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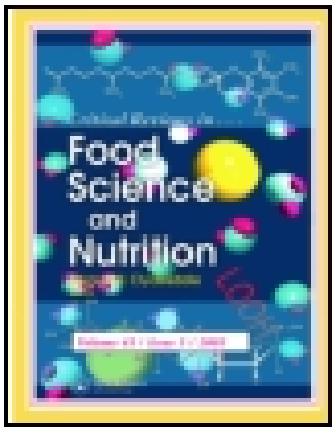

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Food Fortification and Supplement Use - Are there Health Implications?

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Abstract

Dietary supplements are a multi-billion dollar industry in the U.S., and their use is increasing exponentially. Additionally, many foods and beverages are increasingly being fortified with single or multiple vitamins and minerals. Consequently, nutrient intakes are exceeding the safe limits established by the Institute of Medicine. In this paper, we examine the benefits and drawbacks of vitamin and mineral supplements and increasing consumption of fortified foods (in addition to dietary intake) in the U.S. population. The pros and cons are illustrated using population estimates of folic acid, calcium and vitamin D intake, highlighting concerns related to overconsumption of nutrients that should be addressed by regulatory agencies.

Key words: food fortification, dietary supplements, calcium, folic acid

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INTRODUCTION

The U.S. food fortification program began in the early 1900s, with the intention of alleviating nutrient deficiencies. One of the defining principles of the fortification program was that addition of nutrients would not create an imbalance (American Medical Association Council on Foods and Nutrition and National Academy of Sciences, 1968). Fortification, which was initially limited to a few select foods, now includes a range of grain products, snack foods, meal replacements, artificial sweeteners, and even bottled water. In addition to the consumption of fortified foods, intake of multivitamin and mineral supplements and individual nutrient supplements is on the rise. In this paper, we examine the health benefits and consequences of vitamin and mineral excess (from supplements and fortified foods) in the general U.S. population, using the intake of folic acid, calcium and vitamin D to illustrate the pros and cons of this issue, and highlight concerns that regulatory agencies should address issues related to overconsumption of nutrients via food-fortification and supplements.

FOOD FORTIFICATION

A brief chronology of key food fortification milestones is presented in Figure 1. Food fortification is either mandatory or discretionary. Only mandatory food fortification complies with the standards of identity established by the Food and Drug Administration (FDA), which delineates the type and amount of nutrient(s) that should be added to a particular food item. Standards of identity have been established for the addition of thiamin, niacin, riboflavin, folic acid and iron to flour and the fortification of margarine, rice, breads, cereals and other grains and

grain products (The National Academies Press, 2003). The defining principles of the food fortification program include the following (American Medical Association Council on Foods and Nutrition and National Academy of Sciences, 1968):

1. "The intake of nutrient(s) is below the desirable level in the diets of a significant number of people."
2. "The food(s) used to supply the nutrient(s) is likely to be consumed in quantities that will make a significant contribution to the diet of the population in need."
3. "The addition of the nutrient(s) is not likely to create an imbalance of essential nutrients."
4. "The nutrient(s) added is stable under proper conditions of storage and use."
5. "The nutrient(s) is physiologically available from the food."
6. "There is a reasonable assurance against intake to a level of toxicity."

The addition of nutrients to food in all other forms is classified as discretionary fortification (The National Academies Press, 2003). The guiding principles for discretionary fortification were based on the overarching need for fortification based on public health needs primarily due to dietary inadequacies. Although, a need for "scientific justification of discretionary fortification" was identified, there is little research available on this or the impact of fortification on nutrient intakes (The National Academies Press, 2003).

Interestingly, the FDA's food fortification policy is completely voluntary (The National Academies Press, 2003) and cannot be enforced (Backstrand, 2002). Three ways that the FDA can intervene and limit nutrient fortification in foods include: (a) establishing standards of

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identity, (b) monitoring deceptive and erroneous health claims and (c) intervening when a relevant documented public health problem is identified (Backstrand, 2002).

DIETARY REFERENCE INTAKES AND DIETARY SUPPLEMENT REGULATIONS

The Institute of Medicine issues the Dietary Reference Intakes (DRIs) which are comprised of the Estimated Average Requirements (EAR), the Adequate Intake (AI), the Recommended Dietary Allowances (RDA) and the Tolerable Upper Intake Levels (UL). The EAR establishes average daily nutrient intakes *estimated* to meet the requirements of half the population in each age and gender group, whereas AI stipulates average daily nutrient intakes based on *observed or experimentally established* estimate of nutrients. The RDAs define the level of nutrients adequate to meet the needs of approximately 98% of the healthy population and the UL identifies the highest average daily intake, above which a nutrient may cause adverse effects (The National Academies Press, 2003). These DRI categories define the optimal safe level of nutrients that should be consumed to prevent deficiencies and/or to avoid adverse effects of excess consumption.

The term “dietary supplement” refers to any product that supplements the diet and may contain any one or more of a vitamin, mineral, herb or other botanical, an amino acid, “a dietary substance for use by man to supplement the diet by increasing the total dietary intake” or “a concentrate, metabolite, constituent, extract, or combination” of a vitamin, mineral, herb or other botanical (U.S. Food and Drug Administration). This definition of a dietary supplement is part of the 1994 Dietary Supplement Health and Education Act, which relies on the supplement manufacturers to insure the quality and safety of their products, but contains no provisions for

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standardization or testing for safety and effectiveness of these products. The FDA however, issued good manufacturing guidelines pertaining to the manufacturing, preparation and storage of dietary supplements, since nutrient and other dietary supplements are regulated as food and not as drugs (U.S. Food and Drug Administration).

SUPPLEMENT USE AND NUTRIENT INTAKE IN THE US

Dietary supplement use in adults

A steady increase in dietary supplement use has been reported over the years with over 150 million U.S. residents now using dietary supplements (Denham, 2011). Dietary supplement use was reported by 28% of adult men and 38% of adult women in NHANES I (1971-1974), compared to 44% of men and 53% of women in NHANES 2003-2006 (Bailey et al., 2011b). Although, over 50% of adults reported using one dietary supplement in the 2003-2006 NHANES, approximately 20% reported consuming two supplements and over 10% of the population reported using five or more dietary supplements (Bailey et al., 2011b). In the Iowa Women's Study (study to examine the associations between the incidence of cancer and several host, dietary, and lifestyle factors in postmenopausal women) supplement use increased from 62.7% to 85.1% from 1986 to 2004 (Mursu et al., 2011).

