Dietary intake of menaquinones and risk of cancer incidence and mortality

Dear Sir:

In a recent issue of the Journal, Nimptsch et al (1) reported that increased dietary intake of menaquinones (vitamin K2), but not phylloquinone (vitamin K1), is associated with a reduced risk of incidental and fatal cancer. The data are derived from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition, in which 24,340 participants were followed for cancer incidence and mortality for ≥10 y. The prospective study shows that menaquinone intake is particularly associated with the risk of incident and fatal prostate and lung cancer. On the basis of the information obtained from a self-administered, semi-quantitative food-frequency questionnaire, cheese consumption was attributed to be the major determinant of dietary menaquinones. However, in addition to cheese, a number of foods contain a significant amount of menaquinones. In addition, cheeses contain varied amounts of menaquinones depending on the processing conditions, and intestinal microflora may provide parts of the requirement for menaquinones. Menaquinone intake of the participants was also significantly correlated with a number of other dietary intake and information on characteristics and lifestyle factors.

Animals can synthesize the subtype of menaquinones, MK-4, from phylloquinone, which is widely present in green vegetables. Menaquinones with longer isoprene units come mainly from bacterial fermentation (2, 3). Good sources of menaquinones include fermented foods such as cheese, sauerkraut, miso and natto, and animal foods, especially organ meat and pastured dairy products (2, 4, 5). The richest source of menaquinones known is natto, a popular Japanese breakfast food made from steamed and fermented soybeans. A serving (3.5 oz) of natto contains ≈1000 μg MK-7 and 84 μg MK-8. Hard cheeses contain ≈5 μg MK-4 and 70 μg MK-8,9 per serving; soft cheeses contain ≈30% fewer menaquinones. The menaquinone content of fermented cheeses is much higher than that of nonfermented cheeses. The current study does not indicate whether or not the cheeses consumed were fermented. Popular fermented cheeses include aged goat cheese, blue cheese, brie, cheddar, cultured dry cottage cheese, and parmesan; unfermented cheeses include farmers cheese, most cottage cheeses, mozzarella, pot cheese, and processed cheese.

It has long been recognized that several forms of menaquinones are synthesized by intestinal microflora, and that both dietary and microbial vitamin K are widely present in green vegetables. Menaquinones with longer isoprene units come mainly from bacterial fermentation (2, 3). Good sources of menaquinones include fermented foods such as cheese, sauerkraut, miso and natto, and animal foods, especially organ meat and pastured dairy products (2, 4, 5). The richest source of menaquinones known is natto, a popular Japanese breakfast food made from steamed and fermented soybeans. A serving (3.5 oz) of natto contains ≈1000 μg MK-7 and 84 μg MK-8. Hard cheeses contain ≈5 μg MK-4 and 70 μg MK-8,9 per serving; soft cheeses contain ≈30% fewer menaquinones. The menaquinone content of fermented cheeses is much higher than that of nonfermented cheeses. The current study does not indicate whether or not the cheeses consumed were fermented. Popular fermented cheeses include aged goat cheese, blue cheese, brie, cheddar, cultured dry cottage cheese, and parmesan; unfermented cheeses include farmers cheese, most cottage cheeses, mozzarella, pot cheese, and processed cheese.

It has long been recognized that several forms of menaquinones are synthesized by intestinal microflora, and that both dietary and microbial vitamin K are absorbed into intestinal lymph along with other lipids. The most likely absorption site for microbial menaquinones is the terminal ileum, where some menaquinone-producing bacteria as well as bile salts are present. Major forms of microbial menaquinones produced include MK-10 and MK-11 by Bacteroides, MK-8 by Enterobacter, MK-7 by Veillonella, MK-6 by Eubacterium lentum, and MKs 10–13 by Bacteroidce (3, 6). The contribution of intestinal microflora toward the overall requirement of menaquinones, however, is difficult to quantify.

Vitamin K deficiency is common among neonates, and is likely due to poor placental transfer of vitamin K and inadequate production of menaquinones by intestinal microflora. Deficiency in adults resulting from insufficient dietary intake vitamin K is rare. When it occurs, it is usually found in patients with malabsorption syndromes such as cystic fibrosis, celiac disease, and cholestasis (7). Also, vitamin K deficiency occurs in adults with a history of prolonged use of drugs, such as the anticoagulant warfarin and antibiotics that kill the intestinal microflora (8). These findings support the view that microbial menaquinones satisfy parts of the vitamin requirement.

The results obtained from the current study corroborate well with reports of a possible role of menaquinones in the control and regression of atherosclerotic and osteoporotic events (5, 9). However, in addition to the cancer risk, menaquinone intake is also found to be significantly correlated with a number of other dietary intake and lifestyle factors of individuals. For example, the intake of dairy, vegetables, fruit, processed meat, and total energy and age, physical activity, and educational level of participants are all significantly associated with the intake of both phylloquinone and menaquinone (Table 1 in reference 1). It would be of interest if these measures are analyzed for their association with the risk of cancer, osteoporosis, atherosclerosis, and other chronic disorders.

