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Vitamin D and Folic Acid: Critical Micronutrients?
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Abstracts

From vitamin D to hormone D: A consideration of what is important for good health

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Vitamin D is essential for life in higher animals. Classically it has been shown to be one of the most important biological regulators of calcium metabolism and homeostasis via stimulating the intestinal absorption of calcium, facilitating the deposit of calcium in bone, and regulating the excretion of calcium by the kidney.

The molecular structure of vitamin D is closely allied to that of classical steroids (cholesterol) and steroid hormones (e.g., estrogens, glucocorticoids, etc). Current evidence supports the concept that the classical biological actions of the nutritionally important fat soluble vitamin D in mediating calcium homeostasis are not mediated by the parent vitamin D, but by a vitamin D endocrine system which coordinates the metabolism of vitamin D into the steroid hormone 1,25(OH)₂-vitamin D (referred to here as hormone D). Hormone D, like other steroid hormones, can only generate biological responses via interacting with its partner receptor, the vitamin D receptor (VDR) to form a hormone-receptor complex, that interacts selectively with genes to regulate the production of new proteins that are involved in the appearance of the biological response (e.g. stimulation of intestinal calcium absorption).

It is now clear that our body's target organs which possess the VDR include many more tissues than the classical intestine, bone, and kidney. The VDR is also present in the pancreas, pituitary, skin, breast tissue, placenta, hematopoietic cells, immune cells and cancer cells of various origins. Key advances in understanding the mode of action of the hormone D have been made by a thorough study of the VDR as a classical nuclear receptor as well as the emerging studies describing the presence of the VDR in the plasma membrane.

There are clinical applications for hormone D or related drug forms of hormone D for treatment of the bone diseases of renal osteodystrophy, osteomalacia and osteoporosis, as well as psoriasis, and hypoparathyroidism; other clinical targets for hormone D currently under investigation include its use in leukemia, breast, prostate and colon cancer as well as an immunosuppressive agent.

Scientists and nutrition experts agree that about half of the elderly in North America and two-thirds of the rest of the world are not getting enough vitamin D to maintain a healthy bone density, that will lower their risks for fractures. Probably the nutritional Recommended Dietary Allowance (RDA) for vitamin D should be adjusted upwards from the presently approved RDA of 400 IU to levels as high as 2000 IU.

Dr. Norman is a Presidential Chair and Distinguished Professor of Biochemistry and Biomedical Sciences at the University of California in Riverside, California. His bibliography exceeds 770 publications. Several reference citations relevant to this lecture are listed below.

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Health potential of folic acid

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The discovery of folate can be traced to Lucille Wills, a physician who lived in India who first described the occurrence among her patients of “pernicious anemia of pregnancy” or “tropical anemia” In her attempt to cure the anemia, she found that the purified factor from liver extract (B12) was ineffective even though the crude liver extract was effective. She then used instead yeast extract which proved to be highly effective. In 1939 she summarized her observations to suggest that the “tropical macrocytic anemia” is caused by a deficiency of a nutrient which is different from “the extrinsic factor” (B12) which is used to cure pernicious anemia. This new factor was later named folic acid because it was first extracted from green leafy vegetables.

Following the identification of the structure and the successful synthesis of folic acid and other folates and until the early sixties folate continued to be regarded as an hemopoietic factor. The early studies by Hibbard and his colleagues in the sixties suggested that folate metabolism may be deranged in the early weeks of pregnancy at the time of placentation and organogenesis. Smitthels et al later showed that in mothers who gave birth to infants with neural tube defects, first trimester serum folate, red cell folate, were lower than in controls. These authors later confirmed that periconceptional intake of folic acid protected against recurrence of NTD findings which were later substantiated by randomized placebo controlled studies intervention studies.

What is important and different in these studies on foetal development, was the realization that the folate status in women with NTD affected birth was only slightly low and certainly not in the low range which would cause megaloblastic anemia. This observation has opened the field to start explore potential relation between folate and disease under conditions where folate status is only moderately low and certainly within the normal range. A study conducted by Butterworth et al in 1982, has shown that women on oral contraceptives who took folic acid supplement (5mg/d) for a period of 4 months had significantly lower cervical dysplasia scores than women on placebo. None of the women in either group was folate deficient.

