showed that radium-223 was the first radionuclide to improve OS and quality of life in a phase 3 randomised comparison with placebo [4]. The combination of radium-223 with enzalutamide or ABI was considered to be safe, with 21% of patients who received radium-223 discontinuing it because of toxicity [5], a slightly higher rate than the 16% observed in the ALSYMPCA trial without addition of enzalutamide or ABI [4]. In the prospective, nonrandomised, open-label, single-arm, phase 3b study, enzalutamide or ABI combined with radium-223 may have resulted in better outcomes compared to radium-223 monotherapy, although median OS for the combination group was not reached in the initial report, precluding estimation of the statistical significance [5]. The ERA-223 trial showed no survival benefit for the combination of radium-223, prednisone, and ABI, and a higher risk of fractures. On July 26, 2018, the European Medicines Agency issued a warning on the use of radium-223 dichloride in combination with ABI acetate for men with metastasized prostate cancer considering the higher risk of bone fractures and death (www.ema.europa.eu/en/medicines/human/referrals/xofigo). It was suggested that use of prednisone may have increased the risk of fractures when combined with radium-223 [6], and combining radium-223 with enzalutamide may still be valid provided it is taken with bone-protecting agents. It remains remarkable, however, that OS is not improved in the radium-223 arm as it was in the ALSYMPCA trial. Looking at differences in population between ALSYMPCA and ERA-223, median OS was 11.3 mo for the control group in ALSYMPCA and approximately 33.3 mo in ERA-223. This may reflect the higher metastatic load in ALSYMPCA versus ERA-223 (>20 metastases in 30% vs 17%), as well as poorer performance status (25% vs 69% Eastern Cooperative oncology Group score 0) and higher frequency of prior docetaxel use (57% vs 1%). This may imply that radium-223 is of more benefit in the management of later-stage disease, preferably in men with sufficient bone protection without ABI use.

Conflicts of interest: The author has nothing to disclose.

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Henk van der Poel*
Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands

*Department of Urology, Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066CX, The Netherlands.
E-mail address: h.vd.poel@nki.nl.

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Re: Tea's Value as a Cancer Therapy is Steeped in Uncertainty

Eisenstein M

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Experts' summary:

Eisenstein reviews the controversial evidence accumulated over the years on the role of green tea and its constituent molecules as potential anticancer weapons for different types of tumor, including prostate cancer (PC). Epidemiological investigations indicate that the frequency of PC is much lower in eastern countries [1] such as China and Japan, where green tea is widely consumed. Specific large-scale studies also point in the same direction, underlining the beneficial effects of green tea in reducing not only the overall risk of cancer mortality [2] but also cardiovascular diseases [3]. Beneficial effects of green tea have largely been ascribed to a family of polyphenolic molecules known as catechins, mostly epigallocatechin-3-gallate (EGCG), which comprises up to 65% of the total green tea catechin content. However, while EGCG has strong pharmacological effects both in vitro and in in vivo animal models, its therapeutic benefits in humans remain elusive. Several reasons might account for this, the first probably being that the effective dose given to mice would be impractical for use in humans. However, the author also underlines the intriguing outcome of a small-scale Italian study that demonstrated that green tea extracts were effective in preventing high-grade prostate intraepithelial neoplasia from developing into PC [4].

Experts' comments:

The lack of translation of preclinical green tea studies into successful clinical trials is certainly disappointing and underlines the intrinsic difficulties in studying the medical benefits of natural products in humans. However, there are still several avenues of research that could possibly be exploited. For instance, recent studies have confirmed the

importance of fueling lipidogenesis in aggressive PC [5,6]. Very recent data from our group further underline this point: we found that lower ability to perform mitochondrial β-oxidation of fatty acids (FAs), inducing an alternative route to lipidogenesis to preserve high cellular FA levels, is linked to the expression of at least two markers of poor PC prognosis in the large The Cancer Genome Atlas (TCGA) cohort [7] (oncogene *ERG* [8] and long noncoding RNA *TRPM2-AS* [9]). Since it has been shown that EGCG, along with other naturally occurring flavonoids, has the ability to decrease cellular FA levels [10], at least some of its therapeutic potential remains unblunted in principle.

Considering evidence from population studies and the need to using a prohibitive amount of EGCG to achieve therapeutic efficacy, we propose to test green tea consumption during active surveillance (AS) rather than during the more limited treatment time frame. While ensuring curative treatment for patients when actually required, AS is a well-established management option for patients with low- or very low-risk PC that is possible because of the long latency period of this disease [11]. With follow-up periods extending for up to 20 yr [11], it could be hypothesized that prolonged consumption of standard doses of green tea might contribute to achieving a higher body concentration of its active components, which might somehow reproduce the therapeutic benefits observed in animal models at the highest dosage. This could ultimately slow down PC progression to more aggressive disease [12] (primary endpoint), possibly by mimicking some of the benefits observed in Eastern populations, with the possibility to test the latter hypothesis even at the molecular level [13,14] (secondary endpoint).

Finally, molecular tumor classification, possibly via mining of large data sets such as the TCGA or from urine or blood specimens [15], could suggest other adjuvant nonpharmacological approaches, such as other dietary supplements, caloric restriction, and physical exercise, to be tested alone or in combination with green tea. This could ultimately lead to a possibly improved active (hyperactive?) surveillance protocol to be tested.

Conflicts of interest: The authors have nothing to disclose.

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Giovanni Lavorgna[a], Francesco Montorsi[a,b], Andrea Salonia[a,b,*]

[a]*Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy*

[b]*University Vita-Salute San Raffaele, Milan, Italy*

*Corresponding author. Department of Urology, University Vita-Salute San Raffaele, Via Olgettina 60, Milan 20132, Italy.

E-mail addresses: salonia.andrea@hsr.it, saloniaandrea@yahoo.com (A. Salonia).

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