nutrients

MDPI

Review

Role of Vitamin K in Selected Malignant Neoplasms in Women

Anna Markowska [1], Michał Antoszczak [2], Janina Markowska [3] and Adam Huczyński [2,*]

[1] Department of Perinatology and Women's Health, Poznań University of Medical Sciences, 60-535 Poznań, Poland
[2] Department of Medical Chemistry, Faculty of Chemistry, Adam Mickiewicz University, 61-614 Poznań, Poland
[3] Department of Oncology, Gynecological Oncology, Poznań University of Medical Sciences, 60-569 Poznań, Poland
* Correspondence: adhucz@amu.edu.pl

Abstract: The main function of vitamin K in the human organism is its activity in the blood clotting cascade. Epidemiological studies suggest that reduced intake of vitamin K may contribute to an increased risk of geriatric diseases such as atherosclerosis, dementia, osteoporosis, and osteoarthritis. A growing number of studies also indicate that vitamin K may be involved not only in preventing the development of certain cancers but it may also support classical cancer chemotherapy. This review article summarizes the results of studies on the anticancer effects of vitamin K on selected female malignancies, i.e., breast, cervical, and ovarian cancer, published over the past 20 years. The promising effects of vitamin K on cancer cells observed so far indicate its great potential, but also the need for expansion of our knowledge in this area by conducting extensive research, including clinical trials.

Keywords: vitamin K; breast cancer; cervical cancer; ovarian cancer

Citation: Markowska, A.; Antoszczak, M.; Markowska, J.; Huczyński, A. Role of Vitamin K in Selected Malignant Neoplasms in Women. *Nutrients* **2022**, *14*, 3401. https://doi.org/10.3390/nu14163401

Academic Editor: Khalid A. El Sayed

Received: 31 July 2022
Accepted: 17 August 2022
Published: 18 August 2022

1. Introduction

Vitamin K is a group of fat-soluble organic chemical compounds containing a 2-methyl-1,4-naphthoquinone ring substituted at C-3 position by various substituents (Figure 1). Natural vitamin K occurs in two forms: (i) vitamin K_1, produced by green plants (phylloquinone), which has a phytyl side chain composed of three saturated and one unsaturated isoprene units at C-3 position; (ii) vitamin K_2, a series of compounds (menaquinones) whose side chain at C-3 position is composed of multiple (mainly 4 to 13) unsaturated isoprene units (Figure 1) and produced generally by bacteria, with the exception of menaquinone-4 which is produced via biosynthetic conversion of vitamin K_1 in the body. Menaquinones can be designated by the general formula MK-X, where X indicates the number of isoprene units in the side chain, for example, menaquinone-6 (MK-6). Vitamin K_3 (menadione) (Figure 1) is of synthetic origin. High levels of vitamin K_1 can be found in green leafy vegetables and some vegetable oils, while other types of vegetables, fruits, cereal grains, or their milled products are poor sources of this nutrient [1]. Animal products (meat, fish, milk products, and eggs) contain rather low levels of vitamin K_1, but the content of menaquinones is higher in the liver. Various menaquinones are present, e.g., in fermented foods [2], shellfish, beef, pork, chicken, eggs (yolk), and butter [3], while cheese contains significant quantities of MK-8 and MK-9 [4].

Vitamin K is active in prothrombin synthesis (the process of blood clotting) and bone metabolism, by regulating calcium metabolism and reducing inflammation, but it may also have an impact on the course of malignancies [5–7]. However, the results of studies on the effects of vitamin K on malignancies are relatively few and inconclusive [8–10]. They seem to be strongly dependent on the type of cancer, the form of vitamin K used, or the type of study conducted, among other factors.

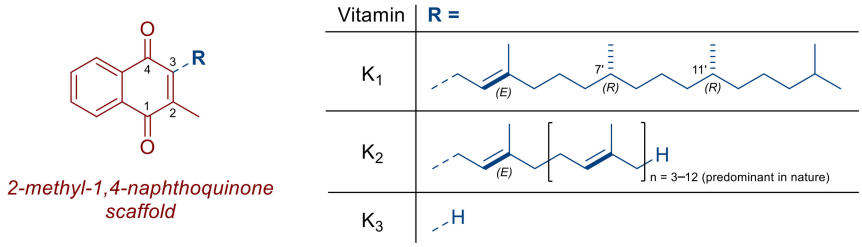

Figure 1. Structure of vitamin K.

Palmer et al. [11], in a Danish prospective cohort study involving more than 56,000 men with a mean age of 56 years, examined the association between dietary vitamin K_1 intake and cancer mortality. After adjusting for demographic and lifestyle factors, they have found that vitamin K_1 contributes to a lower rate of cancer-caused death (Q5 vs. Q1, HR 0.80, 95% CI 0.75, 0.86) [11]. In contrast, an epidemiological study spanning more than eight years and involving a total of 361 pancreatic cancer cases showed differential effects of the supply of different forms of vitamin K on the risk of cancer development [12]. The intake of vitamin K_1 and dihydrovitamin K_1 appeared to reduce the risk of pancreatic cancer (Q4 vs. Q1, HR 0.57, 95% CI 0.39, 0.83), but a similarly favorable relationship was not observed for vitamin K_2 intake [12]. Completely different results have been provided by Nimptsch et al. [13], who have indicated that dietary intake of vitamin K_2, as opposed to vitamin K_1, may be associated with a reduced risk of cancer occurrence and death, particularly in men.

