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„Vitamin K Intake and Status in Relation to Prostate-Cancer – A Systematic Review“ “

verfasst von / submitted by

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Abstract

Prostate cancer cell growth is inhibited by vitamin K, and the aggressiveness of prostate cancers has been linked to changes in the expression of proteins regulated by vitamin K . The impact of vitamin K consumption on prostate cancer in human populations is not well understood.

A systematic review and meta-analysis on vitamin K (intake and status) and prostate cancer risk was conducted according to the PICOS criteria, and following the PRISMA reporting guidelines. Risk of bias and quality of the evidence were graded using the ROBIS-E and GRADE tools.

Out of 144 initial search results, four cohort studies (three on vitamin K intake, one on vitamin K status) were eligible for the present systematic review. In a meta-analysis of three studies, there were no significant associations between total vitamin K intake, phylloquinone intake, or menaquinone intake and prostate cancer risk, with Relative Risks [95 % Confidence Intervals] of 0.96 [0.89, 1.03] , 0.95 [0.85, 1.07], and 1.02 [0.88, 1.33]. No associations between vitamin K intake and advanced prostate cancer risk were observed, while one study suggested an inverse association between low vitamin K status and risk of advanced prostate cancer. The studies showed a high risk of bias and a very low certainty of the evidence.

Overall, the present findings do not indicate that vitamin K intake or status are associated with prostate cancer risk. However, these results need to be interpreted with caution, given the low number of studies with high risk of bias and the low certainty of the evidence.

Abstract

Das Wachstum von Prostatakrebszellen wird durch Vitamin K gehemmt, und die Aggressivität von Prostatakrebs wurde mit Veränderungen in der Expression von Proteinen in Verbindung gebracht, die durch Vitamin K reguliert werden. Die Auswirkungen des Vitamin K-Konsums auf Prostatakrebs in der menschlichen Bevölkerung sind nicht genau bekannt.

Eine systematische Übersichtarbeit und Metaanalyse zu Vitamin K (Einnahme und Status) und Prostatakrebsrisiko wurde gemäß den PICOS-Kriterien und gemäß den PRISMA-Berichtsrichtlinien durchgeführt. Das Risiko einer Verzerrung und die Qualität der Evidenz wurden mit den Tools ROBIS-E und GRADE bewertet.

Von den 144 ersten Suchergebnissen kamen vier Kohortenstudien (drei zur Vitamin K-Aufnahme, eine zum Vitamin-K-Status) für die vorliegende systematische Übersichtarbeit in Frage. In einer Metaanalyse von drei Studien gab es keine signifikanten Zusammenhänge zwischen der gesamten Vitamin-K-Aufnahme, der Phyllochinon-Aufnahme oder der Menachinon-Aufnahme und dem Prostatakrebsrisiko, mit relativen Risiken [95 % Konfidenzintervalle] von 0,96 [0,89, 1,03], 0,95 [0,85, 1,07] und 1,02 [0,88, 1,33]. Es wurden keine Zusammenhänge zwischen der Vitamin K-Zufuhr und dem Risiko für fortgeschrittenen Prostatakrebs beobachtet, während eine Studie einen inversen Zusammenhang zwischen einem niedrigen Vitamin K-Status und dem Risiko für fortgeschrittenen Prostatakrebs nahelegte. Die Studien zeigten ein hohes Verzerrungsrisiko und eine sehr geringe Evidenzsicherheit.

Insgesamt deuten die vorliegenden Ergebnisse nicht darauf hin, dass Vitamin K-Aufnahme oder -Status mit dem Prostatakrebsrisiko verbunden ist. Allerdings müssen diese Ergebnisse angesichts der geringen Anzahl an Studien mit hohem Verzerrungsrisiko und der geringen Vertrauenswürdigkeit der Evidenz mit Vorsicht interpretiert werden.

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Chapter 1

Introduction

1.1 Rationale

Prostate cancer is the second most commonly diagnosed type of cancer in the male population worldwide today. According to the American Cancer Society [26], 288.300 new prostate cases were seen in 2023 and 34.700 people died of prostate cancer. Northern Europe has the highest prevalence of prostate cancer, whereas Southern Asia has the lowest prevalence. In the year 2020, prostate cancer accounted for over 375,000 estimated deaths worldwide, making it one of the leading causes of cancer-related mortality in men [26].

Prostate cancer is a type of cancer that occurs in the prostate gland, which is a small gland located below the bladder in men. There are several factors that can increase or decrease a man's risk of developing prostate cancer, including modifiable and non-modifiable factors. The risk factors for prostate cancer include family history, hereditary syndromes, and race. Potentially modifiable factors are obesity, exercise [7]. Obesity is an established risk factor for advanced prostate cancer, while the role of dietary factors remains to be elucidated. On this matter, however, no firm conclusions have been made [3].

While not much is known about the role of dietary factors in prostate cancer development, there is preliminary evidence to suggest preventive effects of vitamin K intake. For example, laboratory based mechanistic studies have shown that vitamin K may inhibit other cancers, such as colon cancer. However, a systematic review of human studies on vitamin K intake and prostate cancer risk is lacking. Given the high prevalence of prostate cancer worldwide, and the current lack of know targets for is primary prevention, the goal of the present thesis was to carry out a systematic review of human studies on the role of vitamin K in prostate cancer development for the first time. Some researches have indicated that vitamin K could act as a defense against prostate cancer. Both vitamin K1 (phylloquinone) and vitamin K2

(menaquinone) are subtypes of vitamin K. Because prostate cancer affects so many men, it's critical to look at the elements that could shield against its development. There has not previously been a systematic study on the link between vitamin K and prostate cancer despite investigations on both humans and animals. The goal of this thesis is to use a systematic review to bring this topic to the public's notice for the first time. This systematic review could be helpful to understand association vitamin K intake in prostate cancer and can be used in future stages.

1.2 Background

1.2.1 Vitamin K Sources, Metabolism, Biological Functions

Vitamin K is is critical to the blood coagulation process. Vitamin K is mostly found in two forms: vitamin K1 and vitamin K2, the latter of which is primarily found in fermented foods and animal products. Vitamin K1 is primarily found in leafy green vegetables. As a cofactor for the posttranslational -carboxylation of glutamate residues in vitamin dependent proteins, fat-soluble vitamin K develops its critical function. The name "vitamin K" refers to a class of substances that share a 2-methyl-1,4-naphtoquinone ring but differ in the size and composition of their 3-position isoprenoid side chains. Phylloquinone (vitamin K1) and the group of menaquinones (vitamin K2, MK-n), which differ in the amount of prenyl units they contain, are the two forms of vitamin K that naturally exist in foods. Menaquinones are produced by bacteria; consequently, they mostly appear in fermented items like cheese, whereas phylloquinone is plentiful in green leafy vegetables and certain vegetable oils. Menaquinones, particularly MK-4, which are produced in animals either from phylloquinone or the synthetic menadione (vitamin K3) that is frequently added to animal feeds, are also found in meat and meat products. Both vitamin K types contribute to the creation of clotting factors that lessen excessive bleeding. The co-regulation of calcium metabolism, is another function of vitamin K. While vitamin K deficiency is rare, certain groups may be at higher risk, such as newborns, people with digestive disorders, and those taking certain medications. It is important to maintain adequate vitamin K intake for newborns, people with digestive disorders, and those taking certain medications through a balanced diet or supplements, while being mindful of potential interactions and side effects [15].

In addition to its role in blood coagulation, there is growing evidence that vitamin K has another biological functions, including vascular health, brain health, cancer prevention. The activation of the matrix Gla protein (MGP), which works to stop artery walls from calcifying, is facilitated by vitamin K. Adequate levels of vitamin K have been associated with a lower risk of

cardiovascular disease [27]. On the other hand, vitamin K has been shown to play a role in brain function and cognition. It is involved in the production of sphingolipids, a type of lipid that is important for the formation and maintenance of the myelin sheath that surrounds nerve cells [6].

The small intestine absorbs dietary vitamin K from meals like green leafy vegetables and incorporates it into chylomicrons, which are then delivered to the liver. Very-low-density lipoproteins (VLDL) are formed in the liver and carry vitamin K to numerous bodily tissues. Activating certain proteins involved in blood clotting and bone metabolism, carboxylation is a process that vitamin K goes through once it is inside the tissues. Specific amino acid residues in these proteins are converted to gamma-carboxyglutamic acid (Gla) during the carboxylation process. The vitamin K cycle, which involves recycling vitamin K, transforms it back into vitamin K epoxide, which is no longer active [23].

1.2.2 Prostate Cancer: Epidemiology

Prostate cancer is a significant health concern for men worldwide with higher prevalence in developed countries. The incidence and mortality rates of prostate cancer are strongly related to age, with elderly men being at the highest risk. In comparison to White men, African-American men have a greater incidence rate and a more severe form of prostate cancer. According to the World Cancer Research Fund International (WCRFI), prostate cancer is the second most commonly diagnosed cancer in men, accounting for 7.3% of all cancer cases in men worldwide. In 2020, there were an estimated 1.4 million new cases of prostate cancer worldwide. Prostate cancer is also a leading cause of cancer-related death in men, although mortality rates vary widely by country. In 2020, there were an estimated 375,304 deaths from prostate cancer worldwide. The incidence rate of prostate cancer varies significantly across regions and populations worldwide (Figure 1.1) [29].

Globally, 1,276,106 new instances of prostate cancer were reported in 2018, making up 7.1 % of all male malignancies. Age-standardized rates range from 62.1 to 79.1 per 100,000 persons, with the incidence rates being highest in industrialized areas like Oceania, North America, and Europe. In comparison, the incidence rates in Asia and Africa are lower, at 26.6 and 11.5 respectively [21].

Between the populations with the greatest incidence rates (France, Guadeloupe, 189.1) and those with the lowest rates (Bhutan, 1.0), there is a 190-fold disparity in incidence rates. These discrepancies in incidence rates are probably caused by variations in risk factors such genetics, lifestyle, and environmental variables, as well as variations in the use of diagnostic tests. For the purpose of creating efficient preventive and screening techniques that are suited to the particular requirements of various groups, it is crucial

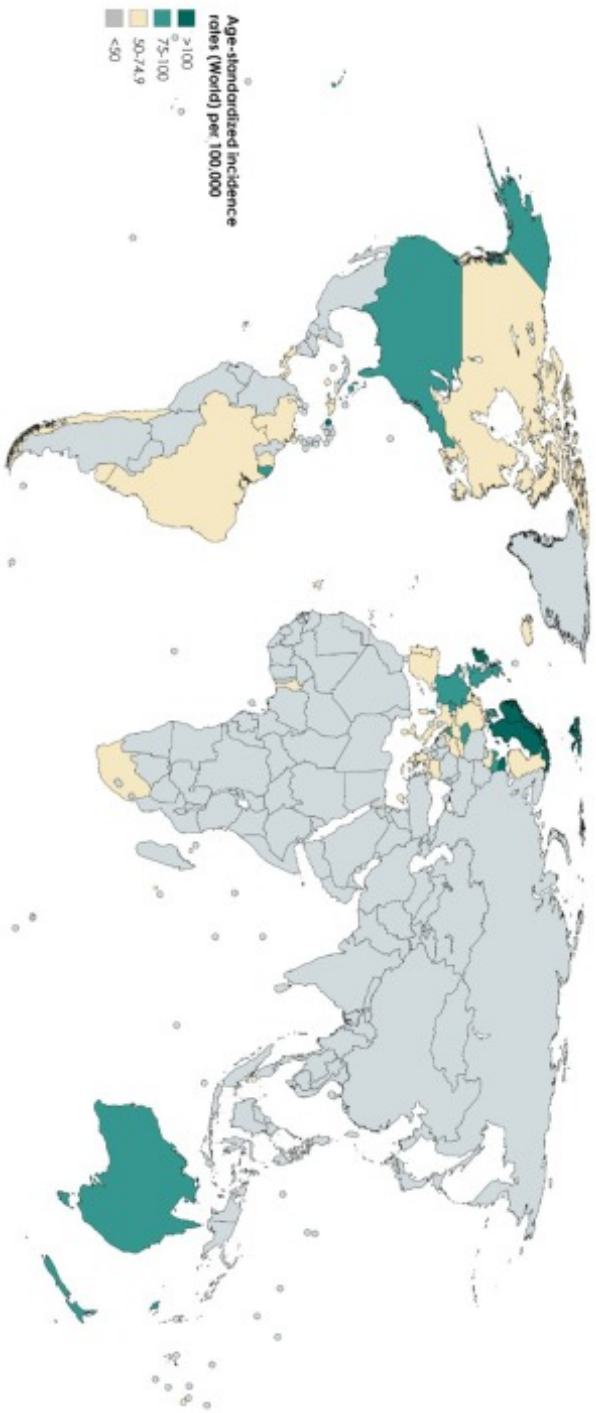

Figure 1.1: Map showing estimated age-standardized incidence rates for prostate cancer worldwide in 2018, in males including all ages, TAKEN FROM RAWLA ET AL. 2019 [21].

to comprehend the differences in prostate cancer incidence rates between populations. The necessity for early identification in high-risk populations and the need of raising knowledge of prostate cancer risk factors are also highlighted [21].

The greatest rates of prostate cancer death were seen in Central America, Australia, New Zealand, and Western Europe in 2018. Prostate cancer mortality rates vary widely throughout the world. Asia and Northern Africa were found to have the lowest rates, according to reports. In (Figure 1.2) Asia and Europe each saw a third of all prostate cancer fatalities. The bulk of deaths from prostate cancer are in males over 65 years old, and the mortality rate rises with age. The variances in risk factors, access to healthcare, and the availability of screening and treatment options may be to blame for these discrepancies in death rates. The burden of prostate cancer can be lessened internationally by creating efficient preventive and screening programs that are adapted to the particular requirements of various populations. Early detection through regular screening tests, such as the PSA test and DRE, can lead to better treatment outcomes and reduce mortality rates. Encouraging men to undergo regular screening, particularly those at higher risk, can play a critical role in reducing the impact of prostate cancer. Additionally, encouraging good lifestyle practices including following a balanced diet, getting regular exercise, and abstaining from tobacco and excessive alcohol usage will help lower the risk of prostate cancer.

1.2.3 Prostate Cancer: Potential nutritional risk factors

Furthermore, death rates and the spread of prostate cancer may be influenced by dietary deficiencies or overconsumption of certain nutrients. Clinical trials have had mixed findings, despite evidence from animal models indicating certain foods, including fat, protein, carbs, vitamins, and polyphenols, may have an impact on prostate cancer. Recent research has also highlighted the potential role of gut microbiota in the development of prostate cancer, with some studies showing an increase in certain gut bacteria in individuals with prostate cancer. In addition, there is a link between prostate cancer and gut microbiota that has drawn a lot of interest recently and is the subject of substantial research (Figure 1.3) [14].