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REFERENCES

Reply to CK Chow

Dear Sir:

We thank Chow for his interest in our article on the association between dietary intake of vitamin K and cancer incidence and mortality in the EPIC (European Prospective Investigation into Cancer and Nutrition) Heidelberg cohort study (1).

In our study, we observed a significant inverse association between dietary intake of menaquinones (MK) and overall cancer mortality. In his letter, Chow states that in addition to cheese, which was the major dietary source of menaquinones in our cohort, a number of other foods contain significant amounts of menaquinones. Besides cheese and other fermented dairy products (eg, yogurt), meat, fish, eggs, and sauerkraut contribute to overall dietary menaquinone intake. Although rarely consumed, animal liver (eg, pork liver, beef liver) and other inwards (eg, kidney) are good sources of menaquinones, especially longer-chain menaquinones (MK-5 to MK-12). In calculating the vitamin K intake of our study participants, we took all foods known to contain vitamin K (2–4) into account, but due to the consumption pattern in our cohort and the high amounts of longer-chain menaquinones (especially MK-8 and MK-9) found in certain types of cheese, cheese remained by far the major food source of menaquinones (as stated in our article, cheese contributes 45% to total menaquinone intake, whereas meat contributes only 9%). Also, in our cohort there was a greater variability in cheese intake (71% of interindividual variation of menaquinone intakes was explained by cheese) than in meat intake (11%). Our food-frequency questionnaire (FFQ) distinguishes between cream cheese, processed cheese, soft cheese (eg, brie) and hard cheese (eg, gouda). We used information from 24-h dietary recalls conducted in a subsample of 2121 study participants to create weights to specify the FFQ items more precisely. By using this method, we could specify which individual types of cheese typically contribute to each FFQ item on cheese in our cohort. Thus, we were able to account for the different amounts of menaquinones found in different types of cheese, as was Chow’s concern.

Furthermore, Chow refers to the intestinal microflora as a potentially relevant contributor to overall vitamin K status. It is well established that the bacterial population of the large intestine synthesizes considerable amounts of predominantly long-chain (MK-9 to MK-12) menaquinones (5). This intestinal production of menaquinones may contribute to vitamin K nutritional status to some extent (6). However, due to the lack of efficient absorption from this part of the bowel, diet is believed to be the major source of menaquinones (5, 7). More recent research has not provided substantial evidence contradicting this assumption (8). It is possible that the terminal ileum, as stated by Chow, is a likely site of absorption of menaquinones synthesized by bacteria, because there are bile acids present that play a role in absorption of menaquinones. However, the predominant site of bacterial menaquinone synthesis (eg, by Bacteroides or Escherichia coli) is the colon, whereas only few constituents of the small intestine microflora produce menaquinones (9). Furthermore, the point raised by Chow that vitamin K deficiency occurs predominantly among patients with malabsorption syndromes would apply for absorption of both dietary and intestinally produced vitamin K, and thus does not seem to substantially support the hypothesis of microbial menaquinones being an important contributor to vitamin K status. Certainly, more studies in humans are warranted to quantify the importance of gut-synthesized menaquinones for overall vitamin K status. With respect to our study, even if menaquinones synthesized by bacteria did contribute to vitamin K supply, our results still indicate that dietary menaquinones may be critical in relation to cancer mortality. We previously showed that both dietary phylloquinone and menaquinones are associated with the ratio of undercarboxylated to total osteocalcin, a functional biomarker of vitamin K status (10). These results underline the importance of dietary vitamin K for overall vitamin K supply.

Finally, in his letter, Chow raises concerns about the correlation between dietary menaquinone intake and potential confounding factors such as dietary factors, physical activity, and education. As shown in Table 1 of our article, dietary intake of menaquinones was in fact significantly associated with total energy intake as well as energy-adjusted intake of vegetables, fruit (inverse association), processed meat, and dairy. None of these dietary factors was independently associated with cancer incidence or mortality. In addition, as we stated in our article, the inverse association between dietary intake of menaquinones and cancer mortality was not substantially attenuated by additional adjustment for consumption of vegetables, meat, and dairy products. We adjusted our models for physical activity and highest attained school degree, which both increased across quintiles of menaquinone intake in our study. Although physical activity was not an independent predictor of either cancer incidence or mortality, lower education was significantly associated with cancer mortality only. Taken together, our data provide no indication for confounding by the factors raised by Chow, although residual confounding cannot be entirely excluded considering possible measurement errors in these variables. Although statistically significant, the association between menaquinone intake and participant age was moderate. In our analysis, we controlled for age by stratifying models by age in 1-y categories.

We are aware that the findings of our study are new and provocative. However, as discussed in our article, the findings of an inverse association between menaquinone intake and cancer mortality are biologically plausible. Certainly, our findings require confirmation in other populations.

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