Dietary vitamin K intake in relation to cancer incidence and mortality: results from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg)[1–3]

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ABSTRACT

Background: Anticarcinogenic activities of vitamin K have been observed in animal and cell studies.

Objective: On the basis of the growth inhibitory effects of vitamin K as observed in a variety of cancer cell lines, we hypothesized that dietary intake of phylloquinone (vitamin K_1) and menaquinones (vitamin K_2) may be associated with overall cancer incidence and mortality.

Design: In the prospective EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition–Heidelberg) cohort study, 24,340 participants aged 35–64 y and free of cancer at enrollment (1994–1998) were actively followed up for cancer incidence and mortality through 2008. Dietary vitamin K intake was estimated from food-frequency questionnaires completed at baseline by using HPLC-based food-composition data. Multivariate-adjusted hazard ratios (HRs) and 95% CIs were estimated by using Cox proportional hazards models.

Results: During a median follow-up time of >10 y, 1755 incident cancer cases occurred, of which 458 were fatal. Dietary intake of menaquinones was nonsignificantly inversely associated with overall cancer incidence (HR for the highest compared with the lowest quartile: 0.86; 95% CI: 0.73, 1.01; *P* for trend = 0.08), and the association was stronger for cancer mortality (HR: 0.72; 95% CI: 0.53, 0.98; *P* for trend = 0.03). Cancer risk reduction with increasing intake of menaquinones was more pronounced in men than in women, mainly driven by significant inverse associations with prostate (*P* for trend = 0.03) and lung (*P* for trend = 0.002) cancer. We found no association with phylloquinone intake.

Conclusion: These findings suggest that dietary intake of menaquinones, which is highly determined by the consumption of cheese, is associated with a reduced risk of incident and fatal cancer. *Am J Clin Nutr* 2010;91:1348–58.

INTRODUCTION

Vitamin K is a fat-soluble vitamin that physiologically acts as a cofactor for the posttranslational γ-carboxylation of vitamin K–dependent proteins (1). Apart from this well-known physiologic function, evidence from in vitro and in vivo studies indicate that vitamin K exerts inhibitory effects on cell growth in several cancer cell lines (2). Phylloquinone (vitamin K_1) and menaquinones (vitamin K_2, MK-n) naturally occur in human food, whereas menadione (vitamin K_3) is a synthetic form of vitamin K (3). Phylloquinone occurs abundantly in green leafy vegetables, whereas cheese and meat are the main food sources of menaquinones. Numerous cell studies (4–18) and a few in vivo studies (19, 20) have shown anticarcinogenic activities of vitamin K. Most such experimental studies were conducted with menadione, which shows strong growth inhibitory effects via oxidative stress in a variety of cancer cell lines (9, 10, 13–15). Anticancer activities via induction of proto-oncogenes such as c-myc or c-fos, which foster cell cycle arrest and apoptosis (5, 12), have been observed for phylloquinone and menaquinones. The antiproliferative potential of menaquinones is ≈5 times stronger than the effects mediated by phylloquinone (12, 16). Anticarcinogenic activities of menaquinones have been observed in a variety of cancer cell lines, including liver (5, 6, 11), lung (17, 18), colorectum (20), stomach (12), and breast (16). Fewer studies explicitly investigated the growth-inhibitory effects of phylloquinone (5, 8, 16, 21), and distinct effects were observed for liver (16) and colorectal cancer (8, 16). In addition to these experimental studies, the anticarcinogenic potential of menaquinones has also been shown in a randomized trial in 43 women with viral cirrhosis of the liver, in which the treatment group received mega-doses of menaquinone-4 (45 mg/d) for 2 y. After follow-up of >6 y, the risk ratio of hepatocellular carcinoma was 0.20 (95% CI: 0.04, 0.91) in a comparison of the treatment group with the control group (22).

Epidemiologic studies investigating the association of dietary vitamin K with the risk of malignant diseases are scarce. One reason for the lack of such studies may be that, until recently, no comprehensive vitamin K food-composition data, especially data comprising the whole variety of menaquinones that are relevant for human nutrition, were available (23). We previously in-

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vestigated the association between dietary intake of phylloquinone and menaquinones and prostate cancer in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) (24). Whereas no effect was observed for phylloquinone intake, dietary intake of menaquinones was inversely associated with prostate cancer, especially advanced prostate cancer. On the basis of the anticancer activities of vitamin K, especially menaquinones, as observed in a variety of cancer cell lines, we hypothesized that dietary intake of vitamin K may be associated with overall cancer incidence and mortality. In addition, we present the association between dietary intake of vitamin K and the most frequently diagnosed specific cancer sites, ie, cancers of the lung, colorectum, breast, and prostate.

SUBJECTS AND METHODS

Study population

The EPIC-Heidelberg cohort study is contributing to the multicenter cohort study EPIC. EPIC-Heidelberg comprises a total of 25,540 participants aged 40–64 y (men) and 35–64 y (women) at recruitment, which took place between 1994 and 1998. The study was approved by the local ethics committee, and all study participants gave their written informed consent at the beginning of the study.

Assessment of habitual dietary intake and other variables at baseline

Habitual dietary intake during the 12 mo preceding recruitment was assessed by using a validated semiquantitative food-frequency questionnaire (FFQ) (25, 26) including 148 food and beverage items. Participants were asked to specify the typical portion size and consumption frequency for each food item. In addition to the self-administered FFQ, information on characteristics and lifestyle factors, including smoking habits, physical activity, and reproductive variables in women, was assessed by self-administered questionnaires and a personal interview as described elsewhere (27, 28).

