**Review Article**

**Vitamin E and Prostate Cancer: A Review**

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**Abstract**

The incidence of prostate cancer is increasing and there is continuing research into possible preventive treatments. Vitamin E, an antioxidant, has been studied as a chemoprotective agent in recent literature with $\alpha$-Tocopherol being the most prominently studied. Although $\alpha$-Tocopherol is found in highest concentration in the body, there are seven other isomers of vitamin E as tocopherols and tocotrienols, most notably $\gamma$-Tocopherol, which is most common in nature. Chemoprotective evidence of high dose $\alpha$-Tocopherol is lacking however there is promising evidence indicating the benefit of $\gamma$-Tocopherol in prevention and treatment of carcinoma of the prostate. Recent studies showing a correlation between high $\alpha$-Tocopherol and prostate cancer is likely due to this specific isomer’s effect on decreasing $\gamma$-Tocopherol levels. This review thoroughly analyzes the relationship and impact of vitamin E on prostate cancer covering biogenesis, mechanism of action and review of animal and human trials. It is the purpose of this review to expose the evidence behind all vitamin E isomers and prostate cancer. Our review indicates further research is required as there is promising evidence of the role of vitamin E, particularly $\gamma$-Tocopherol, and prostate cancer prevention.

**INTRODUCTION**

Prostate cancer has been a disease always concerning to physicians. In the most recent statistics, a total of 238,590 American men will be diagnosed with prostate cancer this year with 29,720 dying from the disease [1]. In 2010 it was approximated that 32,050 men would die from prostate cancer [2]. Although the current data is showing rates of prostate cancer mortality is decreasing, there is indication that incidence is increasing [3,4]. With advancements in medicine allowing physicians to better diagnose, identify and treat in a timely fashion the increase in prostate cancer incidence does warrant an approach to prevent this deadly disease.

Vitamin E as a chemopreventative agent has gained exposure in the medical field. The idea behind chemoprevention is the ability of a specific naturally occurring compound to prevent, slow or reverse the incidence of cancer [5]. Vitamin E consists of eight different isomers, which includes four different tocopherols ($\alpha$, $\beta$, $\gamma$ and $\delta$) and four different tocotrienols ($\alpha$, $\beta$, $\gamma$ and $\delta$), and all have been researched for their impact on prostate cancer. With the conflicting evidence exposed to patients and Americans, this study aims to clarify the story behind vitamin E and prostate cancer including all vitamin E isoforms and their biological impact on prostate cancer.

**VITAMIN E**

Vitamin E is divided into two subgroups, tocopherols (T) and tocotrienols (TT). The tocopherol isomers consist of a chromanol ring and a saturated 16-carbon side chain with methyl groups attached to the ring. The designation of the methyl group determines whether the tocopherol is $\alpha$, $\beta$, $\gamma$ or $\delta$. The tocotrienol isomers are structured similarly and identified as $\alpha$, $\beta$, $\gamma$ or $\delta$ by the methyl positions, however the carbon side chain is unsaturated at the 3', 7' and 11' carbons [6].

The human body cannot synthesize Vitamin E and of these eight forms $\gamma$-tocopherol ($\gamma$-TP) is the most commonly found in the US diet. It can be found in plant foods such as soybeans, corn, walnuts, peanuts, sesame seeds, and other vegetable oils [7]. Although $\gamma$-T is the most consumed, $\alpha$-T seems to be the predominant form of vitamin E found in human tissue and blood plasma [8].

**Vitamin E absorption and metabolism**

All isoforms of vitamin E are found in the diet and are absorbed similarly. Tocopherols freely enter micelles in the intestinal track before the micelle enters the enterocyte. However, there are tocopherols and tocotrienols that are not in free form but instead are esters. Under these circumstances pancreatic esterase and duodenal mucosal esterase hydrolyze the tocotrienols and tocopherols before they can enter the micelle, from which they enter the lymphatic system and mature to react with specific receptor mediated cells.

