Progress in Nutrition 2018; Vol. 20, N. 4: 545-548 DOI: 10.23751/pn.v20i4.7329

Original article

Lycopene and prostate cancer: an overview

*Francesco Carini[1], Marie Noel Zeenny[1], Margherita Mazzola[1, 2], Benedetto Di Trapani[2], Vincenzo Palumbo[2], Alice Geagea Gerges[1], Emanuele Sinagra[2,4], *Angelo Leone[2, 3], *Giovanni Tomasello[1]*

[1] Department of Experimental Biomedicine and Clinical Neuroscience, Section of Human Anatomy, (BIONEC), University of Palermo, Italy - E-mail: giovanni.tomasello@unipa.it; [2]Euro Mediterranean Institute of Science and Technology–IEMEST Palermo, Italy; [3]Department of Experimental Biomedicine and Clinical Neuroscience, Section of Histology and Embryology, (BIONEC), University of Palermo, Italy; [4]Endoscopic Unit, Hospital of Cefalù, Italy

Summary. Prostate cancer is one of the most common cancers in the world. Its pathogenesis is multifactorial and is linked to risk factors such as age, diet, cigarette smoking, family history and the onset of oxidative stress. In recent times, therefore, we are investigating the use of antioxidants as primary and tertiary prevention of prostate cancer. Numerous studies in the literature focused on lycopene, a molecule belonging to the family of carotenoids that is commonly found in tomatoes and products derived from it. The literature analyzed in the last two years shows how lycopene inhibits different mechanisms linked to carcinogenesis and tumor progression. However, there are still many points to be clarified the real antitumoral capacity of this substance.

Key words: lycopene, prostate cancer, antioxidants, oxidative stress, tomato

Introdution

Prostate cancer is one of the most widespread male diseases in the world, and is defined as a tumor that originates from the uncontrolled proliferation of prostate tissue cells (1,2). It is an initially asymptomatic pathology whose pathogenesis is multifactorial and includes factors such as age (the elderly are more at risk), inheritance, metabolic diseases, smoke of cigarette, diet, alcohol consumption and sexually transmitted diseases (2) In addition, another possible cause of prostate cancer is represented by oxidative stress (3), which is an imbalance between oxidizing agent and antioxidant species that leads to the production of free oxygen radicals (ROS). ROS causes structural damage to cell membranes and DNA and may be responsible for the release of inflammation mediators (4-6). In the specific case of prostate cancer, it has been highlighted that the production and accumulation of ROS in prostate cells is related to the presence of serum androgens (3).

For this reason, lately we are focusing on the use of antioxidants, such as lycopene, as prevention of prostate cancer.

Lycopene

Lycopene is a pigment belonging to the carotenoid family, which is mainly found in tomatoes, to which it gives the typical red color (7-9). Thanks to its particular chemical structure it is considered a strongly antioxidant substance, whose main actions take place at the level of stimulation of endogenous antioxidant enzymes (such as glutathione peroxidase, glutathione reductase and glutathione-S-transferase), inhibition of cytochrome P450 2E1 (responsible for the transformation of xenobiotics into carcinogens), inhibition of

*A.L. and G.T. share last authorship

IGF-1 (responsible for many inflammatory processes) and inhibition of metalloproteinases (which play a fundamental role in tumor angiogenesis) (9).

Lycopene also promotes apoptosis by increasing the activity of pro - apoptotic molecules (such as Bax and Bim) and reducing the activity of anti - apoptotic molecules (such as Bcl-2) (9,10)

Analysis of the literature

Our literature analysis took into consideration studies done in the last two years (2016 and 2017) to understand where we are with lycopene research and its effects on prostate cancer. Studies with valuable qualities were included in this review. Most of the articles were taken from PubMed and EMBJ. Cohort studies including 10 women and four men were used to collect more data on the effect of lycopene on prostate cancer. Large cohort studies collected pre-diagnosis data of 8,898 men of whom 526 died of prostate cancer in 2012 with another post-diagnosis dietary data of 5,643 men of whom 363 died of prostate cancer through 2012. Data was also collected from in vitro and clinical studies. Evidence was taken from prospective cohort population of 46,719 men from Health Professionals Follow-Up Study during a follow-up of 23 years. Most of the used data was published in the last two years.

A first study (2) shows how a tomato sauce is consumed 2 to 4 times a week, reduces the risk of prostate cancer by 35% . Furthermore, in the same study it is highlighted as a food supplementation of 15 mg of lycopene (twice a day for at least three weeks) reduces the plasma levels of IGF - I, which as we have seen previously appears to be one of the risk factors for the development of prostate cancer (2).