Dietary supplements use is more prevalent among women, the elderly, and those with higher education (> high school education; 61%) (Bailey et al., 2011b), non-Hispanic Whites, former smokers, normal/underweight, more physically active and those who perceived excellent/very good self-reported health (Radimer et al., 2004). A multivitamin and mineral supplement is the most commonly consumed supplement (Bailey et al., 2011b, Murphy et al.,

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2011, Timbo et al., 2006, Sebastian et al., 2007, Millen et al., 2004). Individuals who consume dietary supplements have a better diet quality. Examining data from NHANES 2003-2006, Bailey et al. (2011a, 2012) reported that participants who used dietary supplements containing vitamin and minerals also ingested more nutrients from food sources, had a lower prevalence of inadequate intake of several nutrients, but also had an increased risk of potentially excessive intakes for several key nutrients such as folic acid, vitamins A, B-6, C, calcium, iron, zinc and magnesium (Bailey et al., 2011a, Bailey et al., 2012). Evaluating the effect of a multivitamin and mineral supplement on the overall nutrient intake among the Hawaii-Los Angeles Cohort, Murphy et al. (2007) reported that addition of a multivitamin and mineral supplements significantly increased the proportion of 45-75 year old participants who achieved nutrient adequacy (Murphy et al., 2007). Although, adequacy of vitamin E, vitamin A and zinc improved with multivitamin and mineral supplement use, 10-15% of the cohort exceeded their DRI intake of vitamin A, zinc, niacin and folate. The overarching finding however, was that nutrient intake from the diet was similar among participants who used and those who did not use a multivitamin and mineral supplement (Murphy et al., 2007).

Dietary supplement use in children

Dietary supplement use is prevalent among children as well and is reflective of parental practice patterns (Martin et al., 2008). Thirty-two percent of children from birth to 18 years who participated in NHANES 1992-2002 used dietary supplements. Dietary supplement use was highest among 4 to 8 year old children (48.5%) followed by 14 to 18 years olds (25.7%) (Picciano et al., 2007). Although multivitamin and multimineral supplements were the most commonly consumed dietary supplement (18.3%), ascorbic acid (28.6%), retinol (25.8%),

vitamin D (25.6%), calcium (21.1%), and iron (19.3%) were the primary supplemental nutrients consumed (Picciano et al., 2007). Shaikh et al. (2009) reported that 34% of 2-17 year old participants of NHANES 1999-2004 reported using vitamin and mineral supplements in the past month (Shaikh et al., 2009). Although 37% of the National Health Interview Survey participants <18 years of age used dietary supplements, multivitamin supplement use was reported by 31% of the participants (Dwyer et al., 2013).

Similar to adult nutrient intake patterns, adolescents who used vitamin and mineral supplements consumed more healthy, nutrient dense diets (Martin et al., 2008, Stang et al., 2000, Reaves et al., 2006, Dwyer et al., 2013, George et al., 2011) and supplements increased nutrient adequacy of several key nutrients such as vitamin A, C, E (Martin et al., 2008, Dwyer et al., 2001). Martin et al. (2008) reported that use of dietary supplements by 8-11 year old Native Hawaiian and Pacific Islanders increased nutrient adequacy for vitamins A, C and E. Most 6-8 year olds consumed 97-100% of most nutrients from diet alone, except for vitamins A, C and E which met only 63%, 86% and 90% of the recommended intake. Addition of supplements increased intake of vitamins A, C and E to 89%, 95% and 98% respectively (Martin et al., 2008).

Reaves et al. (2006) explored the relationship between using multivitamin and mineral supplements and lifestyle and health behaviors in 8-12 grade participants of the Child and Adolescent Trial for Cardiovascular Health (CATCH) (Reaves et al., 2006). Only 25% of the CATCH participants reported using multivitamin, but when compared with non-supplement users fewer supplement users reported smoking ($p = 0.04$), were overweight ($p = 0.004$) and maintained a sedentary lifestyle ($p = 0.006$). After adjusting for age, sex, race, center, and energy intake, supplement users were still less likely to be overweight (OR = 0.81; 95% CI:

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0.68-0.99) or smoke (OR = 0.80; 95% CI: 0.66-0.97) compared to nonusers. Although supplement users consumed slightly more calories (2008±29 vs 1935±17 kcal; p = 0.03), they consumed less total fat (p < 0.001), saturated fat (p < 0.001), soft drinks (p < 0.001), fried foods (p < 0.001) and more fruits (p<0.001), vegetables (p = 0.003) and whole grains (p < 0.001). In a cohort of 11th graders in Texas, George et al. (2011) reported healthy dietary and physical activity behaviors among supplement users. Supplement users were more likely than non-users to eat breakfast regularly (OR = 1.91, 95% CI:1.34-2.70), consume ≥3 meals daily (OR = 1.56, 95% CI:1.15-2.12), more low fat foods and watch less television (OR = 0.53, 95% CI:0.33-0.84), (George et al., 2011).

Higher prevalence of dietary supplement use is reported in chronically ill children or those with special health care needs (Kemper et al., 2008, Ball et al., 2005). Dietary supplements may be a part of the care regimen for these patients either to prevent or treat their symptoms/conditions (Dwyer et al., 2013). Although, vitamins and minerals are critical in several physiologic functions and for maintaining health, disproportionate intake of vitamins and minerals can lead to nutrient imbalances that may cause adverse health outcomes. For instance, vitamin B12 deficiency can be masked by excessive supplemental folic acid intake and chronic excessive intake of supplemental zinc can reduce the absorption of copper and iron, leading to anemia, bone abnormalities and cognitive deficits. Multivitamin and mineral supplements are not intended to replace food, but should complement current diets and help bridge the gap between inadequacy and sufficiency. Since there is limited federal oversight of the supplement industry (U.S. Food and Drug Administration), nutrients in dietary supplements may be present in amounts equal to or higher that the recommended DRIs, making it relatively easy to exceed the

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UL. Although a healthy well balanced diet can insure provision of the nutrients required to maintain optimal health, many consumers of multivitamin and mineral supplements ingest these supplements to prevent chronic diseases. Conversely, several large clinical trials such as the Alpha Tocopherol Beta-Carotene (ATBC) cancer prevention trial (The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994), Beta-Carotene and Retinol Efficacy Trial (CARET) (Omenn et al., 1996), and Women's Health Initiative (Bolland et al., 2011a) have demonstrated an increase in disease incidence and mortality with increased supplement use. We now discuss the benefits and adverse health outcomes related to nutrient excess from food fortification and vitamin and mineral supplement use.

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THE BENEFITS OF FORTIFICATION AND SUPPLEMENTATION

Food enrichment and fortification programs in the U.S. have contributed to increased nutrient intakes in the general population and the eradication of several diseases linked to vitamin or mineral deficiency. For example, iodine fortification of salt eradicated goiter (The National Academies Press, 2003) and similarly, folic acid fortification has significantly decreased the incidence of neural tube defects (Honein et al., 2001).