The reason for $\alpha$-T being the predominant form of vitamin E found in human tissues and blood plasma relates to a specific...
Prostate cancer and Vitamin E research

The recent SELECT trial showed a positive correlation between vitamin E intake (all rac-α-tocopherol acetate) and prostate cancer [19]. One of the other large studies is the Alpha-Tocopherol Beta-Carotene study conducted by the U.S. National Cancer Institute and National Institute for Health and Welfare of Finland found giving male smokers 50mg/day of α-T resulted in a 32% decrease in prostate cancer (PCa) incidence and a 41% decrease in PCa mortality [20]. These two trials, and all in between, have brought about an interesting debate.

Tocopherols and prostate cancer

Pre-clinical In-vitro: The conversation for vitamin E impact on prostate cancer oftentimes begins in evidence brought out by pre-clinical in-vitro studies. γ-T may not be the most commonly studied tocopherol however there is evidence exposing its benefits in prostate cancer. γ-T administered to PCa cells was shown to inhibit PCa growth by various mechanisms. It promoted expression of 15-S-HETE (15-S-Hydroxyeicosatetraenoic acid), which acts as an endogenous PPAR (peroxisome proliferator-activated receptor) ligand and thus impacting cell differentiation and proliferation. In this study the upregulation of 15-S-HETE arrested PC-3 cell growth. Furthermore it was also able to upregulate 15-Lipoxygenase-2, a tumor repressor. The data suggests that γ-T is best as an agent that may help defend against abnormal cell growth as it works on pathways involved in carcinogenesis [21].

Although α-T is assumed to be dominant form of vitamin E in the body, its ability to increase PCa growth inhibition is challenged by γ-T and δ-T. In treating human PC-3 cells, δ and γ isoforms of the tocopherols were superior in growth inhibitions than α-T [22]. Although α-T did inhibit growth, it did so at greater dosages and time than the other tocopherol isoforms. In androgen-dependent human prostate cancer cells (LNCaP), α-T appeared to enhance cell growth whereas γ-T and δ-T inhibited growth [22].

Tocopherols have been tested independently as there is research indicating there is more beyond just vitamin E intake. Tocopherol transfer protein (TTP) plays an essential role in transporting vitamin E to lipoproteins and other parts of the human body that requires the nutrient [10]. However it was also shown that TTP plays an important role in PCa cells. TTP acts by sensitizing PCa cells to vitamin E allowing a greater intracellular concentration of α-T [23]. This then allowed for vitamin E’s anti-oxidative effects to have an impact within the PCa cell leading to a decrease in Reactive Oxygen Species (ROS). Overexpression of TTP largely sensitized PCa cells to α-T, whereas knocking out TTP expression resulted in vitamin E resistance [23]. Thus suggesting that α-T impact on prostate cancer may be dependent on TTP.

The impact of α-T alone may not always show a benefit for patients with prostate cancer [24,25], however it is suspected that vitamin E does not work alone in prostate cancer. Increasing concentrations of α-tocopherol succinate (α-TOS) were shown to significantly decrease PCa viability [26]. Further the study identified the impact of a combination of α-TOS, vitamin K3 (menadione) and ascorbic acid (AA); finding that when combining the three in sub-apoptotic doses, PCa cell death was induced in an autoschizis cell death manner. With just AA and vitamin
**Table 1:** Summary of tocopherol pre-clinical in-vitro studies and final outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tocopherol (T) isomer</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell, 2011</td>
<td>γ-T &amp; δ-T</td>
<td>δ-T and γ-T both inhibited PC-3 and LNCaP cell growth greater than α-T.</td>
</tr>
<tr>
<td>Tomasetti, 2010</td>
<td>α-tocopherol succinate (α-TOS)</td>
<td>Combining menadione and ascorbic acid with and only with α-TOS stimulated PCa cell death in an autoschizis cell death manner. Reactive oxygenated species and DNA damage occurred to PCa cells only with α-TOS.</td>
</tr>
</tbody>
</table>

