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## AN OVERVIEW OF ANTI-CANCEROUS BEHAVIOR OF VITAMIN E

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**ABSTRACT:** Imbalance of reactive oxygen species and their body neutralizing mechanisms defines oxidative stress. ROS play a vital role in cancer progression by taking part in DNA damage and induction of inflammatory processes. Studies reveal that natural anti-oxidant levels are reduced to a much lower extent in the serum of cancer patients in contrast to the healthy ones. Vitamin E subgroups like tocopherols and tocotrienols, being anti-oxidants, show anti-cancer abilities in human and animal cancer models. Cancer patients taking vitamin E diet are observed to have lowered reactive species; however, specific tocopherols in exception act as antagonists against chemotherapeutic drugs. This article reviews the role of pro-oxidants and anti-oxidants in cancer therapy, either alone or in combination with medications. It also highlights the drawbacks of taking vitamin supplements on cancer risks, incidences, and mortality rates.

**INTRODUCTION:** The body normally produces reactive oxygen species (ROS) for a succession of cellular activities. Anti-oxidants remove excess ROS thus maintaining balance. A contrast in ROS and anti-ROS levels cause oxidative stress<sup>1</sup>. Electron transport pathway of mitochondria is one of the major pathways of ROS generation. Excess ROS lead to various types of DNA damages including removal of nitrogenous bases, single and double - stranded DNA breaks and sugar conversions. Cancer occurs if these modifications become long lasting and mutagenic<sup>2</sup>. Increased ROS not only causes cellular damage but can also lead to cancer through chronic inflammation. ROS and inflammatory mediators activate the transcription factors involved in cell proliferation and apoptosis.

Free radical damage to mitochondria can also give rise to cancer by insertion of mitochondrial DNA (mtDNA) fragments in the nuclear genome thus activating oncogenes<sup>3</sup>. According to specific reports, patients with different types of cancers are observed to have increased pro-oxidant levels with a rise in lipid peroxidation products<sup>4</sup>. For example, prostate cancer patients contain high levels of oxidants but the levels of anti-oxidants (Vitamin D and E) are low which indicates that cancer is caused due to either raised free radicals or reduced anti-oxidants<sup>5</sup>. In the case of multiple myeloma (MM) patients, anti-oxidant levels are different from those of control ones<sup>6</sup>. Cancer treatments including chemotherapy<sup>7</sup> and drugs like fluorouracil<sup>8</sup>. Further, reduce patient anti-oxidant levels.

Vitamin E is known to occur in eight forms. Among these, four are the tocotrienols ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ) and four are tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ )<sup>9</sup>. Tocotrienols are known to show apoptotic effects (*i.e.*, nuclear fragmentation, chromatin condensation, *etc.*) in leukemia cell lines<sup>10</sup>. Tocopherols when given separately or in the mixture, cause inhibition

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of inflammation and carcinogenesis in lung and colon cancer models (human and animal) by decreasing amounts of nitrotyrosine in tumors<sup>11</sup>. Dietary intake of vitamin E, vitamin C, alpha and beta carotene also showed an inverse relationship with gastric cancer risk<sup>12</sup>. Alpha-tocopherol, when taken in the form of diet, 34-53% risk of lung cancer<sup>13</sup>. However, tocotrienols have been reported to work even better as anti-oxidants than all forms of tocopherols<sup>14</sup>. Anti-oxidants have been proven beneficial in eliminating the side effects of radiation therapy in cancer patients and also act as the shield for tumor cells against these radiations<sup>15</sup>. However, some studies report that the diet of alpha-tocopherol increases the occurrence rate of prostate cancer, making the role of anti-oxidant diet uncertain<sup>5</sup>.

Vitamins in combination with chemotherapeutic drugs like irinotecan<sup>16</sup>, statins<sup>17</sup> and celecoxib<sup>18</sup> show improved antitumor activity. Alpha-tocopherol behaves as an anti-cancer molecule by inhibiting several protein kinase inhibitors (KI) which are the targets of many anti-cancer drugs. In short, antioxidants and anti-cancer agents can act synergistically as well<sup>19</sup>.

**Anti-Oxidants Level in Serum of Cancer Patients:** It is reported that oxidants remain low while anti-oxidants (vitamin A, E, C, glutathione, etc.) are present in the high level in breast cancer<sup>20</sup>, colorectal cancer (CRC)<sup>4</sup>, lung cancer<sup>7</sup>, multiple myeloma (MM)<sup>6</sup> and cervical carcinoma patients<sup>21</sup>. Patients with CRC contain high levels of lipid peroxides in their serum due to the harmful activity of ROS. Patients also have reduced anti-oxidant status which made them susceptible to cancer development<sup>4</sup>.