In recent years, food fortification has helped meet the nutrient needs of a large proportion of the U.S. population (Fulgoni et al., 2011, Sebastian et al., 2007). Based on their analysis of NHANES 2003-2006 data, Fulgoni et al. (2011) reported that the food fortification and enrichment programs were key contributors of nutrient sufficiency and, along with nutrient supplements helped decrease the percentage of the population that consumed less than the EAR of key nutrients (Fulgoni et al., 2011). Only 7.6% of the population ≥ 2 years of age, consuming

fortified foods and supplements failed to meet the EAR for folate, compared to 88% of the population consuming naturally occurring food sources of folate (Fulgoni et al., 2011). Although, 54% of the population ≥ 2 years of age failed to meet the EAR for calcium, when consuming foods that were naturally good sources of calcium, this proportion was reduced to 38% when accounting for calcium from fortified foods and supplements (Fulgoni et al., 2011). RDAs for folic acid, calcium and vitamin D are provided in Table 1

The RDAs were established to meet the nutritional needs of the majority of the healthy population (The National Academies Press, 2003). However, guidelines for nutrient requirements for disease specific states are lacking and the current RDAs may be insufficient in these patient populations. For example, Reid et al. (1995) reported results of a two year follow-up in postmenopausal women enrolled in a randomized placebo controlled trial to evaluate the effectiveness of 1000 mg calcium supplementation on bone loss and fractures. Mean dietary calcium intake was approximately 700 mg. Despite consuming approximately 1700 mg total calcium well above the RDA (1200 mg for women 51-70 years), the women in the intervention group continued to lose bone mineral density. The rate of bone loss in the intervention group was lower than the placebo group (no supplemental calcium). Fracture rates observed between the two groups were also significantly different ($p = 0.037$), with fewer fractures observed in the calcium supplemented group (Reid et al., 1995). In 111 renal transplant patients on prednisone containing immunosuppressive therapy, participants receiving 1000 mg calcium along with 0.25 mcg vitamin D/day had significantly lower bone loss compared to participants who did not receive supplemental calcium and vitamin D (de Sévaux et al., 2002). Similarly, in men with prostate cancer receiving androgen deprivation therapy (ADT), calcium supplementation up to

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1000 mg was insufficient in preventing treatment related bone loss (Table 2). In a recent review Datta and Schwartz (2012) summarized the clinical trial evidence of calcium and/or vitamin D supplementation in men undergoing androgen deprivation therapy for prostate cancer. They found that despite calcium supplementation of 500-1000 mg calcium and 200-500 IU vitamin D men undergoing androgen deprivation therapy continued to lose bone mineral density (Datta and Schwartz, 2012). Although no clinical trials are available to compare outcomes with and without calcium and/or vitamin D supplementation, bone loss could have been potentially higher in these participants without calcium supplementation, leading to higher fractures and other secondary complications.

In addition to its role in maintaining bone health, calcium supplementation may also reduce the risk of secondary comorbidities such as certain cancers. Bolland et al. (2011b) have reported that daily 1000 mg calcium and 400 IU vitamin D supplementation decreased the risk of total breast cancer (Hazard Ratio (HR) = 0.82, 95% confidence interval (CI): 0.70-0.97; P = 0.021), invasive breast cancer (HR = 0.80, 95% CI: 0.0.66-0.96; P = 0.015) and total cancers (HR = 0.86, 95% CI: 0.78-0.96; P = 0.007) among postmenopausal women who did not take additional calcium and/or vitamin D supplements (Bolland et al., 2011b). Calcium supplementation may actually reduce mortality among elderly women (Mursu et al., 2011, Langsetmo et al., 2013). Data from the Iowa Women's Healthy Study indicated that women who consumed calcium supplements had an absolute risk reduction of 3.8% (HR = 0.91; 95% CI: 0.88-0.94) (Mursu et al., 2011). Similarly, results from the Canadian Multicenter Osteoporosis Study (a population based longitudinal study with a 10 year followup) indicate that calcium supplements of up to 1000 mg/d were associated with reduced mortality in women (HR = 0.78

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(95% CI: 0.66-0.92). No associations between mortality was found in men or women consuming ≥ 1000 mg calcium supplements (Langsetmo et al., 2013). Data from select prospective cohorts and randomized clinical trials on the effectiveness of calcium supplement in disease prevention in women are summarized in Table 3.

Folate is critical in the synthesis of purines and pyrimidines, particularly during times of stress, rapid cell growth and synthesis of RNA and DNA (Blom and Smulders, 2011). The U.S. folic acid fortification program began in 1998 (The National Academies Press, 2003) and its primary objective was to reduce neural tube defects (Yetley and Rader, 2004). Gibson et al. (2011) observed a decreased risk of colorectal cancer, in the participants of a large prospective cohort study (NIH-AARP Diet and Health Study), 8.5 year after folic acid fortification began in the U.S. (Gibson et al., 2011). Emerging research additionally suggests that inadequate consumption of folate may also increase the risk of breast cancer (Tjonneland et al., 2005, Zhang et al., 1999) and stroke (Weng et al., 2008). In a case-controlled study, Tjonneland et al. (2005) reported that postmenopausal women who consumed at least 10 gm of alcohol daily and had lower folic acid intake (< 300 mcg) had higher incidence of breast cancer (Tjonneland et al., 2005). Similarly from a prospective cohort study, Zhang et al. (1999) reported that the risk of alcohol intake associated breast cancer was highest among women who consumed < 300 mcg of folic acid per day (RR=1.32; 95% CI 1.15-1.50) (Zhang et al., 1999). Weng et al. (2008) reported a significantly higher incidence of ischemic stroke in adults with folate intake <369.45 mcg/day (Weng et al., 2008). In a retrospective cohort study of 437 head and neck squamous cell carcinoma patients, Kawakita et al. (2012) reported significantly higher survival in patients consuming ≥ 320 mcg folate daily pretreatment (Kawakita et al., 2012).

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Folic acid supplementation is considered to be a "double edged sword"(Kim, 2006). On the one hand it is critical in the synthesis of RNA and DNA, and on the other hand it may contribute to and promote inflammation, leading to destabilization off the atherosclerotic plaque, contributing to adverse health outcomes (Blom and Smulders, 2011), some of which are discussed below.

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THE DRAWBACKS OF FORTIFICATION AND SUPPLEMENTATION

We now examine the adverse health outcomes associated with excessive intake of nutrients. In addition to toxicities related with chronic, excessive intake of fat-soluble vitamins; excess intake of some nutrients can interfere with the metabolism of other key nutrients (for example, chronic excessive intake of supplemental zinc can reduce the absorption of copper and iron). We discuss below adverse health outcomes and implications of calcium and folic acid excess.

Adverse effects of excess calcium intake have been reported in both men and women. Warensjo et al. (2011) recently reported that older women consuming > 1137 mg of calcium daily (highest quintile) showed a higher rate of hip fracture (HR = 1.19; 95% CI:1.06-1.32) (Warensjö et al., 2011). In men, higher dietary calcium has been linked with increased incidence of prostate cancer. Following analysis of 1012 documented cases of prostate cancer among 20,885 men who participated in the Physician's Health Study, Chan et al. (2001) reported that men consuming the highest amount of dairy products (2.5 servings/day), had a higher risk of developing prostate cancer (Relative Risk (RR) = 1.34; 95% CI 1.04-1.71) (Chan et al., 2001). Giovannucci et al. (2006) reported higher advanced and fatal prostate cancer risk with sustained

daily calcium intake of >1500 mg (Giovannucci et al., 2006). Adverse health outcomes are not limited to calcium from dairy products, plant sources of calcium and supplements have also been implicated. Butler et al. (2010) reported a 25% increase in the risk of developing prostate cancer among a cohort of Singapore Chinese men with total daily calcium intake <700 mg (Butler et al., 2010). Intake of calcium in this cohort was primarily from non-dairy sources.

