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'Mealthy' food: meat as a healthy and valuable source of micronutrients

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Over the last two or three decades meat and especially liver have been looked upon as unhealthy food with high fat content and carcinogenic potential. In addition, its content of highly valuable micronutrients has mostly been ignored. As a result, the mean uptake and serum levels of several micronutrients in the population are below the recommended levels. In the meantime, the contamination of liver with heavy metals and other contaminants has fallen far below the allowed thresholds and sometimes even below the detection limit while its content of micronutrients like iron, folate, selenium or zinc are still high. As a further advantage, the bioavailability of many micronutrients often is better from meat and liver then from plant sources. Considering these advantages and the low content of contaminants in meat and liver leads us to propose that meat – including liver – should be a regular part of a mixed and balanced healthy diet along with vegetables and fruits as the major components to ensure an optimal supply of micronutrients.

Keywords: health, meat, micronutrients.

Introduction

Meat, especially red meat is frequently regarded as an unhealthy food, mainly due to its 'high' fat content and its 'reputation' to be a cancer promoter. As a consequence, low meat intake is often recommended to avoid or minimise the risk of cancer, obesity and metabolic syndrome. However, it is not taken into account that meat is an important source for some micronutrients such as iron, selenium, vitamins A, B12 and folic acid. Some of these are not present in plants at all or have such a low bioavailability that eating only plant-derived food might lead to deficiencies. In addition, the content of fat in (red) meat has decreased over the past years, proteins are high and carbohydrates are low which contributes to a low glycaemic index that is assumed to be 'beneficial' with respect to obesity, development of diabetes and cancer.

Taken together, meat is an important nutrient as an essential part of a mixed diet that ensures adequate delivery of essential micronutrients and amino acids. We will show in more detail in this article that the hypothesis of an almost meat-free diet as a cancer-preventive strategy seems more and more unlikely and that the consumption of meat might have more benefits than risks.

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Meat as an important source of micronutrients

Meat including liver is an important source of several micronutrients due to the fact that some of them are exclusively present in meat or their bioavailability is much higher than from plant sources.

Vitamin A and vitamin B12 occur only in meat and can hardly be compensated for by plant-derived provitamins: provitamin B12 does not exist and provitamin A, β-carotene, would have to be taken up in large amounts due to its poor conversion rate of 1:12.

Iron has a higher bioavailability when derived from meat as heme iron than plant-derived iron. Similarly folic acid has nearly 10-fold higher bioavailability from meat (especially liver) and eggs than from vegetables. Consequently a low or no intake of meat (including liver) is associated with a risk for deficiencies in selected micronutrients.

From these facts the question arises, as to whether the 'normal' eating population is at a risk of deficiencies or whether there are special groups at risk of a low intake of meat-derived micronutrients.

One risk group are elderly people who are generally considered at risk of developing vitamin and trace element deficiencies, especially for the vitamins A, D, E, and for folate as well as iron and calcium (Anderson, 2001; Bates *et al.*, 2002; Martins *et al.*, 2002; Viteri and Gonzalez,

2002). The causes of this health hazard comprise quantitative and qualitative decreased food intake, reduced energy expenditure due to sedentary life style and loss of metabolic active body cell mass, and the development of chronic age-associated disorders. As the digestive and absorptive capacity of the digestive tract is well retained through ageing a decreased absorption of macronutrients seems to be the result of a disease rather than ageing itself (Black, 2001). An exception to this rule is the impaired bioavailability of dietary iron due to gastric mucosal atrophy, which is age-related and in many cases could be regarded as a disorder rather than a disease. Nevertheless, the frequently occurring atrophic gastritis in elderly, which also affects vitamin B12 absorption, should be one reason to recommend meat intake in this risk group.

Malnutrition is far more common among institutionalised and chronically hospitalised elderly subjects rather than free-living subjects in the community and the prevalence of malnutrition is associated with the severity of morbidity, functional impairments and mental state. Such deficiencies affect a broad spectrum of micronutrients, such as the B vitamins, especially B1, B6, folate and B12, vitamin C, vitamin D and E, essential fatty acids and selenium. Thiamine and folate status need special attention in this respect, as a deficiency of these nutrients is associated with depression and impaired cognition and dementia. Intervention trials with micronutrient supplementation consisting of zinc and selenium, vitamin C, β-carotene and α-tocopherol have been associated with a reduction of infectious events, probably due to the micronutrients administration rather than the supplementation of vitamins (for detailed literature cf. Biesalski (2005)).

Pregnant women are another group at risk of micronutrient deficiencies and their adequate nutrition plays an important role in the well being of mother and child and also influences the health of the offspring, not only during the intrauterine life but also during childhood and adolescence (intra-uterine or prenatal programming). While the enhanced requirements during pregnancy normally are met by dietary intake and physiological adaptive processes, the micronutrient status of vitamin D, folic acid, iron, and zinc may become compromised without supplementation (Draper *et al.*, 1993; Fogelholm, 1999; Saletti *et al.*, 2000) especially when meat is avoided, which can be frequently seen in women of child-bearing age. Very often a healthy diet is interpreted as a meat-free diet. Folic acid supplementation is generally recommended to decrease the risk of serious birth defects (e.g. neural tube defects). Especially in multiparious women the essential fatty acid status may become impaired and this can negatively affect the neurological and cognitive development of the offspring (Lowik *et al.*, 1992; Reynolds, 2002).

