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Review Article

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A Review of the Effects of Vitamin E in Ovarian Cancer

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ABSTRACT

Vitamin E is made up of two substances, tocopherols (TOCs) and tocotrienols (TCTs). These substances are present in four different subtypes namely alpha, beta, delta and gamma and these subtypes differs in their chemical structures. Vitamin E has been made known to exert anticancer effects for decades-long ago. This vitamin, which is also a well-known lipid-soluble antioxidant, has been extensively studied and its effects on cancer cells progressions are widely reported. These include its effects on the progressions of the breast, cervix, colon, liver, lung, pancreas, prostate, skin, and stomach cancers. Despite the widely available reports on vitamin E as an anticancer, the particular reports on the effects of this vitamin for reproduction in ovarian cancer are remarkably limited. Hence, this review is written to provide a summary of the reported effects from the studies published between the year 2010-2020 and the possible future research on vitamin E in ovarian cancer. This review will contribute to a more organized finding on the effects of vitamin E and ovarian cancer.

Key words: *Anticancer, Antioxidant, Ovarian cancer, Vitamin E*

INTRODUCTION

Gynecological cancers are the type of cancers occurring in women's reproductive organs such as the ovaries, uterus (endometrium), and cervix [1]. The treatments for these cancers vary on the etiology, type, and severity (stage of cancer). The limitations encountered in the existing treatments have encouraged the alternative search for options that come with reduced side effects and cost consumption [2], and this includes the natural products and micronutrients as one the possible synergistic remedies [3].

One of the micronutrients that attracted the attention of researchers is vitamin E, the vitamin for reproduction. This powerful fat-soluble vitamin is well known for its role as antioxidant [4, 5] and anticancer, and extensive research was conducted to search for its potential use in cancer treatments. However, the reviewed literature showed that most of the efforts were spent on other types of cancers [6], but the gynecological ones. The studies involving gynecological cancers were shown to be limitedly available [7], with ovarian cancer being one of them. Hence, the present paper is written to provide a review of the reported effects from the studies published between the year 2010-2020 and the possible future research on vitamin E in ovarian cancer. This review is anticipated to provide summarized information for future researchers.

RESULTS AND DISCUSSION

Sources of vitamin E

Vitamin E can be found in several plants and foods that include palm, oat, barley, rice bran, annatto, wheat, and coconut. Besides, vitamin E derivatives have also been detected in human milk [8] and palm date (Phoenix canariensis) [9]. Vitamin E is an essential micronutrient that has an important role in maintaining normal human physiological function, but it needs to be consumed through diet as it is not synthesized by the body [10].

Characteristics of vitamin E

Vitamin E is a fat-soluble vitamin and is present in two major compounds, tocopherol (TOC) and tocotrienol (TCT) [11]. Tocopherol and tocotrienols are present in four forms of subtypes, namely alpha (α), beta (β), gamma (γ), and delta (δ). Structurally, both compounds have an isoprenoid side chain of a 6-chromanol ring [12]. These subtypes are named based on the position and the presence of the methyl group and its location on the chromanol ring [12]. The chromanol ring forms the hydrophilic part of the molecules, whereas the isoprenoid side chains form the lipid-soluble part of the vitamin E structure [13]. This amphipathic property makes vitamin E compounds present mostly in the membrane. The difference between TOCs and TCTs is that TOCs possess side chains consisting of three fully saturated isopentyl units while TCTs possess a farnesyl, an isoprenoid compound [12].

Anticancer effect of vitamin E on cancers

The anticancer effects of vitamin E have been extensively shown with most researches proving vitamin E suppression of the proliferation and growth of cancer cells through various signaling pathways and mechanisms [6]. The reported studies were conducted on various cancer types as shown in **Figure 1**.

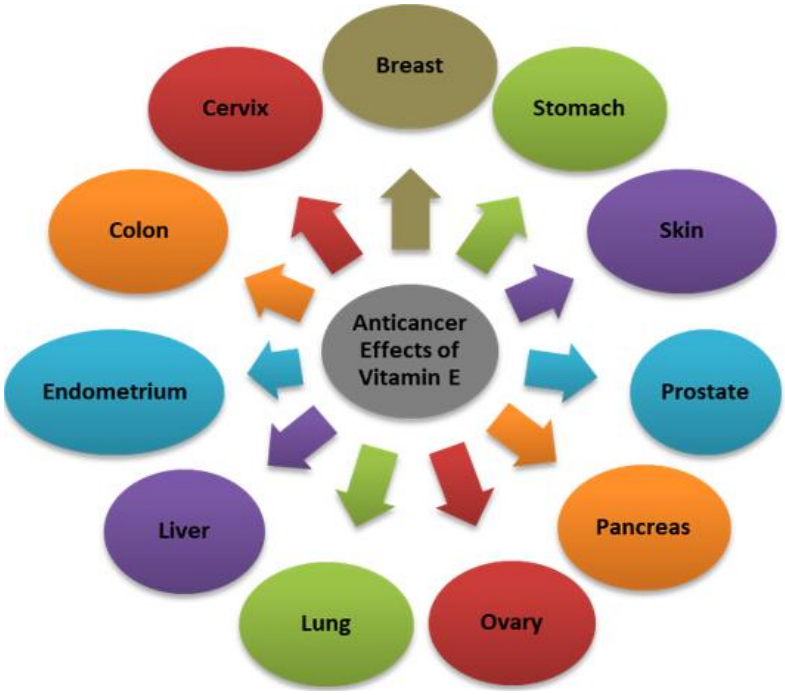

Figure 1. Types of cancers reported in vitamin E studies [4]