**Table 2:** Summary of tocopherol pre-clinical in-vivo studies and final outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tocopherol (T) isomer</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi, 2009</td>
<td>γ-T &amp; α-T</td>
<td>γ-T was shown to be superior to α-T in suppressing the progression from PIN to adenocarcinoma in the prostate ventral lobe in TRAP mice. Mice treated with γ-T showed an increase in apoptotic cells with no observed toxicity.</td>
</tr>
<tr>
<td>Barve, 2009</td>
<td>γ-T</td>
<td>Mice fed an γ-T rich diet exhibited a slowed PIN and tumor progression.</td>
</tr>
<tr>
<td>Lindshield, 2010</td>
<td>γ-T</td>
<td>γ-T fed to Copenhagen mice showed no impact on final tumor area, weight and tumor weight/body weight ratio.</td>
</tr>
<tr>
<td>Ni, 2009</td>
<td>RRR-α-tocopherylxybutyl sulfonic acid (VEBSA)</td>
<td>On LNCaP and PC-3 cells, VEBSA was shown to decrease androgen receptor protein expression, induce apoptosis and enhance VDR expression.</td>
</tr>
<tr>
<td>Zheng, 2011</td>
<td>γ-T rich mixture</td>
<td>SCID mice given the γ-T rich mixture showed dose-dependent inhibition of LNCaP cell growth.</td>
</tr>
</tbody>
</table>

**Table 3:** Summary of tocopherol human studies and final outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tocopherol (T) isomer</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein, 2011</td>
<td>α-T (all-rac-α tocopherol acetate)</td>
<td>Men consuming 400 IU/day of α-T showed a 17% increase in PCa risk.</td>
</tr>
<tr>
<td>ATBC, 1994</td>
<td>α-T</td>
<td>Male smokers consuming 50 IU/day of α-T showed a 35% reduction in PCa risk.</td>
</tr>
<tr>
<td>Tsavachidou, 2009</td>
<td>all-rac-α tocopherol acetate</td>
<td>Men treated with 400 IU/day of α-T showed an increased in PCa cell proliferation. γ-T levels were also significantly reduced after α-T administration.</td>
</tr>
<tr>
<td>Gaziano, 2009</td>
<td>Synthetic α-T</td>
<td>Men treated with 400 IU/day of α-T showed no benefit in PCa and did not decrease PCa occurrence.</td>
</tr>
<tr>
<td>Rodriguez, 2004</td>
<td>α-T</td>
<td>Men consuming 400 IU/day of α-T was not shown to decrease or prevent PCa risk in nonsmokers. However a slight benefit was seen in smokers.</td>
</tr>
<tr>
<td>Weinstein, 2007</td>
<td>α-T</td>
<td>Analysis of the ATBC trial shows that men with the highest quintile of serum α-T have a decreased PCa risk. A progression was noticed from advanced disease to non-advanced disease.</td>
</tr>
<tr>
<td>Helzlsouer, 2000</td>
<td>γ-T</td>
<td>Men in the highest fifth of γ-T plasma concentration had a five-fold reduction in PCa risk, most notable in men with stage II or greater disease.</td>
</tr>
<tr>
<td>Huang, 2003</td>
<td>α-T &amp; γ-T</td>
<td>γ-T concentrations were inversely correlated in men with diagnosed PCa.</td>
</tr>
<tr>
<td>Wright, 2007</td>
<td>α-T &amp; γ-T</td>
<td>Increase dietary γ-T intake was associated with a reduced risk of PCa. Supplemental α-T did not show protective benefits.</td>
</tr>
</tbody>
</table>
Tocotrienol rich fraction γ-TT γ-TT & δ-TT

Tocotrineol (TT) isomer PCa and LNCaP cells treated with γ-TT showed a significant growth inhibition in a

24-hour treatment. The study거나 showed that γ-TT & δ-TT had a similar effect on tumor growth in TRAMP mice [27]. Further, γ-T showed activation of caspases 3 and 7, inactivation of Erk1/2 and decreased expression of bcl-2 in the ventral prostate whereas α-T did not show significant results. The numbers of apoptotic cells in TRAP mice prostate treated with γ-T were significantly increased compared to control. With no observed toxicity γ-TT potentially is an ideal agent for PCa chemoprevention [27].

The mechanism as to how γ-T works may not be known, however TRAMP (transgenic rat adenocarcinoma of prostate) mice fed a γ-T-rich diet showed PIN and tumor progression. γ-TT upregulated expression of Nrf2 and thus the expression of phase 170.