Selected micronutrients from meat and liver

Meat and liver are excellent sources for a number of micronutrients: low-fat pork contains 1.8 mg iron, 2.6 mg zinc, pig liver contains 360 mg magnesium, 20 mg iron and 60 μg selenium per 100 g. Thus, meat and liver (100 g/day) can cover up to 50% of the recommended daily allowance (RDA) for iron, zinc, selenium, vitamins B12, B1, B2, B6, and 100% of vitamin A. Another reason to include liver in the diet is that recent results show porcine as well as bovine liver to be almost free of harmful substances like heavy metals (a former reason to avoid the uptake of liver) which are far below the allowed threshold or even below the technical detection limit (Deutsche Gesellschaft für Ernährung, 2004).

Vitamin A during foetal lung development

Vitamin A is essential for growth and development of cells and tissues. In its active form, retinoic acid, it controls the regular differentiation as a ligand for retinoic acid receptors (RAR, RXR) and is involved in the integration (gap junction formation) of cell formations (Morree, 1992; Kurokowa *et al.*, 1994). Vitamin A plays a substantial role, especially in the respiratory epithelium and the lung. During moderate vitamin-A deficiency, the incidence for diseases of the respiratory tract is considerably increased and repeated respiratory infections can be influenced therapeutically by a moderate vitamin-A supplementation (Sommer, 1993). Kohlhäufl *et al.* (2002) showed that inhalation of vitamin A for 3 months can lead to a substantial remission of lung meta- or dysplastic epithelium. In addition to the importance of this vitamin for lung function, vitamin A is also responsible for the development of many tissues and cells as well as for the embryonic lung development. Recent studies proved that the control occurs by different expressions of retinoid receptors. In fibroblast-like cells close to the alveolar cells, in type-II-cells as well as in the respiratory epithelium of the foetal lung retinyl-esters are present as local extrahepatic stores. The importance of these retinyl-esters as 'acute reserve' during the development of the lung becomes apparent during the late phase of gestation and the beginning of lung maturation. During this period a rapid emptying of the retinyl-ester stores in the lung of rat embryos was shown by Geevarghese and Chytil (1994). This depletion is the result of an increased demand in the process of the lung development, because the retinoic acid is 'instantly' needed for the process of cellular differentiation (e.g. proximalisation) and metabolic work (surfactant).

The prenatal lung development is also influenced by glucocorticoids. The steroid hormones have a similar effect on lung development as vitamin A, i.e. these two factors complement each other. This is not surprising, because the receptors for steroids and retinoids belong to the same multireceptor-complex. The application of dexamethasone leads to an increase of the maternal and foetal retinol-binding protein. Thus, the vitamin A-supply is improved via the regular hepatic export pathway. Such an increase of the vitamin-A concentration in the systemic circulation obviously diminishes morbidity and mortality of premature infants due to bronchopulmonal dysplasia (Shenai *et al.*, 1990). After administration of

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dexamethasone, as well as after administration of steroids, a significant reduction of retinyl-esters in the maturing lung can be detected, together with a moderate increase of retinol, the hydrolysation product of retinyl-ester. This observation may explain the therapeutical success with steroids but also their failures during the therapy of lung-distress-syndrome of premature infants. As far as an insufficient supply is concerned, inappropriate retinyl-ester stores, caused by a shortage of supply to the foetal lung during the late pregnancy can prevent the regulatory effect of glucocorticoids for the vitamin-A-metabolism of the lung cells.

Very low plasma vitamin-A levels are recurrently found in premature infants, especially in cases with lung-distress-syndrome. This can, amongst other things, be attributed to the relative immaturity of the liver for the synthesis of retinol-binding proteins. The neonate is almost exclusively dependent on the mother in its supply, this includes the lung retinyl-esters which are either absorbed by the cells directly (from chylomicrons) or by esterification of retinol after uptake into the cells. These lung retinyl-ester stores can only be sufficiently filled if the mother guarantees an appropriate vitamin-A supply especially during the late pregnancy. This can be either done by supplementation or by an appropriate intake of meat or especially liver but not by the uptake of provitamin A (β-carotene). In a recent pilot study Schulz *et al.* (2006) found that even in Germany in women with twins or with short birth rates there was insufficient retinol uptake and, as a consequence, low plasma levels although their β-carotene uptake was more than sufficient as were their β-carotene plasma levels.

Vitamin A in the postnatal lung

A disease seen recurrently in connection with vitamin-A supply is the bronchopulmonary dysplasia (BPD). The pathogenesis of BPD certainly depends on a multitude of factors, however some of the observed morphological changes are very similar to those seen in vitamin-A deficiency of humans and animals. In particular, there is focal loss of ciliated cells with keratinising metaplasia and necrosis of the bronchial mucosa as well as an increase of mucous secreting cells (Stofft *et al*., 1992).

Especially because focal keratinising metaplasia may occur as a consequence of vitamin-A deficiency, is strengthening the assumption of an impairment of the differentiation on the level of the gene-expression. Since vitamin A regulates the expression of different cytokeratins and therefore influences the terminal differentiation, it seems obvious to suppose common mechanisms. Consequently, the premature, but especially the neonate, are dependent on a sufficient supply of vitamin A. The earlier a child is born before due date, the lower are its serum-retinol-levels (Mupanemunda *et al*., 1994). Since a further decrease of the serum-retinol-level and RBP-level occur postnatally, the plasma value at the time of birth is considered to be a critical parameter regarding the lung development.

Reduced plasma levels during the first months of life have a considerable influence on the overall development as well as on the susceptibility of infants to infections. With reduced retinol-plasma-levels, repeated infections are more often described and they are counted among the main complications of a poor vitamin-A supply in developing countries. In addition, the serum vitamin-A level during infectious diseases, particularly of the respiratory tract, continues to drop which might be explained by an increased metabolic demand and/or with an increased renal elimination of retinol and of RBP during acute infections (for literature see Biesalski (2005)).