Anti-oxidants and pro-oxidants function as antagonists in sporadic CRC. It is reported that specific oxidative stressors like smoking, high intake of polyunsaturated fatty acids and alcohol lead to increased risk of CRC<sup>22</sup>. The levels of anti-oxidants were reported to be high in MM patients<sup>6</sup>. It is also found in some reports that reduction in anti-oxidants levels leads to a high risk of cancer<sup>23</sup>.<sup>24</sup> Patients with non-small cell lung cancer have low levels of antioxidants (vitamin A, C, E) in their blood and these levels further reduced after chemotherapy<sup>7</sup>.

**Effects of Vitamin E on Cancer Cells:** Among the two major groups of vitamin E, tocotrienols have better anti-oxidant and anti-cancer activity than tocopherols<sup>14</sup>.

There are three isomers of tocotrienol ( $\alpha$ ,  $\gamma$ , and  $\delta$ ) which are useful for the apoptosis of different cancer cells like human T lymphoblastic leukemia cell lines (CEM-SS). They cause changes in a structure including peripheral chromatin condensation, fragmentation of nucleus and externalization of phosphatidylserine<sup>10</sup>.  $\alpha$ -,  $\gamma$ -, and  $\delta$ -tocotrienols reduce tumor cell proliferation in MCF-7 and MDA-MD-231 breast cancer cell lines along with an alteration in expression of phase 2 anti-oxidant enzymes<sup>25</sup>.

Gamma-tocotrienol suppresses cell growth by cell cycle arrest, decreasing Bcl-2 and upregulating Bax thus promoting apoptosis in HT-29 colon cancer cell lines<sup>26</sup>. It also induces the paraptosis inhuman in a dose-dependent manner in SW620 and HCT8 cells. It inhibits the expression level of beta-catenin, cyclin D1, and c-jun and also causes suppression in signaling pathway in SW620 cells<sup>27</sup>. It shows antiproliferative effects in all cancer cell types. When used on mouse and human cancer cell lines, it causes an increase in lysosome-mediated autophagy which leads to apoptosis. Evidence indicates an increase in autophagosome formation with the corresponding decrease in mTOR/AKT/P3K pathway, increase in cleaved caspase 3, cleaved poly ADP ribose polymerase and PARP levels<sup>28</sup>. It inhibits the growth of pancreatic tumors by decreasing Nf-kb pathway, cyclin D1, COX-2, Bcl-2, and other regulatory proteins of growth.

Moreover, it also promotes the apoptotic activity of gemcitabine<sup>29</sup>. It acts as an anti-proliferative agent by inhibiting the JAK-STAT pathway of cell proliferation. It inactivates STAT 3 in human liver cancer cell lines<sup>30</sup>. Treatment of colon cancer cells SW620 with delta tocotrienol has been reported to inhibit the wnt pathway and down-regulate wnt-1, beta-catenin, c-jun, and cyclin D1<sup>31</sup>. Delta-tocotrienol succinyl amide enhances the apoptotic activity of human breast adenocarcinoma cell line (SKBR3) which was associated with mitochondrial destabilization<sup>32</sup>. Delta-tocotrienol when added to non-small cell lung cancer cells (NSCLC), cause a

reduction of miR-34a (a type of micro RNA causing transcriptional silencing). This micro RNA further inactivates Notch-1 pathway, disturbing downstream signaling of the-1, cyclin D1, survivin, and Bcl-2, thus inducing apoptosis and inhibiting cancer cell proliferation<sup>33</sup>.

Tocopherols inhibit the growth of mammary, colon and lung cancers. Tocopherol mixture (having high conc. of gamma tocopherol) when given to CL13 murine lung cancer cells and A/J mice subcutaneous tumor cells, inhibited the growth of tumor cells by increasing necrosis<sup>34</sup>. Gamma and delta tocopherols show more anti-inflammatory properties than alpha-tocopherol which are more abundant than others in blood and tissues<sup>11</sup>. Gamma tocopherol has been observed to act as chemo-protective agent in rat ventral prostate cancer cell lines by inducing apoptosis<sup>35</sup>. Gamma-tocopherol independently or in a mixture with other tocopherols is very effective as an anti-cancer agent, and among all vitamins, its preventive role in cancer is high<sup>36</sup>.

**Vitamin E Supplementation for Cancer Patients:** Risk of disease increases in breast cancer patients who take fewer anti-oxidants in their diet<sup>37</sup>. Vitamin intake below the recommended dose increases the risk of cardiovascular diseases and cancer<sup>38</sup>. Dietary anti-oxidants reduce the signs of glioma by decreasing the expression of different tumor linked markers (Mn-SOD, IGFBP5, Ki-67, PDGFRb)<sup>39</sup>. Intake of vitamin E, vitamin C, alpha and beta carotene are inversely associated with gastric cancer risk<sup>12</sup>. Cured meat can lead to pre-neoplastic lesions and increase the risk of colon cancer in rats. Calcium and other agents like alpha-tocopherol when given in diet to humans or rats, reduce specific biomarkers increased by processed meat intake<sup>40</sup>. Different anti-oxidants impart different effects on prostate cancer with alpha-tocopherol increasing and gamma tocopherol decreasing the risk<sup>5</sup>.