In another review several potential links between nutrients and prostate cancer risk are summarized [19]. For example, the authors discuss that high-fat diets have been linked to an increased risk of prostate cancer development. The possible mechanisms linking high-fat diets to prostate cancer development are related to hormonal regulation and androgen levels, oxidative stress, exposure to toxic pesticides, specific effects of individual fatty acids, alteration of growth factor signaling, and lipid metabolism (Figure 1.4)[19]. The authors further suggest that due to intraepithelial neoplasia and prostate

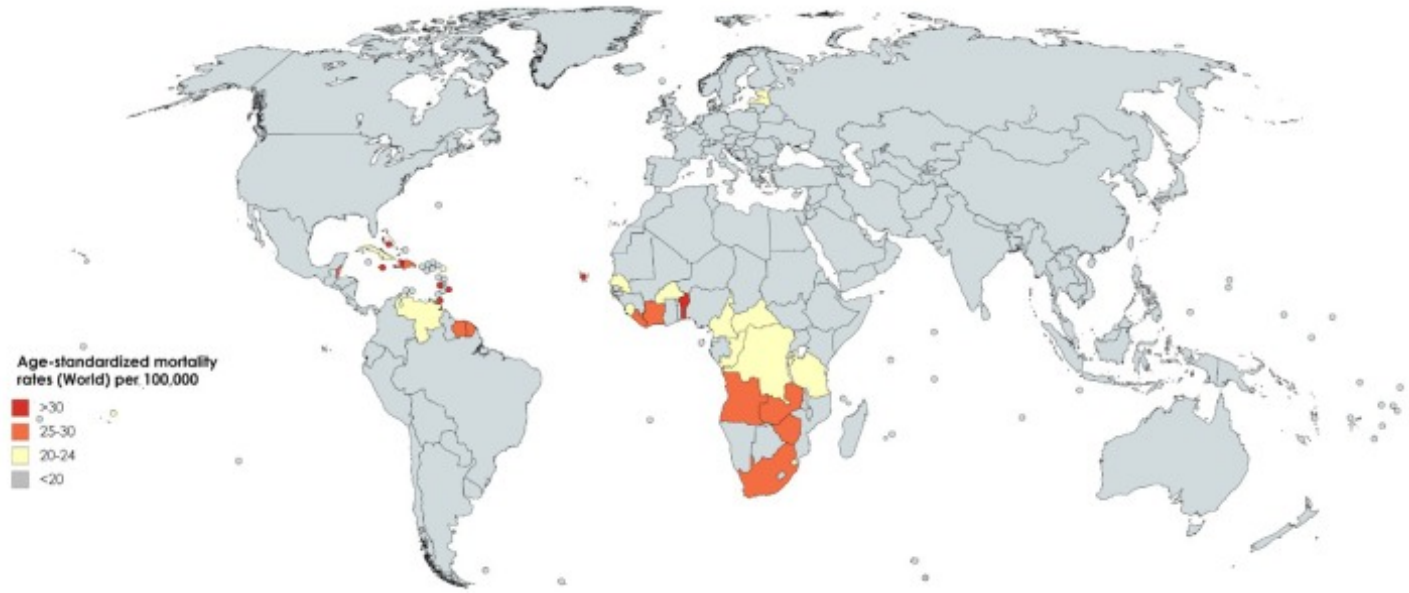

Figure 1.2: Map showing estimated age-standardized mortality rates for prostate cancer worldwide in 2018, in males including all ages, TAKEN FROM RAWLA ET AL. 2019 [21].

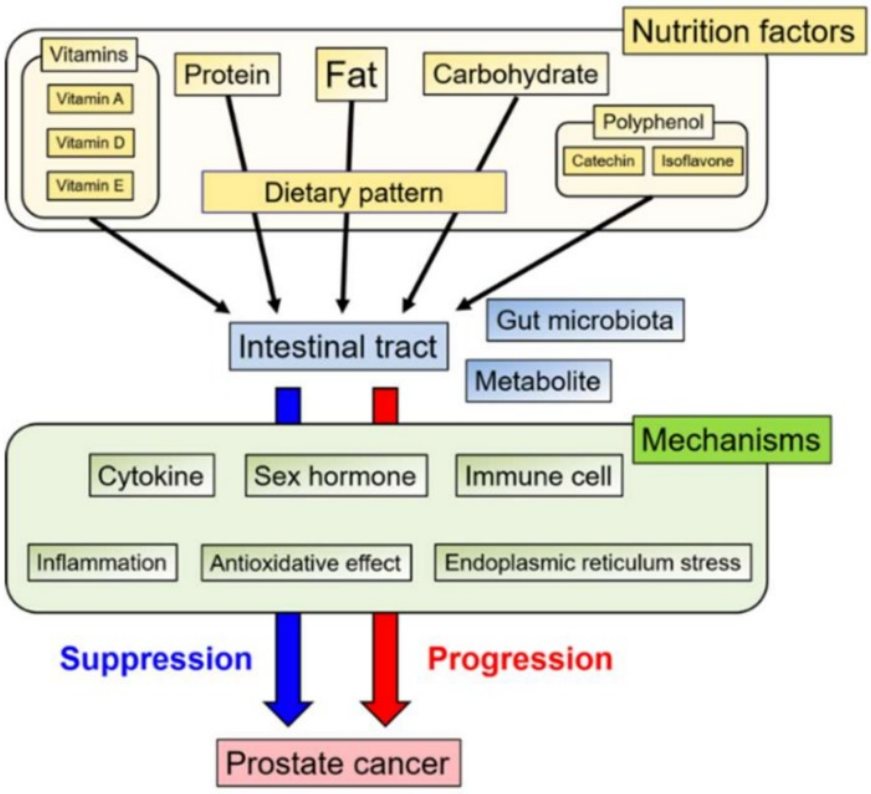

Figure 1.3: Schema of various nutrition factors and mechanisms involved in the progression or suppression of prostate cancer via the intestinal tract, TAKEN FROM MATSUSHITA ET AL. 2020 [14].

cancer, high-fat diets are also known to cause intraprostatic inflammation and cellular proliferation of the mouse prostate gland. The activation of signaling pathways involving the transcription factors STAT-3 and NF-*alpha*B is another effect of a high-fat diet, which also results in a notable rise in proinflammatory cytokines. A hormone-dependent neoplasm highly correlated with androgen levels is prostate cancer. It has been demonstrated that men who are vegetarian or who consume less dietary fat have lower serum testosterone levels. Enhanced 5-*alpha* reductase activity, which is involved in the conversion of testosterone to DHT, has also been linked to excessive fat consumption in laboratory studies [19]. Linolenic, EPA, and DHA acids, which are polyunsaturated fatty acids (PUFAs), lower the overall risk of prostate cancer and its advanced stages. The prevalence of advanced prostate cancer is raised by alpha-linolenic and myristic acids. A role of the linoleic to alpha-linolenic acid ratio has been proposed [19], but that human evidence for such a role is generally lacking [28]. According to WCRF many of the proposed links between diet and prostate cancer risk have been proven just by some human studies [28]. There is still a need for further research to

fully understand the relationship between high-fat diets and prostate cancer development [19].

The consumption of meat, particularly red and processed meat, has been associated with an increased risk of prostate cancer in some studies. The National Institutes of Health (NIH)-AARP Diet and Health Study found that participants who consumed more than 66.1 g of red meat per 1000 kcal had a 12% increased risk of all prostate cancer, and a more than 30% higher risk of advanced disease compared to those consuming small amounts. The intake of processed meat was also associated with an increased risk of advanced prostate cancer [25]. The cooking method of grilling/barbecuing was also found to increase the risk. According to a different study, eating a lot of hamburgers, processed meat, grilled red meat, and well-done processed meat increases your chance of developing advanced prostate cancer compared to not eating any processed red meat at all. However, some studies have shown that the consumption of processed meat did not influence the risk of developing prostate cancer, and the results of some meta-analyses have not supported an independent, positive association between the intake of red or processed meat and the development of prostate cancer. It should be noted that eating white meat has not been associated with an increased risk of prostate cancer [19].

Essential trace elements zinc and selenium may play a part in DNA repair, oxidative stress reduction, and immunological response. Additionally, these trace elements are parts of various enzymes that control important biochemical procedures in living things. Grain, meat, fish, and dairy products are the primary food sources of selenium, and the amount of this trace element in the soil determines how much selenium is present in food. For an adult male, 70 *mu*g of selenium per day is the recommended daily consumption. In organisms that include selenocysteine or selenomethionine, selenium is present in the form of selenoproteins. Iodothyronine deiodinase types I and III, thioredoxin reductase, and antioxidant enzymes like glutathione peroxidase (GPx) and superoxide dismutase (SOD), which are components of the body's antioxidant defense system, are among the selenium-dependent enzymes found in humans. The risk of prostate cancer is significantly correlated with blood selenium content, according to a number of prospective studies and meta-analyses (Figure 1.5) [10].

Prostate cancer risk was shown to be considerably reduced in those who had greater blood selenium concentrations. Additionally, persons whose toenail selenium content was in the range of 0.85-0.94 *mu*g/g were characterized by a considerably decreased risk of prostate cancer. Selenium concentrations in plasma or serum up to 170 ng/mL were also associated with a lower risk of the illness [19].

Additionally, selenium intake was linked to a decreased relative risk of

Figure 1.4: The possible effects of high total fat, saturated fatty acids (SFAs) and trans fatty acids (TFAs) intake on prostate cancer progression. IGFBP: insulin growth factor binding protein (inhibited activity/protein level reduction). NF-αB: nuclear factor kappa B (increased expression). STAT-3: signal transducer and activator of transcription 3 (increased expression). T, DHT, E2: testosterone, dihydrotestosterone, 17β-estradiol (increased secretion). ROS: reactive oxygen species (increased generation). AR: androgen receptor, TAKEN FROM OCZKOWSKI ET AL. 2021 [19].

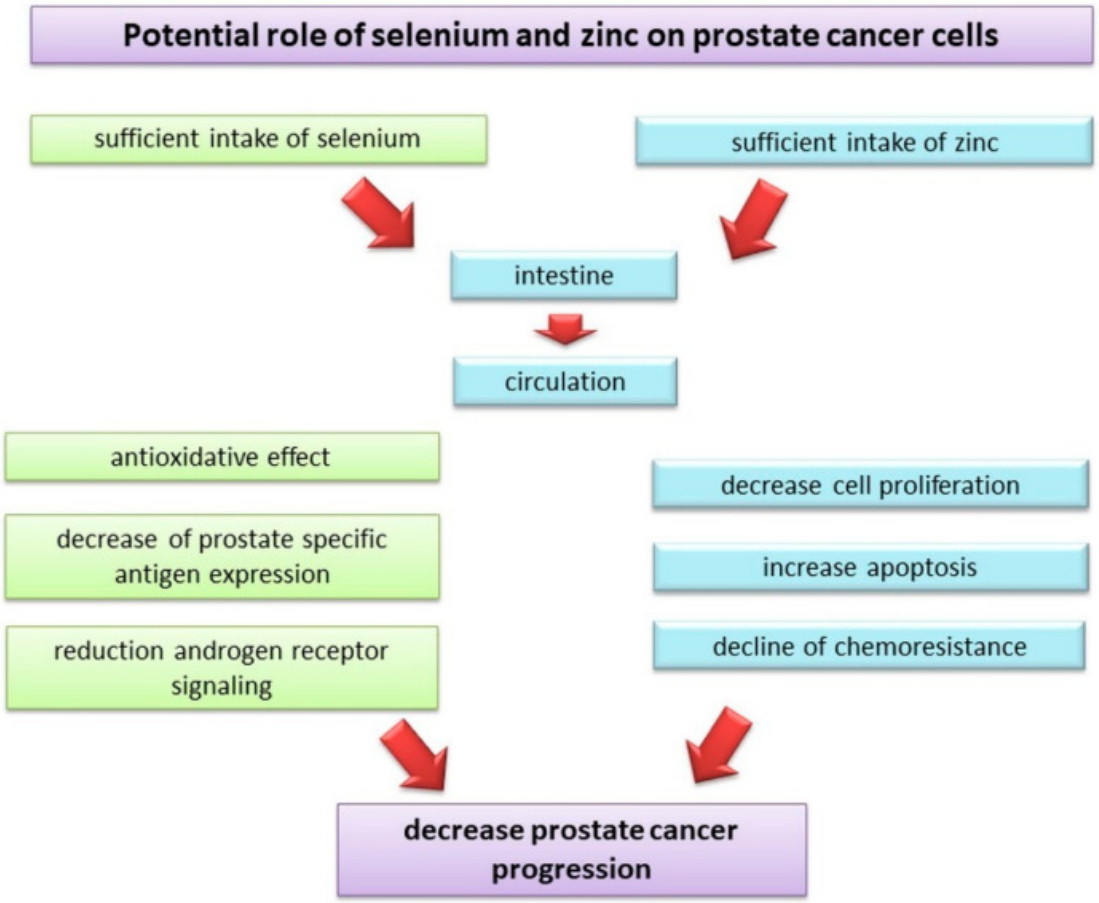

Figure 1.5: Potential role of selenium and zinc on prostate cancer progression, TAKEN FROM OCZKOWSKI ET AL. 2021 [19].

prostate cancer and a lower likelihood of the illness progressing to advanced stages, according to a meta-analysis of 38 studies. The risk of aggressive prostate cancer was shown to be decreased in people with high blood selenium levels. Men who took 200 g of selenium supplements daily were shown to have a 65% lower chance of developing prostate cancer. However, a decline in selenium is seen with age, which may lead to an increase in the incidence of prostate cancer [19].

In a randomized placebo-controlled experiment, selenium supplementation alone or in conjunction with vitamin E did not significantly reduce the risk of prostate cancer as compared to the placebo group in a group of generally healthy men aged 50 or older. In contrast, a prospective trial of men with nonmetastatic prostate cancer found that those who took selenium supplements had a two-fold greater crude mortality rate than men who did not. In comparison to nonusers, such a high amount of selenium supplementation was likewise linked to a very high chance of dying from prostate cancer [12].

In addition, there are inconsistent and ambiguous findings about the association between dairy consumption, particularly whole milk, and the risk of prostate cancer. While some research have revealed a substantial link between a high diet of milk and dairy products and a reduced risk of prostate cancer, other studies have not.The involvement of calcium is one potential explanation for the association between dairy consumption and risk of prostate cancer. Dairy products are a major source of calcium, and higher calcium consumption has been linked to an increased risk of prostate cancer. Prostate cancer may occur as a result of abnormalities in calcium homeostasis brought on by higher calcium consumption and lower levels of vitamin D. Calcium ions are essential for controlling cell growth, division, and differentiation. It is significant to note that calcium supplementation was not linked to a higher risk of prostate cancer in certain studies, indicating that the source of calcium consumption may be a crucial aspect to take into account. In order to fully understand the connection between dairy consumption, calcium consumption, and the risk of developing prostate cancer, further study is required [19].

On the other hand, World Cancer Research Fund (WCRF) study offers a thorough examination of the scientific data about the link between a high calcium intake, a low plasma alpha-tocopherol concentration, and a low plasma selenium level with the risk of developing prostate cancer. To completely comprehend the processes behind these relationships and to create practical preventative methods, further study is necessary [28].

There are several risk factors for prostate cancer, including age, family history, race/ethnicity, and diet. Understanding these risk factors is important for developing effective prevention and early detection strategies for prostate cancer. Additionally, the importance of modifiable risk factors, such as

lifestyle and food in particular, which are linked to the chance of developing prostate cancer, is receiving more and more attention. Contrary to minimally processed food items, the Western-type dietary pattern is thought to be related with a greater risk of cancer occurrence. A high intake of processed food, meat, and meat products with a high fat content, as well as a decrease in the consumption of fruits and vegetables, characterize this pattern. [19].

The widespread use of prostate-specific antigen (PSA) testing has led to increased detection of prostate cancer, particularly in developed countries. Screening for prostate cancer is highly recommended at age 45 for men with familial history and African-American men. Early detection through screening tests such as the prostate-specific antigen (PSA) test and digital rectal exam (DRE) can lead to a better prognosis and treatment outcomes. However, there is ongoing debate about the benefits and harms of prostate cancer screening, and the decision to undergo screening should be made after considering the individual's risk factors and preferences [21].

1.3 Associations between Vitamin K and Prostate Cancer

Vitamin K has become more crucial in the prevention and treatment of cancer because of the quinone structure, which serves as a functional component of various chemotherapeutics in cancer therapy. In research involving phylloquinone and menaquinones, antitumor effects were seen in a variety of cancer cell lines, including prostate cancer. In the case of menaquinones, many studies used MK-4, one used MK-1-3, and others did not identify the kind [17].