The discussion of whether liver should be avoided as a component of a healthy diet is primarily based on questionable contaminants suspected in the liver (e.g. hormones, xenobiotics, metals etc.) which nowadays are hardly detected (see above). If β-carotene from vegetables were the only source of vitamin A, more than 500 g mixed and β-carotene rich vegetables per day would need to be eaten to reach the recommended 1 mg retinol. Concerning contaminants, it has not been evaluated whether this amount of vegetables contains more contaminants than a portion of liver, especially as their concentration in vegetables and fruits seems to have increased during the late 1990s and early 2000s (Deutsche Gesellschaft für Ernährung, 2004). Thus, a small portion of liver (100 g) twice a month is neither toxic nor teratogenic and contributes to a sufficient supply of the body with vitamin A.

Iron

Iron supports oxidative metabolism. It is essential for gas exchange at the tissue and cellular levels through haemoglobin oxygenation in red cells and myoglobin in skeletal muscle. Moreover, iron-containing enzymes are involved in cellular energy metabolism and in host-defence responses. These various roles are due to the biological catalytic activity of iron. Like many other transition elements, it possesses unfilled atomic orbitals that allow it to co-ordinate electron donors and participate in redox processes.

Iron is one of the most abundant elements in the Earth's crust, paradoxically, iron deficiency is the most common and widespread nutritional disorder in the world. Due to biological losses, such as cyclical monthly menstruation in fertile-aged women, excessive infestation with blood-feeding parasites, or poor bioavailability of iron from plant-based diets, it is estimated that as many as 4 to 5 billion people, 66 to 80% of the world's population, may be iron deficient (World Health Organisation (WHO), 1992). At any given time, 2 billion people – over 30% of the world's population – are anaemic, mainly due to iron deficiency, and in developing countries this is frequently exacerbated by malaria and worm infections (WHO, 1992).

Iron deficiency is a particular risk for women and girls of child-bearing age, because of menstrual losses. In a recent Irish food consumption survey, almost half of women aged 18 to 50 years had inadequate iron intakes when compared with national average requirements. In the British

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National Diet and Nutrition Survey, iron intakes were found to be low in girls (aged 7 to 18 years), with iron intakes decreasing with age. Adolescent females (15 to 18 years) were found to have extremely low intakes of iron when compared with UK dietary reference values. Depending on the composition of the individual diet the bioavailability of iron can differ 5- to 10-fold. The different bioavailability depends on the presence or absence of different ligands (phytates from cereal products, tannins from coffee and tea and oxalates from vegetables) which form complexes with iron and zinc and block their absorption. A diet which is primarily composed of vegetables, rice, beans and maize is associated with a poor iron bioavailability which at least explains the high incidence of anaemia in developing countries. Around 100 g pork meat added to the vegetarian diet described above increases the iron absorption 3.6-fold as does an even lower amount of liver.

Folate

In European countries the average folate intake in adults was found to be remarkably similar, around 300 μg/day in adult males and 250 μg/day in adult women (De Bree *et al*., 1997). This is slightly below the recommended intake level of 400 μg/day and even lower than that recommended for pregnant women and women planning a pregnancy. For these groups an intake of 600 μg/day is considered protective against neural tube defects (NTD), which appear around 700 times per year in Germany, and some other possible malformations (e.g. lip cleft). More than 90% of women of childbearing age have dietary folate intakes below this optimal level while an optimal level can reduce the risk to develop NTD by up to 70%. If there is an anamnestic risk for NTD, a daily uptake of 4000 μg is recommended.

The link between poor folic acid status and NTD is well documented but poorly characterised. Poor status is also linked to raised plasma homocysteine, a risk indicator for cardiovascular diseases and poor status may also increase the risk of neurological disorders and cancers. As the 'protective' folate levels are most important during the first 3 weeks after conception, a sufficient 'in time' supplementation cannot always be planned and therefore folate levels should always be in the recommended range. This might either be assured by a supplementation with folate (100% bioavailability) – in the US salt and flour are generally folate-supplemented – or again regarding the bioavailability, by an adequate uptake of liver.

Vitamin B12

Vitamin B12 is found only in animal products. In a recent UK study of 250 vegetarian and 250 vegan men, approximately one quarter of vegetarians and more than half of vegans had sub-optimal intakes of vitamin B12. Plasma vitamin B12 levels were low in the vegetarians and extremely low in the vegan group, with more than a quarter below the threshold level where neurological signs may develop (130 ng/l; Lloyd-Wright *et al*., 2001). The elderly are also at risk of vitamin B12 deficiency, due to physiological changes resulting in reduced absorption. In one study in the UK, vitamin B12 status in some people aged 65 and over was inadequate in both men and women even though vitamin B12 intakes were adequate when compared with UK dietary reference values (Finch *et al*., 1998). To assure the RDA of vitamin B12 (3 μg/day for adults), again meat (bovine 5 μg/100 g) and especially liver (depending on the species 30 to 65 μg/100 g) are the best sources.

Selenium

Selenium is often considered as belonging to the group of antioxidant nutrients, since it is incorporated into the enzyme glutathion peroxidase, which acts as a cellular protector against free radical oxidative damage. A secondary end-point analysis of a randomised placebo-controlled skin cancer prevention trial suggested that supplemental selenium might reduce the incidence of and mortality from cancers at several sites (Clark *et al*., 1996). However, the efficacy of selenium as a cancer-preventive agent should await the results of large on-going controlled studies. Selenium is, like many other nutrients, necessary for a well functioning immune system, and has been pointed out as particularly efficacious against HIV and AIDS. However, a systematic review found no evidence for a clinical relevant function of selenium in that respect (Ozsoy and Ernst, 1999).