Evidence of impaired folate metabolism in persons with a folate status which is traditionally considered to be in the normal range also derives from epidemiological studies which showed associations of low folate status with cardiovascular disease, neuropsychiatric dysfunctions, cancer, osteoporosis and others. These studies were greatly facilitated by the use of plasma homocysteine concentration as, among other things, an indicator of folate and other B vitamin status.

In recent years a number of countries have adopted a program of folic acid fortification of a number of food staples for the prevention of neural tube defects (NTD) with good results. Nevertheless this program has also created concern about potential harmful effects on the elderly because of high prevalence of vitamin B12 deficiency and increased risk of colorectal cancer.

In summary in spite of more than sixty years, the area of the role of folic acid in health and disease remains to be fully determined.

NVS II: The German perspective

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Aim of the second German National Nutrition Survey (NVS II) is to provide current information on food consumption, energy and nutrient intake as well as nutritional behaviour of the German population. Within this cross-sectional study food consumption was assessed by diet history interviews. Interviews were carried out from November 2005 until November 2006 with 15,371 women and men all over Germany. Nutrient intake was calculated by using a preliminary version of the German Nutrient Database II.4.

In general the German population is well provided with vitamins and minerals. However, the median intake of folate equivalents is below the recommended intake of the German, Austrian and Swiss (D-A-CH) reference values for nutrient intake (folate equivalents: women 252 µg/d and men 283 µg/d). 86 % of women and 79 % of men don't reach the recommended intake of folate equivalents. These proportions increase with increasing age. Main food sources of folate are non alcoholic beverages followed by vegetables for women and men, respectively. The median intake of vitamin D is also below the recommended intake for all age groups (vitamin D: women 2.2 µg/d and men 2.9 µg/d). However, the synthesis of cholecalciferol in the skin is not considered. 91 % of women and 82 % of men are below the recommendations for vitamin D intake. Thereby the proportions of adolescents and young adults as well as elderly subjects are the highest. Main food sources of vitamin D are fish and dishes based on fish for both sexes. Within the NVS II five groups of socio-economic status were classified by education of the participants, and by income and occupational classification of the household. The intake of folate equivalents increases from the lowest group up to the highest group of socio-economic status for both women and men. For vitamin D intake only minor differences can be found between the different groups of social-economic status for women and men, respectively.

About 31 % of women and 24 % of men take vitamin and mineral supplements. Folic acid supplements are used by 10 % of the German population. Thereby no differences between women and men are found. The highest proportion of folic acid supplement intake can be shown for subjects at the age between 25-34 years. About 5 % of the German population use vitamin D supplements. A higher proportion of women take vitamin D supplements compared to men. The highest proportion of vitamin D supplement use is found for older women at the age between 51-80 years. Subjects who take folic acid supplements on average don't reach the recommended intake by food consumption (women 66 % and men 74 % of the recommended intake). However, intake of folate equivalents increases to about 150 % of the recommended intake by use of dietary supplements. Comparable results can be found for vitamin D. Subjects who use vitamin D supplements don't reach the recommended intake by food consumption (women 40 % and men 48 % of the recommended intake). In consideration of vitamin D supplement use the vitamin D intake increases to about 120 % of the recommendations.

In addition the results of the NVS II are compared with intake of folate equivalents and vitamin D in other European countries. Therefore the data of the European Nutrition and Health Report 2009 are used. Within this European project nutrient intake data of 25 European countries was collected. Except for Estonian adult men the D-A-CH reference value for folate equivalents of 400 µg/d is not reached by adult women and men of any European country. Vitamin D intakes of adults of most European countries are below the recommended intake of 5 µg/d. Only adult women and men from Norway and Finland as well as men from Lithuania, Sweden and Poland are above the recommended intake.

Thus, it can be summarised that folate and vitamin D are critical nutrients for the German population.

