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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 the long-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 intakes 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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A simple explanation for the inverse association between height and waist in men

Dear Sir:

In the study by Wells et al (2), the authors report 2 main conclusions. The first conclusion was that the relations between body mass index and shape differed significantly between the sexes, particularly in association with age. However, their second conclusion was more obscure, reporting that the inverse association between height and waist in men suggested either a genetic contribution or a link between early growth pattern and predisposition to obesity. Their conclusion was based on a multiple log-log regression analysis of height on components of shape that included a negative association with the fleshy site of waist but positive associations with the “less fleshy” sites of head, knee, hip, and so forth (reported in their Table 6). Also reported in their Table 6 were inverse relations between height and the more fleshy components of thigh, arm, and waist but positive associations with the less fleshy sites of head, knee, and hip in women.

We welcome the analysis of Wells et al (2), which signified an important step toward using appropriate techniques to address shape variation. However, we believe there is a much simpler explanation than the one reported by Wells et al (2). Nevill et al (1) reported that the sum of 8 skinfold thicknesses (including the abdominal site, 5 cm to the right of the midpoint of the navel) increase at a much greater rate relative to body size than that assumed by geometric similarity. They also reported taller subjects had less rather than more adiposity. Hence, the inverse association reported between height and waist in men by Wells et al (2) is likely to be caused by a smaller skeleton to distribute a given increase in adiposity in shorter men, thus causing the waist to expand disproportionately (to that assumed by geometric similarity). The same mechanism likely operates in women, with the smaller skeleton to distribute adiposity in shorter women causing the thigh, arm, and waist to expand disproportionately in a way similar to that observed for the waist in men.

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