Although selenium is widely distributed in the environment, the selenium content of foods is greatly affected by soil on which crops grow or animals graze. Recent evidence suggests that selenium intakes in most parts of Europe are falling and are low when compared with recommended intakes (Rayman, 2000). Declining intakes in the last three decades have been attributed mainly to a change in the source of wheat for bread and cereal products, from predominantly North American to European origin (from a high to a low selenium content). These are reflected in decreasing plasma or serum selenium levels. Due to its antioxidant effects, selenium may be protective against chronic degenerative diseases. In the UK, selenium intakes were low in the majority of the elderly (aged 65 and over) in the British National Diet and Nutrition Survey when compared with UK dietary reference values (Thane and Bates, 2001). Selenium intakes decreased with increasing age in this population subgroup.

Zinc

Zinc-deficient individuals demonstrate slower wound healing and are more prone to infections. However, studies of the effect of zinc supplementation aimed at the healing rate of venous leg ulcers have been inconclusive. A Cochrane review concluded that oral zinc did not appear to aid the healing of leg ulcers, and that there was only weak evidence for a benefit in patients with venous leg ulcers and low serum zinc (Wilkinson and Hawke, 2002). Zinc has been found to inhibit rhinovirus replication *in vitro*. Some studies have demonstrated that zinc may beneficially affect cold symptoms; however a meta-analysis of randomised controlled trials concluded that there is no evidence for the

effectiveness of zinc in reducing the duration of common cold symptoms (Jackson *et al.*, 2000). Finally, in settings with high rates of stunting and low plasma zinc concentrations, zinc supplementation may improve children's growth (Brown *et al.*, 1998). Until now, supplementation studies did not reveal consistent results. However, a low intake of zinc is associated with a weakened immune system. T-cell-count, T-cell-proliferation and function and NK-cell activity are all reduced. Especially in elderly a reduced zinc status is evident (Lukito *et al.*, 2004). In the same group, a higher protein intake (together with slight exercise) stops sarkopenia, a progressive loss of lean body mass. The RDA for zinc is about 12 to 15 mg/day, during pregnancy and lactation a higher need of zinc is documented (20 to 25 mg/day) as well as during chronic inflammatory diseases (Rink and Gabriel, 2000). Again, meat and liver are the best sources.

Protecting micronutrients in meat with respect to cancer

The authors are well aware that meat is under suspicion as a carcinogen, particularly if barbecued and eaten in large quantities. Also the total amount of the energy taken up by the food and its composition of proteins, fat and carbohydrates seems to be of great relevance. However, this is not part of the present consideration but can be considered in relation to other published reviews (Biesalski, 2002 and 2005)

Folate

It is frequently argued that the increased risk of different types of cancer resulting from low intake of fruits and vegetables is a result of a folate deficient diet, because fruits and vegetables are important sources for folate. While this is true, the bioavailability of folate from meat and liver is much better than from fruits and vegetables. Several studies have claimed that a low folate intake has been related to an increased occurrence of colon adenomas (Giovannucci *et al.*, 1993a; Benito *et al.*, 1991) and cancer (Freudenheim *et al.*, 1991). Zhang *et al.* (1999) studied the effect of alcohol and folate on breast cancer. The increased cancer risk associated with alcohol consumption (>15 g/day) was reduced in women who consumed at least 300 μg folate per day which still is under the RDA of 400 μg/day. The major source of folate was supplements, a form which has a very good bioavailability compared with vegetable-derived folic acid. In another study, folate supplementation decreases the risk of colon cancer significantly (Giovannucci *et al.*, 1993b).

An additional aspect, also involved in methylation reactions, which might contribute to the individual colon cancer risk, is a genetic polymorphism of a key enzyme of folate metabolism: the methylenetetrahydrofolate-reductase (MTHFR). This enzyme converts 5,10- methylenetetrahydrofolate to 5- methyltetrahydrofolate, the major circulatory form of folate in the body and primary methyl donor for the methylation of homocysteine to methionine. This pathway is a critical to the methylation of DNA. As described above alterations in the methylation process can result in abnormal expression of oncogenes and tumour suppressor genes (Baylin *et al.*, 1991). The polymorphism of the human MTHFR gene (alanine to valine substitution, coding for a thermolabile enzyme with reduced activity) results in elevated plasma homocysteine levels. Homozygous individuals have 30% normal enzyme activity, heterozygous 65%. Up to now there are controversial results in correlating this polymorphism with individual colon cancer risk. However, supplementation of folate or a diet rich in folate with optimum bioavailability (meat and liver better than vegetables and fruit) will lower homocysteine and might therefore influence the individual risk (Bronstrup *et al.*, 1998).

Vitamin A

On the basis of a few reports it is assumed that a 'local' vitamin-A deficiency exists in meta- and dysplastic areas of the bronchial wall. Measurements of vitamin-A concentrations in metaplastic areas of the respiratory epithelium and the cervix epithelium proved that vitamin A was no longer to be found, in contrast to the surrounding healthy tissues. At the moment it is difficult to distinguish between cause and effect. Studies carried out by Edes (1991) and co-workers point to an induction of metaplasia caused by a vitamin-A deficit. These studies showed that a depletion of vitamin-A ester stores in different tissues is caused by toxins that are present in cigarette smoke (predominantly polyhalogenated compounds).

