

PROSTATE CANCER

Neither vitamin E nor selenium prevent prostate cancer

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Data on the value of dietary supplements in reducing the risk of developing prostate cancer have been conflicting; however, two large randomized trials have indicated that prostate cancer risk is not reduced by the long-term use of vitamin E, vitamin C or selenium supplements.

Preventing prostate cancer with cheap, nontoxic nutritional supplements would be a great achievement. Secondary analyses of two randomized controlled trials in the 1990s raised the possibility that both vitamin E and selenium might have protective effects, but the results from two trials specifically designed to test these hypotheses, published in *JAMA* in January 2009, have largely dashed these hopes.^{1,2}

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), the largest randomized, placebo-controlled cancer chemoprevention trial conducted to date, was designed to test whether supplements of selenium (200 µg per day), vitamin E (400 IU per day), or both could prevent prostate cancer and other diseases in relatively healthy men. The study followed about 35,000 participants from across the US, Canada and Puerto Rico for an average of 5 years, but was prematurely discontinued because there was no evidence of a benefit in terms of reducing prostate cancer incidence in those taking selenium, vitamin E, or both supplements together.¹ The Physicians' Health Study II (PHS II) was designed to test whether supplemental vitamin E (400 IU on alternate days) and/or vitamin C (500 mg per day) could prevent cancer, including prostate cancer. The study followed approximately 15,000 male physicians in the US for an average of 8 years. Overall, neither vitamin E nor vitamin C reduced the incidence of prostate cancer or total cancer.² Participants in both of these well-conducted studies had high levels of adherence to the supplements over several years' duration, and the study

populations were large enough to detect a clinically relevant effect on prostate cancer risk, if one existed.

These null findings highlight the importance of testing candidate chemopreventive agents by conducting large randomized trials with prostate cancer as a prespecified primary end point. Both SELECT and the PHS II trial were established following provocative results from secondary end point analyses of previous trial data. In the mid 1990s the Nutritional Prevention of Cancer (NPC) trial, the aim of which was to examine whether selenium supplementation could prevent the recurrence of non-melanoma skin cancer, found that selenium had no effect on the primary outcome but was associated with a reduction in prostate cancer incidence of 65% (95% CI 35–82%).³ Concurrently, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial was designed to determine whether vitamin E and/or β-carotene supplements could reduce the risk of lung cancer in male smokers. This trial also found no benefit of either supplement on the primary outcome, but reported a reduction in prostate cancer incidence of 34% (95% CI 14–48%) in men taking vitamin E (although this reduction in risk was attenuated after extended follow-up).⁴ These tantalizing findings stimulated great interest in the potential beneficial effects of selenium and vitamin E on

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prostate cancer risk, especially because there are persuasive biological hypotheses for chemoprotective effects of these micronutrients. However, a large trial published in 2005 found no effect of supplementary vitamin E on the incidence of prostate cancer,⁵ and the results of observational studies on the association between prostate cancer and circulating concentrations of selenium and vitamin E have been inconsistent.^{6–8} Overall, the null results from the two 2009 trials add substantial weight to the conclusion that these micronutrients are ineffective in reducing the risk of prostate cancer.

Some may argue that the null findings from these latest trials might, in part, be because these studies were conducted in well-nourished populations already replete in selenium and vitamin E. In particular, it has been suggested that a beneficial effect of selenium supplementation might only be evident among individuals with relatively low plasma selenium concentrations, as suggested by the extended follow-up data of the NPC trial.⁹ Further analyses of SELECT to explore this possibility are planned. It also remains possible that a protective effect might have been seen if these micronutrients had been given at different doses, in different formulations, at different ages, or over a longer period.

Whilst the results of these latest trials are disappointing, perhaps their most important contribution will be to move the focus in research on the chemoprevention of prostate cancer away from nutrients purported to have a general preventive effect, such as antioxidants. The etiology of prostate cancer remains largely unknown, but the one successful trial conducted to date showed that the 5α-reductase inhibitor finasteride can reduce the risk, presumably by reducing intraprostatic levels of dihydrotestosterone. It is possible that dietary factors may influence 5α-reductase activity in the prostate, and this should be further explored. Another important clue is the evidence that high circulating levels of insulin-like growth factor-I (IGF-I) are positively associated with prostate cancer risk.¹⁰ It is known that diet can affect IGF-I

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metabolism, and dietary changes which reduce the exposure of the prostate to IGF-I might be a more productive chemopreventive approach for prostate cancer than the general addition of micronutrients to the diet.

