	2.9%	0.66 [0.45, 0.97]
Thompson03 (PCPT)	803	4368	1147	4692	48.8%	0.75 [0.69, 0.81]
Total (95% CI)		14387		14259	100.0%	0.77 [0.72, 0.82]
Total events	1614		2210			

Heterogeneity: Tau² = 0.00; Chi² = 7.43, df = 7 (P = 0.39); I² = 6%
Test for overall effect: Z = 7.88 (P < 0.00001)

Favours 5-ARIs   Favours control

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GU DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, GU DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Neil Fleshner
- Grant/support as principal or co-investigator: Unrestricted educational grant from GSK
- Principal investigator for a clinical trial involving the topic: GSK supported clinical trials – REDEEM and REDUCE
- Published on the topic: GU ASCO Meeting Feb 2011:Abstract Submission ID: 72231 Abstract Title: Effect of dustasteride on prostate cancer progression and cancer diagnosis on

rebiopsy in the REDEEM active surveillance study;
Fleshner NE, Kapusta L, Donnelly B, Tanguay S, Chin J, Hersey K, Farley A, Jansz K, Siemens DR, Trpkov K, Lacombe L, Gleave M, Tu D, Parulekar WR. Progression from high-grade prostatic intraepithelial neoplasia to cancer: a randomized trial of combination vitamin-e, soy, and selenium. J Clin Oncol. 2011 Jun 10;29(17):2386-90.

Jack Barkin
- Grant support: Researcher/investigator for CombAT, Reduce and Redeem trials sponsored by GSK

All other Working Group members and GU DSG members declared no conflict of interest.

Report Approval Panel
All Report Approval Panel members declared no conflict of interest.

External Reviewers
- One external reviewer declared ≥$5000.00 in a single year to act in a consulting capacity for the US Prostate, Lung, Colon, and Ovary Screening Trial (Division of Cancer Prevention, National Cancer Institute, Bethesda, MD) and has published extensively on screening, including prostate cancer screening.
- One reviewer has published extensively on chemoprevention of prostate cancer.
- One external reviewer declared ≥$5000.00 in a single year to act in a consulting capacity for Sanofi International Strategy Board, received grants as a principal or co-investigator from EL Lilly, and had managerial responsibility for an organization that has received ≥$5000.00 in a single year from a relevant business entity.

UPDATING
This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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