Epidemiological evidence supports the assumption that the development of obstructive respiratory diseases plays an important role as regards cancer mortality of smokers. It was shown that the relative risk for smokers to be affected by lung cancer, when they suffered from obstructive ventilation disorder (Skillud *et al.*, 1987) was significantly higher than that of comparative groups with normal lung-function parameters.

A survey of the dietary habits within the scope of the 'National Health and Nutritional Examination Survey' showed that an inverse correlation (Morabia *et al.*, 1989) existed between chronic obstructive pulmonary diseases (COPD) and vitamin-A supply as the only one of 12 examined dietary components. COPD increases lung cancer risk significantly. If a diminished supply of vitamin A increases the appearance of obstructive respiratory diseases, a marginal or local vitamin-A deficit could be responsible for the observed changes of the respiratory mucosa. Such a deficit results in a loss of cilia, an increase of secreting cells and finally the formation of squamous metaplasia (Chytil, 1985; Stofft *et al.*, 1992). Such changes (decrease of ciliated cells with simultaneous increase of the secretion) are noted among smokers (Gouveia *et al.*, 1982; Mathe *et al.*, 1983) and cause a reduction of the mucociliary clearance. This reduction of the mucociliary clearance, associated with an increased adsorption of the respiratory syncytial virus (RSV)

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(Donelly, 1996), could explain the extraordinarily high morbidity and mortality for respiratory infections of children with vitamin-A deficiency in developing countries (Sommer, 1993).

There is sound evidence from experimental studies that the alteration of the respiratory mucosa, caused by the vitamin-A deficiency, can be re-differentiated into its functional original epithelium, *in vivo* as well as *in vitro*, following vitamin-A supplementation (for literature cf. Biesalski (2005)). Squamous metaplasia of the bronchial mucosa, which occurs in smokers in spite of a sufficient supply with vitamin A as an effect of inhalative noxae could also be reversed through systemic application of high retinoid concentrations *in vitro* (Lasnitzki and Bollag, 1987) and in humans *in vivo* (Gouveia *et al*., 1982; Mathe *et al*., 1983).

Selenium

The best known biochemical role for selenium is as part of the active site of the enzyme glutathione peroxidase (GPx). The metabolic function of this enzyme is vital for cells, as it is part of a mechanism responsible for the metabolism and detoxification of oxygen. It is assumed that GPx can protect DNA from oxidative damage and consequently from mutation leading to neoplastic transformation of cells (Combs and Clark, 1985). At relatively high levels, selenium protects against the action of certain carcinogens in various animal models (Halliwell and Gutteridge, 1989). As well as in *in vitro* and *in vivo* studies, organic and inorganic selenium have been demonstrated to inhibit proliferation of normal and malignant cells and inhibit tumor growth (Redman *et al*., 1997). Apoptosis may result from competition of selenium for s-adenosyl-methionine with ornithine decarboxylase (ODC). ODC acitivity is indeed critically involved in cancerogenesis. From geographical studies it is documented that in areas with sufficient selenium concentrations in the diet (depending on selenium concentrations of the soil), there is an inverse relationship between selenium status and cancer (Clark *et al*., 1991). Epidemiological studies showed inverse associations of selenium intake or plasma levels and cancers of different sites (prostate, colon, skin etc.). In a recent, double blind, placebo controlled cancer prevention trial 200 μg selenium (approx. three times the RDA) were given daily to patients with histories of basal and squamous skin carcinoma (Clark *et al*., 1996). Selenium supplementation did not influence the primary endpoint prevention of recurrent skin cancers, but surprisingly was inversely associated with the incidence of and mortality from total prostate, lung and colorectal cancers. Recently Yoshizawa *et al.* (1998) reported a strong inverse association of toenail concentration of selenium and prostate cancer risk (65% reduced risk in the highest quintile). Toenail concentration reflects long-term intake of selenium with the diet and is consequently influenced by bioavailability. From intervention trials and from epidemiological studies there is now evidence indicating "that substantially increases in the consumption of selenium by men taking 80 to 90 μg/day or more may have striking impact on prostate cancer rates" (Giovannucci, 1998). Recent surveys indicate that average intake of selenium may be as low as 30 to 40 μg/day (Rayman, 2000). Intake data however do not really reflect the bioavailability. Consequently the diet has a strong influence on total selenium supply of tissues. Especially in areas with low soil selenium dietary sources containing substantial amounts of selenium with good bioavailability should be recommended. In the US selenium is mainly supplied by cereals, breads, meats and meat products. Beef alone is estimated to contribute approximately 17% of the total selenium in the American diet. Two recent studies in humans showed that meat was as good a source of selenium as wheat (Van der Torre *et al*., 1991) and that L-selenomethionine (SeMet) was absorbed more rapidly than selenite in selenium deficient men (Xia *et al*., 1992). In a recent study the bioavailability of selenium was estimated from various portions of fully cooked commercial cuts of beef, including liver, strip loin, round, shoulder and brisket in rats (Shi and Spallholz, 1994). The bioavailability from the beef diets was compared with that of selenium as selenite or SeMet. Liver GPx recovery (after depletion), muscle tissue deposition and plasma levels were taken as markers of bioavailability. Liver GPx-recovery was highest from SeMet $>$ beef muscle $>$ selenite $=$ beef liver. Muscle deposition was highest from SeMet $>$ beef muscle $>$ selenite $=$ beef liver. From these results the authors concluded that the bioavailability of selenium from beef is higher than, or at least equal to, that of selenite and slightly lower than that of SeMet. Again one can assume, as for the other micronutrients, that meat is an important source for bioavailable selenium.