A γ-T rich mixture of tocopherol mixture containing 13% α-tocopherol, 1.5% β-tocopherol, 57% γ-tocopherol and 24% δ-tocopherol was shown to decrease the formation of prostate cancer tumors in immunodeficient SCID (Severe Combined Immunodeficient) mice by up to 70% [28]. This shows the importance of not one form of tocopherols but a mixture with all isomers.

Yet there are suggestions that γ-T has no benefit or impact in treating prostate cancer tumor growth in Copenhagen rats [29]. Vitamin E consumption with lycopene and selenium also did not decrease tumor growth or proliferation, as measured by tumor area, tumor weight and tumor weight to body weight ratio. Thus indicating no benefit for γ-T in PCa treatment under these circumstances. The benefits of γ-T in PCa tumor prevention were not studied.

When analyzing analogues of α-T, one such analogue known as RRR-α-tocopheryl oxybutyl sulfonic acid (VEBSA) was shown to prevent PCa occurrence and progression along with suppressing tumor growth in TRAMP mice [30]. The data then suggests for this analogue to be a means of preventing and therapeutically treating prostate cancer without any toxicity. Although this cannot be applied to each vitamin E stereoisomer, the study does propose that vitamin E may work by inducing apoptosis, repressing androgen receptor protein expression, promoting VDR expression and modulating cell cycle molecule expression [30]. Thus this gives reasoning as to how vitamin E may potential work along with giving the nutrient validity in its impact on PCa.

### Human studies

One of the most recent trials studying the impact of vitamin E (α-T), the SELECT trial has gained much press regarding its findings. A total of 35,553 men were studied and in comparison to placebo, men who were given 400 IU/day of synthetic α-T were significantly higher risk of getting prostate cancer [19]. The men who consumed the 400 IU of α-T and selenium did not show an increased incidence of prostate cancer. Using PSA and DRE as an indicator to identify PCa risk, there was a 17% increase in risk prostate cancer [19].

However in contrast to the SELECT trial is the Alpha-Tocopherol beta-carotene trial (ATBC). The ATBC trial was a double-blind RCT trial that tested the consumption of 50IU/day of α-T on male smokers. The study found a 35% reduction in PCa risk in the men who did consume the 50IU/day of α-T with no impact on total mortality [31]. The SELECT trial α-T dose was 700% that of the ATBC trial. Therefore there is some disparity between the two dosages and their impact on PCa that warrants further research and analysis.

A randomized, placebo controlled, double-blind phase IIIA trial studied synthetic all-rac-α tocopherol acetate (the same type isomer tested in the SELECT trial [19]) on the proliferation of PCa cells in men undergoing prostatectomy biopsy. The study found an increased proliferation in PCa cells after treating with the 400 IU/day of synthetic vitamin E [32]. It was also noted that after administration of all-rac-α tocopherol acetate serum levels of γ-T were significantly reduced. This permits further review as to the role γ-T plays in the proliferation of PCa cells.

The Physicians Health Study II found no benefits of implementing 400IU of synthetic α-T. There was neither a decrease in PCa occurrence in men with no PCa at baseline, nor did it show any benefit in men with PCa [33]. A second study analyzing the Cancer Prevention Study II Nutrition Cohort also showed no benefit for 400 IU of α-T supplementation among men. It was not correlated with benefits in preventing or treating PCa in non-smoking men, however it did show a slight benefit in smokers [24]. A case-control study showed a slight, but not significant inverse correlation between α-T and aggressive PCa.

