



VITAMINS / SUPPLEMENTS

## Vitamin E Succinate Continues to Show Impressive Anti-Cancer Properties

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Several recent short-term intervention studies failed to show that vitamin E supplementation was protective against the development of various cancers, most notably lung and prostate cancer. In fact, in the Select study, individuals taking vitamin E supplements showed a 17% higher incidence of prostate cancer. In this study, researchers used a synthetic form of vitamin E known as dl-alpha tocopherol acetate. Some experts have argued that this form of vitamin E has only half the potency of natural forms of vitamin E and thus was a poor candidate for use in this and other trials. Others argue that synthetic vitamin E competes with natural vitamin E (both tocopherols and tocotrienols) for receptor binding sites and other processes, thereby reducing the cell's vitamin E antioxidant defenses and/or reducing other anticancer effects afforded by natural vitamin E (d-alpha-tocopherol)<sup>1-10,19</sup>. Others have implied that possibly vitamin E succinate should be the form of vitamin E used in intervention trials aimed at reducing cancer incidence, as it is the form of vitamin E with the strongest research support as an anticancer agent.<sup>20</sup>

Adding to the confusion, are recent studies showing that antioxidant supplementation may provide existing cancer cells with a survival advantage and thus, may facilitate the growth of cancer once cancer cells have been initiated. In this respect, it may be that antioxidant supplements reduce free radical build-up in cancer cells, which prevents the induction of programmed cell death (apoptosis).<sup>1-10,19</sup>



Conversely, some long-term epidemiological studies show that higher blood levels of vitamin E and the use of high-dose vitamin E supplements are associated with a decreased risk of many types of cancer, including lung and prostate cancer.<sup>11,12</sup>

One explanation for this conflicting data may be as follows - high-dose vitamin E supplements (above 200 IU per day) may act as an antioxidant to reduce DNA oxidation and mutations that lead to cancer, support immune cells responsible for killing emerging cancer cells, and possibly exert other anticancer epigenetic and genetic effects. However, in cancer cells that have already been formed (initiated), vitamin E may aid in their survival by providing them with antioxidant defences they tend to lack. It is established that cancer cells subjected to excess free radical exposure undergo programmed cell death (apoptosis). Thus, it may be that taking natural vitamin E helps to prevent cancer development (initiation), but vitamin E may also promote cancer progression in cancer cells that have already been initiated (indolent cancer or latent cancers). More studies are required to fully understand the impact of d-alpha tocopherol (natural vitamin E) and dl-alpha tocopherol (synthetic vitamin E) on cancer prevention, development and potential use in adjunctive cancer treatment.<sup>13,14</sup>

### Anti-Cancer Properties

Over a number of years, a unique form of vitamin E known as vitamin E succinate (alpha-tocopheryl succinate) has shown the most impressive anti-cancer properties, compared to all other forms of vitamin E, including the tocotrienols. Experimental studies continue to show that only this form of vitamin E (vitamin E succinate) causes rapid production of reactive oxygen species (free radicals) selectively within cancer cells, triggering cell death (apoptosis), while being non-toxic to normal healthy cells.

In addition, Vitamin E succinate also inhibits the anti-apoptotic function of Bcl-2 and Bcl-xl,

normally expressed by tumor cells. Malignant cells typically try to block signals that lead to programmed cell death (apoptosis). One of the clever ways they do this is by blocking an important apoptotic signaling pathway that is controlled by the p53 tumor suppressor gene. Normally, when a cancer cell is emerging it is detected by a network of internal surveillance genes (tumor suppressor genes), which in turn respond by up-regulating the synthesis of the Bax protein. The Bax protein translocates to the mitochondria and exerts effects that lead to mitochondrial disruption and fragmentation. This prevents cancer cells from generating vital ATP energy, which in turn, triggers programmed cell death (apoptosis).

The synthesis of the Bax protein is under control of the p53 tumor suppressor gene. However, malignant cells block the apoptotic effects of Bax protein by synthesizing the Bcl-2 protein, which inhibits the effects of the Bax protein, thereby enabling cancer cells to survive and thrive, even though tumor suppressor genes are sending signals directed at programmed cell death.