A long-term questionnaire-based study was conducted in the US to evaluate the effects of the intake of vitamin K_1, vitamin K_2, and total vitamin K on the prostate cancer risk [14]. The study included more than 2900 cases, 490 of which were at an advanced stage, but no indication has been found that vitamin K intake had a beneficial effect on reducing the incidence of this type of cancer [14]. Nevertheless, interesting therapeutic effects can be expected when vitamin K is administered in combination with commonly used cancer drugs. For example, Haruna et al. [15], who conducted a randomized phase II trial on 68 patients with hepatocellular carcinoma using sorafenib (a kinase inhibitor), noted that a prolonged median overall survival was achieved in the group of patients responding to treatment (partially or completely) and receiving vitamin K.

Anticancer Mechanism of Action

Despite a growing body of research results, a detailed mechanism of vitamin K's action on cancer cells remains unclear. The observed anticancer effects of vitamin K include: (i) inhibition of proliferation, (ii) induction of differentiation, (iii) inhibition of the potential for metastasis, and (iv) induction of autophagy or apoptosis. The phenomenon of vitamin K-mediated apoptosis proceeds much more slowly than that caused by conventional cancer drugs, making it possible to analyze in detail the various stages involved [16]. The mechanisms of vitamin K action on cancer cells have already been reviewed in literature [17], therefore, only selected molecular targets on which vitamin K acts in vitro and/or in vivo are presented below.

In in vitro tests, Dasari et al. [18], have evaluated the effects of vitamin K_2 on a VCaP cell line derived from hormone-refractory prostate cancer. They observed that vitamin K_2 significantly inhibited tumor cell proliferation in a dose-dependent manner, induced apoptosis, caspase 3/7 activity, increased levels of reactive oxygen species (ROS), and decreased androgen receptor expression [18]. A slightly different vitamin K action mechanism was described on the basis of in vitro studies on colon cancer cell lines SW480 and SW620 [19]. Vitamin K_3 inhibited the epithelial-mesenchymal transition (EMT) and Wnt signaling pathway by affecting various molecular targets, such as cadherins, cyclins, and β-catenin [19]. Some other studies have shown that vitamin K leads to depolarization of the mitochondrial membrane and a release of cytochrome c into the cytosol with the generation of apoptosome, which drives the activation of caspase 9, ultimately leading to the activation of caspase 3 and the initiation of apoptosis [20–22]. In addition, vitamin K_2

can reduce cyclin D1 expression in cancer cells by inhibiting the binding of the nuclear factor κB (NF-κB) to the cyclin D1 promoter, which occurs by arresting the cell cycle in the G1 phase [23]. Furthermore, vitamin K_2 derivatives showed growth inhibitory effects not only on cancer cells derived from various organs but also on those resistant to radiotherapy by generating ROS [24].

As indicated in in vivo studies, vitamin K_2 had an inhibitory effect on bladder cancer development by inducing metabolic stress; vitamin K_2 promoted PI3K/AKT/HIF-1α pathway-dependent glycolysis, leading to AMPK-dependent autophagic cancer cell death [25]. Conversely, vitamin K_2 inhibited hepatocellular carcinoma cell proliferation in in vivo tests, through direct binding to 17β-hydroxysteroid dehydrogenase 4 (HSD17B4), a protein that promotes cell proliferation in this cancer [26]. This resulted in inhibition of the activation of Akt and MEK/ERK signaling pathways, leading to decreased STAT3 activation [26].

The positive effects of vitamin K have been confirmed in many types of cancer. However, to the best of our knowledge, literature provides as yet no article describing the potential effects of vitamin K on the development and course of selected female malignancies. In this review paper, which is part of a series outlining the anticancer effects of vitamins on selected female malignancies [27–29], we focused on the potentially beneficial role of vitamin K on breast, cervical, and ovarian cancers. To this end, we have searched the Google Scholar and PubMed databases in detail for original papers describing the potential anticancer activity of vitamin K in in vitro and in vivo tests (Table 1), as well as in human observational studies published over the last two decades.

Table 1. In vitro (and animal) studies with vitamin K on cancer cell lines.

Cancer Type	Active Form of Vitamin K	Cancer Cell Lines Sensitive to the Action of Vitamin K	Optimal Concentration	Combination Treatment/In Vivo Studies	Reference
Breast cancer	K_2	Hs578T, SUM159PT	5 μg mL^{-1} (supplemented medium)		[30]
	K_2 (MK-4)	BT-474, MDA-MB-231, MDA-MB-468	10–25 μM (supplemented medium)		[31]
	K_2 (MK-4)	MDA-MB-231	124.4 μM (IC_{50})	low-glucose medium (5.5 mM)	[32]
	K_3	BT-474, MCF-7, MDA-MB-231, SK-BR3	11.3–25.1 μM (IC_{50})	in vivo studies	[33]
	K_3	MCF-7	14.2 μM (IC_{50})		[34]
Cervical cancer	K_3	SiHa (HPV-16 positive)	10.8 μM (IC_{50}) 21.7 μM (IC_{90})		[35]
	K_3	HeLa, SiHa		ultraviolet radiation A + in vivo studies	[36]
Ovarian cancer	K_2 (MK-4)	PA-1, TYK-nu	5.0–73.0 μM (IC_{50})		[37]
	K_2 (MK-4)	TYK-nu	73.0 μM (IC_{50})		[38]
	K_3	OVCAR-3, SK-OV-3	7.5 μM (~59% cell death)		[39]
	K_3 (menadione bisulfite)	MDAH 2774, CAOV-3, ES-2	22.0–41.8 μM (CD_{50})	vitamin C	[40]
	K_3 (menadione bisulfite)	MDAH 2774	20.3 μM (supplemented medium)	vitamin C	[41]
	K_3	SK-OV-3	20.0 μM (80% inhibition rate)		[42]

2. Breast Cancer

Breast cancer (BC) is the most common malignancy occurring in women. According to epidemiological data, 2,261,419 women developed BC worldwide in 2020, accounting for 24.5% of all malignancies occurring among women [43,44]. The search for new treatments to improve patients' lives with this type of cancer is extremely important. Unfortunately, the results of studies on the effects of vitamin K on the development and course of BC are inconclusive. The inconclusiveness mainly refers to the in vitro studies concerning the evaluation of vitamin K supply in the population.

