ALINEA

NUTRITION

FEBRUARY 2021

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Sadeghian M, Asadi M, Rahmani S, Sadeghi N, Hosseini SA, Zare Javid A. Lycopene Does Not Affect Prostate-Specific Antigen in Men with Non-Metastatic Prostate Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutr Cancer. 2020 Dec 23:1-12.

What We Know, Think We Know, or Are Starting to Know

Prostate cancer is the second-leading cause of cancer mortality in men. However, there are clear divergences in prognosis relative to the stage of diagnosis: early stage prostate cancer may have a 100% 5yr survival rate, which is slashed in half with late stage, advanced prostate cancer, a 1 in 2 5yr survival rate [(1)]. Therefore, screening and detection have become a focal of prostate cancer research.

The introduction of prostate-specific antigen [PSA] in the early 1990's as a biomarker for screening prostate cancer altered the research landscape [(2)]. PSA screening resulted in biologically indolent [i.e., slow growing] cancers, which are latent or asymptomatic, being diagnosed as cancer, leading to an increase incidence of diagnosis without any corresponding change in prostate cancer mortality [(3)]. A majority of men with elevated PSA have no present prostate cancer, and 10% of diagnoses of prostate cancer based on PSA are false-positives [(4)].

From a nutrition science perspective the ramifications of PSA screening have not been academic. For epidemiology, while cohort studies generally have 'hard' events as endpoints, PSA became considered an 'event', i.e., representative of prostate cancer, rather than a biomarker. For interventions, PSA as an outcome may be unrelated to the effect of a nutrient on actual activity of the cancer, potentially resulting in null findings which may be in error.

With prostate cancer, the focal point of nutrition research has been lycopene. Lycopene is a phytochemical in the carotenoid* family, for which tomatoes account for 85% of dietary intake overall, and cooked tomato products in particular account for 82% of intake.However, in 2018 the World Cancer Research Fund updated its status on lycopene and risk of prostate cancer to "no conclusion possible" [(5)]. The present study was a meta-analysis of the effect of lycopene supplementation on PSA levels.

*Geek Box: Carotenoids

Carotenoids are a dizzying group of compounds, with over 600 known in nature. Carotenoids are pigments, and the diversity in the chemical structures of the compounds is reflected in the spectrum of colour, from dark greens with chlorophyll to yellow with lutein and zeaxanthin, orange with beta-carotene, and red with lycopene. Thus, it is lycopene which gives tomatoes their distinct pigment. It is also the pigments of these compounds which confers antioxidant properties, among other mechanisms of action. Carotenoids are synthesised by plants, algae, and certain bacteria, and cannot be synthesised endogenously in humans, although the only carotenoid with nutritional value is beta-carotene as provitamin A. The remaining carotenoids, while lacking nutritional value, like other phytochemical compounds are biologically active and exhibit a diverse range of functions. Carotenoids are highly fat-soluble, and are absorbed in much the same way as dietary fat - intestinal absorption and packaged into chylomicrons. The bioavailability of carotenoids is strongly influenced by fat content of a meal, food processing, and type of carotenoid. Consuming a higher fat meal results in significantly greater circulation levels of lycopene and beta-carotene, compared to a very low or no-fat meals. In addition, increasing concentration through processing and the effect of heating in food processing results in significantly enhanced uptake and efficiency of absorption. For example, while fresh tomato may contain ~2,900mcg lycopene per 100g, tomato paste may contain a range of 5,400-15,000mcg. Tomato paste may thus yield a 3.8-fold greater bioavailability for lycopene than fresh tomatoes in humans, although there is no difference for alpha-carotene or beta-carotene, which demonstrates how the carotenoids may differ in bioavailability based on structural type. Besides provitamin A activity of beta-carotene, carotenoids act as fat-soluble antioxidants, acting as both a chain-breaking antioxidant [i.e., direct scavenging of free radicals] and also upregulate endogenous antioxidant activity. Carotenoids tend to be stored locally in tissues, and provide cells with resistance to oxidative stress and damage. There are a number of potential mechanisms of action in relation to cancer, including cell DNA repair, apoptosis of cancer cells, reduced cell proliferation, and anti-angiogenic activity. While these remain largely mechanistic, however, carotenoid research has produced some crucial, if unheralded, progress for nutrition science, specifically "golden rice". In the developing world, vitamin A deficiency remains the leading nutrient deficiency and cause of morbidity - specifically child blindness - and child mortality. In 2000, scientists Ingo Potrykus and Peter Beyer genetically engineered rice, a crop which lacks carotenoid synthesis capacity, to have a pathway of provitamin A [beta-carotene] synthesis. This gave the rice a yellowy pigment, hence the term "golden rice". Rice with this provitamin A synthesis pathway were able to produce 35mcg beta-carotene per gram - and provide a potential resolution to the scourge of vitamin A deficiency in the developing world. Unfortunately, anti-GMO activists have been successful in preventing the rollout of golden rice, a tragic example of anti-science disinformation successfully derailing the alleviation of needless human suffering.