Dietary intake and biomarker status: vitamin D and folate. EPIC: The european experience

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Epidemiologic evidence suggests that vitamin D and, to a lesser extent, folate may be inversely associated with risk of some cancers and possibly other chronic diseases. In the case of vitamin D, its dietary food sources show great international variation in their level of intake and are primarily limited to fatty fish, cod-liver oil, meat, eggs, milk and some fortified foods. Food content and bioavailability of vitamin D has not been well studied but, depending on the population, it may represent a varying proportion of vitamin D requirements. For some populations, the major sources of vitamin D are sunlight exposure and consumption of dietary supplements or fortified foodstuffs. Folate is found primarily in fruits and vegetables, particularly green leafy ones, although liver is also a rich animal source of the vitamin. Foods fortified with folic acid are common in some countries and intake may be contributed to by dietary supplements.

Varying dietary and lifestyle habits may contribute to differences in the intake levels and/or body status of these important nutrients in different regions and countries. However, their comparison is problematic due to lack of standardized dietary intake assessments. To date, little information is available comparing the intake and blood levels of these nutrients in Western European countries. The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large epidemiologic study of over 520,000 subjects (men and women, aged 25-70yrs) from 23 sub-cohorts in 10 European countries (Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom), providing a wide range of lifestyle and dietary habits. Dietary intake data was collected within EPIC using detailed and validated country-specific dietary questionnaires. In addition, an 8% (approximately 37,000 subjects) sub-set of the cohort was subjected to a standardized 24-hour dietary recall for the purposes of calibration of the dietary questionnaires and reduction of measurement errors. EPIC has also collected biological samples (stored in liquid nitrogen), for measurement of dietary biomarkers.

Data from EPIC will be presented comparing dietary vitamin D intake collected using standardized 24-hour dietary recalls. In addition, biomarker data of blood vitamin D and folate levels will also be presented and dietary and lifestyle correlates and determinants of these nutrients will also be discussed.

NHANES: The US perspective

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The National Health and Nutrition Examination Survey (NHANES) is a nationally representative sample of the noninstitutionalized civilian population of the United States. Each year, household screening, standardized interviews and physical exams take place in homes and mobile examination centers around the 50 states and District of Columbia. Approximately 5,000 persons are examined per year. Information collected includes the use of dietary supplements, intake of selected nutrients estimated from a 24-hr dietary recall interview, and collection of other behavioral and health information designed to estimate the prevalence of chronic conditions. Furthermore, biological specimens are collected to assess nutritional status based on biochemical indicators.

Assessment of vitamin D status has been ongoing in NHANES since 1988. Major factors contributing to vitamin D status are sun exposure, dietary intake of selected foods and beverages that contain naturally occurring or added vitamin D, and consumption of dietary supplements.

Sun exposure data collected in NHANES are of limited scope. NHANES participants are questioned to assess the frequency with which they practice sun protection behaviors and participate in selected outdoor physical activities. Participant recall of details regarding the areas of skin exposed, direct versus indirect sun exposure, and sunscreen usage provides the basis for the assessment of sun protection behaviors. Age, skin pigmentation, latitude, altitude, and seasonal differences add to the complexity of categorizing typical exposures. Information about the length of time spent in outdoor activities or time of day of activities is not collected.

The USDA first published data on the vitamin D content of a limited selection of foods in 1991; the database was updated in 1999, 2007 and 2009. The lawful addition of vitamin D to foods has expanded in the US during the past few years. More foods including cheese and soy products are permitted to be fortified with either vitamin D₂ or D₃. Nonetheless, usual dietary intake data from NHANES 2005-2006 demonstrated that only about 1/3 of individuals ≥ 1 y met the recommended average daily intake (AI; varies with life-stage from 5-15 ug/day) recommended by the National Academy of Sciences, Food and Nutrition Board. Women were less likely than men to meet the AI. As in NHANES III (1988-1994), less than 10% of persons >50 y met the AI from dietary intake alone. Based on dietary intake, $<3\%$ of persons ≥ 1 y had intakes above the tolerable upper intake levels (UL; 50 ug/day).

Since 1988, NHANES has collected data on dietary supplements used by participants. In NHANES 2001-2004, the regular usage of supplements containing 400 IU vitamin D was relatively low (4%) in children and adolescents 1-21 y. Any usage of vitamin D-containing supplements in children and adolescents (<1 -18 y) in 1999-2002 was 26%, and in adults 20-59 y olds was 42% and 54% in NHANES III and 2003-2004, respectively.