Calculation of vitamin K intake

Dietary intakes of phylloquinone and menaquinones were calculated by using HPLC-based food-composition data. In the case of phylloquinone, published and unpublished (Bolton-Smith et al, personal communication, 2005) data from a UK database for the phylloquinone content of foods was used (29). The menaquinone content of relevant foods was derived from a Dutch publication (23) and supplemented with data by Hirauchi et al (30). The average daily intake of phylloquinone and menaquinones was calculated by multiplying the portion size, the daily frequency of intake, and the content of phylloquinone and menaquinones of each food item.

Follow-up and outcome assessment

Active follow-up has been conducted since 1998 by means of follow-up questionnaires that are mailed to the study participants at regular time intervals. The response rates for all follow-up intervals were >91%. All self-reported incident cancer cases are being verified by pathology reports, medical records, and/or death certificates on the basis of the second revision of the *International Classification of Diseases for Oncology* (ICD-O-2). Death certificates were obtained from the mortality registries for all deceased participants. The underlying cause of death was coded according to the ICD-10.

The primary outcome of the present analysis was incidence (ICD-O-2 codes C00-C77 and C80, excluding nonmelanoma skin cancer) and mortality (ICD-10 codes C00-C97 and B21) of total invasive cancer. Information on cancer stage at diagnosis was extracted from medical records, and incident cancer cases were classified as regional/localized and metastatic cancer following the staging guidelines of the Surveillance, Epidemiology and End Results Program (31). In addition, the following frequent cancer sites were analyzed separately: lung cancer incidence and mortality (C34), colorectal cancer incidence (C18-C20), female invasive breast cancer incidence (C50), and prostate cancer incidence (C61).

Follow-up data ascertained up to August 2008 was included. In analyses of cancer incidence, person-years of follow-up were calculated from the date of recruitment until the date of diagnosis of cancer, date of death, or date of last known contact, whichever came first. For the separate analysis of individual cancer sites, subjects with a cancer diagnosis other than the cancer of interest (except nonmelanoma skin cancer) were censored at the date of diagnosis of that cancer. When cancer mortality was modeled as the outcome variable, follow-up time was calculated from the date of recruitment until the date of death from cancer, date of death from any other cause, or date of last known contact, whichever was earliest. Median follow-up time was 10.2 y for the analyses of cancer incidence and 10.7 y for the analyses of cancer mortality.

Statistical analysis

Subjects with prevalent cancer, except for nonmelanoma skin cancer (n = 955), and with the sex-specific top and bottom 0.5 percentile of total energy intake (<888 kcal/≥5585 kcal for men and <705 kcal/≥4316 kcal for women) were excluded from the present analysis, which left a total of 24,340 participants (11,438 men and 12,902 women). Cox proportional hazards regression models were fitted to estimate hazard ratios (HRs) and corresponding 95% CIs of cancer incidence or mortality. Age was used as the underlying time variable, with subjects contributing person-time from their age at recruitment to their age at cancer diagnosis/death or censoring, respectively. In addition, all models were stratified by sex and age at recruitment (1-y categories) to avoid violations of the proportional hazards assumption. Dietary intakes of phylloquinone and menaquinones were entered simultaneously into the models categorized into sex-specific quartiles based on the distribution of the whole study population, with the lowest quartile being the reference category. Tests for linear trend were performed by modeling the median values of phylloquinone or menaquinone quartiles, respectively, as continuous variables. In addition, continuous models were calculated per 10-μg increment in intake of phylloquinone or menaquinones. Multivariate analyses of cancer incidence and mortality were adjusted for total energy intake (kcal/d), alcohol intake (<1, 1 to <5, 5 to <15, 15 to <30, or ≥30 g/d), BMI (kg/m^2), waist circumference (cm), smoking category (never; former, quit ≥10 y ago; former, quit <10 y

TABLE 1
Baseline characteristics of 24,340 EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition–Heidelberg) participants by quartile (Q) of phylloquinone and menaquinone intakes