Zinc

The situation about zinc levels in cancer patients is still unclear, as some studies describe lower zinc levels in their patients (Mellow *et al*., 1983; Rogers *et al*., 1993), while others did not find this association (Kok *et al*., 1988; Kabuto *et al*., 1994). There is good evidence that zinc may contribute to prostate cancer incidence. Total zinc levels in the prostate are 10 times higher than in other soft tissues (Mawson and Fisher, 1952). Uptake of zinc via a membrane transporter into prostatic epithelial cells is under the control of hormones (testosterone, prolactin) (Costello *et al*., 1999). Physiological concentrations of zinc inhibit growth of androgen sensitive and androgen-independent prostate cancer cell lines via cell cycle arrest, apoptosis and necrosis (Iguchi *et al*., 1998; Liang *et al*., 1999). Epidemiological findings are not consistent and a few studies estimating the effect of supplementation on prostate cancer risk are still controversial (for review, see Platz and Helzlsouer (2001)). One important reason for this inconsistency might be the high variability of zinc content of different sources, especially meat and sea-food. Furthermore zinc has a much better bioavailability from meat than from vegetables and other factors, present in the diet may have additional effects: citric acid, histidine and cysteine increase, phytate and oxalate decrease the absorption of zinc (Groff and Groopper, 2000). Better biomarkers are required to help estimate the individual zinc status and consequently the individual risk. At present there is no clear-cut evidence for

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a preventive effect of zinc on prostate cancer from epidemiological studies. Some small case control studies indicate low plasma zinc or low prostatic zinc levels in patients with prostate cancer compared with healthy controls (for review see Platz and Helzlsouer (2001)). One factor contributing to low intake might be a decline in red meat consumption which has been reported in New Zealand, UK, USA and Canada (cf. Biesalski, 2005), concomitant with an increase in intakes of unrefined cereals, nuts and legumes. Red meat is a rich source of readily available zinc, whereas cereals contain different levels of phytic acid, thus decreasing the uptake of zinc. Indeed, the recommendation to decrease or even avoid meat intake may result in a low zinc status as recently documented in women from New Zealand (Gibson *et al.*, 2001). In a cross sectional study of 330 women, the authors assessed the interrelationship of dietary intakes, biochemical zinc status and anthropometric indices. Changes in food selection patterns (reduction of red meat) were suggested to be responsible for the lower biochemical zinc nutrition. This study is an example that a mixed and balanced diet, including meat and meat products, is the best way to ensure sufficient intake of all essential and potentially cancer preventive components.

Meat consumption, especially red meat, is not carcinogenic *per se*, even if it contains components that are assumed to contribute to cancer formation. On the other hand, a reduced cancer risk in persons with a high intake of fruit and vegetables is described attributing the preventive effect to protecting factors such as carotenoids, flavonoids, further phytochemicals and also folic acid, selenium, zinc and other components. Why should these compounds be less effective if they reach the body via meat? The balance of promoting and protecting factors within the diet is important for the protection against cancer. Furthermore the insulin-resistance hypothesis shows that a nutritional behaviour leading to a metabolic syndrome (high energy, high glycaemic carbohydrates) might favour colon cancer or even cancers from other sites. Willett (1999) gave a very good and comprehensive advice: "Current nutritional recommendations for the prevention of cancer include increased consumption of fruits and vegetables; reduced consumption of red meat and animal fat; and avoidance of excessive alcohol. For many individuals a daily multivitamin that contains folic acid may also be part of a reasonable cancer prevention strategy." Only a reasonable amount of exercise should be added to this advice.

Conclusions

Any kind of an unbalanced diet, either avoiding meat or fruit or vegetables more or less leads to (micro-) nutrient deficiencies and consecutive disorders or diseases like metabolic syndrome and cancer, especially in groups with higher needs (pregnant or lactating women, excessive exercise, growing children, elderly, etc.). At this time one has to assume, that a mixed and balanced diet with higher amounts of fruits and vegetables and moderate amounts of meat including liver, paired with body exercise is recommended and seems to be the best recipe for nutritional support for the prevention of deficiencies and physiological malfunctions.

References

Anderson AS 2001. Symposium on 'Nutritional adaptation to pregnancy and lactation'. Pregnancy as a time for dietary change? Proceedings of the Nutrition Society 60, 497-504.

Bates CJ, Benton D, Biesalski HK, Staehelin HB, Van Staveren W, Stehle P, Suter PM and Wolfram G 2002. Nutrition and aging: a consensus statement. Journal of Nutrition, Health and Aging 6, 103-116.

Baylin SB, Makos M and We J 1991. Abnormal patterns of DNA methylation in human neoplasia: potential consequences for tumor progression. Cancer Cells 3, 382-390.

Benito E, Stiggelbout A and Bosch FX 1991. Nutritional factors in colorectal cancer risk: a case control study in Majorca. International Journal of Cancer 49, 161-167.

Biesalski HK 2002. Meat and cancer: meat as a component of a healthy diet. European Journal of Clinical Nutrition 56, (suppl 1) S2-S11.

Biesalski HK 2005. Meat as a component of a healthy diet – are there any risks or benefits if meat is avoided in the diet? Meat Science 70, 509-524.

Black RE 2001. Micronutrients in pregnancy. British Journal of Nutrition 85, (suppl 2) S193-S197.

Bronstrup A, Hages M, Prinz-Langenohl R and Pietrzik K 1998. Effects of folic acid and combinations of folic acid and vitamin B-12 on plasma homocysteine concentrations in healthy, young women. American Journal of Clinical Nutrition 68, 1104-1110.

Brown KH, Peerson JM and Allen LH 1998. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibliotheca Nutritio et Dieta 54, 76-83.