Serum concentration of 25-hydroxyvitamin D (25OHD) is the most widely accepted indicator of vitamin D status. In NHANES 2000-2004, 5% of the US population was vitamin D deficient based on a 25OHD cutoff <11 ng/mL. Using this cutoff, $\leq 1\%$ of infants and children ≤ 11 y, 5% 12-19 y olds and 6% of adults ≥ 20 y had vitamin D insufficiency. Non-Hispanic whites tended to have higher 25OHD concentrations than non-Hispanic blacks. BMI and 25OHD were inversely related. Investigation of the decline in 25OHD concentrations between NHANES III and NHANES 2000-2004 demonstrated that assay differences explained most of the difference rather than an actual decline in the status of the US population.

For NHANES 2007-2008 forward, the laboratory will use an isotope dilution tandem mass spectrometry assay to measure 25OHD for NHANES. Shortcomings of the immunoassay used in the past and advantages of the chemistry-based assay will be discussed.

Determinants of vitamin D status in humans

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Vitamin D can be produced through sun exposure of the skin as well as from dietary intake. A low vitamin D status has been implied in the pathogenesis of several common chronic diseases. Against this background, we analysed the prevalence of vitamin D deficiency in the German population and identified determinants of vitamin D status.

We therefore measured serum 25-hydroxyvitamin D (25-OHD) concentrations in population-representative samples of 10,015 children and adolescents (aged 1 to 17 years) and 4,030 adults (aged 18 to 79 years). Analyses are based on data from the German Nutrition Survey 1998 (GeNuS) and the German National Health Interview and Examination Survey for Children and Adolescents (KiGGS), conducted between 2003 and 2006. Children and adolescents with a migrant background were included in proportion to their presence in the population.

Inadequate serum vitamin D levels are defined as < 50 nmol/L, according to current knowledge. Overall, 62 % of boys and 64 % of girls as well as 57 % of men and 58 % of women had vitamin D concentrations under this threshold. There was a strong seasonal variation in vitamin D status with lower levels in winter and higher levels in summer. During wintertime, the prevalence of inadequate vitamin D levels across all age groups ranged from about 50 % among 1- to 2-year-old children to more than 60 % among 18- to 79-year-old adults to more than 80 % among 11- to 17-year-old girls and boys. Even during summertime, elderly women aged 65 to 79 years (75 %) and migrant boys and girls aged 3 to 17 years (65 %) showed inadequate vitamin D concentrations.

Among children and adolescents, independent determinants of vitamin D levels included season of examination and physical activity or outdoor/indoor activities across all age groups. Additionally, age, use of vitamin D supplements and living in non-metropolitan areas were independent determinants of vitamin D status among 1-to 2-year-old infants, whereas age, migrant background and socio-economic status contributed independently to the model among 3- to 10-year-old children. Among 11- to 17-year-old children and adolescents, body mass index and migrant background were additional independent determinants of vitamin D levels. Residence in East Germany and use of supplements contributed to the model in boys, as well as Tanner stage of sexual maturation, and oral contraceptive use in girls.

Apart from seasonal influences and leisure-time physical activity in both genders, age in 18 to 79 year old women as well as low and high body mass index in men of the same age group were the main independent determinants of vitamin D levels. In addition, dietary vitamin D intake and being married or living with partner were independent determinants in both sexes as well as treatment with menopausal hormone therapy in women and outdoor working in men.

Low vitamin D levels are common in the German population, especially among elderly women as well as among children and adolescents with a migrant background. Examination during winter, lower physical activity/playing outdoors correlated most consistently and independently with lower serum vitamin D across all age groups.

Vitamin D and cardiovascular disease

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In the middle of last century, supra-physiological doses of vitamin D were found to induce arteriosclerosis in animals, which resulted in the widely-held opinion that vitamin D was a cause of cardiovascular disease (CVD). This was challenged in the 1970s by small case control studies, using the newly developed methods to measure 25-hydroxyvitamin D (25(OH)D), the main marker of vitamin D status. Contrary to expectations, these studies, including one from Heidelberg,¹ found that myocardial infarction cases had similar or lower 25(OH)D levels than controls.