Vitamin K is thought to have a primary mode of action that is mediated by oxidative stress and has anticancer properties. Redox-cycling of the Quinone produces ROS such hydroxyl, the superoxide radical, and hydrogen peroxide, which causes oxidative stress. Cell death happens when redox cycling and ROS levels exceed the cell's ability to combat oxidative stress. ROS are chemically reactive compounds with oxygen molecules that are created by eukaryotic cells through a variety of methods during regular oxidative metabolism. Oxidative stress is caused by an imbalance between a cell's defensive mechanisms and its internal production of ROS. Increased levels of oxidative stress cause DNA damage, lipid and protein oxidative changes, and cell death or cancer-causing cell transformation. As a result, the majority of pathological illnesses and diseases, including cancer, are caused by oxidative stress. The majority of pathological disorders and diseases, including cancer, which is defined by increased cell proliferation, accumulating mutations or other DNA damage, and genomic instability, are therefore affected by oxidative stress. It is well known that compared to healthy cells, cancer cells

create more ROS [2].

In cellular systems, Vitamin K undergoes reduction to produce semiquinone (one electron), followed by hydroquinone (two electrons). NADPH:cytochrome p450 reductase catalyzes the reduction of (one electron) VK. Semiquinone is oxidized back to VK in the presence of oxygen (O2), which causes O2 to be reduced into ROS. NQO1, on the other hand, employs NADH or NADPH as electron donors and catalyzes the reduction of VK (menaquinone), which has two electrons, to hydroquinone, without the creation of semiquinone or ROS. The ROS generated as a result of VK's cyclic conversion to semiquinone and back to quinone may have a negative impact on the target cells. Due to the production of hydroxyl radicals, oxidative stress accelerates DNA damage. Oxidative stress causes more DNA damage because of the hydroxyl radicals that VK2 produces, which causes cancer cells to die through cytotoxicity (Figure 1.6) [2].

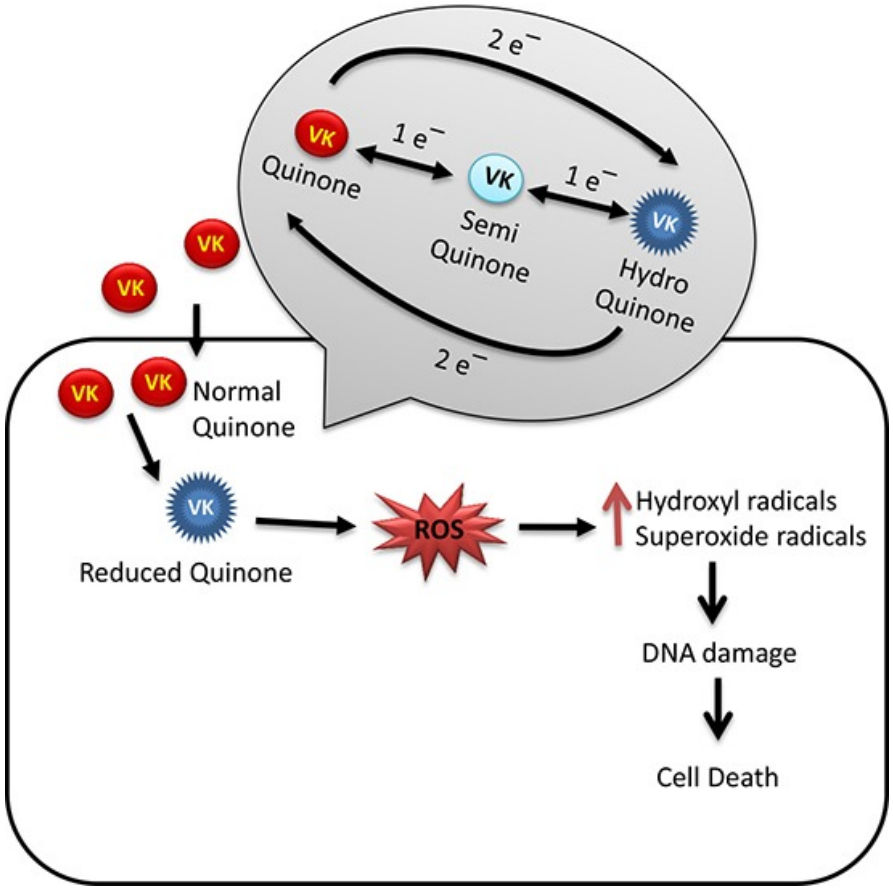

Figure 1.6: Oxidative stress mediated anticancer mechanism of Vitamin K, TAKEN FROM DASARI ET AL. 2017 [2].

However, it was recently shown that administration with VK2 significantly decreased the ability of PCa cells to proliferate, both androgen-dependent and androgen-independent, through molecular mechanisms such as activation of apoptosis and decrease of the PCa cells' angiogenic capability.The findings of the aforementioned investigation and other experiments. It was shown that hepatoma-derived growth factor (HDGF), a heparin-binding growth factor protein, plays a significant role in mediating the anti-proliferative impact of VK2 in hepatic cell lines. A recent study found that HDGF controls the division, apoptosis, and invasion of human PCa cells via the AKT and NF-kB pathways. Therefore, HDGF may be employed as a therapeutic target for VK2 in PCa (Figure 1.7 [24].)

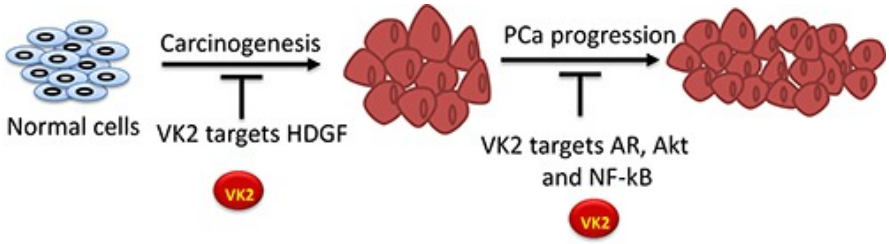

Figure 1.7: Proposed molecular mechanism of VK2 in prostate cancer.VK2 targets HDGF protein during the development of carcinogenesis and targets androgen receptors (AR), Akt and NF-kB during the progression of PCa, TAKEN FROM DASARI ET AL. 2017 [2].

On the other hand, vitamin K has a function in the calcification of varicose veins as well as the proliferation of smooth muscle cells in the media layer of the venous wall, according to recent studies. Varicose vein development is closely related to vitamin K. The idea is that a vitamin K deficiency condition fundamentally manifests as poor prostate health. It is conceivable that great prostate health may be maintained for a lot longer and that bad prostate health could even be restored by giving the correct kind and amount of vitamin K, together with other dietary supplements and phytochemicals. In EPIC-Heidelberg cohort [17], vitamin K was previously demonstrated to have a preventive effect against advanced prostate cancer. Studies studying the relationship between vitamin K and varicoceles as well as the relationship between varicoceles and benign prostatic hyperplasia can be used to further investigate this idea. If this theory is confirmed, changes can be observed in the health of prostate. Prostate enlargement could be seen as the result of poor vein health in general and prostate health may be affected by this result. Research on elements that improve vein health, such as vitamin K's function, will become more prominent [5].

1.4 Aims and Objectives

The aim of this thesis was to investigate association of vitamin K intake and prostate cancer risk in prospective epidemiological studies.Specifically, the following aims were addressed:

1) to examine the associations between total vitamin K intake and total/advanced prostate cancer,

2) to analyze the association of phylloquinone on total/advanced prostate cancer,

3) to analyze the association of menaquinone on total/advanced prostate cancer,

4) to analyze the association of vitamin K status on total/advanced prostate cancer.

Chapter 2

Methods

2.1 PICOS Criteria

The inclusion criteria were given by the Population, Intervention, Control, Outcomes, Study design (PICOS) framework as seen in (Table 2.1) This included (1) population: men with a risk of prostate cancer (2) intervention/exposure: any vitamin K intake form (menaquinone, phylloquinone, vitamin K status, total vitamin K) (3) control: comparison between high vs. low habitual vitamin K intake/high vs. low vitamin K status on risk of having prostate cancer. (4) outcomes: Prostate cancer (5) Study design: Cohort studies. Only full-text English articles of human trials, published in peer-reviewed journals were included in the search process. All steps were carried out through the search method in publications clearly to reach all results.

Table 2.1: Description of the Population, Intervention, Control, Outcome, Study design (PICOS) criteria.

Criteria	**Description**
Participants	Men with a risk of having prostate cancer
Intervention(s)	Total Vitamin K intake, Menaquinone intake, Phylloquinone intake, Vitamin K status
Comparison(s)	Comparison between high vs. low habitual vitamin K intake/high vs. low vitamin K status on risk of having prostate cancer
Outcome(s)	Prostate Cancer
Study design	Cohort studies

2.2 Search Terms and Databases

Firstly, the titles and abstracts of papers were analyzed through the search method in excluding publications. The disagreements were discussed and resolved. One author (AS) extracted the data, while a second author (TK) double-checked it. The following information for each published meta-analysis were gathered: initial author's name, publication year, exposure (including dose of exposure), the number of studies included, the primary studies' research design, the total number of cases and participants, and the comparison method (high-low meta-analysis or dose-response meta-analysis). The data extraction procedure followed the PRISMA statement. In order to compile the available data on vitamin K consumption and the risk of prostate cancer, systematic review was searched through PubMed and Web of Science from the beginning through April 2023. Publications were only in English. This systematic review aimed to find randomized control trials, cohort studies, and studies that looked at the association between vitamin K consumption and risks of prostate cancer incidence. The following keywords were used in search strategy: ("vitamin K intake AND prostate cancer" and "vitamin+K AND prostate+cancer"). PubMed extracted 73 results according to search term "vitamin K intake AND prostate cancer" and Web of Science extracted 71 results from "vitamin+K AND prostate+cancer"). Overlapped study results were 69. (66 excluded, 3 included) (Figure 2.1)

The systematic research resulted in 144 records; details of the search process are shown in Figure 2.2. Abstracts of these records were assessed for eligibility; full texts of the remaining 5 articles were independently examined by A.S and T.K. A total of 4 studies met the inclusion criteria; including cohort studies in this systematic review. One study included a total vitamin K, phylloquinone and menaquinone intake as a intervention, two studies included phylloquinone and menaquinone intake as a intervention, one study included vitamin K supply score and ucOC/iOC exposures.

As a result of PubMed and Web of Science research, 69 studies removed because of dublication. 63 researches were excluded from title and abstract. Reasons for 63 studies to be removed: A meta analysis, case control study, not a human study, not a randomized trial, systematic review, not related with prostate cancer and also vitamin K intake.

The GRADE methodology takes into account the included studies' quality and research design. Observational studies are originally seen as lower-quality evidence than randomized controlled trials (RCTs), which are typically thought of as high-quality evidence. Considerations for evaluating the risk of bias in specific research include randomization, allocation concealment, blinding, and attrition [22].

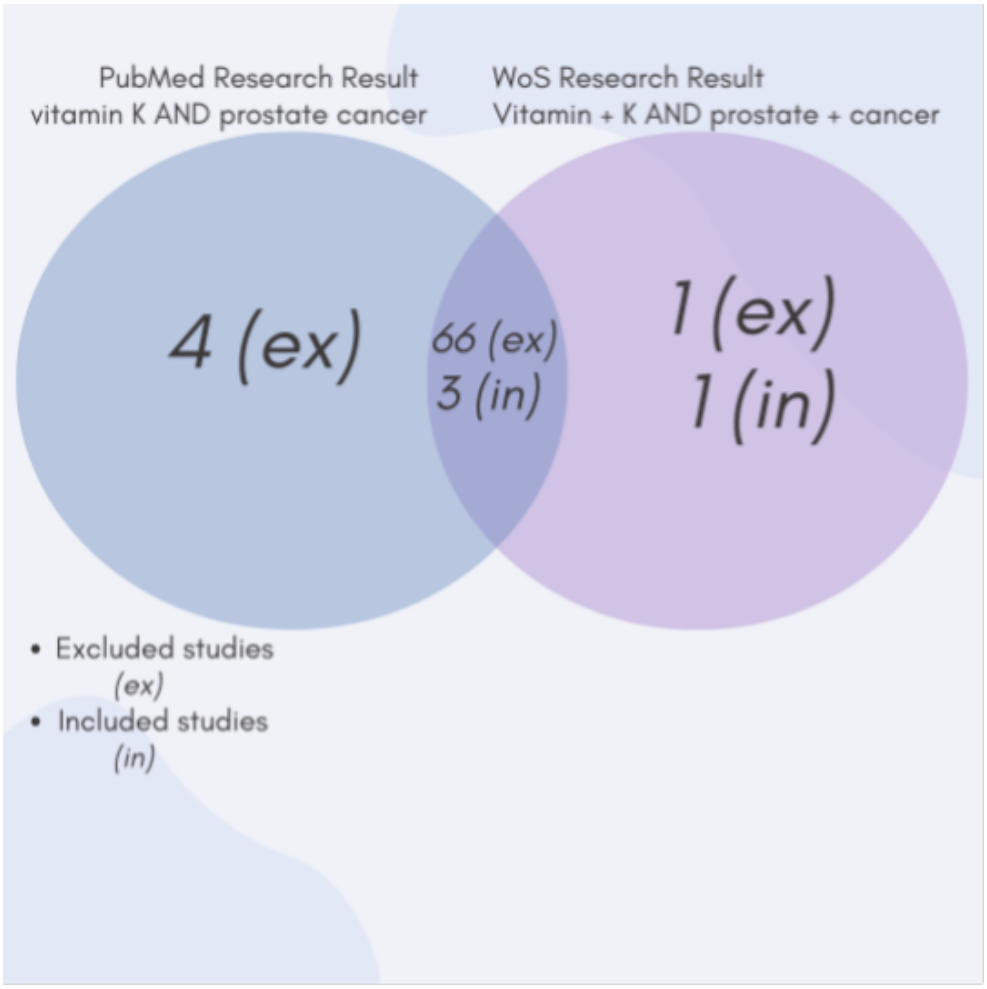

Figure 2.1: PubMed and Web of Science study

2.3 Risk of Bias Assessment and Certainty of the Evidence

The term "risk of bias" refers to systemic mistakes or defects in the planning, execution, or analysis of a research that may produce results that are deceptive or erroneous. These biases may result from a number of factors, including poor study design, biased participant selection, measurement issues, or conflicts of interest [8].

The GRADE method was used to evaluate the caliber of the studies that were part of our evaluation. Only observational studies are covered by this instrument, which evaluates variables that may lower (risk of bias, inconsistent results, accuracy, indirect evidence, and publication bias) or

Figure 2.2: Search process flow chart

raise (magnitude of impact, dose-response gradient, and fewer confounders) the quality of the evidence. The present meta-analysis is independently assessed the quality of all included cohort studies by using the ROBINS risk of bias tool. The quality of evidence for outcomes using the grading of recommendations assessment, development, and evaluation (GRADE) approach were also examined.

The overall findings and conclusions of a systematic review can be impacted by the existence of bias in individual research. The evaluation of the risk of bias often entails assessing a number of important study areas, including randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and other potential sources of bias particular to the research issue under consideration. The assessment process may be guided by a variety of instruments and frameworks, including Cochrane Risk of Bias tool. Each included study's risk of bias is individually evaluated by reviewers, who then rate each category (e.g., low risk, uncertain risk, or high risk) according to their assessment. The verdicts take into account the possibility of bias in that specific study component. [8] .

All included studies' risk of bias is assessed, and the results are then compiled and presented in the systematic review. For readers to appreciate the strength and limits of the evidence and to make well-informed judgments based on the results, this information is essential [8].

In systematic reviews, determining the risk of bias is a crucial step in assuring the reliability and validity of the included research. It provides a basis for evidence-based decision-making by assisting reviewers and readers in understanding the quality of the evidence and the potential influence of bias on the outcomes [8].