Increased risk of cardiovascular events, particularly myocardial infarctions has been reported with calcium supplementation of ≥ 500 mg with or without vitamin D (Bolland et al., 2011a, Bolland et al., 2010, Pentti et al., 2009, Li et al., 2012, Wang et al., 2010). Pentti et al. (2009) evaluated the impact of calcium supplementation on coronary heart disease in 52-62 year old women and concluded that calcium alone or administered concurrently with vitamin D increased the risk of coronary heart disease in women (HR = 1.24; 95% CI: 1.02-1.52) (Pentti et al., 2009). After re-examining the Women's Health Initiative data, Bolland et al. (2011a) similarly concluded that ≥ 500 mg calcium supplements with or without vitamin D increase the risk of cardiovascular events, especially myocardial infarction, and called for reassessing the role of calcium supplements in osteoporosis management (Bolland et al., 2011a). Due to the positive association between calcium supplementation and increased risk of cardiovascular disease, the American Society for Bone and Mineral Research has issued a statement of caution regarding "potential cardiovascular risks associated with calcium supplements" (American Society for Bone and Mineral Research, 2010).

Approximately 6% of NHANES 2003-2006 participants over age two, consuming folic acid supplements along with fortified/enriched food participants exceeded the UL of folate (Fulgoni et al., 2011). Higher total folate intake has been linked with increased incidence of

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several cancers (Hirsch et al., 2009, Ebbing et al., 2009, Uccella et al., 2011) and higher mortality (Ebbing et al., 2009). Uccella et al. (2011) reported an increased risk of type II endometrial cancer in postmenopausal women who consumed >228.6 mcg/day supplemental folate (RR = 1.80; p trend = 0.027) (Uccella et al., 2011). Hirsch et al. (2009) reported a 162% increase in hospital discharges from colon cancer among 45-64 year old (rate ratio 2.6; 99% CI: 2.58-2.93) and 190% increase among 65-79 year old patients (rate ratio 2.9; 99% CI: 2.86-3.25) (Hirsch et al., 2009). In a double blind, placebo controlled study designed to assess the safety and efficacy of daily 1 mg folic acid supplementation in preventing colorectal cancers, Cole et al. (2007) observed higher rates of advanced adenomas (RR = 1.35; 95% CI: 0.98-1.86, p = 0.07) and multiple adenomas (unadjusted RR = 2.32; 95% CI: 1.23-4.35; p = 0.007) in the folic acid intervention group participants (Cole et al., 2007).

The Iowa Women's Health Study researchers evaluated the association of mortality with the use of multivitamins and several individual nutrients (pyridoxine, folic acid, magnesium, iron, zinc and copper) in more than 38,000 women > 60 years of age. Folic acid intake was associated with higher mortality among older women (absolute risk increase 5.9%; HR = 1.15; 95% CI: 1.0-1.32) (Mursu et al., 2011). Ebbing et al. (2009) compiled results from two randomized double-blind placebo controlled trials to evaluate whether folic acid and vitamin B12 supplementation could reduce morbidity and mortality from cardiovascular disease in patients diagnosed with ischemic heart disease (Ebbing et al., 2009). These researchers reported higher lung cancer incidence in the intervention groups and higher all-cause mortality in patients with ischemic heart disease (HR = 1.18; 95% CI 1.04-1.33; p = 0.01). Cancer related mortality in the

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intervention group was also significantly higher (HR = 1.38; 95% CI 1.07-1.79; p = 0.01) (Ebbing et al., 2009).

Additionally, multivitamin and mineral supplements, the most frequently consumed dietary supplement was associated with increased mortality (HR = 1.06; 95% CI: 1.02-1.10; absolute risk increase 2.4%) in the Iowa Women's Study (Mursu et al., 2011). Antioxidant supplements promoted to fight oxidative damage by free radicals have demonstrated significant adverse effects with use in several large clinical trials. The ATBC trial evaluated the benefit of alpha-tocopherol (50 mg/day) and/or beta carotene (20 mg/day) on the incidence of lung cancer and other cancers in 29,133 male smokers. Men who received beta carotene had a higher incidence of lung cancer after 18 months which increased progressively thereafter. A higher incidence of cancers of the bladder, stomach, and other sites were diagnosed in the participants who received alpha-tocopherol. Additionally, these men also had a higher overall mortality rate (The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994). Omenn et al. (1996) report the results of their randomized, double-blind, placebo controlled trial evaluating the effects of a combination of 30 mg of beta carotene and 25,000 IU of retinol (vitamin A) on the incidence of lung cancer in 18,314 smokers, former smokers, and workers exposed to asbestos. Participants in the supplement groups had a higher incidence of lung cancer (RR = 1.28; 95% CI, 1.04 to 1.57; P = 0.02) and a higher mortality rate. The relative risk of death from any cause was 1.17 (95% CI, 1.03 to 1.33); from lung cancer, 1.46 (95% CI, 1.07 to 2.00); and death from cardiovascular disease, 1.26 (95% CI 0.99 to 1.61) (Omenn et al., 1996).

With increasing dietary supplement use and availability of more foods and beverages with nutrient fortification, consumption of nutrients above the recommended UL in various life

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stage groups will continue to increase. This raises the potential of adverse events, not only with nutrient toxicities, but secondary complications such as increased cancer incidence and declining organ function. Health implications of these increased intakes are examined below in greater detail.

HEALTH IMPLICATIONS AND RECOMMENDATIONS

Supplemental nutrient intake and disease prevention are topics of interest to many clinicians and researchers. Older adults routinely do not meet the recommended levels of many vitamin and minerals and food fortification programs as well as nutrient supplements are vital for achieving nutrient sufficiency in this population. Supplement use may not completely eliminate dietary inadequacies, but they do help increase the proportion of adults who meet their daily EAR (Sebastian et al., 2007, Fulgoni et al., 2011). Conversely, with > 30% of children (from birth to 18 years) consuming dietary supplements, often without a medical necessity, nutrient intakes from dietary supplements should be included in the total nutrient intake estimate in children (Picciano et al., 2007, Shaikh et al., 2009). More importantly, a majority of complementary and alternative medicine users do not report their use to the primary care physician (Sawni-Sikand et al., 2002, Ndao et al., 2013), creating a potential for dangerous drug-drug or drug-nutrient interactions (Gilmour et al., 2011, Lim et al., 2011). Murphy et al. (2007) proposed that an "ideal" multivitamin and mineral supplement would bridge the gap for specific nutrients, while omitting those that may have the potential of being exceeded when total diet and supplement contributions are considered (Murphy et al., 2007). Such revised multivitamin and mineral formulations, would better serve the public health needs and aid more efficiently in meeting the nutrient needs of the population (Murphy et al., 2007). However, this seemingly

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simple solution would be extremely challenging to implement due to the variability of eating patterns and nutrient intakes/needs of the population. In order for supplements to truly bridge the gap between inadequate dietary intake and nutritional sufficiency, perhaps one solution could be to define a lower percentage of the RDAs that a multivitamin and mineral supplement or an individual nutrient for general/routine use should contain.