These case control findings were supported by a 1981 review of the descriptive epidemiology which showed that CVD rates were lowest in populations when ambient ultraviolet radiation, and therefore vitamin D status, was highest – ie. in summer, and at low latitude and high altitude.² The identification in 1983 of a receptor in cardiac muscle to 1,25-dihydroxyvitamin D, the active metabolite of vitamin D, increased the likelihood that vitamin D had a role in cardiac function.³ The hypothesis that vitamin D reduces the risk of CVD was tested in a large population-based case control study, published in 1990, which found that risk of myocardial infarction was inversely associated with plasma 25(OH)D.⁴ For the remainder of the century, no further epidemiological studies were published, although research continued into the possible mechanisms linking vitamin D with cardiovascular function and morphology (eg. cardiac hypertrophy) in animal models. Interest in the possible link between vitamin D and CVD has been rekindled in the last few years by German researchers, who have shown that vitamin D is associated with cardiac and immune function,⁵ and by cohort studies of US dialysis patients showing that active vitamin D is associated with a 20% reduction in all-cause mortality, mainly from CVD.⁶ Evidence now exists for a range of mechanisms to explain the association between vitamin D and CVD, including beneficial effects of vitamin D on: inflammatory processes and cytokines to prevent plaque and thrombosis formation; tissue remodelling involving reduction in matrix metalloproteinases to prevent both cardiac hypertrophy and also proliferation of smooth muscle tissue to decrease arterial stiffness; down-regulation of the renin-angiotensin system to prevent hypertension; and decreased insulin resistance.

A tipping point was reached in 2008 with the publication of data from three cohort studies of healthy populations showing that low baseline levels of 25(OH)D predict subsequent increased risk of CVD and all-cause mortality.⁷⁻⁹ Similar results were also found in a cohort study of coronary patients from Ludwigshafen.¹⁰ Further convincing evidence has come from a meta-analysis of clinical trials showing that vitamin D supplementation (weighted average dose of 528 IU per day) reduces all-cause mortality by 7%.¹¹ Large scale clinical trials, with higher doses of vitamin D (>2000 IU per day), are urgently needed to confirm the full potential benefit of vitamin D supplementation against CVD. If such trials were to show that vitamin D protected against CVD, the gains in public health would be great, given the low cost of vitamin D and potential contribution from increased safe sun exposure.

References:

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Vitamin D and Cancer

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Ecological studies showing that cancer risk goes up with increasing latitude of residence gave the major stimulus for the hypothesis that vitamin D could be a causal factor behind this observation. Since then, several observational studies and few intervention studies were conducted to further explore the cancer-preventive potential of vitamin D. This review will give an overview of the current epidemiological evidence.

The anti-carcinogenic potential of vitamin D in various cell types, including normal and malignant cells, is well established and is mainly mediated through regulation of cell cycle, proliferation, and apoptosis. In addition, the active form of vitamin D, $1\alpha,25(\text{OH})_2$ vitamin D, can be produced locally in several tissues, including breast and colon.

Most epidemiological studies on vitamin D and breast cancer risk have assessed the effects of dietary intake only, and have yielded inconsistent results. Only a handful of studies investigated the association of the vitamin D status as characterized (mainly) by plasma 25(OH)-vitamin D concentrations with breast cancer risk. While some large population-based studies provided evidence for a distinct cancer-preventive effect associated with a better vitamin D status, the few prospective studies were contradictory in their findings.

Concerning colorectal cancer (and adenoma), the evidence from epidemiologic studies (case-control and cohort studies) in favour of a cancer-protective effect of vitamin D is sound and convincing, thus arguing for the description of the dose-response curve and the identification of optimal plasma ranges of 25(OH)-vitamin D. Also for colorectal cancer, studies dealing with dietary intake data often were unable to show clear effects. For prostate cancer, prospective studies do not show a lower cancer risk for subjects with high levels of circulating 25(OH)-vitamin D. For cancer sites other than breast, colorectal, and prostate, the evidence from observational studies is still limited.