	Sex-specific quartiles[1] of phylloquinone intake					Sex-specific quartiles[1] of menaquinone intake				
	Q1 (n = 6084)	Q2 (n = 6086)	Q3 (n = 6086)	Q4 (n = 6084)	P for trend[2]	Q1 (n = 6084)	Q2 (n = 6086)	Q3 (n = 6086)	Q4 (n = 6084)	P for trend[2]
Men (%)	47	47	47	47	—	47	47	47	47	—
Never smokers (%)	40	40	39	40	—	40	40	39	39	—
Former smokers, quit ≥10 y ago (%)	10	10	9	10	—	10	10	9	10	—
Former smokers, quit <10 y ago (%)	20	22	22	22	—	22	21	23	21	—
Current smokers, <15 cigarettes/d (%)	9	9	9	9	—	9	8	9	10	—
Current smokers, ≥15 cigarettes/d (%)	15	12	13	12	0.90	12	14	12	13	0.03
Physically active (%)	22	25	26	28	<0.0001	24	24	26	27	<0.0001
University degree (%)	26	29	30	35	<0.0001	23	28	33	36	<0.0001
Current postmenopausal hormone use in postmenopausal women (%)	51	49	50	48	0.08	45	51	51	52	0.0002
Age (y)	49.9 ± 7.9[3]	50.3 ± 8.1	50.4 ± 8.1	50.5 ± 8.2	0.001	51.8 ± 8.0	50.5 ± 8.1	50.0 ± 8.0	48.8 ± 8.0	<0.0001
BMI (kg/m^2)	26.2 ± 4.2	26.2 ± 4.2	26.2 ± 4.3	26.0 ± 4.5	0.17	26.3 ± 4.1	26.2 ± 4.2	26.1 ± 4.3	26.0 ± 4.5	<0.0001
Total energy intake (kcal/d)	1613 (1327–1952)[4]	1806 (1502–2192)	1962 (1602–2366)	2091 (1695–2616)	<0.0001	1462 (1215–1748)	1769 (1502–2083)	1963 (1662–2346)	2309 (1939–2820)	<0.0001
Alcohol intake (g ethanol/d)	9.6 (2.8–24.0)	10.3 (3.3–23.9)	10.3 (3.0–24.1)	10.1 (3.0–24.4)	0.16	8.8 (2.2–22.9)	10.1 (3.1–24.2)	10.8 (3.6–24.3)	10.7 (3.5–24.8)	0.0002
Vegetable intake (g/d)[5]	75.1 (57.7–93.7)	99.7 (82.8–120.7)	116.5 (94.9–142.3)	153.5 (119.4–192.8)	<0.0001	101.8 (77.1–134.1)	104.5 (81.1–135.3)	108.7 (83.7–142.6)	111.4 (84.8–149.2)	<0.0001
Fruit intake (g/d)[5]	80.2 (44.1–107.5)	95.0 (63.1–148.5)	98.7 (69.2–164.4)	107.6 (80.1–185.2)	<0.0001	97.1 (59.1–151.3)	94.8 (62.3–149.5)	95.8 (64.9–154.8)	96.7 (66.0–163.2)	<0.0001
Meat intake (g/d)[5]	91.8 (61.3–124.5)	89.5 (61.0–121.6)	84.7 (56.1–117.2)	82.2 (50.5–118.4)	<0.0001	86.8 (56.0–119.7)	87.6 (59.8–119.8)	87.1 (58.0–119.9)	87.8 (54.6–122.0)	0.83
Red meat intake (g/d)[5]	78.9 (51.9–110.3)	76.5 (50.3–105.4)	71.1 (46.1–100.6)	68.8 (39.6–100.9)	<0.0001	73.8 (46.8–105.4)	74.2 (49.2–103.4)	73.5 (46.9–104.0)	74.2 (44.2–105.9)	0.54
Processed meat intake (g/d)[5]	48.7 (29.6–71.5)	46.3 (28.2–66.9)	42.3 (25.6–62.7)	39.6 (21.1–60.6)	<0.0001	42.1 (24.4–63.0)	43.5 (27.1–63.2)	45.4 (26.3–66.2)	46.4 (26.1–69.3)	<0.0001
Dairy intake (g/d)[5]	188.6 (103.6–296.8)	187.7 (109.3–294.4)	197.4 (116.5–309.4)	199.1 (119.8–317.2)	<0.0001	163.0 (81.9–277.2)	183.9 (106.7–295.7)	199.7 (120.8–308.5)	218.1 (141.1–330.4)	<0.0001
Cheese intake (g/d)[5]	22.9 (14.0–38.3)	25.6 (15.3–38.5)	26.1 (15.6–37.8)	27.9 (16.5–39.4)	<0.0001	13.8 (8.0–19.3)	21.2 (14.8–29.9)	32.3 (21.9–40.3)	40.9 (32.1–61.2)	<0.0001

[1] Quartile ranges were <26, 26 to <35, 35 to <46, and ≥46 μg/d in men and <23, 23 to <32, 32 to <42, and ≥42 μg/d in women.
[2] Likelihood-ratio test or Jonkheere-Terpstra test.
[3] Mean ± SD (all such values).
[4] Median; 25th–75th quartiles in parentheses (all such values).
[5] Energy-adjusted by using the residual method.

TABLE 2
Distribution of incident and fatal cancer cases, by most frequent cancer sites, in 24,340 participants of the EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition–Heidelberg) cohort study (n = 11,438 men and 12,902 women)[1]

		Cancer incidence			Cancer mortality		
Cancer site	ICD-O-2 codes	Total no. of subjects	No. of men	No. of women	Total no. of subjects	No. of men	No. of women
Breast	C50	361	2	359	28	1	27
Prostate	C61	328	328	—	15	15	—
Colorectum	C18-21	180	114	66	52	31	21
Skin (melanoma)	C44	138	89	49	—	—	—
Lung	C34	128	97	31	88	70	18
Kidney	C64	62	43	19	6	3	3
Hematopoietic system	C42	56	37	19	28	23	5
Bladder	C67	47	38	9	11	10	1
Stomach	C16	45	35	10	26	22	4
Pancreas	C25	39	26	13	38	25	13
Lymph nodes	C77	37	23	14	—	—	—
Liver	C22	35	26	9	30	24	6
Corpus uteri	C54	29	—	29	4	—	4
Ovary	C56	27	—	27	17	—	17
Thyroid gland	C73	15	2	13	—	—	—
Esophagus	C15	14	11	3	9	7	2
Cervix uteri	C53	9	—	9	3	—	3
Other	—	205	126	79	103	71	32
Total	—	1755	997	758	458	302	156

[1] ICD-O-2, *International Classification of Diseases for Oncology.*

ago; or current, 1–4, 5–14, 15–24, 25–34, or ≥35 cigarettes/d), smoking duration (<10, 10–19, 20–29, 30–39, or ≥40 y), physical activity (inactive, moderately inactive, moderately active, or active), and education level (none/primary, technical, secondary, or university).

