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Sofia Dahlberg<sup>1</sup> and Ulf Schött<sup>1,2\*</sup>

<sup>1</sup>Department of Anesthesia and Intensive Care, Institution of Clinical Science Lund, Medical Faculty, Lund University, Sweden.

<sup>2</sup>Department of Anesthesiar and Intensive Care, Skane University Rrsity Hospital Lund, Lund,

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**\*Corresponding author:** Ulf Schött, Department of Anesthesia and Intensive Care, Skåne University Hospital, Lund, S-22185 Sweden and Institution of Clinical Science Lund, Medical faculty, Lund University, Sweden, Tel: 46-(0)46-171319; Alt: 171000; Fax: 46-(0)46-176050; E-mail: ulf.schott@skane.se

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## Review Article

# Vitamin K: A potential Liver Cancer treatment way

## Abstract

A review on different vitamin K<sub>1-3</sub> effects on hepatocellular cancer and their tumour cell biology mechanism indicate possible synergistic treatment strategies. Monitoring of dysfunctional carboxylation of the vitamin K dependent coagulation factor II, with the commercial ELISA test PIVKA-II has been used as a hepatocellular cancer marker. Its relevance is also reviewed. Currently the PIVKA-II test has been withdrawn due to marketing reasons by Stago.

## Performance of PIVKA-II as a HCC tumour marker

Multiple studies have shown increased PIVKA-II in HCC patients, and PIVKA-II is considered a valuable complement to AFP. Whereas the AFP measure reflects intrahepatic tumour burden, PIVKA-II correlates with vascular invasion and extra hepatic disease [6]. A suggested mechanism of action of PIVKA-II is that it facilitates the secretion of matrix metalloproteinase (MMP) 9 and MMP-2 through the ERK1/2MAPK pathway [7]. These proteolytic enzymes have the ability to degrade extracellular matrix and facilitate metastasis [8]. PIVKA-II has also been suggested to function as an autocrine/paracrine mitogen for HCC cells by stimulating the Met-JAK-STAT pathway [9]. The mechanism underlying the PIVKA-II increase is not completely understood, but several explanations have been proposed. For instance, animal experiments have shown decreased gamma-carboxylase activity in hepatic tumour tissue [10]. Other suggestions are vitamin K insufficiency in the tumour cells [11], defective vitamin K uptake [12] and excessive synthesis of prothrombin precursors [13].

Several studies comparing the diagnostic capability of different biomarkers for HCC exist. Using PIVKA-II in combination with AFP has been reported to improve accuracy [14]. Other studies looking exclusively at hepatitis B infected individuals suggest PIVKA-II is superior to AFP, and that the combination of both measures may enhance early detection [15]. A recent study comprising roughly 2 000 participants concluded that 230 HCC cases would have been neglected if using AFP alone, and that PIVKA-II levels increased over a year before image discovery [16]. Also, high PIVKA-II levels where associated with greater risk of developing HCC within a 2-year period in high risk populations with chronic hepatitis B. Furthermore, PIVKA-II has also been associated with portal

## Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and roughly 75% of cases are attributed to viral infections with hepatitis B or C [1]. Furthermore, HCC is the second leading cause of cancer death surpassed only by lung malignancies [2], and is often unresectable at diagnosis. The most commonly used tumour marker for HCC is alpha-fetoprotein (AFP) but its diagnostic efficiency is poor, especially in hepatitis infected individuals [3]. Hence, better diagnostic and prognostic markers would aid in early detection and treatment of HCC.

Vitamin K is best known for its involvement in haemostasis, where it functions as a cofactor in  $\gamma$ -carboxylation of hepatic clotting factors II, VII, IX and X as well as protein C, S, Z and M. This post-translational modification induces a conformational change which allows the protein to bind calcium ions, a crucial step for their involvement in haemostasis [4]. In addition to aforementioned clotting factors several vitamin K dependent proteins originating from extra hepatic tissues have been identified and are collectively referred to as Gla proteins. Accumulating evidence from pre-clinical studies suggest that vitamin K and the Gla proteins are involved in a wide range of diseases, such as cardiovascular disease, osteoporosis and cancer [5].

Proteins induced by vitamin K absence for factor II (PIVKA-II, or des-gamma-carboxy prothrombin, DCP) is a measure of hypocarboxylated prothrombin and has been suggested to function as a tumour marker for HCC. In the following sections, the efficacy of PIVKA-II as a tumour marker and the role of vitamin K in HCC treatment are discussed.

vein thrombosis [17] and microvascular invasion, which is a major prognostic factor in HCC [18]. In addition to PIVKA-II and AFP, several other HCC biomarkers have been proposed. Due to the heterogeneity of HCC it seems that a combination of biomarkers is favorable, but currently no large scale studies investigating the optimal biomarker combination have been performed [19].