2.1. In Vitro and In Vivo Studies

A study by Beaudin et al. [30], showed differential effects of vitamin K on cancer cells from the triple-negative BC (TNBC) cell line. Vitamin K_1 was observed to increase the growth of cancer cells and the expression of γ-carboxyglutamate (GLA), the matrix amino acid responsible for binding calcium cations in the cell [30]. In contrast, the exposure of Hs578T, MDA-MB-231 and SUM159PT cells to vitamin K_2 had an antiproliferative effect and caused a decrease in cancer cell activity; however, GLA protein expression was not affected [30]. Miyazawa et al. [31], have conducted in vitro studies on established TNBC cell lines (MDA-MB-231 and MDA-MB-468) using vitamin K_2. In doing so, they have confirmed previous findings [30], indicating that vitamin K_2 has cytotoxic properties against this subtype of BC [31]. On the other hand, adding an inhibitor of the autophagy process, 3-methyladenine, to the cell culture has attenuated this effect [31]. This indicated the involvement of the autophagy-dependent cell death rather than typical apoptosis, which was further supported by the absence of known features of the latter process, such as chromatin condensation and caspase 3 [31]. Another study on the effects of vitamin K_2 on TNBC has reported a significant dose-dependent effect of menaquinone-4, MK-4, that inhibited the growth of MDA-MB-231 and MDA-MB-453 cells, the HER-2^+ BC cell line; vitamin K_2 at concentrations ranging from 100 μM to 150 μM caused inhibition of cell growth in both the adhesion and proliferation phases [32].

Yamada et al. [33], documented the effects of vitamin K on a subcutaneous model of TNBC in a mouse study. The addition of vitamin K_3 significantly inhibited tumor growth, in a manner dependent on the vitamin dose and exposure time, with extracellular signal-regulated kinase (ERK) playing a key role in inhibiting tumor growth induced by vitamin K_3 application [33]. According to the authors of this publication, the observed anticancer effect should be a step forward in the development of molecular therapeutics against TNBC. Vitamin K_3 showed cytotoxicity that induced DNA fragmentation in MCF-7 cells with IC_{50} value of 14.2 μM; detailed mechanistic studies revealed that vitamin K_3 caused mitochondrial dysfunction, including the loss of mitochondrial membrane potential, while mitochondrial damage was induced by ROS generation and subsequent caspase 7/9 activation [34].

A variety of vitamin K_3 derivatives also showed activity against BC cell lines [45,46], including those resistant to doxorubicin (Figure 2) [47]. For example, CR108, a vitamin K_3 derivative, induced apoptosis via ROS and the mitochondrial damage pathway associated with p38 MAP kinase and survival, both in MCF-7 BC cells lacking HER-2 overexpression and in BT-474 cells with HER-2 overexpression [45]. Wellington et al. [46], described that other thioether derivatives of vitamin K_3 might also show anticancer properties. The in vitro tests, using the MCF-7 BC cell line, revealed the ROS generation and disruption of the mitochondrial membrane potential, indicating that the cells underwent apoptosis [46]. The selectivity of sulfide derivatives of vitamin K against cancer cells was generally higher than against normal cells (WI-38) [46], which should encourage further research into chemical modification of vitamin K structure.

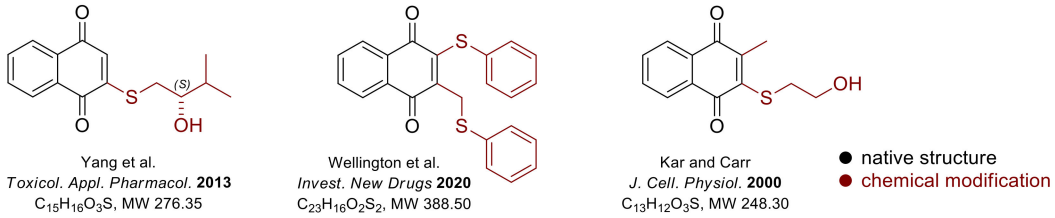

Figure 2. Structure of vitamin K_3 derivatives showing promising activity against BC cell lines [45–47].

2.2. Effects in Cancer Patients

Wang et al. [10], have examined the effect of vitamin K intake on morbidity and mortality among women in the US population diagnosed with BC in a cohort of 2286 cases and 207 deaths from BC. Total vitamin K_2 intake was associated with increased BC risk (Q5 vs. Q1, HR 1.26, 95% CI 1.05–1.52, p = 0.01) and death in a statistically significant manner (Q5 vs. Q1, HR 1.71, 95% CI 0.97–3.01, p = 0.04) [10]. In contrast, this relationship was not observed for vitamin K_1 and total vitamin K intake [10]. This suggests that reduction of the amount of vitamin K_2 in the diet could lower the risk of developing BC. Further results on the relationship between dietary vitamin K content and BC incidence have been provided by Nasab et al. [48]. They compared the indicators of dietary content in BC patients and healthy subjects; this included dietary composition with regard to both mineral (Ca, Mg, and Zn) and vitamin (A, B_2, B_6, B_7, B_{12}, C, E, and K) content in a group of 180 patients diagnosed with BC and 360 healthy women [48]. The authors found a significant association between the reduced risk of BC spread and the dietary vitamin K intake (OR 0.58, 0.37–0.90) [48].