The primary analyses of cancer incidence and mortality were conducted in all study participants as well as separately for men and women. Primary analyses of cancer incidence were repeated after exclusion of incident cancer cases that had occurred during the first 2 y of follow-up. Referring to our earlier findings for prostate cancer (24), in which we observed stronger associations of menaquinones with advanced than with nonadvanced prostate cancer, we divided overall cancer incidence into regional/localized and metastatic cancer and analyzed these as separate outcomes. Site-specific analyses were conducted for lung cancer incidence and mortality as well as for colorectal, breast cancer (separate analyses for pre- and postmenopausal women), and prostate cancer incidence, for which multivariate-adjusted HRs were calculated. In addition to the potentially confounding variables adjusted for in the overall cancer incidence and mortality models, site-specific adjustment variables were included in the models for specific cancer sites. For colorectal cancer, additional adjustment included red and processed meat intake (g/d), fiber intake (mg/d), folate intake (μg/d), calcium intake (mg/d), and family history of colorectal cancer. Breast cancer analyses were conducted separately for pre- and postmenopausal breast cancer and were additionally adjusted for parity (nulliparous; age at first pregnancy ≤19, 19–29, or ≥30 y; or missing), age at menarche (≤12, 12–13, ≥14 y, or missing), oral contraceptive use (never, ever, current, or missing), and family history of breast cancer. In postmenopausal breast cancer models, age at menopause (<45 y, ≥45 y, or missing) and hormone replacement therapy use (never, former, current, or missing) were additionally included as covariates. Models for prostate cancer were additionally adjusted for tomato sauce intake (g/d), calcium (mg/d), and vitamin D intake (μg/d) as well as family history of prostate cancer.

We tested for the heterogeneity of effects of vitamin K on different types of cancer by application of the data augmentation approach on competing risks as described by Lunn and McNeil (32).

Analyses were repeated stratified by sex, smoking status, age at baseline (<50 or ≥50 y), and BMI groups (in kg/m^2; <25, 25 to <30, or ≥30) to assess potential interaction by these factors. Tests for interaction were performed by using cross-product terms comparing multivariate models with and without interaction terms according to the log-likelihood statistic to obtain the P for interaction. All statistical tests were 2-sided, and P values <0.05 were considered statistically significant. All statistical analyses were performed by using SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS

The distributions of potential confounders across quartiles of dietary intake of phylloquinone and menaquinones among the 23,340 male and female subjects included in the analysis are shown in **Table 1**. Subjects with higher intakes of phylloquinone or menaquinones were more likely to be physically active and to have a university degree. Postmenopausal hormone use was more likely among postmenopausal women with higher menaquinone intakes. Mean consumption of vegetables, the major food source of phylloquinone (60% contribution), in the upper quartile of phylloquinone intake, was more than twice as high as in the first quartile. Dietary intake of dairy and cheese increased with growing phylloquinone quartiles. With increasing quartiles of menaquinone intake, consumption of the main food source cheese (45% contribution) increased clearly, whereas

TABLE 3
Association between dietary intake quartile (Q) of vitamin K and risk of incident and fatal cancer in 23,340 participants of the EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition–Heidelberg) cohort study[1]

	Sex-specific quartile of vitamin K intake					
	Q1	Q2	Q3	Q4	*P* for trend	Continuous HR[2]
Cancer incidence						
Phylloquinone						
Cases/noncases	447/5637	423/5663	455/5631	430/5654		
HR[3]	1	0.95	1.02	0.96		1.00
95% CI		(0.83, 1.09)	(0.89, 1.16)	(0.83, 1.10)	0.71	(0.99, 1.01)
Menaquinones						
Cases/noncases	507/5577	435/5651	427/5659	386/5698		
HR[3]	1	0.91	0.91	0.86		0.97
95% CI		(0.80, 1.04)	(0.79, 1.04)	(0.73, 1.01)	0.08	(0.93, 1.00)
Cancer incidence[4]						
Phylloquinone						
Cases/noncases	373/5637	346/5663	386/5631	371/5654		
HR[3]	1	0.93	1.03	0.98		1.00
95% CI		(0.80, 1.08)	(0.89, 1.19)	(0.84, 1.14)	0.93	(0.99, 1.01)
Menaquinones						
Cases/noncases	414/5577	371/5651	358/5659	333/5698		
HR[3]	1	0.93	0.90	0.87		0.97
95% CI		(0.81, 1.08)	(0.78, 1.05)	(0.73, 1.04)	0.11	(0.94, 1.01)
Cancer incidence, regional or localized						
Phylloquinone						
Cases/noncases	249/5637	258/5663	261/5631	254/5654		
HR[3]	1	1.02	1.04	1.02		1.00
95% CI		(0.86, 1.22)	(0.87, 1.25)	(0.85, 1.23)	0.85	(0.99, 1.01)
Menaquinones						
Cases/noncases	292/5577	271/5651	251/5659	208/5698		
HR[3]	1	1	0.95	0.86		0.97
95% CI		(0.84, 1.19)	(0.79, 1.14)	(0.70, 1.07)	0.14	(0.92, 1.02)
Cancer incidence, metastatic						
Phylloquinone						
Cases/noncases	71/5637	43/5663	51/5631	56/5654		
HR[3]	1	0.64	0.76	0.80		1.00
95% CI		(0.44, 0.95)	(0.53, 1.11)	(0.55, 1.18)	0.49	(0.97, 1.03)
Menaquinones						
Cases/noncases	74/5577	50/5651	50/5659	47/5698		
HR[3]	1	0.73	0.78	0.75		0.96
95% CI		(0.50, 1.05)	(0.52, 1.15)	(0.48, 1.17)	0.23	(0.87, 1.06)
Cancer mortality						
Phylloquinone						
Cases/noncases	128/5956	104/5982	111/5975	115/5969		
HR[3]	1	0.88	0.89	0.93		1.01
95% CI		(0.68, 1.14)	(0.69, 1.16)	(0.71, 1.22)	0.70	(0.99, 1.02)
Menaquinones						
Cases/noncases	156/5928	114/5972	90/5996	98/5986		
HR[3]	1	0.77	0.64	0.72		0.92
95% CI		(0.60, 0.99)	(0.49, 0.85)	(0.53, 0.98)	0.03	(0.86, 1.00)