Concerning the evidence from intervention studies, the Women's Health Initiative (WHI) randomized controlled trial (10 μg vitD₃ over 7 years) found no indication for a lower breast or colorectal cancer risk, while the Nebraska Trial (27.5 μg vitD₃ over 4 years) reported a significantly lower cancer incidence in the vitD+Ca intervention arm; however, after using the correct statistical model this association disappeared. In addition, a meta-analysis of RCT with short-term vitamin D intervention showed that the mortality in the intervention groups was significantly decreased. A reduced risk of colorectal mortality was also reported from an observational study.

Several studies in cancer survivors gave indication for a better prognosis in subjects with higher plasma 25(OH)-vitamin D concentration at diagnosis. Since this phenomenon is also observed with other chronic diseases, a causal role for vitamin D remains to be demonstrated.

In summary, a causal relationship between vitamin D status and cancer risk is still not proven, although the evidence from observational studies gives strong support for an inverse association between vitamin D status and colon cancer (and adenoma) risk. The unclear results arising from studies using data on dietary vitamin D intake can be explained by the small proportion that dietary vitamin D provides to the overall vitamin D status; up to 90 % of vitamin D in the body is of endogenous origin, for which UV exposure to the skin is the rate limiting factor. Since UV exposure is an accepted and important risk factor for skin cancer, not only the optimal plasma levels of a vitamin D biomarker but also the recommended way of how to reach such a goal is under discussion.

Intervention effects + optimal dietary intake: Vitamin D

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Based on intervention trials, strong evidence indicates that many or most adults in the United States and Europe would benefit from vitamin D supplements with respect to fracture and fall prevention. This review will discuss the amount of vitamin D supplementation needed and desirable 25-hydroxyvitamin D level to be achieved for optimal musculoskeletal health.

Vitamin D modulates fracture risk in two ways: by decreasing falls and increasing bone density. Two most recent meta-analyses of double-blind randomized controlled trials came to the conclusion that fall and fracture reduction with vitamin D is dose- dependent and benefits are increased with higher achieved 25-hydroxyvitamin D levels.

Based on these evidence-based data derived from the general older population, vitamin D supplementation should be at least 700 to 1000 IU per day and taken with good adherence to cover the needs for both fall and fracture prevention. Ideally, the target range for 25-hydroxyvitamin D should be at least 75 nmol/l, which may need more than 700 to 1000 IU vitamin D in individuals with severe vitamin D deficiency or those overweight.

Smaller intervention trials will be discussed for vitamin D supplementation and other endpoints beyond muscle and bone.

Folic acid and cardiovascular disease

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Intake and status of folic acid may play an important role in cardiovascular disease. This role is primarily discussed in respect to the ability of folic acid to provide methyl-groups converting homocysteine to methionin. The elimination of homocysteine in tissues and blood stream is important since this amino acid has consistently been related to risk of myocardial infarction and stroke. It has been shown in controlled studies that up to a dietary provision 400 microgram folic acid per day there is an inverse relation with the homocysteine level in blood. This fact motivated nutritional societies to set the recommend intake of folic acid at this level.

In the transfer of methyl groups more essential nutrients than folic acid are involved. In the conversion of homocysteine to methionin, cobalamin, called Vitamin B12, act as a cofactor. Pyridoxal-5-phosphate, called Vitamin 6, is a coenzyme converting homocysteine to cysteine. Thus, in respect to lowering homocysteine levels in blood, the joint effects of folic acid, vitamin B12 and Vitamin B6 should be considered.

Observational studies provide information in as much blood levels of homocysteine, folic acid, and the vitamins B12 and B 6 relate to risk of myocardial infarction and stroke taking other risk factors into account. Such studies may not directly provide evidence of causal relationships but form the basis for intervention studies. Intervention studies are often of short term nature and address rarely hard endpoints. If both types of studies show consistency in results the evidence that this compound play a causal role for the development of hard endpoints is high.

There are several prospective studies that investigated the role of folic acid, and the vitamins B12 and B6 for risk of cardiovascular disease in one study population. Only a few studies based their results on blood values. Recently, a group from Umea, Sweden, reported from their cohort studies that folic acid levels are inversely related to risk of myocardial infarction but not vitamin B12 levels. In a previous study they found an inverse relation between folic acid status and hemorrhagic stroke but not for vitamin B12 and ischemic stroke. In an analysis from the EPIC-Potsdam-Study and folic acid, vitamin B12 and B6 status, the risk of ischemic stroke was increased for a combination of low values of folic acid and B12.