ROBINS E includes seven domains of bias:

• D1: Were all essential confounders considered ?, Were some important confounders considered ? Were only a few important confounders considered?

• D2: Was the dietary assessment questionnaire-based? Was the dietary assessment validated to capture vitamin K intake? Were objective biomarkers measured?

• D3: Were the study participants reflective of the general population of men in the respective country? Was there some kind of specific selection putting into question generalizability of results?

• D4: Could vitamin K intake / status have changed over time?

• D5: How many participants had missing values?

• D6: Was the outcome prostate cancer validated by medical records?

• D7: Were some results likely not shown?

Chapter 3

Results

3.1 Overview of Identified Studies

The comparison of the results was made by the meta-analysis through RevMan method and examined the quality according to Grade assessment. In the table below (Table 3.1), the results of the 4 selected studies are summarized. All of the studies were cohort research types. 2 studies were conducted in the USA and the other 2 were conducted in Germany. Participant's total prostate cancer and advanced prostate cancer were calculated based on the reference and high quintile ranges of vitamin K intake.

There were 4 included studies in this systematic review. First included study was about vitamin K intake and PLCO. The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial was a large-scale randomized controlled trial conducted between 1993 and 2001 in the United States. The study aimed to determine the effectiveness of screening tests for the early detection of cancer in the four aforementioned sites. In the identified publication, the PLCO data were used for merely observational analyses into the association between vitamin K consumption and the incidence of prostate cancer, which is why PLCO is considered as a cohort in the present systematic review [9].

76.685 men between the ages of 55 and 74 who were initially clear of prostate cancer participated in the trial. 28,356 males were left in the cohort DQX (dietary questionnaire data type) following the exclusions, with 2978 incident cases of prostate cancer(including 490 advanced cases) throughout the course of an 11.8-year median follow-up. When comparable exclusion criteria were employed, 48,090 males were left in the cohort and finished the DHQ (dietary history questionnaire data type) [9].

From the 48,090 males, 2973 incident of prostate cancer (including 647 advanced cases) were found throughout the course of a median follow-up of 8.5 years. The males were subsequently observed by the researchers for an

Figure 3.1: Study Results

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Total vitamin K, Phylloquinone, Menaquinone Exposures categories: Total vit.K: Q5:≥221.7μg/d, Q4: 167.2–221.6μg/d, Q3:131.9–167.1μg/d, Q2: 100.0–131.8μg/d, Q1 : <99.9μg/d Phylloquinone: Q5: ≥204.7μg/d,Q4:152.8–204.6μg/d, Q3: 118.9–152.7μg/d, Q2: 89.2–118.8gμ/d, Q1 : ≤89.1μg/d Menaquinone: Q5: ≥18.4μg/d, Q4: 12.7–18.3μg/d, Q3: 9.4–12.6μg/d, Q2: 6.6–9.3μg/d, Q1 : ≤6.5μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Total vitamin K total prostate cancer Table 3.1, Total vitamin K advanced prostate cancer Table 3.2, Phylloquinone intake total prostate cancer Table 3.2, Phylloquinone intake advanced prostate cancer Table 3.3, Menaquinone intake total prostate cancer Table 3.4, Menaquinone intake advanced prostate cancer Table 3.5	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene
Nimptsch K. (2008)	EPIC Heidelberg 8.6 y	11.928 part. 40-65 y 268 incident cases (113 advanced)	Exposure assessment: FFQ, HPLC Exposures: Phylloquinone, Menaquinone Exposures categories: Phylloquinone: Q1: <71μg/d Q2: 71-94μg/d Q3: 94-124μg/d Q4: ≥ 124 μg/d Menaquinone: Q1: <26μg/d Q2: 26-35μg/d Q3: 35-46μg/d Q4: ≥46μg/d Outcome assessment: Self-reported primary prostate cancer during follow-up or on death certificates, Study physician, medical records	Total prostate cancer Phylloquinone: Q1 : 1.00 - Q2 : 0.85 (0.59, 1.25) Q3 : 0.90 (0.60, 1.36) - Q4 : 1.02 (0.64, 1.61) Menaquinone: Q1 : 1.00 - Q2 : 0.75 (0.52, 1.07) Q3 : 0.68 (0.45, 1.04) - Q4 : 0.61 (0.36, 1.02)	Smoking, education, vigorous physical activity, energy from fat, alcohol, nonfat-nonalcohol energy, calcium, vitamin D, tomato or tomato products, BMI, history of diabetes, and family history of prostate cancer, intake of vegetables, dairy products, and meat or meat products (quartiles).
Nimptsch K. (2009)	EPIC Heidelberg 2 to 3 y	25.540 part. 40-65 y 250 case subjects and 494 control subjects	Exposure assessment : Self-administered questionnaires Personal computer–guided interview ELISA Exposures: Vitamin K supply score Exposure categories: Cases: Total vitamin K (μg/d) 124.7 (101.0-167.0) ucOC/iOC ratio: 0.16 (0.12-0.22) Controls: Total vitamin K (μg/d) 132.5 (104.8-169.4) ucOC/iOC ratio: 0.17 (0.12-0.23) ucOC/iOC Outcome assessment: Medical records, death certificates	Total prostate cancer ucOC/iOC: Q1 : 1.00 Q2 : 1.12 (0.71-1.77) Q3 : 1.09 (0.70-1.71) Q4 : 0.91 (0.56-1.47) Vitamin K supply score: Q1 : 1.00 Q2 : 1.04 (0.65-1.66) Q3 : 0.87 (0.53-1.43) Q4 : 0.76 (0.43-1.35) Advanced prostate cancer ucOC/iOC : Q1 : 1.00 Q2 : 0.88 (0.34-2.30) Q3 : 1.31 (0.54-3.19) Q4 : 1.38 (0.53-3.61) Vitamin K supply score: Q1 : 1.00 Q2 : 1.53 (0.53-4.38) Q3 : 0.55 (0.20-1.49) Q4 : 0.25 (0.07-0.96)	Season of blood collection, smoking status, education, vigorous physical activity, and family history of prostate cancer, dietary intake of phylloquinone, total energy, calcium, vitamin D, tomato products (all nutrients entered as quartiles).
Nimptsch K. (2015)	Prospective Health Professionals USA (1986 -2006) 20 y	44.087 part. 6.293 prostate cases (1.034 advanced and 4.585 organ cases)	Exposure assessment: FFQ Exposures: Phylloquinone, Menaquinone Exposure categories: Phylloquinone intake, Menaquinone intake Outcome assessment: Hazard ratios Confidence intervals	Total prostate cancer Phylloquinone: 0.96 (0.88, 1.04) Menaquinone: 0.97 (0.89, 1.05)	

average of 11.8 years to determine if prostate cancer appeared. Two different methods were used as exposure assessment (DQX, DHQ). Risk ratios are different for each assessment. For example, 2488 cases were examined for DQX total prostate cancer and 2326 cases for DHQ total prostate cancer. For DQX, the group with the highest total vitamin K intake 0.94 (0.80, 1.10) has no association with total prostate cancer. For DHQ, the group with the highest total vitamin K intake 0.91 (0.74, 1.11) has again no association with total prostate cancer. Quintile were used in all models. The most comprehensively adjusted model which was model 3 included, because it accounted for the highest number of confounders [9].

The PLCO study's findings demonstrated that neither total vitamin K consumption nor vitamin K1 intake were significantly associated with the risk of developing prostate cancer and advanced prostate cancer (Table 3.1 and Table 3.2). When total intakes of vitamin K, phylloquinone, and menaquinone all of which were measured by the DHQ were employed in the data analysis, there were no relationships with the risk of either advanced or overall prostate cancer. After analyses were expanded to include patients included in both the intervention and control arms, the null relationships found for vitamin K consumption data collected from the administration of the DHQ remained [9].

However, it has been shown that high vitamin K1 intake has no association with total prostate cancer, advanced prostate cancer. (Table 3.2) (Table 3.3). In the result of DQX evaluation, it was seen that higher vitamin K1 intake was not statiscally significant and there was no relationship with risk of developing advanced prostate cancer and also there is no association between vitamin K1 and total prostate cancer (Table 3.2).Males who consumed the most vitamin K2 had again no association with risk of developing advanced prostate cancer and risk of having total prostate cancer. All of the results were not significant so that there is no prevention effect. (Table 3.4) (Table 3.5)

Secondly, the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) was a large population-based study that investigated the relationship between dietary factors and the risk of various types of cancer, including prostate cancer.The specific study on dietary intake of vitamin K and risk of prostate cancer analyzed data from 11,319 men between the ages of 50 and 74 who were recruited into the EPIC-Heidelberg cohort between 1994 and 1998. (Table 3.2) The participants completed detailed dietary questionnaires at the time of recruitment, which were used to estimate their intake of vitamin K.

The researchers followed up with the participants over an average of 8.6 years and identified 268 cases of prostate cancer. (Table 3.2) The incidence of prostate cancer was then compared between participants with different

Table 3.1: Study results on total vitamin K and total prostate cancer

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Total vit. K Exposures categories: Total vit.K: Q5: $\geq$221.7μg/d, Q4: 167.2–221.6μg/d, Q3: 131.9–167.1μg/d, Q2: 100.0–131.8μg/d, Q1 : $<$99.9μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Total prostate cancer DQX Total vitamin K Q1 : Ref. Q2 : 0.98 (0.87, 1.10) Q3 : 1.00 (0.88, 1.13) Q4 : 0.98 (0.86, 1.12) Q5 : 0.94 (0.81, 1.10) Total prostate cancer DHQ Total vitamin K Q1 : Ref. Q2 : 1.09 (0.94, 1.26) Q3 : 0.88 (0.75, 1.03) Q4 : 0.99 (0.84, 1.17) Q5 : 0.91 (0.74, 1.11)	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene

Table 3.2: Study results on total vitamin K and advanced prostate cancer

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Total vit. K Exposures categories: Total vit.K: Q5: $\geq$221.7μg/d, Q4: 167.2–221.6μg/d, Q3: 131.9–167.1μg/d, Q2: 100.0–131.8μg/d, Q1 : $<$99.9μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Advanced prostate cancer DQX Total vitamin K : Q1 : Ref. Q2 : 1.24(0.92, 1.68) Q3 : 1.25(0.92, 1.71) Q4 : 1.20 (0.86, 1.67) Q5 : 1.33 (0.90, 1.96) Advanced prostate cancer DHQ Total vitamin K : Q1 : Ref. Q2 : 0.82 (0.57, 1.19) Q3 : 0.73 (0.49, 1.07) Q4 : 0.87 (0.58, 1.29) Q5 : 0.77 (0.48, 1.23)	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene

levels of vitamin K intake. In the outset, self-administered questionnaires and a personal interview with questions on marital status, education, employment status, smoking history, physical activity, use of medication, and history of disease were used to gather information on dietary and nondietary variables. A professional interviewer used established techniques to collect anthropometric data at the research site, including participant weight and height. Active follow-up was done by mailing follow-up questionnaires to track down any new cases of various illnesses. First follow-up, 1998–2000, response rates were 93.5 %, second follow-up, 2001–2004, response rates were 91.8 %; and third follow-up, 2004–present, response rates were 92.0 %. (3rd follow-up, 2004–2007). Inquiries regarding PSA screening test participation were made at the second and third follow-up visits [17].

The results of the study suggested that there was no significant association between dietary intake of vitamin K1 and the risk of prostate cancer. Whether the highest consumption of phylloquinone nor lowest consumption had an association with risk of having total prostate cancer and risk of having advanced prostate cancer because the findings were not statistically significant. (Table 3.2) (Table 3.3). This was true for both forms of phylloquinone (vitamin K1) and menaquinones (vitamin K2), as well as for specific food sources of vitamin K, such as leafy green vegetables and dairy products. However, after excluding cases diagnosed within the first 2 years of follow-up and further adjusting for food group intake, intake of menaquinones was found to be significantly and related to lower the total prostate cancer after excluding cases within the 2 years in third 0.64(0.41, 0.99) and fourth 0.57 (0.33, 0.98) quartiles [17]. (Table 3.4)

The only menaquinones linked with a significantly decreased risk of advanced prostate cancer were those found in dairy products. The risk estimate for greater menaquinones, which are mostly (85 % of total consumption) obtained from dairy products, was therefore near to significance (RR: 0.82; 95 % CI: 0.67, 1.02), but the risk estimate for menaquinone not significant [17].

Overall, this study suggests that dietary intake of vitamin K is not a major factor in the development of prostate cancer. The relationship of vitamin K and prostate cancer was evaluated in order to understand about vitamin K and prostate cancer, its relationship [17].

Thirdly, phylloquinone and menaquinone consumption in the diet and the risk of prostate cancer were examined in 44,087 men taking part in the prospective Health Professionals Follow-up Study. The US Department of Agriculture database was used to estimate individuals' dietary vitamin K consumption using food frequency questionnaires they completed every four years between 1986 and 2006. Cox Proportional Hazards regression was used to generate the multivariable adjusted hazard ratios (HRs) and 95 % confidence intervals (CI).(Table 3.4) [16].

Figure 3.2: Study results on phylloquinone and total prostate cancer

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Phylloquinone Exposures categories:Phylloquinone: Q5: $\geq$204.7μg/d, Q4: 152.8–204.6μg/d, Q3: 118.9–152.7μg/d, Q2: 89.2–118.8μg/d, Q1 : $\leq$89.1μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Total prostate cancer DQX Phylloquinone: Q1 : Ref. Q2 : 0.97 (0.87, 1.10) Q3 : 1.02 (0.91, 1.15) Q4 : 0.97 (0.85, 1.10) Q5 : 0.94 (0.81, 1.10) Total prostate cancer DHQ Phylloquinone: Q1 : Ref. Q2 : 1.04 (0.90, 1.20) Q3 : 0.91 (0.77, 1.06) Q4 : 0.91 (0.77, 1.08) Q5 : 0.90 (0.74, 1.10)	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene
Nimptsch K. (2008)	EPIC Heidelberg 8.6 y	11.928 part. 40-65 y 268 incident cases (113 advanced)	Exposure assessment: FFQ, HPLC Exposures: Phylloquinone Exposures categories:Phylloquinone: Q4: $\geq$124μg/d Q3: 94-124μg/d Q2: 71-94μg/d Q1: $<$71μg/d Outcome assessment: Self-reported primary prostate cancer during follow-up or on death certificates, Study physician, medical records	Total prostate cancer Phylloquinone: Q1 : 1.00 Q2 : 0.85 (0.59, 1.25) Q3 : 0.90 (0.60, 1.36) Q4 : 1.02 (0.64, 1.61)	Smoking, education, vigorous physical activity, energy from fat, alcohol, nonfat-nonalcohol energy, calcium, vitamin D, tomato or tomato products, BMI, history of diabetes, and family history of prostate cancer, intake of vegetables, dairy products, and meat or meat products (quartiles).
Nimptsch K. (2015)	Prospective Health Professionals USA (1986 - 2006) 20 y	44.087 part. 6.293 prostate cases (1.034 advanced and 4.585 organ cases)	Exposure assessment: FFQ Exposures: Phylloquinone Exposure categories: Phylloquinone intake Outcome assessment: Hazard ratios Confidence intervals	Total prostate cancer Phylloquinone: 0.96 (0.88, 1.04)	