### Table 4: Summary of tocotrienol pre-clinical in-vitro studies and final outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tocotrienol (TT) isomer</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srivastava, 2006</td>
<td>Tocotrienol rich fraction</td>
<td>Increased concentrations of TRF resulted in decreased growth in LNCaP, DU145 and PC-3 cells. Anchorage-independent growth and colony formation was inhibited with no impact on non-cancerous cells.</td>
</tr>
<tr>
<td>Conte, 2004</td>
<td>γ-TT</td>
<td>PCa and LNCaP cells treated with γ-TT showed a significant growth inhibition in a dose dependent manner.</td>
</tr>
<tr>
<td>Luk, 2011</td>
<td>γ-TT &amp; δ-TT</td>
<td>Both γ-TT and δ-TT exhibited an 8 to 10-fold difference in growth inhibition. Pretreatment of PC-3 cells with γ-T3 was found to suppress tumor initiation ability of the cells.</td>
</tr>
<tr>
<td>Constantinou, 2009</td>
<td>γ-TT &amp; δ-TT</td>
<td>LNCaP cells treated with γ-TT &amp; δ-TT separately showed caspase activation. γ-TT &amp; δ-TT in combination induced cell death in AR-PC-3 and DU145 cells.</td>
</tr>
</tbody>
</table>
Higher levels of α-T were correlated with lower incidences of aggressive PCa, however they were not statistically significant [25].

There was however an inverse relationship between α-T and PCa risk in advanced disease and cancer diagnosed in the early-post trial period in an analysis of the ATBC study. An inverse correlation between serum α-T and PCa was identified after post-intervention [34]. Therefore men with higher serum α-T had a reduced risk of PCa, which was done with only 50 IU of α-T intake. The study also showed a progression from advanced disease to non-advanced disease incidence among men in the highest quintile of serum α-T. This may indicate a greater indicator of tumor progression among men with a greater bioavailability of α-T with a dosage of 50 IU [34]. A secondary study showed in the highest versus lowest tertiles of α-T and γ-T serum levels, there was an inverse correlation with PCa [35].

In two case-control studies correlations were found between serum γ-T levels and the risk of prostate cancer, finding men with higher serum γ-T levels had a statistically significant decreased risk of PCa, with no such impact from α-T. Helzlsouer et al. noticed the correlation to be more significant in men with stage II disease or higher [36,37]. A prospective study analyzing the National Institute of Health American Association of Retired Persons Diet showed an increase in dietary γ-T was associated with a decreased incidence of prostate cancer (RR, 0.68; 95% CI, 0.56-0.84; P trend = 0.001). In the same study, there was no association with supplemental α-T [38]. This suggests there is a significant difference in the biological impact between the different isomers of supplemental and dietary forms of vitamin E.

**TOCOTRIENOLS AND PROSTATE CANCER**

**Pre-clinical in-vitro**

LNCaP, DU145 and PC-3 cells were exposed to tocotrienol rich fraction (TRF), which contained α-tocotrienol 14.77%, γ-tocotrienol 33.97%, δ-tocotrienol 26.11%, α-tocopherol 18.10%, and other γ-tocopherol and tocotrienol-like compounds 7.05%, respectively. Each cell type was impacted in a dose-dependent manner, where increased concentrations of the TRF resulted in a decrease in cell growth. The TRF also inhibited anchorage-independent growth and colony formation [39]. One of the more interesting aspects of this study indicated that the tocotrienols did not have the same impact on non-cancer cells, thus indicating the impact of TRF as a broad spectrum anti-proliferative agent in PCa with little to no threat to non-cancerous cells [39].

Further investigating the impact of tocotrienols on PCa in comparison to tocopherols exposed a benefit of tocotrienols over tocopherols. Supplementation of in-vitro PCa cells and LNCaP cells with γ-T and γ-TT showed a significant inhibition of growth in cells treated with γ-TT in a concentration dependent manner [40]. The research also showed γ-TT to be superior to α-T in the ability to inhibit PCa cell and LNCaP cell growth. γ-T, γ-TT, δ-T, and δ-TT each were shown to increase growth inhibition on PC-3 cells, further these select isomers were superior to α-T [22]. Some data also showed that γ-TT and δ-TT exhibited an 8 to 10-fold difference in growth inhibition. It is suggested that γ-TT works by down regulating expression of prostate cancer stem cell markers, thus giving a possible mechanism as to the how γ-TT may fight PCa [41].