[1] HR, hazard ratio.
[2] Per 10-μg/d increment.
[3] Age- and sex-stratified and adjusted for total energy, alcohol intake (<1, 1 to <5, 5 to <15, 15 to <30, or ≥30 g/d), BMI (continuous; in kg/m^2), waist-to-hip ratio (continuous), smoking (never; former, quit ≥10 y ago; former, quit <10 y ago; current: 1–4, 5–14, 15–24, 25–34, or ≥35 cigarettes/d; or other smoking), smoking duration (<10, 10–19, 20–29, 30–39, or ≥40 y), physical activity (inactive, moderately inactive, moderately active, or active), and educational level (none/primary, technical, secondary, or university).
[4] Cases occurring in the first 2 y of follow-up were excluded.

meat intake (18% contribution) increased marginally. Intake of cheese explained 71% of the between-subject variation in menaquinone intake, whereas meat explained 11%.

The distribution of cancer sites among incident and fatal cancer cases in the whole study cohort as well as separately for men and women are shown in **Table 2**. Overall, during the follow-up time of >10 y, 1755 incident cancer cases were identified. The most frequent cancer sites were prostate in men and breast in women. Cancer as the underlying cause of death was documented in 458 study participants, with lung cancer

TABLE 4
Association between dietary intake quartile (Q) of vitamin K and risk of incident cancer in 23,340 participants of the EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition–Heidelberg) cohort study by sex[1]

	Men (n = 11,438)						Women (n = 12,902)						
	Q1	Q2	Q3	Q4	P for trend	Continuous HR[2]	Q1	Q2	Q3	Q4	P for trend	Continuous HR[2]	P for interaction
Cancer incidence													
Phylloquinone													
Cases/noncases	251/2608	235/2625	261/2599	250/2609			196/3029	188/3038	194/3032	180/3045			
HR[3]	1	0.96	1.04	1.00		1.00	1	0.96	1.00	0.91		1.00	
95% CI		(0.80, 1.15)	(0.87, 1.24)	(0.83, 1.21)	0.83	(0.98, 1.01)		(0.78, 1.17)	(0.82, 1.23)	(0.74, 1.13)	0.46	(0.99, 1.02)	0.90
Menaquinones													
Cases/noncases	309/2550	245/2615	229/2631	214/2645			198/3027	190/3036	198/3028	172/3053			
HR[3]	1	0.83	0.79	0.78		0.95	1	1.04	1.10	1.01		1.00	
95% CI		(0.70, 0.99)	(0.66, 0.95)	(0.63, 0.96)	0.03	(0.91, 1.00)		(0.85, 1.28)	(0.89, 1.36)	(0.79, 1.30)	0.86	(0.94, 1.05)	0.05
Cancer incidence[4]													
Phylloquinone													
Cases/noncases	213/2608	196/2625	225/2599	217/2609			160/3029	150/3038	161/3032	154/3045			
HR[3]	1	0.95	1.07	1.02		1.00	1	0.93	1.00	0.93		1.01	
95% CI		(0.78, 1.15)	(0.88, 1.30)	(0.83, 1.26)	0.63	(0.98, 1.01)		(0.74, 1.16)	(0.80, 1.25)	(0.74, 1.18)	0.71	(0.99, 1.02)	0.96
Menaquinones													
Cases/noncases	259/2550	212/2615	188/2631	192/2645			155/3027	159/3036	170/3028	141/3053			
HR[3]	1	0.84	0.76	0.81		0.96	1	1.08	1.14	0.98		0.99	
95% CI		(0.70, 1.02)	(0.62, 0.93)	(0.64, 1.01)	0.06	(0.91, 1.01)		(0.86, 1.36)	(0.90, 1.45)	(0.74, 1.29)	0.89	(0.93, 1.05)	0.02

[1] HR, hazard ratio.
[2] Per 10-μg/d increment.
[3] Age- and sex-stratified and adjusted for total energy, alcohol intake (<1, 1 to <5, 5 to <15, 15 to <30, or ≥30 g/d), BMI (continuous; in kg/m^2), waist-to-hip ratio (continuous), smoking (never; former, quit ≥10 y ago; former, quit <10 y ago; current: 1–4, 5–14, 15–24, 25–34, or ≥35 cigarettes/d; or other smoking), smoking duration (<10, 10–19, 20–29, 30–39, or ≥40 y), physical activity (inactive, moderately inactive, moderately active, or active), and educational level (none/primary, technical, secondary, or university).
[4] Cases occurring in the first 2 y of follow-up were excluded.