In addition to viral hepatitis, alcohol-induced liver damage is a major risk factor for developing HCC [20]. In a study investigating PIVKA-II levels in patients with benign alcoholic liver disease (ALD), 21% of cases had PIVKA-II levels above the cut-off value commonly used for the tumour marker [21]. Similar results were demonstrated in a more recent study [22]. The causative mechanism of the PIVKA-II increase is unknown. Vitamin K deficiency has been suggested [23], but no correlation between plasma vitamin K levels and PIVKA-II has been demonstrated [21, 24]. The confounding effect of ALD on PIVKA-II levels should be taken into account when interpreting PIVKA-II levels, and a different cut-off value might be needed to avoid false-positive results in ALD patients.

### HCC treatment with vitamin K

Due to the aforementioned effects of PIVKA-II on HCC tumour cells, and that PIVKA-II seems to predispose for more aggressive disease [25], studies have investigated whether vitamin K administration could affect the disease course. Vitamin K occurs naturally in two forms, vitamin K<sub>1</sub> and vitamin K<sub>2</sub>, which is further subdivided depending on the length and saturation of its side chain [26]. In addition, synthetic forms vitamin K<sub>3</sub>-K<sub>5</sub> exist. Vitamin K<sub>2</sub> subspecies MK-4 is a ligand to the steroid and xenobiotics receptor (SXR) which regulates cell growth. In vitro studies have demonstrated vitamin K<sub>2</sub>-dependent suppression of proliferation and motility of HCC cells [27]. Furthermore, administration of vitamin K to patients with HCC subsequently decreased plasma PIVKA-II levels [28]. This study also demonstrated that PIVKA-II levels were not correlated with plasma levels of vitamin K derivatives, suggesting that the increase is not due to vitamin K deficiency but rather related to tumour metabolism.

In 2004 vitamin K<sub>2</sub> supplementation was reported to prevent HCC in women with viral cirrhosis [29]. Since then, several supplementation studies with MK-4 to HCC patients have been performed with mixed results. Although a few smaller studies have demonstrated a reduction of HCC recurrence when administering MK-4 [30], this effect was not confirmed in larger study populations using MK-4 [31]. In a recent meta-analysis of five randomized control trials evaluating the effect of vitamin K<sub>2</sub> on HCC recurrence after resection, survival was not improved [32]. However, synergistic effects were observed when MK-4 and the multikinase inhibitor sorafenib were administered together [33]. The vitamin K<sub>2</sub> derivative MK-7 has a longer half-life and better bioavailability for both hepatic and extra hepatic Gla proteins [34]. Several clinical trials investigating the effects of MK-7 on vascular disease are currently ongoing [35], but its effects on HCC has not been investigated.

Vitamin K<sub>3</sub> has been investigated in several studies due to its reported ability to generate ROS. In a clinical trial where vitamin K<sub>3</sub> was administered to patients with advanced HCC reduction of tumour size was demonstrated in 17% of the patient population. These patients also demonstrated increased mean survival time, but overall mortality was not affected [36]. Vitamin K<sub>3</sub> has also been used as a radio-sensitizer, and older studies have demonstrated increased survival time compared to radiotherapy alone in bronchial carcinoma patients [37]. Similar potentiation have been demonstrated in animal experiments [38, 39], but whether this can be used as adjuvant therapy in humans have not been studied in recent years. Vitamin K<sub>3</sub> has not been extensively studied in humans due to its hematological toxicities related to erythrocyte glutathione metabolism [40]. However, if administered concomitant with vitamin C, the necessary dose decreases due to synergistic effects. A small clinical trial investigating the effect of vitamin K<sub>3</sub> and vitamin C on therapy-resistant prostate cancer demonstrated a decrease in the rate of prostate specific antigen (PSA) increase after 12 weeks [41], but the combination has not been studied on HCC patients.

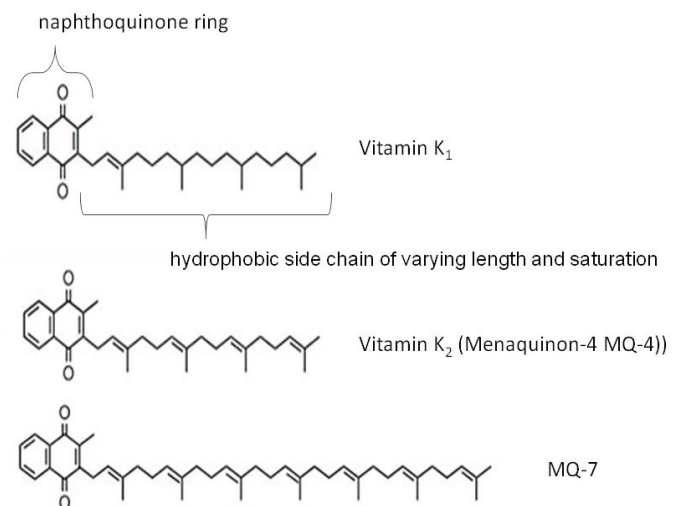


Figure 1:

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