3. Cervical Cancer

Cervical cancer (CC) is the most common malignancy in women in the countries with lower living standards. It results from a long process of changes in the normal cervical epithelium under the influence of persistent HPV infection [49,50]. As its high incidence, the search for new and effective ways to combat CC is a highly timely challenge for researchers. However, only a few papers describing the effect of vitamin K on this type of cancer can be found in the scientific literature.

3.1. In Vitro and In Vivo Studies

The effects of vitamin K_3 on the morphology and volume of cancer cells, cell membrane integrity, mitochondrial membrane potential, and oxidative balance have been investigated in HPV 16-transformed CC (SiHa) cell cultures [35]. Vitamin K_3 has been shown to induce an increase in ROS levels in SiHa cells and their morphological and biochemical changes [35]. In addition, vitamin K_3 triggered mechanisms inducing cancer cell death by apoptosis [35]. On the other hand, Xin et al. [36], in a heterotransplant model from HeLa cells, have demonstrated the efficacy of vitamin K_3 against CC also in in vivo tests. The study used ultraviolet A (UVA) photodynamic therapy with vitamin K_3 as a photosensitizer [36]. The combined therapy resulted in a significant reduction in cancer cell viability in a dose-dependent manner, activation of the apoptosis pathway, and inhibition of tumor growth [36]. These observations were accompanied by an increase in cleaved caspase 3 and cleaved caspase 9 expression, as well as a decrease in the expression of the anti-apoptotic protein Bcl-2 [36].

3.2. Effects in Cancer Patients

A cohort study conducted in China (Sanxi CIN Cohort Study) based on dietary questionnaires on a group of 218 randomly selected subjects was aimed at the assessment of the effect of dietary vitamins on the development of cervical intraepithelial neoplasia [51]. Vitamin K was found to show a protective effect (Q2 vs. Q4, OR 1.60, 95% CI 1.05–2.44) if the

dose was optimal [51]. Similarly, beneficial effects were observed of vitamin B_3, B_6, B_9 and C intake, indicating that deficiencies in these nutrients may affect the development of CC.

4. Ovarian Cancer

Ovarian cancer (OC) has the worst prognosis of all gynecological cancers. It is estimated that about 70% of OC cases are diagnosed only in advanced clinical stages; for this reason, 5-year survival is recorded among 27% of patients in clinical stage III and only among about 13% in stage IV disease [26,52,53], justifying the need to search for new ways to combat this type of cancer.

In Vitro and In Vivo Studies

Kim et al. [39], conducted tests on two OC cell lines (OVCAR-3, SK-OV-3) and found that vitamin K_3 could induce apoptotic death of cancer cells through activation of the mitochondrial pathway and pathways dependent on caspase 8 and the proapoptotic cytoplasmic protein Bid. The observed proapoptotic effect of vitamin K_3 may have been due to ROS generation and glutathione depletion [39]. Vitamin K_3 also inhibited focal adhesion kinase (FAK)-dependent cell adhesion [39], indicating that this vitamin may be beneficial in the adjunctive treatment of OC. Furthermore, von Gruenigen et al. [40], conducted studies on established OC cell lines to determine the mechanistic and cytotoxic effects of vitamin K_3 (and vitamin C) on this type of cancer. Anticancer activity was demonstrated by both vitamins [40]. Importantly, the use of vitamin K_3 in combination with vitamin C resulted in a synergistic effect, blocking the G1 phase of the cell cycle, and ultimately to autoschizis, cell death with characteristics of both apoptosis and necrosis [40]. Similar results have been reported by other researchers [41]; human OC cells MDAH 2774 treated with a combination of vitamin K_3 and vitamin C showed changes observed when the vitamins were used separately (for vitamin K_3: damage to the cytoskeleton and self-cleavage; for vitamin C: damage to the plasma membrane). In addition, after 1-h exposure to the combination of the two vitamins, autoschizisis (43%), apoptosis (3%), and oncosis (1.9%) of the cancer cells tested were observed [41].

Xia et al. [42], examined the response of SK-OV-3 OC cells and cisplatin-resistant OC cells (SK-OV-3/DDP) to vitamin K_3. The authors of the study showed a diverse response of these cell lines to vitamin K_3; it induced apoptosis in SK-OV-3 cells by increasing ROS production, while SK-OV-3/DDP cells with high levels of p62 protein, involved in autophagy, redox signaling, and apoptosis, were less sensitive to its effects [42]. At the same time, it has been shown that downregulation of p62 protein expression can increase susceptibility to apoptosis in SK-OV-3/DDP cells [42]. It is important to note that SK-OV-3/DDP OC cells show higher basal Nrf2 levels than those of the parental SK-OV-3 cell line, which allows them to tolerate higher concentrations of ROS. In this context, vitamin K_3 was identified as an agent that activates the Nrf2 signaling pathway, a key modulator of OC chemoresistance and progression [54], protecting SK-OV-3/DDP cells from the proapoptotic action of vitamin K_3. As vitamin K_3 is a safe nutrient for human consumption and could be an important supplement to prevent OC progression, vitamin K_3-induced upregulation of Nrf2 pathway may protect non-tumor ovarian cells from oxidative stress damage.