Folic acids spread over a wide range of foods such as dark green, leafy vegetables, whole wheat bread, lightly cooked beans and peas, nuts and seeds, sprouts, oranges and grapefruits, liver and other organ meats, poultry, and fortified breakfast cereals and enriched grain products. B12 can be found in animal products, particularly seafood and fish. Recommendations regarding food sources improving the status of folic acid and vitamin B12 should include only foods that show a similar risk relation than the nutrient of interest. This is not always given. In the EPIC-Potsdam Study we applied the approach of food pattern analysis predictive for blood values of these B-vitamins. The test data set had been the CORA study, a case-control study conducted in Hamburg. In both studies, a food pattern consisting of mushrooms, olive oil, fresh fruit, wine, cruciferous vegetable, nuts, whole-grain bread and less fried potatoes was associated with reduced risk of heart diseases.

In conclusion, it seems to be a long way to convert an apparent well founded hypothesis into a sound public health strategy.

Folic acid and colon cancer

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Folate is a water-soluble B vitamin that is present naturally in foods whereas folic acid is the synthetic form of this vitamin that is used in supplements and in fortified foods. The sole biochemical function known for folate is mediating the transfer of one-carbon units involved in nucleotide synthesis and biological methylation reactions. In this role, folate may play an important role in cancer development and progression. Indeed, epidemiologic studies suggest that folate intake (dietary and supplemental) and blood folate levels are inversely associated with the risk of several malignancies including cancer of the colorectum, oropharynx, esophagus, stomach, pancreas, lungs, cervix, ovary, and breast and neuroblastoma and leukemia. The best epidemiologic evidence for the inverse association between folate status and cancer risk exists for colorectal cancer and its precursor, adenoma. Collectively, epidemiologic studies suggest a 20-40% reduction in the risk of colorectal cancer and adenomas in individuals with the highest folate intake compared with those with lowest intake. The role of folate in colorectal carcinogenesis has been further strengthened by the observations that genetic polymorphisms in the folate metabolic pathway modify colorectal cancer risk.

However, animal studies suggest that folate possesses dual modulatory effects on colorectal carcinogenesis depending on the stage of cell transformation at the time of folate intervention as well as the dose of folate supplementation. Folate deficiency has an inhibitory effect whereas folate supplementation has a promoting effect on the progression of established colorectal (pre)neoplasms. In contrast, folate deficiency in normal colorectal mucosa appears to predispose it to neoplastic transformation, and modest levels of folic acid supplementation suppress, whereas supraphysiologic supplemental doses enhance, the development of cancer in normal colorectal mucosa. Although small human intervention trials have suggested potential beneficial effects of folic acid supplementation on biomarkers of colorectal cancer, more recent large intervention trials do not support these earlier observations. In the Aspirin-Folate Polyp Prevention Study, folic acid supplementation (1 mg/d for up to 6 years) increased the risk of developing advanced lesions with a high malignant potential (OR=1.67; 95% CI, 1.00-2.80) and of developing multiple (>2) adenomas (OR=2.32; 95% CI, 1.23-4.35) compared with placebo in 1021 subjects with previously resected adenomas (JAMA 2007; 297: 2351). One explanation for this observation is that folic acid supplementation might have promoted the progression of already existing, undiagnosed microscopic preneoplastic lesions in these predisposed patients. Another secondary finding from this trial was that the risk of cancers other than colorectal cancer was significantly increased in the folic acid supplemented group (P=0.02) largely due to an excess of prostate cancer in the folic acid group (P=0.01) (JAMA 2007; 297: 2351 and J Natl Cancer Inst 2009; 101: 432).