Figure 3.3: Study results on phylloquinone and advanced prostate cancer

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Phylloquinone Exposures categories:Phylloquinone: Q5: $\geq$204.7μg/d, Q4: 152.8–204.6μg/d, Q3: 118.9–152.7μg/d, Q2: 89.2–118.8μg/d, Q1 : $\leq$89.1μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Advanced prostate cancer DQX Phylloquinone: Q1 : Ref. Q2 : 1.28(0.95, 1.73) Q3 : 1.28(0.94, 1.74) Q4 : 1.24 (0.89, 1.72) Q5 : 1.32 (0.90, 1.94) Advanced prostate cancer DHQ Phylloquinone: Q1 : Ref. Q2 : 0.80 (0.55, 1.17) Q3 : 0.84 (0.58, 1.23) Q4 : 0.85 (0.58, 1.26) Q5 : 0.75 (0.47, 1.20)	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene
Nimptsch K. (2008)	EPIC Heidelberg 8.6 y	11.928 part. 40-65 y 268 incident cases (113 advanced)	Exposure assessment: FFQ, HPLC Exposures: Phylloquinone Exposures categories:Phylloquinone: Q4: $\geq$124μg/d Q3: 94-124μg/d Q2: 71-94μg/d Q1: $<$71μg/d Outcome assessment: Self-reported primary prostate cancer during follow-up or on death certificates, Study physician, medical records	Advanced prostate cancer Phylloquinone: Q1 : 1.00 Q2 : 1.18 (0.67, 2.06) Q3 : 1.11 (0.59, 2.08) Q4 : 1.09 (0.52, 2.27) Q5 : 0.75 (0.47, 1.20)	Smoking, education, vigorous physical activity, energy from fat, alcohol, nonfat-nonalcohol energy, calcium, vitamin D, tomato or tomato products, BMI, history of diabetes, and family history of prostate cancer, intake of vegetables, dairy products, and meat or meat products (quartiles).
Nimptsch K. (2015)	Prospective Health Professionals USA (1986 - 2006) 20 y	44.087 part. 6.293 prostate cases (1.034 advanced and 4.585 organ cases)	Exposure assessment: FFQ Exposures: Phylloquinone Exposure categories: Phylloquinone intake Outcome assessment: Hazard ratios Confidence intervals	Advanced prostate cancer Phylloquinone: 1.09 (0.88, 1.33)	

Figure 3.4: Study results on menaquinone and total prostate cancer

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Menaquinone Exposures categories:Menaquinone: Q5: $\geq$18.4μg/d, Q4: 12.7–18.3μg/d, Q3: 9.4–12.6μg/d, Q2: 6.6–9.3μg/d, Q1 : $\leq$6.5μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Total prostate cancer DQX Menaquinone: Q1 : Ref. Q2 : 0.98 (0.88, 1.10) Q3 : 0.96 (0.85, 1.08) Q4 : 0.98 (0.86, 1.12) Q5 : 0.98 (0.84, 1.14) Total prostate cancer DHQ Menaquinone: Q1 : Ref. Q2 : 1.01 (0.87, 1.17) Q3 : 1.06 (0.91, 1.24) Q4 : 1.03 (0.87, 1.21) Q5 : 1.05 (0.86, 1.27)	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene
Nimptsch K. (2008)	EPIC Heidelberg 8.6 y	11.928 part. 40-65 y 268 incident cases (113 advanced)	Exposure assessment: FFQ, HPLC Exposures: Menaquinone Exposures categories:Menaquinone: Q4: $\geq$46μg/d Q3: 35-46μg/d Q2: 26-35μg/d Q1: $<$26 μg/d Outcome assessment: Self-reported primary prostate cancer during follow-up or on death certificates, Study physician, medical records	Total prostate cancer Menaquinone: Q1 : 1.00 Q2 : 0.75 (0.52, 1.07) Q3 : 0.68 (0.45, 1.04) Q4 : 0.61 (0.36, 1.02)	Smoking, education, vigorous physical activity, energy from fat, alcohol, nonfat-nonalcohol energy, calcium, vitamin D, tomato or tomato products, BMI, history of diabetes, and family history of prostate cancer, intake of vegetables, dairy products, and meat or meat products (quartiles).
Nimptsch K. (2015)	Prospective Health Professionals USA (1986 - 2006) 20 y	44.087 part. 6.293 prostate cases (1.034 advanced and 4.585 organ cases)	Exposure assessment: FFQ Exposures: Menaquinone Exposure categories: Menaquinone intake Outcome assessment: Hazard ratios Confidence intervals	Total prostate cancer Menaquinone: 0.97 (0.89, 1.05)	

Figure 3.5: Study results on menaquinone and advanced prostate cancer

Author, year	Cohort name, country, Follow up	Number of participants, age, Number of cases	Exposure assessment, Exposures, Exposure categories, Outcome assessment	Risk Ratio (95 % CI)	Adjustment factors
Hoyt M. (2019)	PLCO US 11.8 y	76.685 men 55-74 y DQX (2978 cases including 490 advanced) DHQ (2973 cases including 647 advanced)	Exposure assessment: DQX, DHQ, Exposures: Menaquinone Exposures categories:Menaquinone: Q5: $\geq$18.4μg/d, Q4: 12.7–18.3μg/d, Q3: 9.4–12.6μg/d, Q2: 6.6–9.3μg/d, Q1 : $\leq$6.5μg/d Outcome assessment: Antigen blood test, digital rectal examination, death certification Diagnosis of prostate cancer was confirmed primarily through the review of medical records of men who were suspected of having prostate cancer.	Advanced prostate cancer DQX Menaquinone: Q1 : Ref. Q2 : 1.01(0.76, 1.33) Q3 : 0.96(0.72, 1.29) Q4 : 0.91(0.66, 1.26) Q5 : 1.07(0.74, 1.54) Advanced prostate cancer DHQ Menaquinone: Q1 : Ref. Q2 : 0.98 (0.68, 1.42) Q3 : 0.77 (0.52, 1.18) Q4 : 1.17 (0.80, 1.73) Q5 : 1.09 (0.69, 1.73)	Age,race, family history of prostate cancer,intakes of energy,total fat, calcium (including supplements) and β-carotene
Nimptsch K. (2008)	EPIC Heidelberg 8.6 y	11.928 part. 40-65 y 268 incident cases (113 advanced)	Exposure assessment: FFQ, HPLC Exposures: Menaquinone Exposures categories:Menaquinone: Q4: $\geq$46 μg/d Q3: 35-46μg/d Q2: 26-35μg/d Q1: $<$26 μg/d Outcome assessment: Self-reported primary prostate cancer during follow-up or on death certificates, Study physician, medical records	Advanced prostate cancer Menaquinone: Q1 : 1.00 Q2 : 0.77 (0.45, 1.31) Q3 : 0.63 (0.33, 1.19) Q4 : 0.33 (0.14, 0.80)	Smoking, education, vigorous physical activity, energy from fat, alcohol, nonfat-nonalcohol energy, calcium, vitamin D, tomato or tomato products, BMI, history of diabetes, and family history of prostate cancer, intake of vegetables, dairy products, and meat or meat products (quartiles).
Nimptsch K. (2015)	Prospective Health Professionals USA (1986 - 2006) 20 y	44.087 part. 6.293 prostate cases (1.034 advanced and 4.585 organ cases)	Exposure assessment: FFQ Exposures: Menaquinone Exposure categories: Menaquinone intake Outcome assessment: Hazard ratios Confidence intervals	Advanced prostate cancer Menaquinone: 0.86 (0.70, 1.05)	

1,034 occurrences of advanced-stage or deadly prostate cancer were detected between 1986 and 2010, totaling 6,293 cases. Higher phylloquinone consumption was not significantly linked with a reduced risk of overall prostate cancer (HR 0.96, 95 % CI 0.88, 1.04, P-trend 0.15) or advanced/fatal prostate cancer (HR 1.09, 95 % CI 0.88, 1.33, P-trend 0.51) (Table 3.2) but was substantially associated with a lower risk of organ-confined prostate cancer (HR 0.90, 95 % CI 0.81, 0.99, P-trend 0.003). Consuming menaquinones was not associated with total prostate cancer (HR 0.97, 95 % CI 0.89, 1.05, P for trend 0.19), organ-confined prostate cancer (HR 1.01, 95 % CI 0.92, 1.12, P-trend 0.57), but it was non-significantly associated with a 14 % lower risk of advanced/fatal prostate cancer (HR 0.86, 95 % CI 0.70, 1.05, P-trend 0.14) (Table 3.4) (Table 3.5) [16].

Last but not least, a nested case-control research done within the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) examined the relationship between blood undercarboxylated osteocalcin (ucOC), a biomarker of vitamin K consumption, and the risk of prostate cancer [18].

The study included 250 cases of prostate cancer and 494 matched controls selected from the EPIC-Heidelberg cohort. The researchers measured serum levels of ucOC/iOC as a biomarker of vitamin K intake. A semiquantitative food frequency questionnaire was used to measure baseline dietary consumption in the habitual manner. Participants were asked to describe each food item's average serving size and frequency of intake, which ranged from once or fewer per month to five or more times per day. The food frequency questionnaires were used to quantify dietary intakes of phylloquinone and menaquinones (MK-4 to MK-14) using previously published food composition data based on high-performance liquid chromatography studies [18].

The laboratory staff was completely blinded to the case-control status for all laboratory analyses. Total intact osteocalcin (iOC, Metra Osteocalcin EIA Kit, Quidel Corporation), which equates to total osteocalcin independent of carboxylation status, was measured in serum concentrations using a commercially available ELISA based on monoclonal antibodies [18].

In this nested case-control research, dietary consumption of menaquinones was likewise negatively correlated with the risk of prostate cancer. In comparing the 2nd, 3rd, and 4th quartiles with the first quartile, the multivariate adjusted ORs for total prostate cancer were 0.60 (95 % CI, 0.38-0.95), 0.63 (95 % CI, 0.36-1.08), and 0.36 (95 % CI, 0.19-0.68), respectively. The probability of developing total prostate cancer was significantly reduced by 11 % for every increase in dietary menaquinones consumption of 10 g/d (multivariate adjusted OR, 0.89; 95 % CI, 0.76-1.00). Comparing the fourth and first quartiles of menaquinone consumption, the OR of aggressive prostate cancer was

considerably lower (multivariate adjusted OR, 0.35; 95 % CI, 0.13-0.95; and OR per 10 g/d increase, 0.87; 95 % CI, 0.72-1.06). Phylloquinone use was not linked to prostate cancer [18].

The serum ucOC/iOC ratio was not linked to overall prostate cancer, as indicated in Table 3.3 per 0.1 increase in the ucOC/iOC ratio, the multivariate adjusted continuous OR was 1.01 (95 % CI, 0.91-1.13). Each 0.1 increase in the ucOC/iOC ratio was linked to a substantial 38 % increase in the chance of developing advanced-stage prostate cancer (OR, 1.38; 95 % CI, 1.03-1.86). (Table 3.4) The ucOC/iOC ratio's third and fourth quartiles had higher ORs of aggressive, high-grade, and advanced prostate cancer than the first quartile, although these differences were not statistically significant [18].

Insignificantly negatively related to all prostate cancer was the vitamin K supply score. (Table 3.5) (Table 3.6) However, as compared to patients in the first quartile, those in the fourth quartile of the vitamin K supply score had a substantially lower probability of being identified as having advanced-stage prostate cancer (OR, 0.25; 95 % CI, 0.07-0.96) (P for linear trend = 0.01) [18].

The results of this nested case-control research support the previously anticipated negative connection between dietary consumption of menaquinones and risk of prostate cancer when taking into account the ucOC/iOC ratio as a biomarker of vitamin K status. Serum ucOC/iOC ratio was not linked with overall prostate cancer but was significantly positively associated with advanced-stage prostate cancer. The vitamin K supply score, which incorporates data on dietary menaquinones consumption and blood ucOC/iOC ratio, was substantially inversely related to advanced-stage prostate cancer. Although the VKORC1 gene polymorphism +2255 was not linked to the likelihood of developing prostate cancer, there was some evidence that it could affect the relationship between dietary menaquinones and prostate cancer. In addition, the researchers observed that the association between ucOC levels and prostate cancer risk was stronger among men with a low intake of vitamin K1 [18].

Menaquinone consumption, but not phylloquinone intake, was found to be negatively correlated with the incidence of prostate cancer. This finding is in line with experimental research indicating menaquinones to have far more growth-inhibitory effects than phylloquinone. It was anticipated that there would be a positive correlation between ucOC/iOC ratio and risk of prostate cancer since a larger ucOC/iOC ratio denotes a poorer vitamin K status. The serum ucOC/iOC ratio and advanced-stage prostate cancer were shown to be significantly positively correlated [18].

In conclusion, the elevated risks of high-grade and advanced-stage prostate cancer with rising blood ucOC/iOC ratio support the idea that vitamin K status may be involved in the development and genesis of prostate cancer. The results of this nested case-control study may serve as inspiration for

larger-scale research on the relationship between serum ucOC/iOC ratio or other vitamin K status indicators, such as plasma menaquinones, and prostate cancer [18].

Table 3.3: Study results on ucOC/iOC and total prostate cancer

Author, year	**Cohort name, country, Follow up**	**Number of participants, age, Number of cases**	**Exposure assessment, Exposures, Exposure categories, Outcome assessment**	**Risk Ratio (95 % CI)**	**Adjustment factors**
Nimptsch K. (2009)	EPIC Heidelberg 2 to 3 y	11.928 part. 40-65 y 250 case subjects and 494 control subjects	Exposure assessment: Self-administered questionnaires Personal computer–guided interview ELISA Exposures: ucOC/iOC Exposures categories: ucOC/iOC : Cases ucOC/iOC ratio: 0.16 (0.12-0.22) Controls ucOC/iOC ratio: 0.17 (0.12-0.23) Outcome assessment: Medical records, death certificates	Total prostate cancer cases/controls ucOC/iOC : Q1 : 1.00 Q2 : 1.12 (0.71-1.77) Q3 : 1.09 (0.70-1.71) Q4 : 0.91 (0.56-1.47)	Season of blood collection, smoking status, education, vigorous physical activity, and family history of prostate cancer, dietary intake of phylloquinone, total energy, calcium, vitamin D, tomato products (all nutrients entered as quartiles).

Table 3.4: Study results on ucOC/iOC and advanced prostate cancer

Author, year	**Cohort name, country, Follow up**	**Number of participants, age, Number of cases**	**Exposure assessment, Exposures, Exposure categories, Outcome assessment**	**Risk Ratio (95 % CI)**	**Adjustment factors**
Nimptsch K. (2009)	EPIC Heidelberg 2 to 3 y	11.928 part. 40-65 y 250 case subjects and 494 control subjects	Exposure assessment: Self-administered questionnaires Personal computer–guided interview ELISA Exposures: ucOC/iOC Exposures categories: ucOC/iOC : Cases ucOC/iOC ratio: 0.16 (0.12-0.22) Controls ucOC/iOC ratio: 0.17 (0.12-0.23) Outcome assessment: Medical records, death certificates	Advanced prostate cancer cases/controls ucOC/iOC : Q1 : 1.00 Q2 : 0.88 (0.34-2.30) Q3 : 1.31 (0.54-3.19) Q4 : 1.38 (0.53-3.61)	Season of blood collection, smoking status, education, vigorous physical activity, and family history of prostate cancer, dietary intake of phylloquinone, total energy, calcium, vitamin D, tomato products (all nutrients entered as quartiles).

Table 3.5: Study results on vitamin K supply score and total prostate cancer

Author, year	**Cohort name, country, Follow up**	**Number of participants, age, Number of cases**	**Exposure assessment, Exposures, Exposure categories, Outcome assessment**	**Risk Ratio (95 % CI)**	**Adjustment factors**
Nimptsch K. (2009)	EPIC Heidelberg 2 to 3 y	11.928 part. 40-65 y 250 case subjects and 494 control subjects	Exposure assessment: Self-administered questionnaires Personal computer–guided interview ELISA Exposures: Vitamin K supply score Exposures categories: Vitamin K supply score: Cases Vitamin K supply score(μg/d): 124.7 (101.0-167.0) Controls Vitamin K supply score(μg/d): 132.5 (104.8-169.4) Outcome assessment: Medical records, death certificates	Total prostate cancer cases/controls Vitamin K supply score: Q1 : 1.00 Q2 : 1.04 (0.65-1.66) Q3 : 0.87 (0.53-1.43) Q4 : 0.76 (0.43-1.35)	Season of blood collection, smoking status, education, vigorous physical activity, and family history of prostate cancer, dietary intake of phylloquinone, total energy, calcium, vitamin D, tomato products (all nutrients entered as quartiles).