In addition to vitamin K_3, the effect of vitamin K_2 (menaquinone-4, MK-4) against OC cells has also been assessed [38]. Vitamin K_2 induced apoptosis in the TYK-nu cell line, associated with the release of cytochrome c and decreased Bcl-2 protein [38]. This process was inhibited by cycloheximide and starvation at a low concentration of serum [38]. In PA-1 cells, vitamin K_2 ($IC_{50} = 5.0 \pm 0.7$ μM) induced apoptosis due to increased TR3/Nur77 levels and its accumulation in mitochondria and cell nuclei [37]. On the other hand, SK-OV-3 cells proved resistant to vitamin K_2 in the concentration range tested [37].

5. Conclusions

Vitamin K is an essential nutrient. In recent years, it has also increasingly become the subject of research into its potential use as a promising adjuvant to anticancer therapy. The

effects of vitamin K on selected female malignancies, i.e., breast cancer, cervical cancer, and ovarian cancer, have so far been observed primarily in in vitro and animal tests and have indicated diverse phenotypic effects exerted by different forms of the vitamin. While most studies have focused on the effects of vitamin K_2 and vitamin K_3, there have been far fewer concerning vitamin K_1. Exemplary effects of vitamin K on breast, cervical, and ovarian cancers are schematically shown in Figure 3.

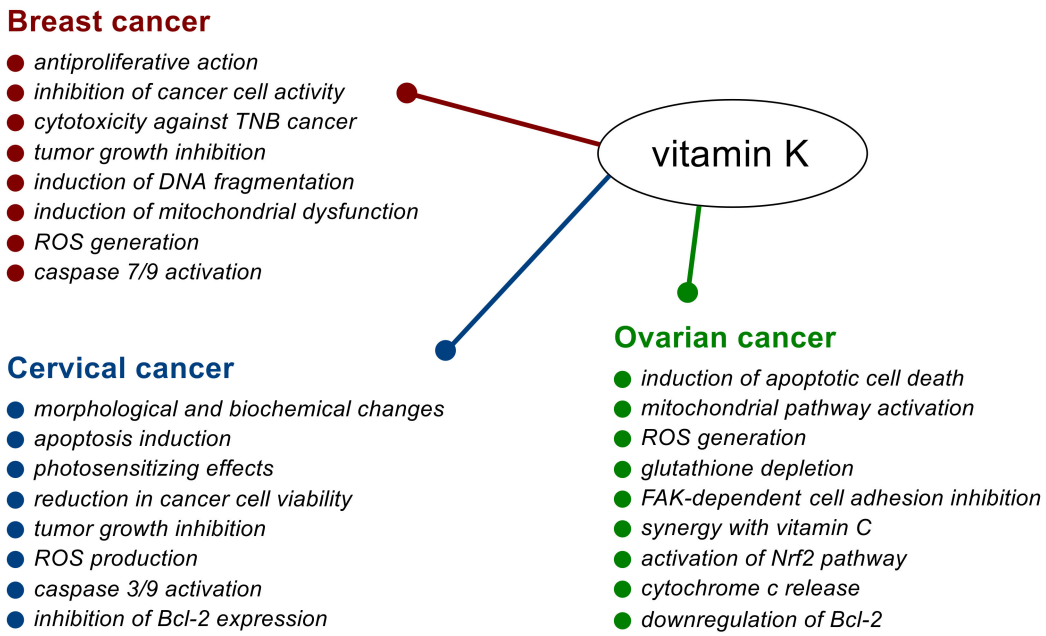

Figure 3. Effects of vitamin K on malignant neoplasms in women.

Dietary vitamin intake may play an essential role in carcinogenesis. A few observational studies, mainly on breast cancer, have indicated an association between the reduced risk of morbidity, disease progression and mortality, and the dietary vitamin K intake. In addition, combined administration of vitamin K and standard chemotherapeutic drugs may contribute to better outcomes with fewer observed side effects, which could lead to improvements in efficacy and reduced costs of conventional cancer therapy. However, this approach still requires further intensive research, including clinical trials. On the other hand, in an animal study, it has been confirmed that all dietary forms of vitamin K can be converted to tissue menaquinone-4 (MK-4) [55], thus, further investigations of the physiological role of MK-4 in certain malignant neoplasms developing in women, that may be independent of classical function of vitamin K, are bound to be undertaken.

Chemical modification of the structure of vitamin K is also an exciting line of research. Various derivatives of vitamin K_3 have proven effective against breast cancer cells, including those resistant to commonly used cytostatic drugs. This substantiates the validity of the ongoing synthetic work and justifies its continuation in the coming years.