Chytil F 1985. Function of vitamin A in the respiratory tract. Acta Vitaminologica et Enzymologica 7, 27-31.

Clark LC, Cantor KP and Allaway WH 1991. Selenium in forage crops and cancer mortality in US countries. Archives of Environmental Health 46, 37-42.

Clark LC, Combs GF, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JL, Park HK, Sanders BB, Smith CL and Taylor JR 1996. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. Journal of the American Medical Association 276, 1957-1963, For the Nutritional Prevention of Cancer Study Group.

Combs GF and Clark LC 1985. Can dietary selenium modify cancer risk? Nutrition Reviews 43, 325-331.

Costello LC, Liu Y and Zou J 1999. Evidence for a zinc uptake transporter in human prostate cancer cells which is regulated by prolactin and testosterone. Journal of Biological Chemistry 274, 17499-17504.

De Bree A, Van Dusseldorp M, Brouwer IA, Van het Hof KH and Stegers-Theunissen RPM 1997. Folate intake in Europe: recommended, actual and desired intake. European Journal of Clinical Nutrition 51, 643-660.

Deutsche Gesellschaft für Ernährung. 2004. Ernährungsbericht 2004. DGE, Bonn, Germany.

Donelly BI 1996. Vitamin A and respiratory syncytial virus infection. Archives of Pediatrics and Adolescent Medicine 150, 882-892.

Draper A, Lewis J, Malhotra N and Wheeler E 1993. The energy and nutrient intakes of different types of vegetarian: a case for supplements? British Journal of Nutrition 69, 3-19.

Edes TE 1991. Exposure to the carcinogen benzopyrene depletes tissue vitamin A. Nutrition and Cancer 15, 159-166.

Finch S, Doyle W, Lowe C, Bates C J, Prentice A, Smithers G and Clarke P 1998. National diet and nutrition survey: people aged 65 years or over: volume 1, *Report of the diet and nutrition survey.* The Stationery Office, London.

Fogelholm M 1999. Micronutrients: interaction between physical activity, intakes and requirements. Public Health Nutrition 2, 349-356.

Freudenheim JL, Graham S and Marshall JR 1991. Folate intake and carcinogenesis of the colon and rectum. International Journal of Epidemiology 20, 368-374.

https://doi.org/10.1017/S1751731107657796 Published online by Cambridge University Press

Geevarghese SK and Chytil F 1994. Depletion of retinyl esters in the lungs coincides with lung prenatal morphological maturation. Biochemical and Biophysical Research Communications 200, 529-535.

Gibson RS, Heath AL and Limbaga ML 2001. Are changes in food consumption patterns associated with lower biochemical zinc status among women from Dunedin, New Zealand? British Journal of Nutrition 86, 71-80.

Giovannucci E 1998. Selenium and risk of prostate cancer. Lancet 352, 755-756.

Giovannucci E, Stampfer MJ and Colditz GA 1993a. Folate, methionine, and alcohol intake and risk of colorectal adenoma. Journal of the National Cancer Institute 85, 875-884.

Giovannucci E, Stampfer MJ and Colditz GA 1993b. Multivitamin use, folate, and colon cancer in women in the nurse's health study. Annals of Internal Medicine 129, 517-524.

Gouveia J, Mathe G and Hercend T 1982. Degree of bronchial metaplasia in heavy smokers and its regression after treatment with retinoid. Lancet 1, (8274) 710-712.

Groff JL and Groopper SS 2000. Advanced nutrition and human metabolism. Wadsworth, Belmont, CA.

Halliwell B and Gutteridge JM 1989. Free radicals in biology and medicine. Oxford University Press, New York.

Iguchi K, Hamatake M and Ishida R 1998. Induction fo necrosis by zinc in prostate carcinoma cells and identification of proteins increased in association with this induction. European Journal of Biochemistry 253, 766-770.

Jackson JL, Lesho E and Peterson C 2000. Zinc and the common cold: a meta-analysis revisited. Journal of Nutrition 130, 1512S-1515S.

Kabuto M, Imai H and Yonezawa C 1994. Prediagnostic serum selenium and zinc levels and subsequent risk of lung and stomach cancer in Japan. Cancer Epidemiology, Biomarkers and Prevention 3, 465-469.

Kohlhäufl M, Häussinger K, Stanzel F, Markus A, Tritschler J, Mühlhöfer A, Morresi-Hauf A, Golly I, Scheuch G, Jany BH and Biesalski HK 2002. Inhalation of aerosolized vitamin A: reversibility of metaplasia and dysplasia of human respiratory epithelia - a prospective pilot study. European Journal of Medical Research 7, 72-78.

Kok FJ, Van Duijn CM and Hofman A 1988. Serum cooper and zinc and the risk of death from cancer and cardiovascular disease. American Journal of Epidemiology 128, 352-359.

Kurokowa R, DiRenzo J and Boehm M 1994. Regulation of retinoid signalling by receptor polarity and allosteric control of ligand binding. Nature 371, 528-531.

Lasnitzki I and Bollag W 1987. Prevention and reversal by non-polar carotenoid (Ro 150778) of 3,4-benzpyrene and cigarette smoke condensate-induced hyperplasia of rodent respiratory epithelia grown *in vitro*. European Journal of Cancer and Clinical Oncology 23, 861-865.

Liang JY, Liu YY and Zou J 1999. Inhibitory effect of zinc on human prostatic carcinoma cell growth. Prostate 40, 200-207.

Lioyd-Wright Z, Allen N, Key TJA and Sanders TAB 2001. How prevalen is vitamin B12 deficiency among British vegetarians and vegans. Proceedings of the Nutrition Society 60, 174A.