It is evident that vitamin and mineral needs for disease prevention and management are dissimilar and that adverse health outcomes with excess intake are prevalent (Warensjö et al., 2011, Giovannucci et al., 2006, Butler et al., 2010, Bolland et al., 2010, Bolland et al., 2011a, Pentti et al., 2009). Additionally, cancer patients undergoing treatment are cautioned to avoid certain nutrient supplements due to possible interference with therapy. However, no limitations are placed on food consumption, since there are no data indicating that fortified nutrients from foods cause any harm. With discretionary fortification and addition of "synthetic" (source other than naturally occurring in food) nutrients to food, should patients be advised to limit intake of fortified foods during treatment? We do not know whether fortification has the potential to disrupt the synergistic effect of naturally present nutrients. We also do not know the long term impact of discretionary fortification on the health of consumers, since adverse outcomes may not necessarily be evident immediately.

In a recent position paper on "food and nutrition for older adults: promoting health and wellness" (based on a systematic review of the literature using the Evidence Analysis Process), the Academy of Nutrition and Dietetics recommends against antioxidant supplementation in patients with diagnosed cognitive impairment or Alzheimer's disease. The evidence indicates that antioxidant supplements have no effect on cognition or delay in cognitive decline (Bernstein

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and Munoz, 2012). Martinez and colleagues (2012) examined the benefits and harms of antioxidant supplements, folic acid, vitamin D and calcium. They reviewed the evidence from experimental and observational studies and convincingly argued against marketing of dietary supplements for cancer prevention, due to lack of evidence to support such claims (Martínez et al., 2012). Although their focus was limited to supplemental nutrient intake only, we include in our review data on nutrient availability from food fortification in addition to nutrient supplements to highlight the benefits and adverse effects of vitamin and mineral excess. Lack of a national database linking nutrient contributions from supplements as well as fortified and natural food sources, provides an incomplete picture and leaves the data subject to bias (Fulgoni et al., 2011).

Current levels of discretionary food fortification seem to violate the key elements of the Food and Nutrition Boards recommendations. Chief amongst them is the condition that "addition of the nutrient is not likely to create an imbalance of essential nutrients" (American Medical Association Council on Foods and Nutrition and National Academy of Sciences, 1968). The time has come to define a therapeutic and non-therapeutic effect of nutrients and to limit the amounts that can be added to foods. Discussions to revise the 1943 FDA policy statement to make it enforceable, to ensure that fortified foods do contribute to the nutritional well-being of individuals who consume them, and to "do no harm" are urgently needed, a sentiment previously echoed by other researchers (Backstrand, 2002).

The issues surrounding the combined use of food fortification and supplement use are complex. These issues present a pressing public health concern that should be addressed. For example, should discretionary or indiscriminate food fortification be allowed to continue?

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Should discretionary fortification be regulated? Which foods should be fortified and which foods should be exempt from fortification? Which nutrients should be included in the fortification program? And finally, what range of nutrient fortification should be considered? Stratification of the nutrient requirements for different age groups makes different levels of food fortification an enormous challenge. In light of increasing dietary supplement use, indiscriminate food fortification is ill advised, and should be better enforced and regulated. Additionally, it may be time for the regulatory agencies to define and then enforce what percentage of RDAs dietary supplements can provide, so they can complement dietary intake while minimizing excess intake of nutrients. A research priority should be to identify populations with higher nutrient needs and those at risk for adverse health outcomes with increased nutrient intake from both fortified food and supplements.

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References

American Medical Association Council on Foods and Nutrition, National Academy of Sciences (1968). Improvement of Nutritive Quality of Foods. *JAMA* **205:**868-869.

American Society for Bone and Mineral Research. Statement on Potential Cardiovascular Risks Associated with Calcium Supplements. Available from: American Society for Bone and Mineral Research, Washington, DC. Available at: http://www.asbmr.org/about/detail.aspx?cid=80efb4d9-d696-46c8-b83b-3e0940c9dddd.

Backstrand, J. R. (2002). The History and Future of Food Fortification in the United States: A Public Health Perspective. *Nutr Rev* **60:**15-26.

Bailey, R. L., Fulgoni III, V. L., Keast, D. R., et al. (2012). Examination of Vitamin Intakes among US Adults by Dietary Supplement Use. *J Acad Nutr Diet* **112:**657-663.

Bailey, R. L., Fulgoni, V. L., Keast, D. R., et al. (2011a). Dietary supplement use is associated with higher intakes of minerals from food sources. *Am J Clin Nutr* **94:**1376-1381.

Bailey, R. L., Gahche, J. J., Lentino, C. V., et al. (2011b). Dietary Supplement Use in the United States, 2003–2006. *J Nutr* **141:**261-266.

Ball, S. D., Kertesz, D., Moyer-Mileur, L. J. (2005). Dietary supplement use is prevalent among children with a chronic illness. *J Am Diet Assoc* **105:**78-84.

Downloaded by [Ondokuz Mayis Universitesine] at 12:46 06 November 2014

 ACCEPTED MANUSCRIPT

Bernstein, M., Munoz, N. (2012). Position of the Academy of Nutrition and Dietetics: Food and Nutrition for Older Adults: Promoting Health and Wellness. *J Acad Nutr Diet* **112:**1255-1277.

Bhoopalam, N., Campbell, S. C., Moritz, T., et al. (2009). Intravenous Zoledronic Acid to Prevent Osteoporosis in a Veteran Population With Multiple Risk Factors for Bone Loss on Androgen Deprivation Therapy. *J Urol* **182:**2257-2264.

Bishai, D., Nalubola, R. (2002). The History of Food Fortification in the United States: Its Relevance for Current Fortification Efforts in Developing Countries. *Econ Dev Cult Change* **51:**37-53.

Blom, H., Smulders, Y. (2011). Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. *J Inherit Metab Dis* **34:**75-81.

Bolland, M. J., Avenell, A., Baron, J. A., et al. (2010). Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *Br Med J* **341**.

Bolland, M. J., Grey, A., Avenell, A., et al. (2011a). Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *Br Med J* **342**.

Bolland, M. J., Grey, A., Gamble, G. D., et al. (2011b). Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr* **94:**1144-1149.

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ACCEPTED MANUSCRIPT

Butler, L. M., Wong, A. S., Koh, W.-P., et al. (2010). Calcium Intake Increases Risk of Prostate Cancer among Singapore Chinese. *Cancer Res* **70:**4941-4948.

Chan, J. M., Stampfer, M. J., Ma, J., et al. (2001). Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. *Am J Clin Nutr* **74:**549-554.

Cole, B. F., Baron, J. A., Sandler, R. S., et al. (2007). Folic Acid for the Prevention of Colorectal Adenomas. *JAMA* **297:**2351-2359.

Datta, M., Schwartz, G. G. (2012). Calcium and Vitamin D Supplementation During Androgen Deprivation Therapy for Prostate Cancer: A Critical Review. *Oncologist* **17:**1171-1179.

de Sévaux, R. G. L., Hoitsma, A. J., Corstens, F. H. M., et al. (2002). Treatment with Vitamin D and Calcium Reduces Bone Loss after Renal Transplantation: A Randomized Study. *J Am Soc Nephrol* **13:**1608-1614.

Denham, B. E. (2011). Dietary Supplements—Regulatory Issues and Implications for Public Health. *JAMA* **306:**428-429.

Devine, A., Dick, I. M., Heal, S. J., et al. (1997). A 4-year follow-up study of the effects of calcium supplementation on bone density in elderly postmenopausal women. *Osteoporos Int* **7:**23-28.