TABLE 5
Association between dietary intake quartile (Q) of vitamin K and risk/mortality of cancer at different sites in 23,340 participants of the EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition–Heidelberg) cohort study[1]

	Sex-specific quartiles of vitamin K intake					
	Q1	Q2	Q3	Q4	*P* for trend	Continuous HR[2]
Lung cancer incidence						
Phylloquinone						
Cases/noncases	31/6053	27/6059	35/6051	34/6050		
HR[3]	1	1.06	1.30	1.19		0.98
95% CI		(0.62, 1.81)	(0.77, 2.20)	(0.63, 2.21)	0.54	(0.93, 1.03)
Menaquinones						
Cases/noncases	47/6037	33/6053	24/6062	23/6061		
HR[3]	1	0.62	0.43	0.38		0.87
95% CI		(0.39, 0.98)	(0.25, 0.75)	(0.20, 0.71)	0.002	(0.75, 1.01)
Lung cancer mortality						
Phylloquinone						
Cases/noncases	20/6064	21/6065	25/6061	22/6062		
HR[3]	1	1.23	1.36	1.08		0.99
95% CI		(0.65, 2.33)	(0.72, 2.57)	(0.50, 2.32)	0.90	(0.94, 1.05)
Menaquinones						
Cases/noncases	30/6054	25/6061	19/6067	14/6070		
HR[3]	1	0.76	0.55	0.41		0.88
95% CI		(0.43, 1.33)	(0.29, 1.04)	(0.19, 0.92)	0.02	(0.74, 1.06)
Colorectal cancer incidence						
Phylloquinone						
Cases/noncases	44/6040	39/6047	41/6045	49/6035		
HR[4]	1	0.90	0.95	1.15		0.98
95% CI		(0.58, 1.41)	(0.60, 1.51)	(0.68, 1.95)	0.50	(0.94, 1.03)
Menaquinones						
Cases/noncases	50/6034	48/6038	41/6045	34/6050		
HR[4]	1	1.07	0.94	0.89		0.93
95% CI		(0.70, 1.61)	(0.59, 1.49)	(0.50, 1.59)	0.57	(0.80, 1.07)
Premenopausal breast cancer incidence						
Phylloquinone						
Cases/noncases	21/1357	30/1344	21/1347	22/1369		
HR[5]	1	1.39	0.98	0.90		0.98
95% CI		(0.78, 2.47)	(0.51, 1.87)	(0.43, 1.88)	0.58	(0.92, 1.04)
Menaquinones						
Cases/noncases	23/1104	16/1309	30/1415	25/1589		
HR[5]	1	0.61	1.00	0.72		0.90
95% CI		(0.32, 1.17)	(0.55, 1.82)	(0.35, 1.48)	0.70	(0.76, 1.07)
Postmenopausal breast cancer incidence						
Phylloquinone						
Cases/noncases	61/1193	53/1246	51/1237	35/1263		
HR[6]	1	0.90	0.85	0.61		0.99
95% CI		(0.61, 1.32)	(0.56, 1.31)	(0.35, 1.07)	0.51	(0.95, 1.04)

(Continued)

TABLE 5 (*Continued*)

	Sex-specific quartiles of vitamin K intake					
	Q1	Q2	Q3	Q4	*P* for trend	Continuous HR[2]
Menaquinones						
Cases/noncases	56/1458	57/1266	50/1191	37/1024		
HR[6]	1	1.13	0.99	0.80		0.98
95% CI		(0.76, 1.66)	(0.64, 1.52)	(0.47, 1.36)	0.57	(0.87, 1.11)
Prostate cancer incidence						
Phylloquinone						
Cases/noncases	83/6001	76/6010	85/6001	84/6000		
HR[7]	1	0.89	1.00	1.00		1.00
95% CI		(0.64, 1.23)	(0.72, 1.39)	(0.67, 1.48)	0.84	(0.97, 1.04)
Menaquinones						
Cases/noncases	111/5973	83/6003	71/6015	63/6021		
HR[7]	1	0.79	0.67	0.65		0.92
95% CI		(0.59, 1.06)	(0.48, 0.93)	(0.44, 0.97)	0.03	(0.84, 1.01)

[1] HR, hazard ratio.

[2] Per 10-μg/d increment.

[3] Age- and sex-stratified and adjusted for total energy, alcohol intake (<1, 1 to <5, 5 to <15, 15 to <30, or ≥30 g/d), BMI (continuous; in kg/m^2), waist-to-hip ratio (continuous), smoking (never; former, quit ≥10 y ago; former, quit <10 y ago; current: 1–4, 5–14, 15–24, 25–34, or ≥35 cigarettes/d; or other smoking), smoking duration (<10, 10–19, 20–29, 30–39, or ≥40 y), physical activity (inactive, moderately inactive, moderately active, or active), and educational level (none/primary, technical, secondary, or university).

[4] Additionally adjusted for family history of colorectal cancer and intakes of red and processed meat, fiber, folate, and calcium.

[5] Additionally adjusted for fat intake, parity (nulliparous; age at first pregnancy <19, 19–29, or ≥30 y; or missing), age at menarche (<12, 12–13, or ≥14 y or missing), pill use (never, ever, current, or missing), and family history of breast cancer.

[6] Additionally adjusted for fat intake, parity (nulliparous; age at first pregnancy <19, 19–29, or ≥30 y; or missing), age at menarche (<12, 12–13, or ≥14 y or missing), pill use (never, ever, current, or missing), and family history of breast cancer and age at menopause (<45 y, ≥45 y, or missing), hormone replacement therapy use (never, ever, current, or missing).