Table 3.6: Study results on vitamin K supply score and advanced prostate cancer

Author, year	**Cohort name, country, Follow up**	**Number of participants, age, Number of cases**	**Exposure assessment, Exposures, Exposure categories, Outcome assessment**	**Risk Ratio (95 % CI)**	**Adjustment factors**
Nimptsch K. (2009)	EPIC Heidelberg 2 to 3 y	11.928 part. 40-65 y 250 case subjects and 494 control subjects	Exposure assessment: Self-administered questionnaires Personal computer–guided interview ELISA Exposures: Vitamin K supply score Exposures categories: Vitamin K supply score: Cases Vitamin K supply score(μg/d): 124.7 (101.0-167.0) Controls Vitamin K supply score(μg/d): 132.5 (104.8-169.4) Outcome assessment: Medical records, death certificates	Advanced prostate cancer cases/controls Vitamin K supply score: Q1 : 1.00 Q2 : 1.53 (0.53-4.38) Q3 : 0.55 (0.20-1.49) Q4 : 0.25 (0.07-0.96)	Season of blood collection, smoking status, education, vigorous physical activity, and family history of prostate cancer, dietary intake of phylloquinone, total energy, calcium, vitamin D, tomato products (all nutrients entered as quartiles).

3.2 Overview of Meta-Analysis

In this systematic review, meta-analysis of 3 different studies and meta-analysis of 8 different forest plot was carried out, using RevMan 5.4.1. The association of phylloquinone and menaquinone intake on total prostate cancer and on advanced prostate cancer were investigated in 8 different forest plots in the studies conducted on Pubmed and Web of Science. The inverse of the variance of the treatment effect, or one over the square of the standard error, is calculated to allocate weights to individual studies based on their contributions to the pooled estimate. The weight and sample size of a research are strongly connected [4].

In a meta-analysis, heterogeneity refers to differences in findings that may be related to the population, an intervention, a comparator, an outcome measure, a risk of bias, a research technique, healthcare systems, and other elements of the individual studies [1].

The comparison of phylloquinone intake on total prostate cancer was examined in 3 different studies: Hoyt et al. 2019 DQX, Nimptsch et al. 2008, Nimptsch et al. 2015. Not all studies contribute equally to the pooled results. The P-value was greater than 0.21, we could not reject the hypothesis of no heterogeneity.(3.6) The I2 in Figure 3.6 was 0 % suggesting results were not heterogenous (I2=0). Nimptsch et al. 2015 study had the greatest weight 75.2 % in outcomes of phylloquinone intake on total prostate cancer. All studies were not significant because the confidence interval range was within the number 1. The total 95 % CI 0.96 [0.89, 1.03] showed that there was no effect, no significant association between the studies about phylloquinone intake on total prostate cancer. As a result of all studies, the group with highest intake of phylloquinone was 4 % less likely to develop total prostate cancer compared to the lowest intake but the risk was actually 4 % lower could not be assumed because our result was not statistically significant. (Figure 3.6)

The comparison of phylloquinone intake on total prostate cancer was examined in 3 different studies: Hoyt et al. 2019 DHQ, Nimptsch et al. 2008 and Nimptsch et al. 2015. Not all studies contribute equally to the pooled results. The P-value was greater than 0.19, we could not reject the heterogeneity. (Figure 3.7) The I2 in Figure 3.7 was 0 % suggesting results were not heterogenous (I2=0). Nimptsch et al. 2015 study had the greatest weight 82.6 % in outcomes of phylloquinone intake on total prostate cancer. All studies were not significant and could not be sure because the confidence interval range was within the number 1. The total 95 % CI 0.95 [0.88, 1.02] showed that there was no effect, no significant association between the studies about phylloquinone intake on total prostate cancer. As a result of all studies, the group with highest intake of phylloquinone could be 5 % less likely to develop total prostate cancer compared to the lowest intake but this could not be assumed because it was again statistically not significant. (Figure 3.7)

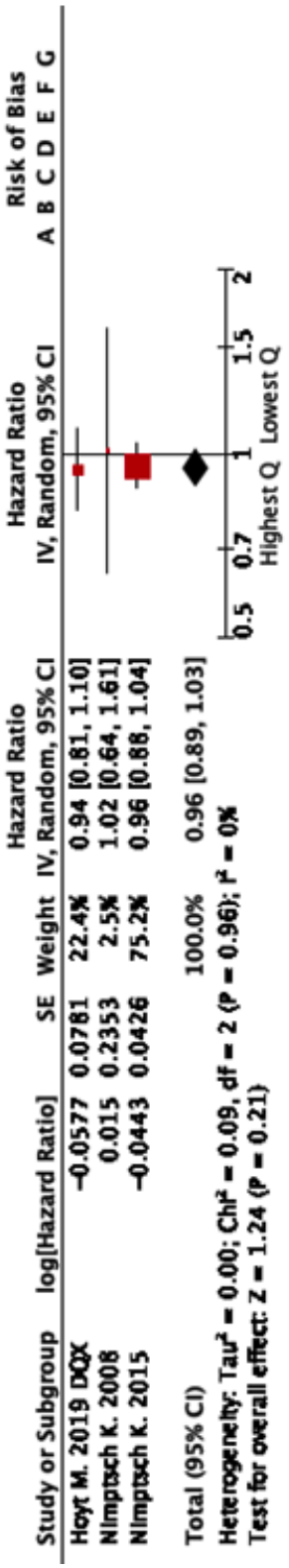

Figure 3.6: The comparison of phylloquinone intake on total prostate cancer (DQX)

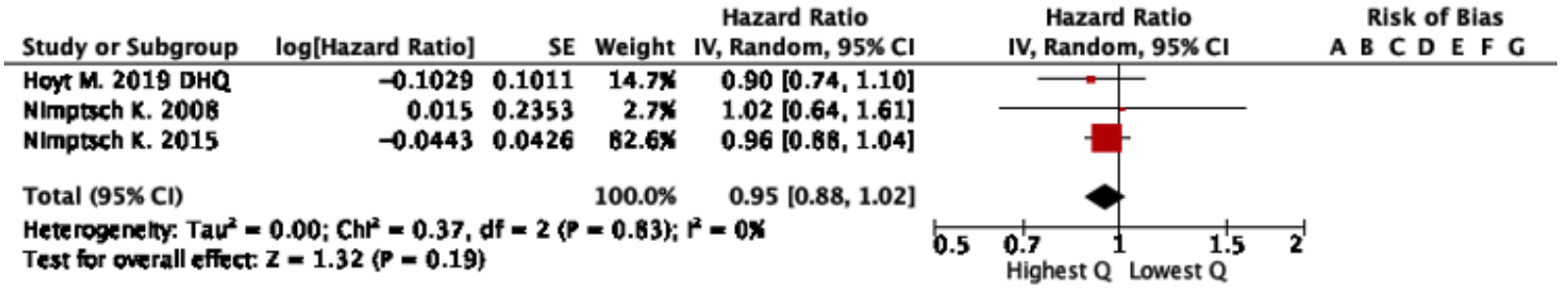

Figure 3.7: The comparison of phylloquinone intake on total prostate cancer (DHQ)

The comparison of phylloquinone intake on advanced prostate cancer was examined in 3 different studies: Hoyt et al. 2019 DQX, Nimptsch et al. 2008, Nimptsch et al. 2015. Not all studies contribute equally to the pooled results. The P-value was greater than 0.17, we could not reject the hypothesis of no heterogeneity.(Figure 3.8) The I2 in Figure 3.8 was 0 % suggesting results were not heterogenous (I2=0). Nimptsch et al. 2015 study had the greatest weight 73.4 % in outcomes of phylloquinone intake on total prostate cancer. All studies were not significant and could not be sure whether the highest intake of phylloquinone had a inverse effect on developing advanced prostate cancer or not. The total 95 % CI 1.13 [0.95, 1.35] showed that there was no effect, no difference between the studies about phylloquinone intake on advanced prostate cancer (Figure 3.8).

The comparison of phylloquinone intake on advanced prostate cancer was examined in 3 different studies: Hoyt et al. 2019 DHQ, Nimptsch et al. 2008, Nimptsch et al. 2015. Not all studies contribute equally to the pooled results. The P-value was smaller than 0.79, we could reject the hypothesis of no heterogeneity. (Figure 3.9) The I2 in Figure 3.9 was 1 % suggesting any heterogeneity might not be important. Nimptsch et al. 2015 study had the greatest weight 78.4 % in outcomes of phylloquinone intake on advanced prostate cancer. All studies were not significant and could not be sure whether the highest intake of phylloquinone had a inverse effect on developing advanced prostate cancer or not because the confidence interval range was within the range 1. The total 95 % CI 1.03 [0.85, 1.23] showed that there was no effect, no difference between the studies about phylloquinone intake on advanced prostate cancer (Figure 3.9).

Three distinct research compared the effects of menaquinone consumption on total prostate cancer: Hoyt et al. 2019 DQX, Nimptsch et al. 2008, and Nimptsch et al. 2015. The aggregated results are not evenly influenced by all research. The null hypothesis of no heterogeneity was ruled out of since the P-value was less than 0.38. (Figure 3.10) In Figure 3.10 the I2 was 35 %, indicating moderate heterogeneity. The results of menaquinone consumption on total prostate cancer were weighed most heavily in Nimptsch et al. 2015 research at 60.7 %. Because the confidence interval range was within the range 1, it was unable to determine whether or not the highest intake of the menaquinone had an inverse effect on developing total prostate cancer. There was no difference between the studies regarding the effects of menaquinone consumption on total prostate cancer, as indicated by the total 95 % CI of 0.95[0.85, 1.07] (Figure 3.10).

Three distinct studies Hoyt et al. 2019 DHQ, Nimptsch et al. 2008, and Nimptsch et al. 2015 compared the effects of menaquinone consumption on total prostate cancer. The results from the combined research do not all contribute equally. Since the P-value was below 0.57, we could rule out

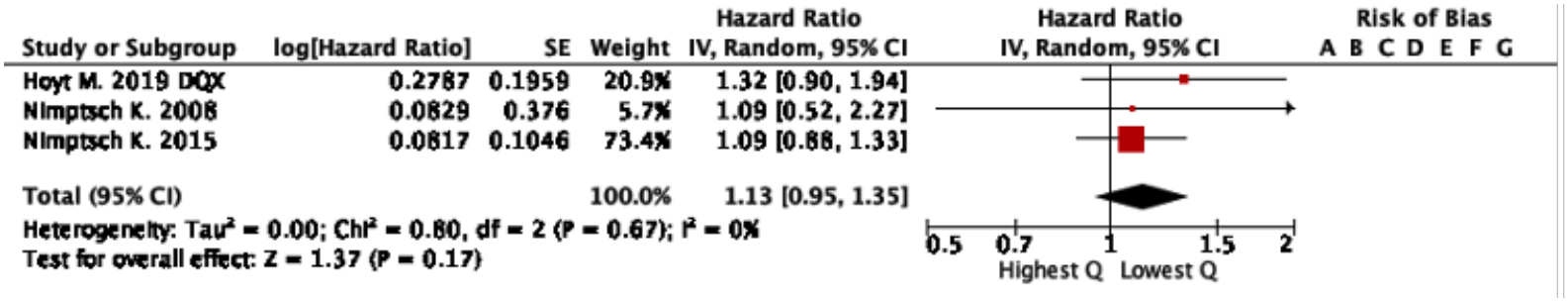

Figure 3.8: The comparison of phylloquinone intake on advanced prostate cancer (DQX)

Figure 3.9: The comparison of phylloquinone intake on advanced prostate cancer (DHQ)

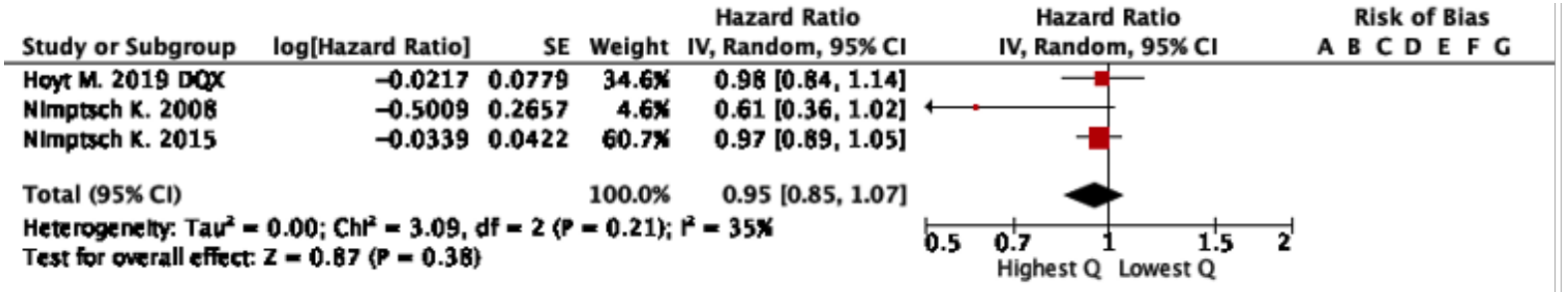

Figure 3.10: The comparison of menaquinone intake on total prostate cancer (DQX)

the existence of heterogeneity. (Figure 3.11) The I2 in Figure 3.11 was 46 %, indicating that there may be some substantial heterogeneity present. The results of menaquinone consumption on total prostate cancer were most heavily weighed in Nimptsch et al. 2015 research (59 %). Because the confidence interval range was within the range 1, it could not be determined whether the highest intake of the menaquinone biomarker had an inverse impact on developing total prostate cancer or not because none of the trials were statistically significant. Among the studies, only one exception was seen in the effect size part of the Hoyt M. 2019 DHQ study.The total 95 % CI 0.96[0.82, 1.12] indicated that there was no difference between the studies in the effect of menaquinone consumption on total prostate cancer and no effect was present (Figure 3.11).