Several potential mechanisms relating to the role of folate in one-carbon transfer reactions and consequent DNA synthesis and epigenetic regulations exist to support the differential effects of folate on the development and progression of colorectal cancer in the normal colorectum and in established colorectal (pre)neoplastic foci. In normal colorectum, folate deficiency may enhance the development of colorectal cancer via DNA stand breaks, impaired DNA repair, increased mutagenesis, and genomic DNA hypomethylation, while folic acid supplementation may prevent the development of colorectal cancer by ensuring DNA stability and integrity, optimal DNA repair, decreased mutagenesis, and prevention of aberrant DNA methylation. In established colorectal cancer and adenomas, folate deficiency causes ineffective DNA synthesis leading to inhibition of tumor growth and progression (similar to chemotherapies using antifolates) and may reverse promoter CpG island methylation of tumor suppressor and other anticancer genes involved in colorectal carcinogenesis, thereby reactivating these genes and leading to inhibition of tumor progression. In established colorectal cancer or adenomas, folic acid supplementation may promote tumor progression by providing

Intervention effects of folic acid

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High levels of homocysteine, a non-protein-forming, sulfur-containing amino acid, are associated with elevated cardiovascular risk in observational studies. Folic acid supplementation has been shown to reduce circulating levels of homocysteine. On the basis of unequivocally supportive data from observational, experimental and mechanistic studies, a series of large randomized controlled trials of homocysteine-lowering through folic acid supplementation were launched in the late 1990's. Unfortunately, the results of these trials have been overwhelmingly negative, showing little effect on the endpoints of interest. The results of three additional large, randomized controlled trials examining the effects of folic acid interventions on cardiovascular diseases and mortality have been reported in the past year: the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), the Western Norway B-vitamin Intervention Trial (WENBIT), and the Women's Antioxidant and Folic Acid Cardiovascular disease Study (WAFACS). The results of the latter 3 trials in combination with those of other major randomized trials of folic acid supplementation (CHAOS-2, VISP, NORVIT, HOPE-2) effectively rule out the possibility of an important effect of folic acid interventions on risk of coronary heart disease, stroke, and all-cause mortality. Although the effects of folic acid supplementation on cardiovascular disease seem to be primarily null, the results of several further trials, including the Supplementation with Folate, vitamin B6 and B12 and/or Omega-3 fatty acids (SU.FOL.OM3) trial, the Folic Acid for Vascular Outcome Reduction in Transplantation Trial, the Vitamins to Prevent Strokes Trial, and the Homocysteine and Atherosclerosis Reduction Trial, have yet to be reported. Truly definitive evidence will come from an individual level meta-analysis planned by the B-vitamin Trialists' Collaboration.

ESCO Working Group on the analysis of risks and benefits of fortification of food with folic acid – what's going on in Europe

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Folic acid intake is effective in reducing neural tube defects. But folic acid fortification remains controversial because of concerns about potential adverse effects. Thus, mandatory fortification does not exist in Europe. However, many countries allow voluntary food fortification with folic acid.

In 2007, the European Food Safety Authority (EFSA) established an EFSA Scientific Cooperation Working Group (ESCO WG) on the “Analysis of risks and benefits of fortification of food with folic acid”, with the aim of sharing experiences and concerns regarding folic acid food fortification amongst Member States.

The ESCO WG on folic acid was asked to consider the following issues as part of their terms of reference:

To review current practice in Member States regarding the level of voluntary fortification of foods and categories of foods to which the addition of folic acid is allowed.

To consider new evidence regarding the risk of high intakes of folic acid and the need for a review of current guidance on safe upper levels of folic acid for all population groups.

EFSA and the Swedish National Food Administration organised a scientific meeting on “Folic Acid: An Update on Scientific Developments”, in Uppsala, Sweden, on 21-22 January 2009. The aim of the meeting was partly to address the second bullet point above by bringing together international scientific expertise to consider the latest scientific developments regarding folic acid and cancer risk.

Over 60 scientific experts from the European Union (EU), Switzerland, the United States and Canada attended the meeting to assess the latest scientific evidence on the possible relationship between dietary intakes (including fortified foods and food supplements) of folate and folic acid, and cancer risks such as colon, breast and prostate cancer.

In an open debate, the latest scientific evidence concerning folate metabolism, animal and mechanistic studies, and human studies were reviewed and discussed. In break-out group discussions, experts considered: whether it was possible to identify an association of folic acid intake with risk of cancer; the population groups concerned; dose-response relationships; the different dietary sources of folic acid; and whether the available data were sufficient to allow a quantitative risk assessment. Areas for further scientific research were also identified.

The major conclusions of the meeting and the discussion of the ESCO WG will be presented.