Lowik MR, Van den Berg H, Schrijver J, Odink J, Wedel M and Van Houten P 1992. Marginal nutritional status among institutionalized elderly women as compared to those living more independently (Dutch Nutrition Surveillance System). Journal of the American College of Nutrition 11, 673-681.

Lukito W, Wattanapenpaiboon N, Savige GS, Hutchinson P and Wahlqvist ML 2004. Nutritional indicators, peripheral blood lymphocyte subsets and survival in an institutionalised elderly population. Asia Pacific Journal of Clinical Nutrition 13, 107-112.

Martins I, Dantas A, Guiomar S and Amorin JA 2002. Vitamin and mineral intakes in the elderly. Journal of Nutrition, Health and Aging 6, 63-65.

Mathe G, Gouveia J, Hercend T, Gros F and Dorval T 1983. Detection of precancerous bronchus metaplasia in heavy smokers and its regression following retinoid treatment. In Modulation and mediation of cancer by vitamins (ed. F Meyskens), pp. 317-321, Karger, Basel.

Mawson CA and Fisher MI 1952. The occurrence of zinc in the human prostate gland. Canadian Journal of Medical Science 30, 336-339.

Mellow MH, Layne EA and Lipman TO 1983. Plasma zinc and vitamin A in human squamous carcinoma of the oesophagus. Cancer 51, 1615-1620.

Morabia A, Sorenson A, Kumanyika H, Abbey H, Cohen BH and Chee E 1989. Vitamin A, cigarette smoking, and airway obstruction. American Review of Respiratory Disease 140, 1312-1316.

Morree DM 1992. Intracellular actions of vitamin A. In International review of cytology (ed. KW Jeon Friedlander), pp. 1-31, Academic Press, San Diego, CA.

Mupanemunda RH, Lee DSC, Fraher LJ, Koura IR and Chance GW 1994. Postnatal changes in serum retinol status in very low birth weight infants. Early Human Development 38, 45-54.

Ozsoy M and Ernst E 1999. How effective are complementary therapies for HIV and AIDS: a systematic review. International Journal of STD and AIDS 10, 629-635.

Platz EA and Helzlsouer KJ 2001. Selenium, zinc and prostate cancer. Epidemiologic Reviews 23, 93-101.

Rayman MP 2000. The importance of selenium to human health. Lancet 356, 233-241.

Redman C, Xu MJ and Peng YM 1997. Involvement of polyamines in selenomethionine induced apoptosis and mitotic alterations in human tumor cells. Carcinogenesis 18, 1195-1202.

Reynolds EH 2002. Folic acid, ageing, depression, and dementia. British Medical Journal 324, 1512-1515.

Rink L and Gabriel P 2000. Zinc and immune system. Proceedings of the Nutrition Society 59, 541-552.

Rogers MAM, Thomas DB and Davis S 1993. A case control study of element levels and cancer of the upper aerodigestive tract. Cancer Epidemiology, Biomarkers and Prevention 2, 305-312.

Saletti A, Lindgren EY, Johansson L and Cederholm T 2000. Nutritional status according to mini nutritional assessment in an institutionalized elderly population in Sweden. Gerontology 46, 139-145.

Schulz C, Engel U, Kreienberg R and Biesalski HK 2006. Vitamin A and beta-carotene supply of women with gemini or short birth intervals (pilot study). European Journal of Nutrition, (Epub ahead print).

Shenai JP, Rush MG, Stahlman MT and Chytil F 1990. Plasma retinol-binding protein response to vitamin A administration in infants susceptible to bronchopulmonary dysplasia. Journal of Pediatrics 116, 607-614.

Shi BB and Spallholz JE 1994. Selenium from beef is highly bioavailable as assessed by liver glutathione peroxidase acitivity and tissue selenium. British Medical Journal 72, 873-881.

Skillud DM, Offord KP and Miller RD 1987. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective matched controlled study. Annals of Internal Medicine 105, 503-507.

Sommer A 1993. Vitamin A supplementation and childhood morbidity. Lancet 342, 1420.

Stofft E, Biesalski HK, Zschaebitz A and Weiser H 1992. Morphological changes in the tracheal epithelium of guinea pigs in conditions of 'marginal' vitamin A deficiency. International Journal of Nutrition Research 62, 134-142.

Thane CT and Bates CJ 2001. Intake and sources of selenium in British elderly people. Proceedings of the Nutrition Society 60, 60A.

Van der Torre HW, Van Dokkum W and Schaafsma G 1991. Effect of various levels of selenium in wheat and meat on blood selenium status indices and on selenium balance in Dutch men. British Journal of Nutrition 65, 69-80.

Viteri FE and Gonzalez H 2002. Adverse outcomes of poor micronutrient status in childhood and adolescence. Nutrition Reviews 60, (suppl) S77-S83.

Wilkinson EAJ and Hawke CI 2002. Oral zinc for arterial and venous leg ulcers (Cochrane Review). In The Cochrane Library, Issue 2. Update Software Oxford.

Willett WC 1999. Goals for nutrition in the year 2000. CA, a cancer journal for clinicians 49, 331-352.

World Health Organisation. 1992. Iron deficiency anemia. assessment, prevention and control. A guide for programme managers. United Nations Children Fund, United Nations University and World Health Organisation, WHO/NHD/01.3.

Xia Y, Zhao X and Zhu L 1992. Metabolism of selenate and selenomethionine by selenium deficient population of men in China. Journal of Nutrition Biochemistry 3, 202-210.

Yoshizawa K, Willet WC and Morris SJ 1998. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. Journal of the National Cancer Institute 90, 1219-1224.