Author Contributions: Writing—original draft preparation, A.M. and M.A.; writing—review and editing, M.A., A.H. and J.M.; supervision, A.H.; funding acquisition, A.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ball, G.F.M. *Vitamins: Their Role in the Human Body*, 1st ed.; Wiley-Blackwell: Hoboken, NJ, USA, 2004.
2. Sakano, T.; Notsumoto, S.; Nagaoka, T.; Morimoto, A.; Fujimoto, K.; Masuda, S.; Suzuki, Y.; Hirauchi, K. Measurement of K vitamins in food by high-performance liquid chromatography with fluorometric detection. *Vitamins* **1988**, *62*, 393–398. [CrossRef]
3. Hirauchi, K.; Sakano, T.; Notsumoto, S.; Nagaoka, T.; Morimoto, A.; Fujimoto, K.; Masuda, S.; Suzuki, Y. Measurement of K vitamins in foods by high-performance liquid chromatography with fluorometric detection. *Vitamins* **1989**, *63*, 147–151. [CrossRef]
4. Shearer, M.J.; Bach, A.; Kohlmeier, M. Chemistry, nutritional sources, tissue distribution and metabolism of vitamin K with special reference to bone health. *J. Nutr.* **1996**, *126*, 1181S–1186S. [CrossRef] [PubMed]
5. Gröber, U.; Reichrath, J.; Holick, M.; Kisters, K. Vitamin K: An old vitamin in a new perspective. *Dermato-Endocrinology* **2014**, *6*, e968490. [CrossRef]
6. Schwalfenberg, G.K. Vitamins K1 and K2: The emerging group of vitamins required for human health. *J. Nutr. Metab.* **2017**, *2017*, 6254836. [CrossRef]
7. Akbulut, A.C.; Pavlic, A.; Petsophonsakul, P.; Halder, M.; Maresz, K.; Kramann, R.; Schurgers, L. Vitamin K2 needs an RDI separate from vitamin K1. *Nutrients* **2020**, *12*, 1852. [CrossRef]
8. Dahlberg, S.; Ede, J.; Schött, U. Vitamin K and cancer. *Scand. J. Clin. Lab. Investig.* **2017**, *77*, 555–567. [CrossRef]
9. Halder, M.; Petsophonsakul, P.; Akbulut, A.; Pavlic, A.; Bohan, F.; Anderson, E.; Maresz, K.; Kramann, R.; Schurgers, L. Vitamin K: Double bonds beyond coagulation insights into differences between vitamin K1 and K2 in health and disease. *Int. J. Mol. Sci.* **2019**, *20*, 896. [CrossRef]
10. Wang, K.; Wu, Q.; Li, Z.; Reger, M.K.; Xiong, Y.; Zhong, G.; Li, Q.; Zhang, X.; Li, H.; Foukakis, T.; et al. Vitamin K intake and breast cancer incidence and death: Results from a prospective cohort study. *Clin. Nutr.* **2021**, *40*, 3370–3378. [CrossRef]
11. Palmer, C.R.; Bellinge, J.W.; Dalgaard, F.; Sim, M.; Murray, K.; Connolly, E.; Blekkenhorst, L.C.; Bondonno, C.P.; Croft, K.D.; Gislason, G.; et al. Association between vitamin K1 intake and mortality in the Danish Diet, Cancer, and Health cohort. *Eur. J. Epidemiol.* **2021**, *36*, 1005–1014. [CrossRef]
12. Yu, D.W.; Li, Q.J.; Cheng, L.; Yang, P.F.; Sun, W.P.; Peng, Y.; Hu, J.J.; Wu, J.J.; Gong, J.P.; Zhong, G.C. Dietary vitamin K intake and the risk of pancreatic cancer: A prospective study of 101,695 American adults. *Am. J. Epidemiol.* **2021**, *190*, 2029–2041. [CrossRef]
13. Nimptsch, K.; Rohrmann, S.; Kaaks, R.; Linseisen, J. Dietary vitamin K intake in relation to cancer incidence and mortality: Results from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg). *Am. J. Clin. Nutr.* **2010**, *91*, 1348–1358. [CrossRef]
14. Hoyt, M.; Reger, M.; Marley, A.; Fan, H.; Liu, Z.; Zhang, J. Vitamin K intake and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial. *Am. J. Clin. Nutr.* **2019**, *109*, 392–401. [CrossRef]
15. Haruna, Y.; Yakushijin, T.; Kawamoto, S. Efficacy and safety of sorafenib plus vitamin K treatment for hepatocellular carcinoma: A phase II, randomized study. *Cancer Med.* **2021**, *10*, 914–922. [CrossRef]
16. Shibayama-Imazu, T.; Aiuchi, T.; Nakaya, K. Vitamin K2-mediated apoptosis in cancer cells: Role of mitochondrial transmembrane potential. *Vitam. Horm.* **2008**, *78*, 211–226. [CrossRef]
17. Xv, F.; Chen, J.; Duan, L.; Li, S. Research progress on the anticancer effects of Vitamin K2. *Oncol. Lett.* **2018**, *15*, 8926–8934. [CrossRef]
18. Dasari, S.; Samy, A.L.P.A.; Kajdacsy-Balla, A.; Bosland, M.C.; Munirathinam, G. Vitamin K2, a menaquinone present in dairy products targets castration-resistant prostate cancer cell-line by activating apoptosis signaling. *Food Chem. Toxicol.* **2018**, *115*, 218–227. [CrossRef]
19. Kishore, C.; Sundaram, S.; Karunagaran, D. Vitamin K3 (menadione) suppresses epithelial-mesenchymal-transition and Wnt signaling pathway in human colorectal cancer cells. *Chem. Biol. Interact.* **2019**, *309*, 108725. [CrossRef]
20. Karasawa, S.; Azuma, M.; Kasama, T.; Sakamoto, S.; Kabe, Y.; Imai, T.; Yamaguchi, Y.; Miyazawa, K.; Handa, H. Vitamin K2 covalently binds to Bak and induces Bak-mediated apoptosis. *Mol. Pharmacol.* **2013**, *83*, 613–620. [CrossRef]
21. Shibayama-Imazu, T.; Sonoda, I.; Sakairi, S.; Aiuchi, T.; Ann, W.; Nakajo, S.; Itabe, H.; Nakaya, K. Production of superoxide and dissipation of mitochondrial transmembrane potential by vitamin K2 trigger apoptosis in human ovarian cancer TYK-nu cells. *Apoptosis* **2006**, *11*, 1535–1543. [CrossRef]
22. Tsujioka, T.; Miura, Y.; Otsuki, T.; Nishimura, Y.; Hyodoh, F.; Wada, H.; Sugihara, T. The mechanisms of vitamin K2-induced apoptosis of myeloma cells. *Haematologica* **2006**, *91*, 613–619. [PubMed]
23. Ozaki, I.; Zhang, H.; Mizuta, T.; Ide, Y.; Eguchi, Y.; Yasutake, T.; Sakamaki, T.; Pestell, R.G.; Yamamoto, K. Menatetrenone, a vitamin K2 analogue, inhibits hepatocellular carcinoma cell growth by suppressing cyclin D1 expression through inhibition of nuclear factor κB activation. *Clin. Cancer Res.* **2007**, *13*, 2236–2245. [CrossRef] [PubMed]
24. Amalia, H.; Sasaki, R.; Suzuki, Y.; Demizu, Y.; Bito, T.; Nishimura, H.; Okamoto, Y.; Yoshida, K.; Miyawaki, D.; Kawabe, T.; et al. Vitamin K2-derived compounds induce growth inhibition in radioresistant cancer cells. *Kobe J. Med. Sci.* **2010**, *56*, E38–E49. [PubMed]
25. Duan, F.; Mei, C.; Yang, L.; Zheng, J.; Lu, H.; Xia, Y.; Hsu, S.; Liang, H.; Hong, L. Vitamin K2 promotes PI3K/AKT/HIF-1α-mediated glycolysis that leads to AMPK-dependent autophagic cell death in bladder cancer cells. *Sci. Rep.* **2020**, *10*, 7714. [CrossRef]
26. Lu, X.; Ma, P.; Kong, L.; Wang, X.; Wang, Y.; Jiang, L. Vitamin K2 inhibits hepatocellular carcinoma cell proliferation by binding to 17β-hydroxysteroid dehydrogenase 4. *Front. Oncol.* **2021**, *11*, 757603. [CrossRef]