The Study

The researchers conducted a meta-analysis, with the following inclusion criteria:

- Randomised controlled trials
- Patients with non-metastatic prostate cancer [defined as PSA progression despite anti-androgen therapy, in the absence of identifiable disease]
- Lycopene supplement or tomato products as intervention treatments
- A comparison group of controls, including placebo, usual care, no treatment, or usual diet
- The study reported means and standard deviations for changes in PSA levels before and after the trial in both groups

Subgroup analyses were conducted based on study duration [>6-weeks vs. <6-weeks] and baseline PSA levels [>6.5mcg/L vs. <6.5mcg/L]. The included studies were also analysed to determine whether one study or group of studies influenced the outcomes.

Results: 6 studies were included in the final analysis. Sample size of the studies ranged from 22 to 77 participants, providing a total of 317 in the meta-analysis, and age ranged from 57-79yrs. 5 trials used lycopene extract supplements, while 1 trial used tomato products: the range of lycopene intake per day was between 15-45mg. Study duration range from 3-28 weeks. All studies measured PSA levels. One study compared three levels of lycopene supplementation, and each dose was treated as a separate effect for the overall meta-analysis.

- ***Qualitative Review:*** Of the 6 included studies, 2 found a statistically significant reduction in PSA levels, 2 found a statistically insignificant reduction in PSA levels, and 2 found no effect of lycopene on PSA levels.
- ***Overall Meta-Analysis:*** Combining the 6 studies [8 effect sizes included the study with doses treated separately] resulted in a statistically insignificant reduction in PSA of 0.60mcg/L [range -2.01 to 0.81mcg/L].
- ***Subgroup Analysis:***
    - **Study Duration**: The mean reduction in PSA in studies <6-weeks was 0.66mcg/L compared to 0.35mcg/L in studies >6-weeks duration; there was no statistically significant difference between groups.
    - **Baseline PSA**: There was a significant effect of lycopene supplementation in studies with participants whose baseline PSA levels were >6.5mcg/L. In these participants, the mean reduction in PSA was 3.74mcg/L [range -5.15 to -2.32mcg/L]. Conversely, in participants with PSA <6.5mcg/L at baseline, the mean reduction in PSA was 0.57mcg/L, which was not statistically significant.

The Critical Breakdown

Pros: The inclusion criteria was clearly defined. Studies were systematically reviewed and qualitatively presented. The statistical method for combining the results of the primary studies was clearly presented. The subgroup and sensitivity analysis explored the included studies for relevant potential mediating factors, e.g., baseline PSA levels.

Cons: There were significant heterogeneity between studies, which is a common challenge for nutrition meta-analysis, but ultimately means that differences between studies on key issues may influence the results. For example, lycopene supplements often contain added fats to aid absorption, however, no information is provided regarding the supplements beyond the lycopene dose.

Key Characteristic

The outcome of any meta-analysis reflects the inclusion criteria, i.e., the input dictates the output. In this case, the trials included patients with progression of PSA [i.e., increasing levels despite treatment]. This is important because in the lycopene literature, the strongest associations for a protective effect of lycopene against prostate cancer [PCa] have been observed in men with a PSA-negative tests at baseline [2]. This is likely because any subsequent diagnoses reflects a true change in the activity of the cancer. A 2015 meta-analysis demonstrated that the association with lycopene was significant in reducing risk in studies pre-PSA [circa. 1994], but not significant subsequent to widespread screening [6]. Why?