Dwyer, J., Nahin, R. L., Rogers, G. T., et al. (2013). Prevalence and predictors of children's dietary supplement use: the 2007 National Health Interview Survey. *Am J Clin Nutr* **97:**1331-1337.

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 ACCEPTED MANUSCRIPT

Dwyer, J. T., Garceau, A. O., Evans, M., et al. (2001). Do Adolescent Vitamin-Mineral Supplement Users Have Better Nutrient Intakes Than Nonusers? Observations from the CATCH Tracking Study. *J Am Diet Assoc* **101:**1340-1346.

Ebbing, M., Bønaa, K. H., Nygård, O., et al. (2009). Cancer Incidence and Mortality After Treatment With Folic Acid and Vitamin B12. *JAMA* **302:**2119-2126.

Fulgoni, V. L., Keast, D. R., Bailey, R. L., et al. (2011). Foods, Fortificants, and Supplements: Where Do Americans Get Their Nutrients? *J Nutr*.

George, G. C., Springer, A. E., Forman, M. R., et al. (2011). Associations among Dietary Supplement Use and Dietary and Activity Behaviors by Sex and Race/Ethnicity in a Representative Multiethnic Sample of 11th-Grade Students in Texas. *J Am Diet Assoc* **111:**385-393.

Gibson, T. M., Weinstein, S. J., Pfeiffer, R. M., et al. (2011). Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. *Am J Clin Nutr* **94:**1053-1062.

Gilmour, J., Harrison, C., Asadi, L., et al. (2011). Natural Health Product–Drug Interactions: Evolving Responsibilities to Take Complementary and Alternative Medicine Into Account. *Pediatrics* **128:**S155-S160.

Giovannucci, E., Liu, Y., Stampfer, M. J., et al. (2006). A Prospective Study of Calcium Intake and Incident and Fatal Prostate Cancer. *Cancer Epidemiol Biomarkers Prev* **15:**203-210.

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ACCEPTED MANUSCRIPT

Greenspan, S. L., Nelson, J. B., Trump, D. L., et al. (2007). Effect of Once-Weekly Oral Alendronate on Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer. *Ann Intern Med* **146:**416-424.

Hirsch, S., Sanchez, H., Albala, C., et al. (2009). Colon cancer in Chile before and after the start of the flour fortification program with folic acid. *Eur J Gastroenterol Hepatol* **21:**346-349.

Honein, M. A., Paulozzi, L. J., Mathews, T. J., et al. (2001). Impact of Folic Acid Fortification of the US Food Supply on the Occurrence of Neural Tube Defects. *JAMA* **285:**2981-2986.

Israeli, R. S., Rosenberg, S. J., Saltzstein, D. R., et al. (2007). The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. *Clin Genitourin Cancer* **5:**271-277.

Kärkkäinen, M., Tuppurainen, M., Salovaara, K., et al. (2010). Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65–71 years: a 3-year randomized population-based trial (OSTPRE-FPS). *Osteoporos Int* **21:**2047-2055.

Kawakita, D., Matsuo, K., Sato, F., et al. (2012). Association between dietary folate intake and clinical outcome in head and neck squamous cell carcinoma. *Ann Oncol* **23:**186-192.

Kemper, K. J., Vohra, S., Walls, R., et al. (2008). The Use of Complementary and Alternative Medicine in Pediatrics. *Pediatrics* **122:**1374-1386.

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 ACCEPTED MANUSCRIPT

Kim, Y.-I. (2006). Folate: a magic bullet or a double edged sword for colorectal cancer prevention? *Gut* **55:**1387-1389.

LaCroix, A. Z., Kotchen, J., Anderson, G., et al. (2009). Calcium Plus Vitamin D Supplementation and Mortality in Postmenopausal Women: The Women's Health Initiative Calcium–Vitamin D Randomized Controlled Trial. *J Gerontol A Biol Sci Med Sci* **64A:**559-567.

Langsetmo, L., Berger, C., Kreiger, N., et al. (2013). Calcium and Vitamin D Intake and Mortality: Results from the Canadian Multicentre Osteoporosis Study (CaMos). *J Clin Endocrinol Metab*.

Li, K., Kaaks, R., Linseisen, J., et al. (2012). Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* **98:**920-925.

Lim, A., Cranswick, N., South, M. (2011). Adverse events associated with the use of complementary and alternative medicine in children. *Arch Dis Child* **96:**297-300.

Martin, C. L., Murphy, S. P., Novotny, R. (2008). Contribution of Dietary Supplements to Nutrient Adequacy among Children in Hawaii. *J Am Diet Assoc* **108:**1874-1880.

Martínez, M. E., Jacobs, E. T., Baron, J. A., et al. (2012). Dietary Supplements and Cancer Prevention: Balancing Potential Benefits Against Proven Harms. *J Natl Cancer Inst* **104:**732-739.

Downloaded by [Ondokuz Mayis Universitesine] at 12:46 06 November 2014

ACCEPTED MANUSCRIPT

Mertz, W. (1997). Food Fortification in the United States. *Nutr Rev* **55:**44-49.

Michaelson, M. D., Kaufman, D. S., Lee, H., et al. (2007). Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol* **25:**1038-1042.

Millen, A. E., Dodd, K. W., Subar, A. F. (2004). Use of vitamin, mineral, nonvitamin, and nonmineral supplements in the United States: the 1987, 1992, and 2000 National Health Interview Survey results. *J Am Diet Assoc* **104:**942-950.

Morabito, N., Gaudio, A., Lasco, A., et al. (2004). Neridronate Prevents Bone Loss in Patients Receiving Androgen Deprivation Therapy for Prostate Cancer. *J Bone Miner Res* **19:**1766-1770.

Moschonis, G., Katsaroli, I., Lyritis, G. P., et al. (2010). The effects of a 30-month dietary intervention on bone mineral density: The Postmenopausal Health Study. *Br J Nutr* **104:**100-107.

Murphy, S. P., White, K. K., Park, S.-Y., et al. (2007). Multivitamin-multimineral supplements' effect on total nutrient intake. *Am J Clin Nutr* **85:**280S-284S.

Murphy, S. P., Wilkens, L. R., Monroe, K. R., et al. (2011). Dietary Supplement Use Within a Multiethnic Population as Measured by a Unique Inventory Method. *J Am Diet Assoc* **111:**1065-1072.

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 ACCEPTED MANUSCRIPT

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Mursu, J., Robien, K., Harnack, L. J., et al. (2011). Dietary Supplements and Mortality Rate in Older Women: The Iowa Women's Health Study. *Arch Intern Med* **171:**1625-1633.

Ndao, D. H., Ladas, E. J., Bao, Y., et al. (2013). Use of Complementary and Alternative Medicine Among Children, Adolescent, and Young Adult Cancer Survivors: A Survey Study. *J Pediatr Hematol Oncol* **35:**281-288.

Omenn, G. S., Goodman, G. E., Thornquist, M. D., et al. (1996). Effects of a Combination of Beta Carotene and Vitamin A on Lung Cancer and Cardiovascular Disease. *N Engl J Med* **334:**1150-1155.

Pentti, K., Tuppurainen, M. T., Honkanen, R., et al. (2009). Use of calcium supplements and the risk of coronary heart disease in 52–62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. *Maturitas* **63:**73-78.