27. Markowska, A.; Antoszczak, M.; Kojs, Z.; Bednarek, W.; Markowska, J.; Huczyński, A. Role of vitamin D3 in selected malignant neoplasms. *Nutrition* **2020**, *79–80*, 110964. [CrossRef]
28. Markowska, A.; Antoszczak, M.; Markowska, J.; Huczyński, A. Role of vitamin E in selected malignant neoplasms in women. *Nutr. Cancer* **2022**, *74*, 1163–1170. [CrossRef]
29. Markowska, A.; Antoszczak, M.; Markowska, J.; Huczyński, A. Role of vitamin C in selected malignant neoplasms in women. *Nutrients* **2022**, *14*, 882. [CrossRef]
30. Beaudin, S.; Kokabee, L.; Welsh, J. Divergent effects of vitamins K1 and K2 on triple negative breast cancer cells. *Oncotarget* **2019**, *10*, 2292–2305. [CrossRef]
31. Miyazawa, S.; Moriya, S.; Kokuba, H.; Hino, H.; Takano, N.; Miyazawa, K. Vitamin K2 induces non-apoptotic cell death along with autophagosome formation in breast cancer cell lines. *Breast Cancer* **2020**, *27*, 225–235. [CrossRef]
32. Kiely, M.; Hodgins, S.J.; Merrigan, B.A.; Tormey, S.; Kiely, P.A.; O'Connor, E.M. Real-time cell analysis of the inhibitory effect of vitamin K2 on adhesion and proliferation of breast cancer cells. *Nutr. Res.* **2015**, *35*, 736–743. [CrossRef]
33. Yamada, A.; Osada, S.; Tanahashi, T.; Matsui, S.; Sasaki, Y.; Tanaka, Y.; Okumura, N.; Matsuhashi, N.; Takahashi, T.; Yamaguchi, K.; et al. Novel therapy for locally advanced triple-negative breast cancer. *Int. J. Oncol.* **2015**, *47*, 1266–1272. [CrossRef]
34. Akiyoshi, T.; Matzno, S.; Sakai, M.; Okamura, N.; Matsuyama, K. The potential of vitamin K3 as an anticancer agent against breast cancer that acts via the mitochondria-related apoptotic pathway. *Cancer Chemother. Pharmacol.* **2009**, *65*, 143–150. [CrossRef]
35. De Carvalho Scharf Santana, N.; Lima, N.A.; Desoti, V.C.; Bidóia, D.L.; de Souza Bonfim Mendonça, P.; Ratti, B.A.; Nakamura, T.U.; Nakamura, C.V.; Consolaro, M.E.L.; Ximenes, V.F.; et al. Vitamin K3 induces antiproliferative effect in cervical epithelial cells transformed by HPV 16 (SiHa cells) through the increase in reactive oxygen species production. *Arch. Gynecol. Obstet.* **2016**, *294*, 797–804. [CrossRef]
36. Xin, Y.; Guo, W.; Yang, C.; Huang, Q.; Zhang, P.; Zhang, L.; Jiang, G. Photodynamic effects of vitamin K3 on cervical carcinoma cells activating mitochondrial apoptosis pathways. *Anti-Cancer Agents Med. Chem.* **2020**, *21*, 91–99. [CrossRef]
37. Sibayama-Imazu, T.; Fujisawa, Y.; Masuda, Y.; Aiuchi, T.; Nakajo, S.; Itabe, H.; Nakaya, K. Induction of apoptosis in PA-1 ovarian cancer cells by vitamin K2 is associated with an increase in the level of TR3/Nur77 and its accumulation in mitochondria and nuclei. *J. Cancer Res. Clin. Oncol.* **2008**, *134*, 803–812. [CrossRef]
38. Shibayama-Imazu, T.; Sakairi, S.; Watanabe, A.; Aiuchi, T.; Nakajo, S.; Nakaya, K. Vitamin K2 selectively induced apoptosis in ovarian TYK-nu and pancreatic MIA PaCa-2 cells out of eight solid tumor cell lines through a mechanism different from geranylgeraniol. *J. Cancer Res. Clin. Oncol.* **2003**, *129*, 1–11. [CrossRef]
39. Kim, Y.J.; Shin, Y.K.; Sohn, D.S.; Lee, C.S. Menadione induces the formation of reactive oxygen species and depletion of GSH-mediated apoptosis and inhibits the FAK-mediated cell invasion. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2014**, *387*, 799–809. [CrossRef]
40. Von Gruenigen, V.E.; Jamison, J.M.; Gilloteaux, J.; Lorimer, H.E.; Summers, M.; Pollard, R.R.; Gwin, C.A.; Summers, J.L. The in vitro antitumor activity of vitamins C and K3 against ovarian carcinoma. *Anticancer Res.* **2003**, *23*, 3279–3287.
41. Gilloteaux, J.; Jamison, J.M.; Arnold, D.; Taper, H.S.; von Gruenigen, V.E.; Summers, J.L. Microscopic aspects of autoschizic cell death in human ovarian carcinoma (2774) cells following vitamin C, vitamin K3 or vitamin C: K3 treatment. *Microsc. Microanal.* **2003**, *9*, 311–329. [CrossRef]
42. Xia, M.; Yan, X.; Zhou, L.; Xu, L.; Zhang, L.; Yi, H.; Su, J. P62 suppressed VK3-induced oxidative damage through Keap1/Nrf2 pathway in human ovarian cancer cells. *J. Cancer* **2020**, *11*, 1299–1307. [CrossRef] [PubMed]
43. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. *CA Cancer J. Clin.* **2020**, *70*, 7–30. [CrossRef] [PubMed]
44. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]
45. Yang, C.R.; Liao, W.S.; Wu, Y.H.; Murugan, K.; Chen, C.; Chao, J.I. CR108, a novel vitamin K3 derivative induces apoptosis and breast tumor inhibition by reactive oxygen species and mitochondrial dysfunction. *Toxicol. Appl. Pharmacol.* **2013**, *273*, 611–622. [CrossRef]
46. Wellington, K.W.; Hlatshwayo, V.; Kolesnikova, N.I.; Saha, S.T.; Kaur, M.; Motadi, L.R. Anticancer activities of vitamin K3 analogues. *Investig. New Drugs* **2020**, *38*, 378–391. [CrossRef]
47. Kar, S.; Carr, B.I. Growth inhibition and protein tyrosine phosphorylation in MCF 7 breast cancer cells by a novel K vitamin. *J. Cell. Physiol.* **2000**, *185*, 386–393. [CrossRef]
48. Behrad Nasab, M.; Afsharfar, M.; Ahmadzadeh, M.; Vahid, F.; Gholamalizadeh, M.; Abbastorki, S.; Davoodi, S.H.; Majidi, N.; Akbari, M.E.; Doaei, S. Comparison of the index of nutritional quality in breast cancer patients with healthy women. *Front. Nutr.* **2022**, *9*, 811827. [CrossRef]
49. Arbyn, M.; Weiderpass, E.; Bruni, L.; de Sanjosé, S.; Saraiya, M.; Ferlay, J.; Bray, F. Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. *Lancet Glob. Health* **2020**, *8*, e191–e203. [CrossRef]
50. Ono, A.; Koshiyama, M.; Nakagawa, M.; Watanabe, Y.; Ikuta, E.; Seki, K.; Oowaki, M. The preventive effect of dietary antioxidants on cervical cancer development. *Medicina* **2020**, *56*, 604. [CrossRef]
51. Wang, Z.; Yang, A.; Yang, J.; Zhao, W.; Wang, Z.; Wang, W.; Wang, J.; Song, J.; Li, L.; Lv, W.; et al. Dietary nutrient intake related to higher grade cervical intraepithelial neoplasia risk: A Chinese population-based study. *Nutr. Metab.* **2020**, *17*, 100. [CrossRef]