Because it appears that the most significant reductions in PCa risk from lycopene relates to advanced stage and/or aggressive PCa [7]. Nordström et al. analysed blood lycopene levels in relation to low-grade or high-grade PCa , and found that the odds for high-grade PCa decreased at the highest levels of lycopene [8]. They also found that in low-grade PCa, lycopene levels reduced prostate genomic instability, a marker of aggressive cancer [8].

So what is all of this telling us? It points to a protective effect of lycopene early in the natural history of PCa, and suggests that the primary role of lycopene is to inhibit PCa progression, not total incidence of diagnoses as defined by PSA [2,6-8]. The effects of lycopene on PSA levels per se may not necessarily reflect the effect of lycopene on PCa risk, where the stage of PCa is highly relevant to the potential effects of lycopene.

Interesting Finding

The significant effect of lycopene supplementation in studies with participants whose baseline PSA levels were >6.5mcg/L may reflect not only the PSA level, but the activity of the disease at that stage. These studies not only demonstrated an 18% reduction in PSA levels, but the intervention group also exhibited smaller tumours compared to controls and had other evidence of inhibited cancer progression [9]. Conversely, let' s contrast this one of the included studies which did not find any effect of lycopene on PSA levels, which despite no change in PSA levels found that 75% of participants taking 30mg lycopene had decreased cell proliferation [10]. These included studies further demonstrate the point under ***Key Characteristic*** above that PSA levels do not necessarily serve as a proxy for the effect of lycopene on PCa risk.

Relevance

PSA screening has had a substantial influence on the evidence relating lycopene to PCa risk. It is important to clarify, however, that this Deepdive is not an assessment of the pros and cons of PSA screening with regard to PCa. It is simply highlighting the discrepancy which emerged in the evidence-base with the introduction of PSA-screening. To clarify the difference from a research perspective, pre-PSA an "event" constituted an overt diagnosis of PCa; post-PSA a diagnosis constituted a positive PSA test [11]. The introduction of screening resulted in more diagnoses, many of which were biologically indolent or asymptomatic, which would not have been diagnosed in the pre-PSA era. Because the associations between lycopene and PCa risk primarily relate to cancer progression to advanced/aggressive PCa, included PSA-positive cases at baseline rendered a true association between lycopene and PCa more difficult to detect [11].

This is important when we consider the present meta-analysis under review. This study is not an evaluation of the efficacy of lycopene in preventing prostate cancer, but an evaluation of the effect of lycopene on reducing PSA levels. As noted above, the included studies found benefits to lycopene supplementation on other markers of PCa, independent of higher or lower baseline PSA levels. The relationship between plasma lycopene levels and PCa may not necessarily be evident through the lens of PSA alone. In a recent example, a study looking at asymptomatic, local-stage PCa failed to find any association with serum lycopene and risk relative to PSA levels [12]. Conversely, higher circulating lycopene levels lower tumour genomic instability and DNA damage, two characteristic features of cancer stage progression [8].

We are probably still somewhat off fully reconciling the evidence in this area. The distinct divergence of research findings between the pre and post PSA era suggests that the the stage of cancer relative to lycopene levels is a crucial modifying factor. Consequently, when considering indolent cancer identified by PSA within the context of total PCa incidence, the literature concludes no association between lycopene and PCa, but in considering only incidence of advanced stage and/or aggressive PCa, there are significant inverse associations between lycopene and PCa [2,6,7]. There are also plausible biological mechanisms of action through which carotenoids and lycopene may inhibit PCa progression.

Perhaps if the present study had also looked at cancer cell proliferation, oxidative stress, DNA damage, etc., rather than PSA alone, a more informative picture would emerge.

Application to Practice

The study has added to the inconclusive evidence for lycopene and prostate cancer. Through the lens of PSA, lycopene may not be considered effective for prevention of PCa. However, through plausible biological mechanisms and at physiological levels obtainable through diet, lycopene may inhibt PCa progression and reduce incidence of advance-stage and aggressive PCa. Further research would be more helpful by focusing on more specific characteristics of cancer metabolism.

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