Picciano, M. F., Dwyer, J. T., Radimer, K. L., et al. (2007). DIetary supplement use among infants, children, and adolescents in the united states, 1999-2002. *Arch Pediatr Adolesc Med* **161:**978-985.

Porthouse, J., Cockayne, S., King, C., et al. (2005). Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ* **330:**1003-1008.

Radimer, K., Bindewald, B., Hughes, J., et al. (2004). Dietary Supplement Use by US Adults: Data from the National Health and Nutrition Examination Survey, 1999–2000. *Am J Epidemiol* **160:**339-349.

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 ACCEPTED MANUSCRIPT

Reaves, L., Steffen, L. M., Dwyer, J. T., et al. (2006). Vitamin Supplement Intake Is Related to Dietary Intake and Physical Activity: The Child and Adolescent Trial for Cardiovascular Health (CATCH). *J Am Diet Assoc* **106:**2018-2023.

Reid, I. R., Ames, R. W., Evans, M. C., et al. (1995). Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: A randomized controlled trial. *Am J Med* **98:**331-335.

Rosenberg, I. H., Abrams, S. A., Beecher, G. R., et al. (2004). Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification. *Nutr Rev* **62:**73-79.

Ryan, C. W., Huo, D., Demers, L. M., et al. (2006). Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. *J Urol* **176:**972-978.

Saad, F., Gleason, D. M., Murray, R., et al. (2002). A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma. *J Natl Cancer Inst* **94:**1458-1468.

Salovaara, K., Tuppurainen, M., Kärkkäinen, M., et al. (2010). Effect of vitamin D3 and calcium on fracture risk in 65- to 71-year-old women: A population-based 3-year randomized, controlled trial—the OSTPRE-FPS. *J Bone Miner Res* **25:**1487-1495.

Sawni-Sikand, A., Schubiner, H., Thomas, R. L. (2002). Use of Complementary/Alternative Therapies Among Children in Primary Care Pediatrics. *Ambul Pediatr* **2:**99-103.

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ACCEPTED MANUSCRIPT

Sebastian, R. S., Cleveland, L. E., Goldman, J. D., et al. (2007). Older Adults Who Use Vitamin/Mineral Supplements Differ from Nonusers in Nutrient Intake Adequacy and Dietary Attitudes. *J Am Diet Assoc* **107:**1322-1332.

Shaikh, U., Byrd, R. S., Auinger, P. (2009). Vitamin and mineral supplement use by children and adolescents in the 1999-2004 national health and nutrition examination survey: Relationship with nutrition, food security, physical activity, and health care access. *Arch Pediatr Adolesc Med* **163:**150-157.

Smith, M. R., Eastham, J., Gleason, D. M., et al. (2003). Randomized Controlled Trial of Zoledronic Acid to Prevent Bone Loss in Men Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer. *J Urol* **169:**2008-2012.

Smith, M. R., Egerdie, B., Toriz, N. H., et al. (2009). Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer. *N Engl J Med* **361:**745-755.

Stang, J., Story, M. T., Harnack, L., et al. (2000). Relationships between Vitamin and Mineral Supplement use, Dietary Intake, and Dietary Adequacy among Adolescents. *J Am Diet Assoc* **100:**905-910.

Taxel, P., Dowsett, R., Richter, L., et al. (2010). Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. *BJU Int* **106:**1473-1476.

Downloaded by [Ondokuz Mayis Universitesine] at 12:46 06 November 2014

 ACCEPTED MANUSCRIPT

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The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group (1994). The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers. *N Engl J Med* **330:**1029-1035.

The National Academies Press (2003) Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification, Washington, DC.

Timbo, B. B., Ross, M. P., McCarthy, P. V., et al. (2006). Dietary Supplements in a National Survey: Prevalence of Use and Reports of Adverse Events. *J Am Diet Assoc* **106:**1966-1974.

Tjonneland, A., Christensen, J., Olsen, A., et al. (2005). Folate intake, alcohol and risk of breast cancer among postmenopausal women in Denmark. *Eur J Clin Nutr* **60:**280-286.

U.S. Food and Drug Administration. Dietary Supplement Health and Education Act of 1994. Available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148003.htm. Accessed January 15, 2013.

Uccella, S., Mariani, A., Wang, A. H., et al. (2011). Dietary and supplemental intake of one-carbon nutrients and the risk of type I and type II endometrial cancer: a prospective cohort study. *Ann Oncol* **22:**2129-2136.

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 ACCEPTED MANUSCRIPT

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Wang, T. K. M., Bolland, M. J., van Pelt, N. C., et al. (2010). Relationships between vascular calcification, calcium metabolism, bone density, and fractures. *J Bone Miner Res* **25:**2777-2785.

Warensjö, E., Byberg, L., Melhus, H., et al. (2011). Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *BMJ* **342**.

Weng, L.-C., Yeh, W.-T., Bai, C.-H., et al. (2008). Is Ischemic Stroke Risk Related to Folate Status or Other Nutrients Correlated With Folate Intake? *Stroke* **39:**3152-3158.

Yetley, E. A., Rader, J. I. (2004). Modeling the Level of Fortification and Post-Fortification Assessments: U.S. Experience. *Nutr Rev* **62:**S50-S59.

Zhang, S., Hunter, D. J., Hankinson, S. E., et al. (1999). A Prospective Study of Folate Intake and the Risk of Breast Cancer. *JAMA* **281:**1632-1637.

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Table 1. Estimated Average Requirements, Recommended Dietary Allowances and Tolerable Upper Intake Levels for Folate and Calcium for children and adults (The National Academies Press, 2003)

Life Stage Group	Folate (µg/d)			Calcium (mg/d)			Vitamin D (IU/d)		
	EAR*	RDA*	UL+	EAR	RDA	UL	EAR	RDA	UL
Males									
1-3 years	120	150	300	500	700	2500	400	600	2500
4-8 years	160	200	400	800	1000	2500	400	600	3000
9-13 years	250	300	600	1100	1300	3000	400	600	4000
14-18 years	330	400	800	1100	1300	3000	400	600	4000
19-30 years	320	400	1000	800	1000	2500	400	600	4000
31-50 years	320	400	1000	800	1000	2500	400	600	4000
51-70 years	320	400	1000	800	1000	2000	400	600	4000
>70 years	320	400	1000	1000	1200	2000	400	800	4000
Females									
1-3 years	120	150	300	500	700	2500	400	600	2500
4-8 years	160	200	400	800	1000	2500	400	600	3000
9-13 years	250	300	600	1100	1300	3000	400	600	4000
14-18 years	330	400	800	1100	1300	3000	400	600	4000
19-30 years	320	400	1000	800	1000	2500	400	600	4000
31-50 years	320	400	1000	800	1000	2500	400	600	4000
51-70 years	320	400	1000	1000	1200	2000	400	600	4000
>70 years	320	400	1000	1000	1200	2000	400	800	4000
Pregnancy									
14-18 years	520	600	800	1100	1300	3000	400	600	4000

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19-30 years	520	600	1000	800	1000	2500	400	600	4000
31-50 years	520	600	1000	800	1000	2500	400	600	4000
Lactation									
14-18 years	450	500	800	1100	1300	3000	400	600	4000
19-30 years	450	500	1000	800	1000	2500	400	600	4000
31-50 years	450	500	1000	800	1000	2500	400	600	4000

*As dietary folate equivalents (DFE) = 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach

+ The UL applies to synthetic forms obtained from supplements, fortified foods or a combination of the two.