The comparison of menaquinone intake on advanced prostate cancer was examined in 3 different studies: Hoyt et al. 2019 DQX, Nimptsch et al. 2008, Nimptsch et al. 2015. Not all studies contribute equally to the pooled results. The P-value was smaller than 0.29, the hypothesis of no heterogeneity could be rejected Figure 3.12.The I2 in Figure 3.12 was 66 % suggesting substantial heterogeneity might be seen. Nimptsch et al. 2015 study had the greatest weight 47.9 % in outcomes of menaquinone intake on advanced prostate cancer. Two studies were not significant but just one study showed significant difference. According to Nimptsch et al. 2008 95 % CI 0.33 [0.14,0.80] high consumption of menaquinone could be effective to reduce the risk of advanced prostate cancer. Lastly, overall result investigated there would not be any significant difference between the high intake of menaquinone on advanced prostate cancer and could not be sure whether the highest intake of menaquinone had a inverse effect on developing advanced prostate cancer or not. The total 95 % CI 0.81 [0.54, 1.20] showed that there was no effect, no difference between the studies in menaquinone intake on advanced prostate cancer. As a result of all studies, the group with highest intake of menaquinone results were not significant therefore can not be sure. (Figure 3.12)

The comparison of menaquinone intake on advanced prostate cancer was examined in 3 different studies: Hoyt et al. 2019 DHQ, Nimptsch et al. 2008, Nimptsch et al. 2015. Not all studies contribute equally to the pooled results. The P-value was smaller than 0.30, we could reject the hypothesis of no heterogeneity 3.13. The I2 in Figure 3.13 was 64 % suggesting substantial heterogeneity. Nimptsch et al. 2015 study had the greatest weight 48.8 % in outcomes of menaquinone intake on advanced prostate cancer. Two studies were not significant but just one study showed significant difference. According to Nimptsch et al. 2008 95 % CI 0.33 [0.14,0.80] high consumption of menaquinone could be effective to reduce the risk of advanced prostate cancer. On the other hand, Hoyt et al. 2019 DHQ positive effect between intake and advanced prostate cancer risk was observed. Lastly, overall result

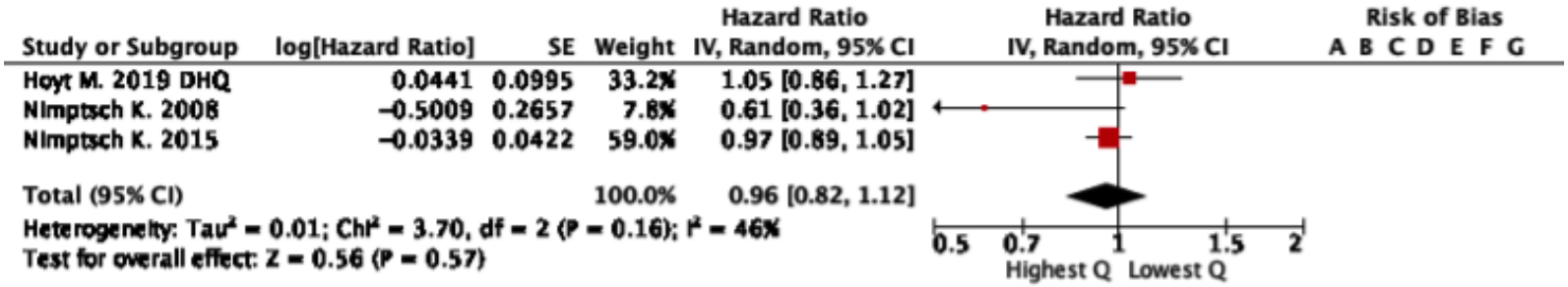

Figure 3.11: The comparison of menaquinone intake on total prostate cancer (DHQ)

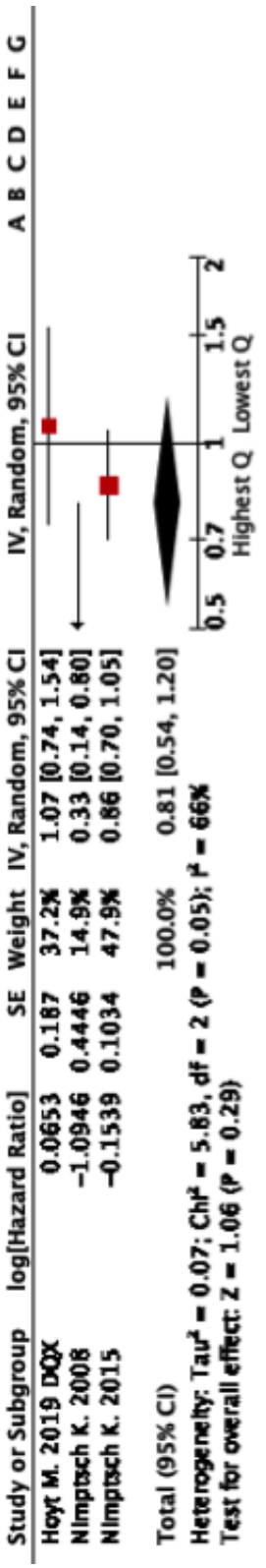

Figure 3.12: The comparison of menaquinone intake on advanced prostate cancer (DQX)

investigated there would not be any significant difference between the high intake of menaquinone on advanced prostate cancer and could not be sure whether the highest intake of menaquinone had a inverse effect on developing advanced prostate cancer or not. The total 95 % CI 0.79 [0.51, 1.23] showed that there was no effect, no difference between the studies in menaquinone intake on advanced prostate cancer (Figure 3.13).

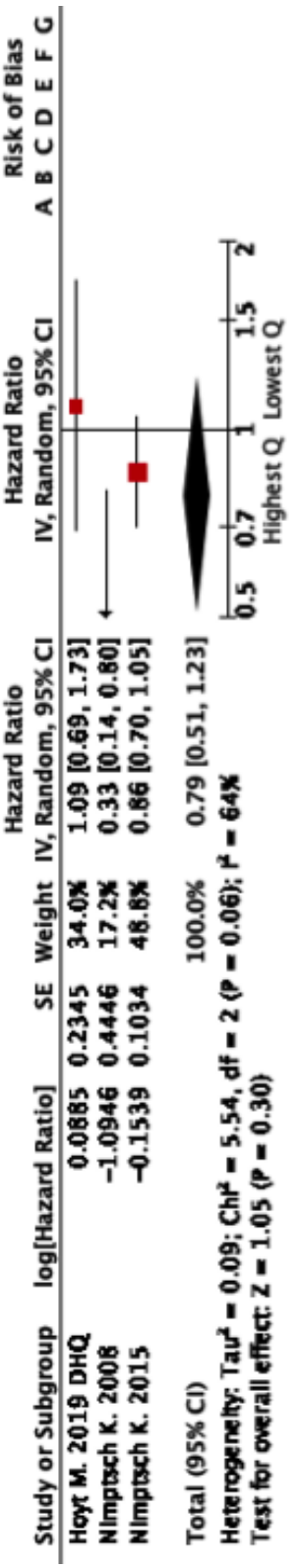

Figure 3.13: The comparison of menaquinone intake on advanced prostate cancer (DHQ)

3.3 Risk of Bias Assessment

In this systematic review on the relationship between vitamin intake and prostate cancer, smoking status, BMI, physical activity and family history of prostate cancer were selected as essential confounders for domain 1. Among these confonders, the risk was in the study by Hoyt et al. 2019 and Nimptsch et al. 2015 high because only one of the confounder (family history of prostate cancer) from our essential confounders is presented in Hoyt et al. 2019 and no information is included in Nimptsch et al. 2015, but Nimptsch et al. 2008 study includes all essential confounders that's why the risk value is low. As only certain confounders are available in Nimptsch et al. 2009, the risk was on some concerns.

The risk assessment of dietary questions or food frequency questions was done in domain 2. If the studies are based on dietary based questions then the risk value was on some concern. If a biomarker was used or evaluated in the study, then the risk was low. In this case, the risk was low, since only the Nimptsch et al. 2009 study contained serum vitamin k values.

All studies had "some Rob" in domain 3. Because the people with high SES were overrepresented in EPIC-HD, the PLCO was a screening trial that´s why again some concern and lastly Nimptsch et al. 2015 study consisted of health professionals only.

Domain 4 examines whether vitamin K intake changes over time or whether this intake remains constant. Vitamin k value can have different amounts in the same quartile. In some studies, vitamin intake has been divided into two as menaquinone and phylloquinone, and their amounts are different in the quartile ranges that changes over time. The amount of vitamin k intake in each study was different and examined in different time periods, so the risk values were on some concern.

Domain 5 evaluates the missing values in studies. If there is a missing value of less than 5 % in a research, then the risk value is low. In this case, the risk value was high just in Nimptsch et al. 2015 study because there were missing information and in the study not reported.

In domain 6, it was measured whether the outcomes were evaluated with the medical records or not. As a result of scientific studies, in most of the studies outcome parameters were measured either with medical records, death certifications and antigen test methods. However, just in one study Nimptsch et al. 2015 did not contain any records but just hazard ratios that´s why risk was high.

Domain 7 plays a role in evaluating the results. Evaluation of the results and their clear visibility are important in risk bias assessment. Results and evaluations of the participants were made in all but not in the Nimptsch et

al. 2015 research. The Nimptsch et al. 2015 study had a high risk because essential data on certain associations were not reported and this study was from a conference abstract rather than a full paper.

The general results showed that,the risk value of the study by Hoyt et al. 2019 and the Nimptsch et al. 2015 study is high. There is bias due to confounding in both of them. Apart from this, the Nimptsch et al. 2015 study has missing data and a high risk value in outcome measurements and outcome results. In the Nimptsch et al. 2008 and Nimptsch et al. 2009 studies, the risk value is some concerns because some of the domain questions, the questions could not be answered completely.If I make an overall judgement than I could say that any high risk value in domains affects all general values. When the risk assessment of the relationship between vitamin K intake and prostate cancer was made, it was concluded that these studies are risky and more studies are needed on this subject and this issue needs to be addressed more.

3.4 Certainty of Evidence

Risk assessment results evaluate the reliability of the result and how concrete it is. Cohort studies on vitamin k, menaquinone, phylloquinone and biomarker. When all general evidence was evaluated, a high risk value was observed. Having a high risk affects the reliability of the results when the domains of the studies are evaluated, Nimptsch et al. 2015- Hoyt et al. 2019 -Nimptsch et al. 2008 and Nimptsch et al. 2009. The most reliable study is Nimptsch 2009 according to the risk assessment.

A popular approach for evaluating the strength of recommendations and the quality of the evidence in systematic reviews and other forms of evidence syntheses is called GRADE (Grading of Recommendations Assessment, Development, and Evaluation). It offers a methodical and open way to assess the certainty (confidence) of the evidence and the potency of suggestions based on that evidence (Table 3.7) [22].

The degree of uniformity in the size and direction of the results across several research is referred to as consistency. Variations in research demographics, treatments, or outcome measures may cause inconsistency. The GRADE method assesses the consistency of the evidence and takes into account how it affects the general degree of certainty of the conclusions [22].

Directness evaluates the evidence's application and relevance to the research topic under consideration. It takes into account whether the studies that make up the review specifically assess the desired outcomes as well as how closely the study populations and interventions correspond to the desired population and interventions [22].

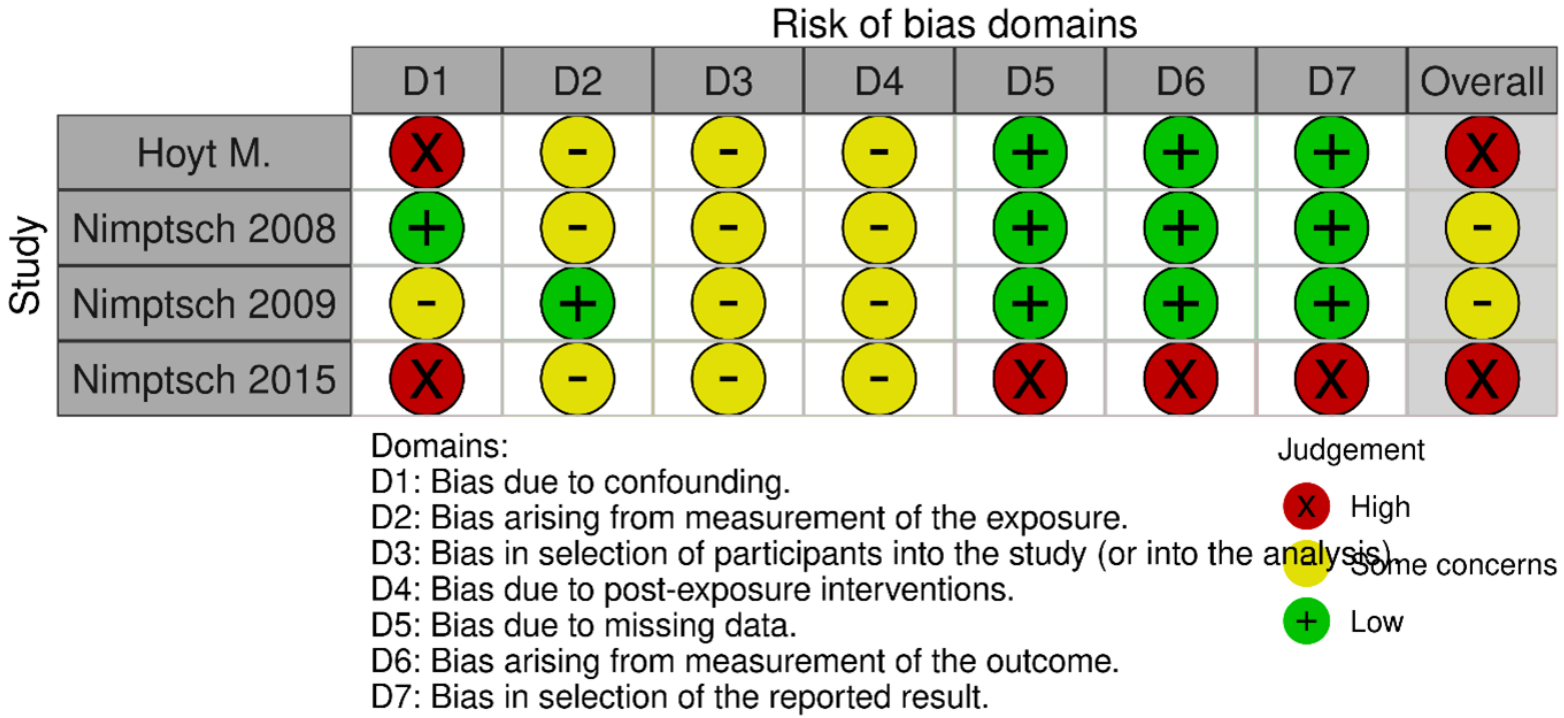

Figure 3.14: Risk of bias assessment for the cohort studies on vitamin K intake and relationship between prostate cancer

Table 3.7: Grade Assessment Overall

	Assessment	Comment
Risk of Bias Factor	Downgraded by two levels	Serious risk of bias in two of the included studies; see risk of bias assessment
Inconsistency Factor	Downgraded due to high I2 values	
Imprecision Factor	Not downgraded	Large sample sizes
Indirectness Factor	Not downgraded	Population based study designs with good generalizability
Publication Bias Factor	Not downgraded	Based on less than 10 studies
Effect Size Factor	Not upgraded	No strong effect size
Overall Assessment	Very low	

The term ”precision” describes the degree of confidence or certainty in the projected impact sizes or outcome measurements. The sample size, the size of the confidence intervals, and the statistical significance of the results all have an impact on it. The GRADE method assesses the accuracy of the evidence and its bearing on the reliability of the findings [22].

In this systematic review, two different studies were high-risk in the overall assessment because very few parameters were used as confounders in the Hoyt et al. 2019 study and these parameters were less compatible with essential confounders. In the Nimptsch et al. 2015 study, the risk of D1, D5, D6, D7 values were high. Inconsistency part in grade assessment is downgraded because I2 values were high in studies that conducted from forest plots. The imprecision part is not downgraded because large sample sizes were used in research. Apart from that, indirectness not downgraded due to population based and good generalizability. Since only 4 different cohort studies were evaluated, the bias in the publication was insufficient that´s why not downgraded. The effect values were not strong when logarithmic values are calculated in RevMan and therefore certainity is very low in general.

More human cohort studies should be conducted on this subject and the evidence should be strengthened. The reliability of the evidence should be supported by different studies that can give similar results on an experimental basis [22].

Chapter 4

Discussion

4.1 Summary

The aim of this systematic study was to investigate the relationship between vitamin K intake and prostate cancer. In this systematic review, a total of 4 different cohort studies were examined from Pubmed and Web of Science. Two cohort studies were on phylloquinone and menaquinone, one cohort study was on both total vitamin k intake, phylloquinone and menaquinone and only one study was identified using a vitamin K status biomarker and a vitamin K supply score based on both intake and biomarker data. Meta-analyses were made among cohort studies and the effect of vitamin K intake on total prostate cancer and advanced prostate cancer was observed. No significant associations were found between vitamin biomarkers and risk of having prostate cancer.

When phylloquinone intake was compared between studies, it was found that there was no relationship between phylloquinone intake in preventing total prostate cancer In only one study by Nimptsch 2008 0.33[0.14 – 0.80], it was seen that the use of menaquinone could prevent 67 % of the risk of advanced prostate cancer, and a significant difference was found between them. According to all the studies screened and their general results, it was observed that the use of vitamin K would neither prevent the risk of total prostate cancer nor prevent advanced total prostate cancer.