[7] Additionally adjusted for family history of prostate cancer and intakes of tomato, calcium, and vitamin D.

being the most frequent cause of cancer death (70 fatal lung cancer cases in men and 18 in women).

Multivariate-adjusted HRs of overall cancer incidence and mortality by sex-specific quartiles of phylloquinone and menaquinone intakes are presented in **Table 3**. Dietary phylloquinone intake was unrelated to overall cancer incidence (HR for the highest compared with the lowest quartile: 0.96; 95% CI: 0.83, 1.10; *P* for trend = 0.71), whereas dietary intake of menaquinones was nonsignificantly associated with a decreased risk of overall cancer incidence in a comparison of the highest with the lowest quartile (HR: 0.86; 95% CI: 0.73, 1.01; *P* for trend = 0.08). Risk estimates changed only slightly when cancer cases that were diagnosed within the first 2 y after recruitment were excluded. Dietary intake of menaquinones was significantly inversely associated with cancer mortality, both across quartiles of intake (HR for the highest compared with the lowest quartile: 0.72; 95% CI: 0.53, 0.98; *P* for trend = 0.03) and in the continuous model. Phylloquinone intake was not associated with cancer mortality.

Sex-specific analyses (**Table 4**) showed that dietary intake of menaquinones was significantly inversely associated with cancer incidence in men but not in women. The interaction between dietary menaquinones and sex was of borderline significance for total cancer incidence (*P* = 0.05) and significant when cases occurring in the first 2 y of follow-up were excluded (*P* = 0.02). There was no indication of effect modification by sex for localized, metastatic, or fatal cancer (*P* for interaction >0.1 for all; data not shown).

The inverse association between dietary intake of menaquinones and cancer mortality in the entire study population persisted when models were additionally adjusted for the main food sources of phylloquinones and menaquinones, ie, vegetables, dairy products, and meat (data not shown). Both MK-4 and the sum of MK-5 to MK-9 were significantly inversely associated with total cancer mortality when modeled separately (data not shown). There was no indication of statistical interaction by age, smoking status, or BMI category (data not shown; $P > 0.05$ for all).

Associations between dietary intake of phylloquinone and menaquinones and cancer at specific sites are presented in **Table 5**. Whereas phylloquinone intake was not associated with lung cancer incidence, we observed an inverse association for dietary intake of menaquinones. Subjects in the fourth quartile of menaquinone intake had a 62% reduced risk of lung cancer. The significant inverse association between dietary intake of menaquinones and lung cancer mortality was of similar magnitude. Neither the phylloquinone nor menaquinone intakes was statistically significantly associated with risk of colorectal cancer. Dietary intakes of phylloquinone and menaquinones were unrelated to pre- and postmenopausal breast cancer. As reported at an earlier stage of follow-up (mean follow-up time: 8.6 y; 268 prostate cancer cases) (22), dietary intake of menaquinones but not of phylloquinone was significantly inversely associated with the risk of prostate cancer. Despite the virtually stronger effects for lung and prostate cancer than for colorectal and breast cancer, there was no indication of significant heterogeneity when different types of cancer were modeled as competing risks, which was not entirely unexpected because of limited power.

When total cancer incidence was modeled excluding prostate and lung cancer, multivariate-adjusted HRs (95% CI) of the second, third, and fourth quartiles compared with the first quartile of menaquinone intake were 0.97 (0.83, 1.14), 1.03 (0.88, 1.21), and 0.98 (0.81, 1.18), respectively (*P* for trend = 0.97). An inverse, but not statistically significant, association was still observed between menaquinone intake and metastatic incident cancer after the exclusion of prostate and lung cancer. Multivariate-adjusted HRs (95% CI) were 0.75 (0.48, 1.16), 0.87 (0.55, 1.39), and 0.80 (0.47, 1.37), respectively (*P* for trend = 0.47) in a comparison of the second, third, and fourth quartiles with the first quartile.

DISCUSSION

In this prospective analysis of the EPIC-Heidelberg cohort, cancer incidence and cancer mortality decreased with higher intakes of menaquinones, whereas phylloquinone was not associated with a decreased cancer risk. Cancer risk reduction with increasing intakes of menaquinones was more distinguished in men than in women. Investigating the most frequent cancer sites individually, significant inverse associations of menaquinones could be established for lung and prostate cancer, the third and first most frequent cancer sites, respectively, in men. To the best of our knowledge, this was the first study to address the association between dietary vitamin K and overall cancer incidence and mortality; it is a follow-up project to our investigation on prostate cancer incidence (24).

The inverse association between intake of menaquinones and overall cancer incidence is in line with the observation of anticarcinogenic effects of vitamin K in a variety of cancer cell lines (4–18). However, sex-specific analyses showed that an inverse association was only seen in male participants, which might be related to the different distribution of cancer sites in men as compared with women. In male participants, the most frequent cancer sites were prostate, colorectum, and lung, of which prostate and lung cancer were individually influenced by dietary intake of menaquinones. In contrast, almost 50% of all cancer cases in women were breast cancer, which was not significantly associated with intake of menaquinones. The effects that menaquinones exert on cancer cells involve cell cycle arrest and apoptosis (5, 12), which are likely to play a role in any form of solid cancer. Nevertheless, differences with respect to cancer site might be expected, for instance, because of the differential tissue distribution of menaquinones. To date, the data on tissue distribution of menaquinones originating from dietary intake, which might give insight to this speculative hypothesis, is quite limited (33). In addition, because of the tissue-specific conversion of MK-4 from phylloquinone (34), it is not known to which extent menaquinones found in extrahepatic tissues are attributable to dietary intake of menaquinones.