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Table 2. Summary of before-after data from clinical trials on the impact of calcium and vitamin D supplementation on changes in bone mineral density in men with prostate cancer treated with androgen derivation therapy.

Authors	N	Population	Dose	Endpoint	Outcome
Taxel et al. (Taxel et al., 2010)	40	Locally advanced PC receiving LHRH-agonist	600 mg calcium, 400 IU vit.D	Change in BMD at 6 months	-
Smith et al. (Smith et al., 2009)	1468	Non-metastatic, hormone-sensitive PC	1000 mg calcium, 400 IU vit.D	Change in lumbar spine BMD	-
Bhoopalam et al. (Bhoopalam et al., 2009)	93	Localized prostate cancer on ADT	1000 mg calcium, 400 IU vit.D	Percent change in BMD at lumbar spine	
Greenspan et al. (Greenspan et al., 2007)	112	Non-metastatic PC	500 mg calcium, 200 IU vit.D	Change in BMD at 12 months	-
Israeli et al. (Israeli et al., 2007)	56	Non metastasized PC patients on ADT	500 mg calcium, 400-500 IU vit.D	Effect on bone loss and bone resorption biomarkers	-
Michaelson et al. (Michaelson et al., 2007)	44	Non- metastatic PC on ADT	500 mg calcium carbonate, 400 IU vit.D	Change in BMD and bone turnover markers	-
Ryan et al. (Ryan et	120	Non metastasized PC patients on	500 mg calcium, 400-	Effect on BMD and bone turnover markers	-

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Saad et al. (Saad et al., 2002)	643	Metastatic PC	500 mg calcium, 400-500 IU vit.D	Effectiveness in reducing skeletal related events associated with metastasis	-
al., 2006)		ADT	500 IU vit.D		
Morabito et al. (Morabito et al., 2004)	48	Osteoporotic PC	500 mg elemental calcium, 400 IU vit.D	Prevention of bone loss during androgen oblation	-
Smith et al. (Smith et al., 2003)	106	Localized PC beginning ADT	500 mg calcium, 400 IU vit.D	BMD after a year of therapy	-

ADT = Androgen Deprivation Therapy; BMD = Bone Mineral Density; PC = Prostate Cancer; LHRH = Luteinizing Hormone Releasing Hormone

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Table 3. Summary of select prospective cohort and randomized clinical trials on the impact of calcium and vitamin D supplementation on disease outcomes in women

Authors	N	Population	Dose	Endpoint	Outcomes	Comments
Bolland et al. (Bolland et al., 2011b)	36282	Postmenopausal women	1000 mg calcium carbonate, 400 IU vit. D	All-cause mortality, risk of hip or total fracture, breast, colorectal or total cancer	+	Significant ↓ in risk of total breast, invasive breast and colorectal cancer in women consuming prescribed calcium & vit.D only
Salovaara et al. (Salovaara et al., 2010)	3432	65-71 year old	1000 mg calcium + 800 IU vit. D	Fracture risk	neutral	Non-significant trend towards ↓ fracture risk
Moschonis et al. (Moschonis et al., 2010)	66	55-65 year old postmenopausal women	1200 mg calcium, 300-900 IU vit.D	Effect of calcium on BMD after a 30 month intervention	+: pelvis, total spine & total body	Lower BMD loss in arms & legs in the calcium group
Karkkainen et al. (Kärkkäinen et al., 2010)	593	66-71 year old women	1000 mg calcium + 800 IU vit. D	Effect of calcium and vitamin D in reducing bone loss in postmenopausal women	+: total body, trochanter	Lower BMD loss at femoral neck, wards triangle, total proximal femur
LaCroix et al. (LaCroix et al.,	36282	Postmenopausal women 51-82 years	1000 mg calcium carbonate, 400	Total and cause specific mortality	neutral	Non-significant trend towards ↓ mortality

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2009)			IU vit. D			
Porthouse et al. (Porthouse et al., 2005)	3314	≥ 70 year old with fracture risk	1000 mg calcium + 800 IU vit. D	Clinical fractures	neutral	Time to fracture and no. of fractures similar between groups
Devine et al. (Devine et al., 1997)	84	54-74 year old postmenopausal women	1000 mg calcium	Change in lumbar spine, distal tibia, fibula, hip and ankle BMD	+	Sustained ↓ in rate of bone density loss at the ankle and hip
Reid et al. (Reid et al., 1995)	78	Healthy postmenopausal women	1000 mg elemental calcium	Effect of calcium supplementation on BMD after 4 years	+: lumbar spine, trochanter BMD; fracture rate	Lower % BMD ↓ at femoral neck & total body in women supplemented with calcium

BMD = Bone Mineral Density; RCT = Randomized Controlled Trial; RPCT = Randomized Placebo Controlled Trial;

RDBPCT = Randomized Double Blind Placebo Controlled Trial

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Year*	Notable events
1924	→ Iodine added to salt to prevent goiter
1933	→ Vitamin D added to milk – by irradiating milk or feeding cattle irradiated yeast
1940	→ Vitamin D added to milk changed to a concentrate → Addition of thiamin, niacin, riboflavin and iron to flour
1941	→ FDA established "standard of identity" for enriched flour → Bread enrichment began → FDA first required nutrition information on food & dietary supplement label+
1942	→ 75% white bread in the US was fortified
1943	→ Flour sold for interstate commerce had to be enriched → FDA policy statement issued due to interest in fortification (this still holds exists) indicating that the nutrients added for fortification should contribute "substantially to the nutritional well-being of the individuals who consume usual amounts of food"
1945	→ Voluntary fluoridation of municipal water#
1953	→ Standard of identity established for enriched flour
1962	→ FDA proposal to limit fortification to only those nutrients that are essential for human health and are also appropriate for supplementation
1966	→ To prevent indiscriminant food fortification, FDA proposed limiting foods for fortification to 8 classes and specified the nutrients that could be added to

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them

1973 → Increase in the niacin, riboflavin and thiamin added to grain products and more than doubled (40 mg/lb) iron content of flour[†]

1974 → Due to objections received during public hearings, the 1966 proposal was abandoned

1976 → Congress limited FDA's authority over vitamin and mineral supplementation

1978 → Iron added to flour reverted to pre-1973 levels (13-16.5 mg/lb) due to concerns about iron overload[†]

1981 → Minimum and maximum range for iron fortification abolished and a single level of 20 mg/lb added to flour[†]

Late 1980 → Introduction of calcium fortified soft-drinks, juices and cereals by the US food industry[§]

1997 → FDA authority was further curtailed by including dietary supplements in food to the 1976 limitations

1998 → Standard of identity for folate fortification of grain products established

Adapted from [*](The National Academies Press, 2003) [+](Rosenberg et al., 2004) [#](Mertz, 1997) [†](Backstrand, 2002) [§](Bishai and Nalubola, 2002)

Figure 1: Brief chronology of key food fortification milestones [adapted from (The National Academies Press, 2003)]