A study comparing all tocopherol isoforms, tocotrienol isoforms and their corresponding succinate synthetic derivatives found δ-TT and its succinate derivative to be the most potent in inducing PCa cell death [42]. DU145 and PC-3 cells treated with γ-TT and δ-TT separately did not show any caspase activation, however they did so in LNCaP cells thus leading to cancer cell death. Interestingly γ-TT and δ-TT in combination were able to synergistically induce programmed cell death in AR – PC-3 and DU145 cells. The study therefore suggests α –T and its succinate derivative are not the most effective in inducing prostate cancer cell death; secondly the study also exposes the selectivity of vitamin E isoforms and impact of various isoforms, even synergistically, in inducing cell death on prostate cancer cell lines [42].

**Pre-clinical in-vivo**

Nude mice injected with PC-3-luc cells and then injected with γ-TT resulted in a decreased development of tumors, thus indicating γ-TT as a viable suppressor of PC-3-luc cells tumorigenicity. Even oral consumption of γ-TT prior to injection of PC-3-luc cells resulted in similar results [41].

**Human studies**

Although analysis of the ATBC trial did not show any significantly correlation between PCa risk and tocotrienol intake, there was a statistically significant lower risk of advanced prostate cancer risk in men with the highest TT intake compared to the lowest TT intake [34].

**DISCUSSION**

With the completion of the recent SELECT trial, the controversy over vitamin E’s health benefits or faults has sprung up great debates among experts. The 1994 ATBC trial was one of the first major studies to exemplify the correlation between vitamin E intake and decreased PCa risk. The SELECT trial identified a correlation between vitamin E intake and increased prostate cancer risk. A third large study, the Physicians Health Study II showed no such correlation between vitamin E and prostate cancer.

From ATBC (using non-synthetic α-T) and SELECT (using synthetic α-T) we know that non-synthetic α-T at doses of 50IU/day has been correlated with decreased prostate cancer risk and death from prostate cancer among male smokers. The SELECT trial, on the contrary, has shown that synthetic α-T at doses of 400IU/day may increase the risk of prostate cancer. In trying to decipher if vitamin E is protective or harmful against prostate cancer, dosages and types of vitamin E may play a role. It is likely that 50IU/day of natural α-T is beneficial and 400IU/day of synthetic α-T may be problematic.

With the major human studies focusing on α-T, the other less known tocopherol, γ-T has exhibited its benefits in prostate cancer prevention and treatment. Pre-clinical in-vitro studies have shown the benefits of γ-T in inhibiting prostate cancer cell growth, superior to α-T [21, 22]. Such in-vitro studies progressed to in-vivo testing of γ-T and results were promising. γ-T was
shown to have profound impacts of decreasing PIN and prostate tumor progression in animal models [27,43]. Additionally, analysis of the ATBC trial showed that the highest tertiles vs the lowest tertiles of γ-T serum levels were associated with a decreased PCA risk [35]. The case-control studies identifying a decrease PCA risk in men with higher γ-T serum levels does warrant further clinical studies with potentially promising outcomes [36,37]. It is possible that this lesser known and more abundant γ-tocopherol may play a larger part in inhibiting PCA development and progression.

Human trials on tocotrienols have not been developed as of yet, however promising pre-clinical in-vitro studies suggest the benefits of γ-TT and δ-TT in inhibiting prostate cancer cell growth [39,40]. Apoptosis was also identified in PCa cells treated with γ-TT and δ-TT [42]. One in-vivo trial exhibited the impact of γ-TT in preventing prostate cancer tumor growth [41]. Albeit the minimal human trials on the tocotrienols, the pre-clinical trials indicate that tocotrienols are non-toxic and have potential in inhibiting PCA cells. Although these results are intriguing, it warrants further investigation into the role of tocotrienols, especially γ-TT and δ-TT.

Although conclusions are inadequate at this time, we propose that all tocopherols and γ-TT and δ-TT at nutritional levels may play an important role in PCA inhibition. The evidence presented demonstrates that the various tocopherol and tocotrienol isomers play a part in prostate cancer prevention and promotion. It is the purpose of this review to expose the evidence behind all isomer vitamin E and prostate cancer and it is proposed that further research be conducted on all vitamin E isomers’ impact on prostate cancer.

REFERENCES


27. Espinosa et al. (2014) Email: Giovanni.Espinosa@nyumc.org