Anticancer effect of vitamin E on ovarian cancer – the reported studies

In overview, the literature search from the year 2010 to 2020 indicated that mostly the protective effects of vitamin E against cancer cells are coming deep from the regulations at the molecular level. In ovarian cancer cells, the preferential mechanism of action of vitamin E was mostly reported to be through the initiation of apoptosis. For instance, this has been shown in a study report by [14]. In this study, two types of ovarian cancer cell lines which were the OVCAR and COV434 were used. Twenty-four hours of exposure of the cell lines to doxorubicin and cyclophosphamide resulted in the generations of reactive oxygen species (ROS), but treatment with 1-hour exposure to gamma-TOC (γ-TOC) reduced the levels of ROS in COV434. Gamma-TOC also maintained the cellular condensed nuclei, demonstrating that γ-TOC exerted its protective effects in ovarian cancer cell lines against chemical-induced oxidative stress. Another study report by Figueroa *et al*. [15] also has shown that the

addition of both γ-TOC and α-TOC to the combination of the chemotherapeutic agents of doxorubicin (Dox) and 4-hydroperoxycyclophosphamide (4-Cyc) has the potential to decrease cytotoxicity towards ovarian granulosa cells.

Next, the potential antineoplastic activity of δ-TCT was demonstrated in a study by Thomsen *et al*. [16]. The study was a phase II clinical trial conducted on 23 patients with stage III multi-resistant ovarian cancer. The study findings indicated that the combination of bevacizumab and δ-TCT could be effective against multi-resistant ovarian cancer. In addition, the effects of δ-TOC in combination with docetaxel (the first-line chemotherapeutic drug for ovarian cancer) on ovarian cancer SKOV3 cells *in vitro* were reported [17]. The combination was shown to synergistically inhibit cell growth, resulting in lower cell viability and more cell arrest at the S-phase, suggesting that δ-TOC could enhance docetaxel's serious side effects.

Other than the reported studies mentioned above, the literature search made for writing the present study returned a limited number of reports and the reports are compiled in **Table 1**.

Table 1. Effects of vitamin E on ovarian cancer (studies reported from 2010 to 2020)

No.	Type of Vitamin E	Mechanism /Effects of Vitamin E	References
1.	δ-TCT	The combination of curcumin with δ-TOC tocotrienol nano-emulsion possesses the anti-neoplastic effect in a concentration and time-dependent manner.	[18]
2.	α-TEA (RRR-α-tocopherol ether-linked acetic acid analog)	α-TEA induced apoptosis through downregulation of the ErbBs and subsequent downstream pro-survival mediators, Akt, and Akt mediated FLIP and survivin.	[19]
3.	Dietary Vitamin E	There is no association between a high intake of vitaminE and the risk for ovarian cancer.	[20]
4.	Dietary Vitamin E	There is little or no association between dietary and individual antioxidant intake such as vitamin E with the risk for ovarian cancer.	[21]
5.	Dietary Vitamin E	There is no association between dietary intake and total vitamin intake, including vitamin E on the risk of ovarian cancer.	[22]

Review of the reported studies and the future directions

Reviewing the limitedly available reported studies shows that vitamin E was reported to may or may not have any associations with ovarian cancer cells. This is somehow contradicting because the results observed in experimental settings are not supported by the results of the clinical trials. There could be many factors to these disagreements, including the 1) nature of the study subjects which were the cell cultures and humans (patients), 2) exposure to vitamin E in the study subjects resulted in different levels of cellular reactions, 3) the molecular mechanisms of reactions of vitamin E differed between the cell lines and human body, depending on the microenvironments inside the cell cultures and the multisystem of the human body. These factors could be the determining factors that need to be explored deeper, thus providing detailed information towards a better understanding of these differences. In addition, the information obtained also could be used to establish effective research strategies targeting the reduction in ovarian cancer incidences [23-25].

CONCLUSION

Vitamin E was first discovered as an essential substance for reproduction, however, its effect on ovarian cancer particularly in humans (patients) remains ambiguous. The external factors introduced to the study subjects could be influencing the results hence, these factors may be the points where future research on vitamin E and ovarian cancer are continued. Future research is also needed to overcome the problem of limitedly available evidence on vitamin E and ovarian cancer.

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