52. Armstrong, D.K.; Alvarez, R.D.; Bakkum-Gamez, J.N.; Barroilhet, L.; Behbakht, K.; Berchuck, A.; Chen, L.; Cristea, M.; DeRosa, M.; Eisenhauer, E.L.; et al. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2021**, *19*, 191–226. [CrossRef]
53. Van Nagell, J.R.; Burgess, B.T.; Miller, R.W.; Baldwin, L.; DeSimone, C.P.; Ueland, F.R.; Huang, B.; Chen, Q.; Kryscio, R.J.; Pavlik, E.J. Survival of women with type I and II epithelial ovarian cancer detected by ultrasound screening. *Obstet. Gynecol.* **2018**, *132*, 1091–1100. [CrossRef]
54. Tossetta, G.; Marzioni, D. Natural and synthetic compounds in ovarian cancer: A focus on NRF2/KEAP1 pathway. *Pharmacol. Res.* **2022**, *183*, 106365. [CrossRef]
55. Ellis, J.L.; Fu, X.; Karl, J.P.; Hernandez, C.J.; Mason, J.B.; DeBose-Boyd, R.A.; Booth, S.L. Multiple dietary vitamin K forms are converted to tissue menaquinone-4 in mice. *J. Nutr.* **2022**, *152*, 981–993. [CrossRef]