For the time being, men should not be advised to take nutritional supplements of selenium or vitamin E over the long term to reduce their risk of prostate cancer, or any other type of cancer.

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Competing interests

The authors declared no competing interests.

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PATHOLOGY

The lottery of conventional prostate biopsy

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Increasing the number of prostate biopsy cores taken does not improve diagnostic accuracy. Instead, urologists need to think in three dimensions and use template guidance to improve cancer detection and characterization.

Conventional prostate biopsy is often misleading. Cancers are frequently missed on initial biopsy and, when detected, are frequently mischaracterized in terms of size, Gleason score and precise location within the prostate. Such information has important implications for treatment selection, and is directly relevant to patient outcomes. The report by Delongchamps *et al.*¹ should be a reminder to every urologist that, as a specialty, we need to do a better job of biopsying the prostate.

This study convincingly shows that merely increasing the number of biopsy cores is not the answer to the problem. A fairly extensive 36-core biopsy (Figure 1) performed in 48 autopsied prostates (median volume 35 ml) missed 5 of 12 (42%) cancers found on whole-mount pathologic analysis. In fact,

the 36-core biopsy offered no benefit over an 18-core protocol in terms of prostate cancer detection. Among the 7 tumors that were discovered, 3 (43%) were incorrectly graded. While all five of the missed tumors were small (index volume <0.5 ml; median 0.08 ml), two were deemed clinically significant on the basis of their relatively high Gleason score, or pathologic stage. These *ex vivo* data represent yet more evidence of the limitations of conventional prostate biopsy, which have been highlighted by a number of other studies.^{2–4}

What then is the urology community to do to improve the situation? Increasing evidence suggests that the solution is to embrace strict template-guidance and three-dimensional techniques for biopsy of the prostate. If we can distribute cores throughout all regions of the prostate that might harbor prostate cancer, we will optimize the detection and characterization of these tumors. Template guidance offers an advantage over merely increasing the number of cores, in that the precise location of each core is known. If an initial biopsy is negative for cancer, subsequent biopsies can be arrayed in such a way as to sample different regions of the prostate. By contrast, non-template-guided biopsies do not precisely record information on the location of cores, and subsequent biopsy might inadvertently resample the same areas. The ability to sample truly unique locations on subsequent biopsies is likely to allow detection of even very small tumors. Although definitive studies to date are lacking, emerging data strongly support that three-dimensional protocols, guided by ultrasound and templates, with biopsy performed via either a transperineal or a transrectal approach, enhance the identification, localization and characterization of prostate cancers, compared with conventional office biopsy.

The three-dimensional transperineal mapping approach to prostate biopsy generally employs a brachytherapy-like grid to array biopsy cores at 5–10 mm intervals

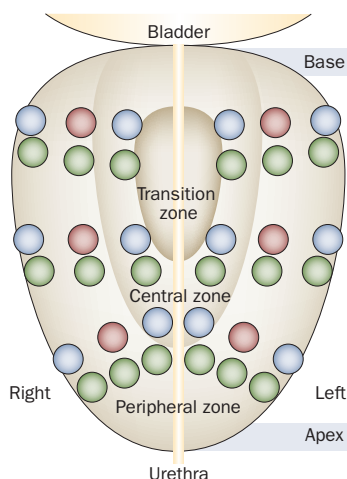


Figure 1 | A 36-core saturation biopsy scheme, as used by Delongchamps *et al.*¹ The red cores represent a conventional sextant biopsy; the addition of the blue cores brings this up to an extended 18-core biopsy. For the 36-core biopsy, each of these sites is resampled (green cores). Modified, with permission, from Delongchamps, N. B. *et al.* *Prostate Cancer Prostatic Dis.* doi:10.1038/pcan.2008.38 (2008) © Macmillan Publishers Ltd. All rights reserved.