Dietary intake of menaquinones was more strongly inversely associated with fatal cancer than with cancer incidence. This observation is consistent with the assumption that factors affecting apoptosis and cell cycle arrest are likely to play a role later in carcinogenesis. In addition, experimental studies suggest an inhibitory role of menaquinones in angiogenesis (35, 36), which is tightly linked to the development of metastasis (37). Dietary intake of phylloquinone was largely unrelated to cancer incidence. This seems plausible considering that the anticancer activities exerted by phylloquinone in cell studies were much lower than those of menaquinones (5, 8, 16, 21). However, it is

conceivable that dietary phylloquinone exerts growth inhibitory effects after endogenous conversion to MK-4 (34) or menadione (vitamin K_3), which shows the strongest anticancer activities of all forms of vitamin K (16) and has been identified as a metabolite of both phylloquinone and menaquinones formed during absorption from the gastrointestinal tract (38). Differences in the biological actions between dietary phylloquinone and menaquinones are also to be expected due to differential transport by lipoproteins (liver as the main target organ of phylloquinone, whereas menaquinones are redistributed by the liver to extrahepatic organs) (39) and poor bioavailability of phylloquinone from vegetables (23).

As a nutritional epidemiologic study without biomarker measurement, this study had several limitations. Of major concern was the relative validity in estimating dietary intake of vitamin K by means of FFQs. The main food sources of phylloquinone are vegetables; those of menaquinones are dairy products and meat. In an earlier validation study, Spearman correlation coefficients between twelve 24-h dietary recalls and the FFQ were reasonable for the main food sources of menaquinones (0.58 for cheese, 0.67 for meat, and 0.65 for processed meat), albeit moderate for vegetables (0.42) (40). A validation study investigating the validity of estimated vitamin K intake has not been conducted in our cohort. However, a comparable validation study has been conducted for the Dutch EPIC FFQ, which showed reasonable relative validity of intakes of menaquinones estimated by using the same data source (23) as in the present study (correlation coefficients between 0.51 and 0.72) (41). In a cross-sectional study, dietary intakes of both phylloquinone and menaquinones (calculated from 24-h dietary recalls by using the same nutrient databases as used herein) were significantly associated with undercarboxylated osteocalcin, a functional biomarker of vitamin K status (42). Furthermore, it has been shown that dietary intakes of phylloquinone estimated with FFQs are significantly associated with plasma phylloquinone (43, 44).

The vitamin K content of foods may vary according to growth and production conditions (23, 45). We used HPLC-based data from the United Kingdom (phylloquinone) and from the Netherlands (menaquinones) for calculation of vitamin K intake. Both databases have been used to estimate vitamin K intakes in previous epidemiologic studies (41, 43, 46, 47). Because growth and production practices as well as the types of foods consumed (ie, types of cheese) are comparable across European countries, the application of the UK/Dutch databases for a German cohort study seems reasonable.

A crucial point in this study is whether the obtained results really show a vitamin K effect or not. Dietary intake of menaquinones is strongly determined by the consumption of cheese, which contributes 45% to the total intake and explains 71% of the between-person variability. Thus, with the use of dietary questionnaire data only, it is difficult to determine whether what has been observed herein is an effect of menaquinones in cheese or an effect of cheese in general. In fact, cheese consumption was independently inversely associated with cancer incidence and mortality in this cohort. The fact that both intakes of MK-4, which is equally derived from meat and dairy products, and intakes of the menaquinones MK-5 to MK-9, which almost exclusively occur in cheese, were independently inversely associated with cancer incidence and mortality, however, argues that the observed effect of menaquinones was an effect beyond a mere cheese effect. Nevertheless, it is possible that the inverse association between menaquinones and incident and fatal cancer was due to constituents of cheese beyond those considered in this analysis. To rule this out, studies involving biomarker measurements are warranted. A first confirmatory backup was provided by a nested case-control study, which showed an increased risk of advanced stage prostate cancer in participants with poor vitamin K status as reflected by serum undercarboxylated osteocalcin (48).

In the present study, the estimation of dietary intake was based on FFQs administered at baseline by the study participants, assuming that dietary habits remain stable over time. This assumption seems justified because the long-term reproducibility of dietary intake of dairy products and meat—the 2 most important sources of menaquinones—is fairly high in our study population (Spearman rank correlations between repeated FFQ measurements at baseline and 5.8 y later of 0.55 for dairy products and 0.62 for meat) (49).

The strengths of this study included its prospective design and the substantial follow-up period. In addition, the comprehensive assessment of potential confounders at baseline allowed for adjustment for a wide range of potentially confounding factors.

In conclusion, this study showed inverse associations between the dietary intake of menaquinones and both overall cancer incidence and mortality. Considering menaquinones in the context of daily food intake, the findings of our study imply that the consumption of cheese may have a beneficial effect with respect to cancer, particularly prostate and lung cancer in men. The hypothesis that habitual dietary vitamin K intake may affect the risk of cancer is rather new and mostly based on evidence from experimental cell studies. Certainly, more studies in humans are warranted before dietary recommendations for cancer prevention can be postulated. Because of the limited accuracy of questionnaire-based calculations of phylloquinone and menaquinone intakes, assessments of vitamin K status via biomarker measurement are desirable.

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