Vitamin E succinate is one of only a few compounds ever shown to inhibit the anti-apoptotic function of Bcl-2 and Bcl-xl (by blocking their BH3 domains). This may also explain, to some extent, how vitamin E succinate has been shown to sensitize cancer cells to other anti-cancer drugs, thereby improving their chemotherapy-killing effects.<sup>14</sup>

### Cancer Cells and Free Radicals

The emerging studies show that cancer cells that are able to protect themselves against reactive oxygen species (free radicals) are less likely to undergo apoptosis. Thus, some experimental studies show that antioxidant fortification via superoxide dismutase, N-acetylcysteine, coenzyme Q<sub>10</sub>, and possibly other forms of vitamin E, provide cancer cells with a survival advantage due to their antioxidant properties.

However, vitamin E succinate has the opposite effect - it increases accumulation of free radicals within cancer cells, which leads to cell death. This has been shown to occur via the unique ability of vitamin E succinate's capacity to bind to complex II within the mitochondria, thus preventing binding of coenzyme Q<sub>10</sub> at this point in the mitochondrial chain. As such, coenzyme Q<sub>10</sub> becomes unable to transfer electrons to complex II, and thereby releases them within the cell. The unpaired electrons interact with cellular oxygen to form various reactive oxygen species, such as the superoxide anion (free radicals), which accumulate and trigger programmed cell death.

This mitochondrial disruption killing effect of cancer cells has recently been demonstrated in a mouse model of breast cancer, in which many tumors showed over-expression the Her-2 receptor. The positive Her-2 receptor breast cancer phenotype is known to be highly aggressive and a stubborn form of cancer to kill.

Anti-cancer agents that target mitochondria disruption leading to programmed cell death are termed mitocans, which represent a new investigative and promising area of oncology research.

Vitamin E succinate is a one of the most promising mitocans discovered to date.<sup>14,15</sup>

In addition, vitamin E succinate has shown other multi-modal anticancer properties that have been reviewed by several researchers over the years.<sup>16,17</sup>

### Human Studies Underway

The impressive experimental cancer-killing effects of vitamin E succinate, coupled with our understanding of its observed anticancer properties (particularly reactive oxygen species-induced

apoptosis, and inhibiting the anti-apoptotic effects of Bcl-2 and Bcl-xl), prompted researchers to test vitamin E succinate in a recent human case of mesothelioma. Malignant mesothelioma is a form of lung cancer caused by exposure to asbestos and is highly resistant to radiation and chemotherapy. In this single case study, administering vitamin E succinate to a patient with malignant mesothelioma the researchers stated, "the data revealed a significant clinical benefit with vitamin E succinate therapy, causing a reduction in tumour volume and improved the well-being of our subject who had a lethal type of neoplastic pathology". This outcome was published in *Lancet* in 2005. These researchers are currently preparing to set-up a larger clinical trial in which a cohort of mesothelioma patients will be treated with vitamin E succinate.<sup>14</sup> Experimental studies in the past have demonstrated the efficacy of vitamin E succinate in killing human malignant mesothelioma cells in-vitro.<sup>15,16</sup>

### My View Point

Due to the conflicting data surrounding the influence of vitamin E on cancer, it may be wise to choose a multiple vitamin that contains vitamin E in the form of vitamin E succinate at a minimum dose of 400 IU for purposes of health promotion and possibly cancer prevention. Human oral supplementation studies using significant (supraphysiological) doses of vitamin E succinate have been shown to raise plasma levels of vitamin E succinate. This is unlikely to occur with low-dose intake, as the pancreatic digestive esterase enzymes typically deconjugate the succinate moiety from vitamin E succinate in the gut. In supraphysiological supplementation, a significant percentage of the vitamin E succinate has been shown to get absorbed into the bloodstream intact (as vitamin E succinate), by-passing deconjugation by esterase enzymes in the gut. This is important because studies show that vitamin E succinate must reach cancer cells intact (in the form of vitamin E succinate) in order to exert its anticancer properties.<sup>17</sup>

It is noteworthy that vitamin E succinate does not possess antioxidant properties, however, some vitamin E succinate is deconjugated by pancreatic digestive enzymes (esterases) and the tocopheryl moiety is available for conversion to d-alpha-tocopherol. This is the natural form of vitamin E that does possess antioxidant properties. The next step is for researchers to begin using vitamin E succinate more aggressively in animal models of cancer prevention and treatment to determine its efficacy and best route of administration. From there, hopefully we will see its adoption in a greater number of human cancer trials, in both prevention and adjunctive cancer treatment.<sup>20</sup>

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