Menaquinone intake was examined amongst studies, it was shown that there was no correlation between consumption and total prostate cancer prevention. Other than that,there is no correlation between menaquinone consumption and avoiding advanced prostate cancer according to a meta-analysis that looked at the subject.

It is only a single study related to biomarkers and since the number of cases is only 250 it should be carefully examined. The total prostate cancer was not

related to the serum ucOC/iOC ratio. The continuous multivariate adjusted odds ratio (OR) per 0.1 increase in the ucOC/iOC ratio was 1.01 (95 % CI, 0.91-1.13). A substantial 38 % increase in risk of advanced-stage prostate cancer was linked to every 0.1 rise in the ucOC/iOC ratio (OR, 1.38; 95 % CI, 1.03-1.86). Insignificantly negatively related to all prostate cancer was the vitamin K supply score. However, as compared to patients in the first quartile of the vitamin K supply score, those in the fourth quartile had a substantially lower probability of being identified as having advanced-stage prostate cancer (OR, 0.25; 95 % CI, 0.07-0.96) [18].

To summarize, there is no clear relationship between vitamin K and prostate cancer. The number of cohort studies conducted is very low and more comprehensive studies are needed on this subject. These findings suggest that there is no prove of anticancer effects vitamin K in humans. On the other hand, human studies are not proven and not available. According to these findings there is no benefit in vitamin K intake and prostate cancer.

4.2 The present findings

Overall the present analysis do not suggest vitamin K intake and relation to prostate cancer. If generalization is to be made between cohorts, it could be said that in this systematic study that whether using more menaquinone nor phylloquinone can prevent total prostate cancer and advanced prostate cancer compared to under use because they have non-significant association.

In the context of the present findings, evidence on Vitamin K agonists should be mentioned. In addition to studies on vitamin K intake and prostate cancer risk, another line of evidence on the protential role of vitamin K comes from studies on the use of vitamin K antagonists. In prostate cancer, vitamin K antagonists may have anticancer benefits. The results of observational research are contradictory, nevertheless. In one meta-analysis the risk of prostate cancer was inversely correlated with the usage of vitamin K antagonists, however this relationship was not statistically significant. Prostate cancer risk may be lowered by using vitamin K antagonists, especially for long-term users [13].

One meta-analysis that compiled the available research was done using Danish demographic and health data registries. The results of this statewide investigation did not show a decreased incidence of prostate cancer related with VKA usage and when combined with those of other studies, it seems doubtful that VKAs have a significant protective impact against prostate cancer. There are a total of 8 studies in the meta-analysis. With significant between-study heterogeneity (I2: 93.9 %), the estimated impact estimates varied from 0.51 (95 % CI, 0.23-1.13) to 1.10 (95 % CI, 0.94-1.40). Using random effect approaches, the pooled impact estimate was 0.86 (95 % CI,

0.70-1.05). However, the observed correlations between VKA usage and the risk of developing prostate cancer are still ambiguous and originate from research that varied greatly in terms of study design, exposure definition, confounder correction, and outcome evaluation [13].

The research on the relationship between VKA usage and the risk of prostate cancer is inconsistent. The data that is now available does not show that using VKA significantly reduces one's chance of developing prostate cancer, and our examination of incident prostate cancers throughout the country revealed no evidence to support this claim. Numerous scientific explanations for VKAs' anti-neoplastic effects against prostate cancer have been put forth. However, it does not seem that these observations translate into any significant protective benefit of VKA usage against prostate cancer in a clinical environment based on prior findings and the results of the present investigations [11].

On the other hand, the relationship between the haemostatic system and tumor stroma growth and metastasis has been supported by several research using both animal models and in vitro models. Numerous research have produced intriguing findings in this context, despite the fact that the mechanisms by which warfarin affects cancer are not fully understood and are instead dependent on supposition. But can adding warfarin to the advised anti-tumor medication increase cancer patients' chances of surviving? Answering this question at this moment is challenging. The literature has little, occasionally incongruous data. Trials are distinguished by significant variations in the cohorts under study, the types of malignancies being assessed histologically, and the treatment regimens [20].

4.3 Strenghts and Limitations

This systematic review is the first review on vitamin K intake and its association with prostate cancer. As it is the first systematic review on this subject, the studies were examined and eliminated in detail. Overall results of the studies and risk assessments were deduced from RevMan through ROBIS and Grade Assessment. State-of- the-art methods were used; PRISMA statements was adhered to make careful considerations when forming risk assessment questions.

The caliber of the studies considered determines how strong a systematic review is. Low-quality individual studies may have an impact on the validity and reliability of the review findings (e.g., small sample numbers, insufficient confounder control). In this case, when risk assessments are made on ROBIS, it is seen that there are certain strenghts and limitations on vitamin K intake and prostate cancer. Both due to the low number of cohort studies on this subject and because the studies do not evaluate missing values we can

conduct that there are certain strenghts and limitations like high risk of bias and low certainty of the evidence.

On the other hand, only the studies from Germany and USA were found, which limits generalizability. The present systematic review can improve the statistical power to find connections by merging data from cohort research. This is especially helpful for subjects like the association between vitamin K intake and prostate cancer, where there may be little data and weak statistical power in the individual research.

This first systematic review can point out areas that need more research and show gaps in the body of existing knowledge and can help focus research efforts in the area of vitamin K consumption and prostate cancer by directing future research objectives.

Other than that, in some studies not all results are shown and outcomes are not evaluated with medical records.

This first systematic study can show a association between vitamin K consumption and prostate cancer, but they can not prove a cause-and-effect relationship. Confounding variables that were insufficiently taken into account in the included studies might have affected the observed correlation. The association between vitamin K consumption and prostate cancer may be impacted by confounding factors including smoking status, family history of prostate cancer, BMI, physical activity.

4.4 Conclusion

This thesis concluded by doing a thorough evaluation of the literature on the link between vitamin K consumption and prostate cancer. A thorough examination of the available material yielded many important conclusions.

Firstly, the results do not point to a potential link between vitamin K consumption and the risk of prostate cancer. No protective effect of both menaquinone and phylloquinone intake of vitamin K on prostate cancer was observed. However, further study is required to corroborate these findings because the data is not yet conclusive.

Secondly, it is important to appreciate the differences across research and the limits of the data that is currently available. Some associations were able to be analyzed which was not too bad but the limited number of studies made it difficult to combine the data because of little amount of evidence. Additionally, some of the research included in the systematic review had high risk of bias and better research on this subject needs to be investigated.

Additionally, it is crucial to take into account any potential confounding variables that may affect the association between vitamin K consumption

and prostate cancer. But, it may not really matter because the present meta-analysis did not show any association between vitamin K and prostate cancer. Future research must rigorously control for variables including smoking status, BMI, family history of prostate cancer, physical activity and genetic variants that may confuse the apparent connection.

The present meta-analysis emphasizes the association of vitamin K intake on total prostate cancer, despite its limitations and the requirement for more study. Additional well planned clinical trials and population-based research are required to fully understand the possible chemopreventive effects of vitamin K, particularly vitamin K2. Future studies should also concentrate on figuring out the precise amount and sources of vitamin K for possible preventative or therapeutic treatments, as well as the underlying processes by which vitamin K affects prostate cancer cells.

In conclusion, more thorough research is needed to establish a conclusive link between vitamin K consumption and prostate cancer risk. This thesis lays the groundwork for future research and highlights the need for a more research on this topic in order to understand the relationship between vitamin K intake and prostate cancer, ultimately opening the door to better methods for the prevention and treatment of this common cancer.

Bibliography

[1] Yuhao Chang, Matthew R. Phillips, Robyn H. Guymer, and et al. The 5 min meta-analysis: understanding how to read and interpret a forest plot. *Eye*, 36(3):673–675, 2022.

[2] Shaloam Dasari, Shafquat M. Ali, Gang Zheng, Allen Chen, Venkata S. Dontaraju, Maarten C. Bosland, Andre Kajdacsy-Balla, and Gnanasekar Munirathinam. Vitamin k and its analogs: Potential avenues for prostate cancer management. *Oncotarget*, 8(34):57782–57799, May 2017.

[3] Kaitlin Defever, Elizabeth A. Platz, David S. Lopez, and Alison M. Mondul. Differences in the prevalence of modifiable risk and protective factors for prostate cancer by race and ethnicity in the national health and nutrition examination survey. *Cancer Causes & Control*, 31(9):851–860, Sep 2020. Epub 2020 Jul 14.

[4] Joseph R. Dettori, Daniel C. Norvell, and Jens R. Chapman. Seeing the forest by looking at the trees: How to interpret a meta-analysis forest plot. *Global Spine Journal*, 11(4):614–616, May 2021.

[5] Michael S. Donaldson. Vitamin k: the missing link to prostate health. *Medical Hypotheses*, 84(3):219–222, Mar 2015. Epub 2015 Jan 9.

[6] Guylaine Ferland. Vitamin k and the nervous system: an overview of its actions. *Advances in Nutrition*, 3(2):204–212, Mar 2012.

[7] Giorgio Gandaglia, Roberta Leni, Freddie Bray, Neil Fleshner, Stephen J. Freedland, Adam Kibel, Pär Stattin, Hendrik Van Poppel, and Carlo La Vecchia. Epidemiology and prevention of prostate cancer. *European Urology Oncology*, 4(6):877–892, Dec 2021. Epub 2021 Oct 26.

[8] Fina N. Hendra, Marco N. Helder, Muhammad Ruslin, Ellen M. Van Cann, and Tymour Forouzanfar. A network meta-analysis assessing

the effectiveness of various radical and conservative surgical approaches regarding recurrence in treating solid/multicystic ameloblastomas. *Scientific Reports*, 13(1):8445, May 2023.

[9] Margaret Hoyt, Michael Reger, Andrew Marley, Hao Fan, Ziyue Liu, and Jianjun Zhang. Vitamin K intake and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial. *The American Journal of Clinical Nutrition*, 109(2):392–401, 01 2019.

[10] Rachel Hurst, Lee Hooper, Teresa Norat, Rosa Lau, Dagfinn Aune, Darren C. Greenwood, Rui Vieira, Rachel Collings, Linda J. Harvey, Jonathan A. Sterne, and et al. Selenium and prostate cancer: Systematic review and meta-analysis. *The American Journal of Clinical Nutrition*, 96(1):111–122, 2012.

[11] Kristina B. Kristensen, Pia H. Jensen, Charlotte Skriver, Søren Friis, and Anton Pottegård. Use of vitamin k antagonists and risk of prostate cancer: Meta-analysis and nationwide case-control study. *International Journal of Cancer*, 144(7):1522–1529, Apr 2019. Epub 2018 Nov 13.

[12] Scott M. Lippman, Eric A. Klein, Phyllis J. Goodman, M. Scott Lucia, Ian M. Thompson, Leslie G. Ford, Howard L. Parnes, Lori M. Minasian, J. Michael Gaziano, JoAnn A. Hartline, J. Kellogg Parsons, James D. Bearden, E. David Crawford, Gary E. Goodman, Jorge Claudio, Eric Winquist, Elise D. Cook, Daniel D. Karp, Paul Walther, Michael M. Lieber, Alan R. Kristal, Amy K. Darke, Kathryn B. Arnold, Patricia A. Ganz, Regina M. Santella, Demetrius Albanes, Philip R. Taylor, Jeffrey L. Probstfield, Tejinder J. Jagpal, John J. Crowley, Frank L. Jr. Meyskens, Laurence H. Baker, and Charles A. Jr. Coltman. Effect of selenium and vitamin e on risk of prostate cancer and other cancers: the selenium and vitamin e cancer prevention trial (select). *JAMA*, 301(1):39–51, Jan 2009. Epub 2008 Dec 9.

[13] Jian-Dong Luo, Jing Luo, Can Lai, Jun Chen, and Hao-Zheng Meng. Is use of vitamin k antagonists associated with the risk of prostate cancer?: A meta-analysis. *Medicine*, 97(49):e13489, Dec 2018.

[14] Masato Matsushita, Kazutoshi Fujita, and Norio Nonomura. Influence of diet and nutrition on prostate cancer. *International Journal of Molecular Sciences*, 21(4):1447, Feb 2020.

[15] Přemysl Mladěnka, Kateřina Macáková, Lenka Kujovská Krčmová, Lenka Javorská, Klára Mrštná, Alejandro Carazo, Michele Protti, Fernando Remião, Lucie Nováková, OEMONOM researchers, and collaborators. Vitamin k - sources, physiological role, kinetics, deficiency,

detection, therapeutic use, and toxicity. *Nutrition Reviews*, 80(4):677–698, Mar 2022.

[16] K. Wu T. Pischon Nimptsch, K. and E. Giovannucci. Dietary intake of vitamin k and risk of prostate cancer in a cohort of us health professionals. *Annals of Nutrition and Metabolism*, pages 67: 392–392, 2015.

[17] Katharina Nimptsch, Sabine Rohrmann, and Jakob Linseisen. Dietary intake of vitamin K and risk of prostate cancer in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg). *The American Journal of Clinical Nutrition*, 87(4):985–992, 04 2008.

[18] Katharina Nimptsch, Sabine Rohrmann, Alexandra Nieters, and Jakob Linseisen. Serum undercarboxylated osteocalcin as biomarker of vitamin k intake and risk of prostate cancer: a nested case-control study in the heidelberg cohort of the european prospective investigation into cancer and nutrition. *Cancer Epidemiology Biomarkers & Prevention*, 18(1):49–56, Jan 2009.

[19] Michał Oczkowski, Karolina Dziendzikowska, Aleksandra Pasternak-Winiarska, Dariusz Włodarek, and Joanna Gromadzka-Ostrowska. Dietary factors and prostate cancer development, progression, and reduction. *Nutrients*, 13(2):496, 2021.

[20] Vittorio Pengo, Gentian Denas, Shibu P. Jose, and Maria-Fabrizia Pengo. Cancer prevention and vitamin k antagonists: an overview. *Thrombosis Research*, 125(Suppl 2):S103–S105, Apr 2010.

[21] Prashanth Rawla. Epidemiology of prostate cancer. *World Journal of Oncology*, 10(2):63–89, Apr 2019. Epub 2019 Apr 20.

[22] Holger Schünemann, Jan Brożek, Gordon Guyatt, and Andrew Oxman. *GRADE Handbook*. GRADE Working Group, Hamilton, ON, October 2013.

[23] Martin J. Shearer. Vitamin k metabolism and nutriture. *Blood Reviews*, 6(2):92–104, Jun 1992.

[24] Anil Shetty, Shaloam Dasari, Sushanta Banerjee, Tyrel Gheewala, Gang Zheng, Aiwen Chen, Andre Kajdacsy-Balla, Maarten C. Bosland, and Gnanasekar Munirathinam. Hepatoma-derived growth factor: A survival-related protein in prostate oncogenesis and a potential target for vitamin k2. *Urologic Oncology*, 34:483, 2016.

[25] Rashmi Sinha, Yikyung Park, Barry I. Graubard, Michael F. Leitzmann, Albert Hollenbeck, Arthur Schatzkin, and Amanda J. Cross. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the united states. *American Journal of Epidemiology*, 170:1165–1177, 2009.

[26] American Cancer Society. Cancer Statistics Center, 2023.

[27] Adriana J. van Ballegooijen and Joline W.J. Beulens. The role of vitamin k status in cardiovascular health: Evidence from observational and clinical studies. *Current Nutrition Reports*, 6(3):197–205, 2017. Epub 2017 Jul 10.

[28] WCRF. Diet, nutrition, physical activity and prostate cancer. 2014.

[29] World Cancer Research Fund International. Prostate Cancer Statistics. https://www.wcrf.org/cancer-trends/prostate-cancer-statistics.