A second study (11) poses the hypothesis that lycopene, being a powerful antioxidant, could reduce the mutations that occur at the DNA level. In particular, the study focuses on the gene rearrangement TMPRSS2:ERG (fusion between the transmembrane protein protease serine 2 or TMPRSS2 and v-ets avian erythroblastosis virus E26 oncogene homolog or ERG) associated with prostate cancer and linked to the synergistic action between stress genotoxic and increased androgen receptor signaling. The results of the study show, in the first instance, how the consumption of lycopene and tomato sauce is inversely proportional to the risk of developing prostate cancer. Secondly, lycopene consumption appears to reduce both genotoxic stress and increased androgen receptor signaling, thereby also reducing the risk of gene rearrangement TMPRSS2:ERG associated with prostate cancer (11).

A third in vitro study (8) shows how the administration of 5 mg/ml of lycopene to cell cultures deriving from prostatic carcinoma, increases the rate of apoptosis and decreases cell viability. Specifically, the consumption of lycopene and products derived from tomatoes, would increase the expression of Bax (pro - apoptotic protein) and decreasing that of Bcl-2 (anti - apoptotic protein) thus favoring the death of cancer cells. It also seems that, with mechanisms that probably involve the over-expression of Bax and the down-regulation of cyclin D1 involved in the cell cycle, lycopene also intervenes at the cell cycle level, inhibiting it, and consequently arresting cell proliferation (8).

A fourth study (12) aimed at understanding whether a diet rich in lycopene (30 mg per day) could modify PSA levels (specific prostate antigen) in patients with non-metastatic prostate cancer. The treatment lasted for three weeks and showed a decrease in PSA of 0.23 mg/mL (12).

Mechanisms of action

Despite the numerous studies that demonstrate its protective role in prostate cancer prevention, little is known about mechanisms by which lycopene inhibits prostate cancer.

The mode of action by which dietary lycopene intake reduces prostate cancer risk is still unclear (13). The use of laboratory rodents as animal models in assessing the association between increase lycopene consumption on prostate cancer risk is hindered due to the poor absorption of carotenoid (14). Lycopene is one of the most potent antioxidants that could potentially induce its protective effect even early in the disease onset. Smoking could inhibit its anticancer roles (15).

More studies should be conducted for a better understanding of the mechanisms by which lycopene induces its chemopreventive role. However, it is well

established so far that lycopene inhibits the prostatic IGF-1 signaling, modulates IL-6 expression, improves gap-junctional communication, reduce DNA damage, improve oxidative stress defense and modulates androgen signaling.

A study performed by Soares et al. showed that lycopene products such as tomato sauce, tomato extract, tomato paste and ketchup inhibit cell viability of prostate cancer by 39.7 %. In addition, Tan et al. showed that the anticancer potential of lycopene in prostate cancer arose in its genetic cleavage impact through its metabolism in TRAMP/ BCO2 dependent model. Studies have shown that epigenetic loss of the enzyme βcarotene 9',10'-oxygenase (BCO2) which catalyzes asymmetric cleavage of several carotenoids, is significantly down regulated in human prostate cancer (16).

Treatment with lycopene increased the expression of BCO2 gene and thus decreased in cell proliferation and colony formation in only androgen-sensitive cell lines signaling. Therefore, epigenetic loss of the BCO2 enzyme is correlated with prostate cancer progression. Treatment with lycopene or its metabolite, apo-10-lycopenal, increases the tumor suppressor gene BCO2 leading to a reduced NF-κB signaling. Consequently, lycopene treatment activated the expression of the tumor suppressor gene BCO2 (17).

Lycopene treatment from tomato extract in primary prostate cancer cells promoted a significant increase of the tumor suppressor gene TP53 protein and Bax transcript levels (18). As in many types of cancers, prostate cancer shows an abnormal loss of Bcl-2 protein associated with the loss of TP53. Quantification of cell apoptosis revealed that lycopene repressed the anti-apoptotic Bcl-2 protein expression.

The pathway through which lycopene products plays an important role in DNA repair, cell cycle arrest and apoptosis is mainly through the transcription-dependent pathways of p53 (18,19). Therefore, tomato-based such as ketchup, tomato sauce, tomato paste and pizza are able to act as anti-tumor agent by arresting cell proliferation and inducing apoptosis (18). Deletion of the important BC02 cleavage enzyme reduces significantly the chemopreventive impact of lycopene in prostate cancer.

The mechanism of action underlying the protective role of lycopene in reducing the proliferation of cancerous prostate epithelial cells is by reducing DNA damage and enhancing the oxidative stress defense (20).

Lycopene and tomato sauce could potentially reduce the common fusion transmembrane protease, serine 2 (TMPRSS2): v-ets erythroblstosis virus E26 oncogene homolog (ERG) (20).