Chemotherapy has many side effects including the reduction of anti-oxidants and increased production of ROS with increased DNA damage. However, the application of vitamin E along with chemotherapy reduces the side effects of chemotherapy leading to anti-oxidant levels near to normal<sup>41</sup>. Radiation therapy in cancer causes cellular injury including

inflammation, tissue damage, and fibrosis, etc. Anti-oxidant diet may reduce the effects of radiation on the body. They alter the expression of interleukin 6 genes which in turn is involved in the activation of inflammation and other pathophysiological processes<sup>42</sup>. Surgical removal of ovarian and endometrial tumors increases malondialdehyde content in the body and oxidative stress, which is reduced by using vitamin E<sup>43</sup>.

It is suggested that anti-oxidants may or may not improve health, even in some cases, they may increase the risk of mortality<sup>44</sup>. Anti-oxidants don't play any vital role in CRC incidence, showing negligible effects on mortality rates<sup>45</sup>. They can prove damaging if taken by patients to reduce the side effects of chemo or radiotherapy and also reduce the therapeutic effects of anti-cancer drugs<sup>46</sup>. No evidence has been found for the prevention of lungs cancer in healthy people by the use of vitamin<sup>47</sup>. Gamma-tocopherol is even associated with an increased risk of high-grade prostate cancer<sup>48</sup>. Hence, mechanism of action (*i.e.*, absorption by intestines, transport, and metabolism), source, form and appropriate dosage in the diet should be considered before using vitamin E as cancer preventive medicine<sup>49</sup>.

**Conjugation Therapy of Vitamin E with Chemotherapeutic Agents:** Anti-oxidants, when taken as supplements cause a reduction in oxidative stress. Patients of cervical cancer receiving cisplatin (an anti-cancer drug) and radiotherapy have lower antioxidant levels than controls<sup>50, 51</sup>. Vitamin E also improves the anti-cancerous ability of irinotecan, a chemotherapeutic agent for cancer<sup>16</sup>. Paclitaxel in combination with Vitamin E succinate shows synergistic effects in reduction of tumor growth in bladder cancer cell lines<sup>52, 53</sup>. Gamma-tocotrienol enhances the anti-cancer activity of capecitabine by inhibition of NF-KB regulated proteins (*i.e.*, COX-2, cyclin D1, Bcl-2, CXCR4, VEGF) and thus affecting the phenomena of apoptosis, metastasis, and angiogenesis in a xenograft model of human gastric cancer<sup>54</sup>.

Celecoxib is effective in cancer, but its high dose causes toxicity in gastrointestinal and cardiac cells. Moreover, gamma-tocotrienol is effective against cancer, but its limited absorption in the body makes it less functional. These two compounds when

given in the combined form to mouse mammary cancer cells, act synergistically to reduce cancer cell growth. The cells were observed with decreased levels of prostaglandin E and a reduction in activated AKT and Nf-kb<sup>18</sup>. Inefficient Met signaling can lead to cancer. Combination of Met inhibitor (SU11274) and gamma tocotrienol reduced tumor cell proliferation in mouse and human mammary cancer cell lines<sup>55</sup>.

Statins when applied alone, cause toxicity in muscles and other tissues. Combined treatment of gamma-tocotrienol and statins in mammary cancer cell lines has been proven to inhibit cell proliferation. This effect is due to the reduction of cyclin proteins, retinoblastoma protein (tumor suppressor) levels and an increase in expression of p27. So a combined treatment of tocotrienols with statins may benefit in breast cancer treatments<sup>56</sup>.

Gamma-tocotrienol and statins both are involved in the reduction of HMG-CoA reductase enzyme thus inhibiting growth. These, when given in the combined form, cause increased induction of apoptosis in human mesothelioma cells. Gamma-tocotrienol is required for CHOP and GRP78 (death-inducing markers), and a statin is necessary for the activity of caspase<sup>3</sup>. In this way, their combined therapy is much effective than alone<sup>17</sup>. Both Atorvastatin and gamma tocotrienol inhibit HMG-CoA reductase, thus inhibiting mevalonate based cell growth<sup>57</sup>.

**CONCLUSION:** According to the findings of the present study, vitamin E has been concluded to have anti-apoptotic effects on cancer cells *in vitro* and *in vivo*, but some contradictory reports are also available. Combination therapy of vitamin E with anti-cancerous drugs improves their efficacy and reduces the side effects but have no significant impact on overall mortality rates. Anti-oxidants behave differently in multiple conditions; therefore, proper dosage, form, and mechanism of action should be studied before taking any anti-oxidant in the diet.

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