Conclusions

Although the results of the studies carried out over the last two years seem encouraging, there are still many points to be clarified regarding the actual antitumor activity of lycopene. The critical points remain the in vitro results, the bioavailability of lycopene when administered in vivo, and the individual parameters of each individual subject that could influence and vary the response to lycopene. However, it is advisable to continue the research in this direction as it could be a great advantage to be able to say that the intake of lycopene, starting from commonly used products such as tomato or tomato sauce, has a real effect on prevention and progression of prostate cancer. We must not underestimate the psychological impact that such a discovery could have on the population. Knowing that, alongside the known therapies, there may also be the possibility of combining completely natural therapies, such as the consumption of tomato, could improve the quality of life in psychological terms as they would feel they had more "weapons" available for to combat tumor pathology.

References

1. Chen J, Song Y, Zhang L. Lycopene/tomato consumption and the risk of prostate cancer: a systematic review and meta-analysis of prospective studies. J Nutr Sci Vitaminol 2013; 59: 213-23
2. Perdana NR, Mochtar CA, Umbas R, Hamid AR. The Risk Factors of Prostate Cancer and Its Prevention: A Literature Review. Acta Med Indones. 2016; 48: 228-238
3. Oh B, Figtree G, Costa D, et al. Oxidative stress in prostate cancer patients: A systematic review of case control studies. Prostate International 2016; 4: 71-87
4. Mazzola M, Carini F, Leone A, et al. Inflammatory bowel disease and colorectal cancer, nutraceutical aspects. Euro-mediterranean biomedical journal 2016; 11: 123-29

5. Scardina GA, Pisano T, Carini F, Valenza V, Messina P. Burning mouth syndrome: an evaluation of invivo microcirculation. J Am Dent Assoc 2008; 139: 940-46.
6. Tomasello G, Mazzola M, Leone A, et al. Nutrition, oxidative stress and intestinal dysbiosis: Influence of diet on gut microbiota in inflammatory bowel diseases. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2016; 160: 461-66
7. Wang Y, Jacobs EJ, Newton CC, McCullough ML. Lycopene, tomato products and prostate cancer-specific mortality among men diagnosed with non metastatic prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Int J Cancer 2016; 138: 2846-55
8. Soares ND, Machado CL, Trindade BB, et al. Lycopene Extracts from Different Tomato-Based Food Products Induce Apoptosis in Cultured Human Primary Prostate Cancer Cells and Regulate TP53, Bax and Bcl-2 Transcript Expression. Asian Pac J Cancer Prev 2017; 18: 339-345.
9. Carini F, David S, Tomasello G, et al. Colorectal cancer: an update on the effects of lycopene on tumor progression and cell proliferation. J Biol Regul Homeost Agents 2017; 31: 769-774
10. Trejo-Solís C, Pedraza-Chaverrí J, Torres-Ramos M, et al. Multiple molecular and cellular mechanisms of action of lycopene in cancer inhibition. Evid Based Complement Alternat Med 2013; 2013:705121
11. Graff RE, Pettersson A, Lis RT, et al. Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. The American Journal of Clinical Nutrition 2016; 103: 851-860
12. Paur I, Lilleby W, Bøhn SK, et al. Tomato-based randomized controlled trial in prostate cancer patients: Effect on PSA. Clin Nutr 2017; 36: 672-679.
13. Chen L, Stacewicz-Sapuntzakis M, Duncan C, et al. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst 2001; 93: 1872–79.
14. Lee C, Boileau A, Boileau T, et al. Review of animal models in carotenoid research. J Nutr 1999; 129: 2271–77.
15. Graham DL, Carail M, Caris-Veyrat C, Lowe GM. Cigarette smoke and human plasma lycopene depletion. Food Chem Toxicol 2010; 48: 2413–20.
16. Tan HL, Thomas-Ahner JM, Moran NE, et al. β-Carotene 9',10' Oxygenase Modulates the Anticancer Activity of Dietary Tomato or Lycopene on Prostate Carcinogenesis in the TRAMP Model. Cancer Prev Res (Phila). 2017; 10: 161-169.
17. Gong X, Marisiddaiah R, Zaripheh S, Wiener D, Rubin LP. Mitochondrial β-Carotene 9›,10› Oxygenase Modulates Prostate Cancer Growth via NF-κB Inhibition: A Lycopene-Independent Function. Mol Cancer Res. 2016; 14: 966-975.
18. Soares N, Teodoro A, Oliveira F, et al. Influence of lycopene on cell viability, cell cycle, and apoptosis of human prostate cancer and benign hyperplastic cells. Nutr Cancer 2013; 65: 1076-85.
19. Tomkova K, Tomka M, Zajac V. Contribution of p53, p63, and p73 to the developmental diseases and cancer. Neoplasma 2008; 55: 177-81.
20. Wertz K, Siler U, Goralczyk R. Lycopene: modes of action to promote prostate health. Arch Biochem Biophys.2004; 430: 127-34.

Correspondence:
Prof. Giovanni Tomasello
Department of Experimental Biomedicine and
Clinical Neuroscience, Section of Anatomy
University of Palermo
E-mail: giovanni.tomasello@unipa.it