VOLUME 28 · NUMBER 26 · SEPTEMBER 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Role of Vitamin and Mineral Supplementation and Aspirin Use in Cancer Survivors

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Submitted November 24, 2009; accepted July 6, 2010; published online ahead of print at www.jco.org on August 9, 2010.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2826-4081/$20.00

DOI: 10.1200/JCO.2009.27.3219

ABSTRACT

Multivitamins and multiminerals are widely used in the United States, but their efficacy and, perhaps more importantly, the potential for harm in individuals who have cancer have received relatively little study. Beyond their general effects on health, the use of vitamins and minerals by patients with cancer has unique implications because of their potential direct effects on existing cancers, effects on factors that may influence carcinogenesis, such as immunity, and interactions with treatment. Some evidence suggests that vitamin D at higher than standard doses may improve cancer-specific and overall survival for several cancer sites. Besides vitamin D, there is little evidence that nutritional supplements lower the risk of recurrence or improve survival from cancer, although some benefits may be possible in specific subgroups. Some data suggest that higher than standard doses of some vitamins or minerals could even enhance carcinogenesis or worsen survival in patients with cancer. For example, evidence suggests that although folate supplementation administered in preneoplastic stages may lower the risk of colorectal cancer, excessive folic acid in patients with established cancer may be harmful. For prostate cancer, some preliminary evidence indicates that excess consumption of one or a combination of components in a multivitamin/multimineral may accelerate cancer progression and increase fatality. Use of aspirin is proven to lower risk of colorectal cancer, and recent evidence suggests that aspirin use in patients with colorectal cancer improves cancer-specific and overall survival, especially in patients with tumors that express cyclooxygenase-2 (COX-2). The potential beneficial or adverse effects of dietary supplements and aspirin in survivors of cancer warrant further study.

J Clin Oncol 28:4081-4085. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The consumption of vitamin and mineral supplements is high in the United States, even among patients with cancer and survivors. However, their efficacy and, perhaps more importantly, the potential for harm in individuals who have cancer has received relatively little study. This brief review summarizes some of the important studies that have examined vitamin and mineral supplement use in relation to cancer progression or mortality. Potential benefits of vitamin D, which can be taken as a supplement but is unique because the major source is from sun exposure, are also considered. Finally, the role of aspirin in cancer survivors is briefly examined. Although aspirin is not a dietary supplement, it is commonly consumed and has been shown to have anticancer properties by inhibiting cyclooxygenase-2 (COX-2).

VITAMIN AND MINERAL SUPPLEMENTS

In the United States in general, approximately 50% of adults use dietary supplements, and 33% use multivitamin/multimineral supplements. Vitamin and mineral supplements are particularly commonly used among the 10 million adults with a diagnosis of cancer. In a systematic review of 32 studies (published between 1999 and 2006) that addressed vitamin and mineral supplement use among adult US patients with cancer and cancer survivors, 64% to 81% reported using a vitamin or mineral supplement and 26% to 77% reported using multivitamins.[1] Between 14% and 32% of cancer survivors initiated supplement use after the cancer diagnosis. By cancer site, patients with breast cancer report the highest and patients with prostate cancer report the lowest prevalence of use. Female sex and higher education were also associated with greater prevalence of supplement use.

Despite the widespread use of these supplements, the associated benefits and risks have not been well studied in patients with cancer. Beyond their general effects on health, the use of vitamins and minerals by patients with cancer has unique implications because of their potential direct effects on existing cancers, effects on factors that may influence carcinogenesis, such as immunity, and

interactions with treatment. The second World Cancer Research Fund/American Institute for Cancer Research report concluded that there is not yet sufficient evidence to provide specific advice to cancer survivors on dietary factors or supplement use. Thus, the advice provided for cancer survivors is to meet nutritional needs through diet alone and to avoid supplement use.[2] The American Cancer Society has developed guidelines for nutrition and physical activity during and after treatment, although they acknowledge that the evidence is incomplete and no evidence was found that nutritional supplements lower the risk of recurrence.[3] The American Cancer Society recommends a standard multivitamin and mineral supplement containing approximately 100% of the daily requirement, primarily because of the difficulty in acquiring these nutrients from diet alone. However, the use of high-dose supplements was discouraged.

Because of lack of data on any beneficial effects of vitamin/mineral supplement use on cancer recurrence and survival, it is critical to consider evidence for any potential adverse effects. The most direct evidence would be studies in cancer survivors. However, because this evidence is essentially nonexistent, studies of the development of fatal or advanced cancer according to long-term supplement use in individuals initially without cancer may provide useful data. Although it may be difficult in these studies to separate whether any effects observed occurred during the prediagnostic or postdiagnostic stages, any evidence of an increase in mortality or cancer progression for a specific supplement may be sufficient to warrant caution against use of this supplement in cancer survivors.

Prostate cancer is a cancer known to have wide variation in aggressive potential, and survivors can live for many years or decades. Some suggestive evidence indicates that some components of a multivitamin/multimineral supplement may increase fatality in patients with prostate cancer. In the Cancer Prevention II Study, among 475,726 men who were cancer free at baseline in 1982, 5,585 died of prostate cancer over an 18-year period.[4] There was a marginally significant 7% increase rate for those who took multivitamin at baseline, with a 12% increase during the initial 4 years of follow-up. The National Institutes of Health–American Association of Retired Persons Diet and Health Study followed 295,344 men who were cancer free for 5 years, over which time 10,241 were diagnosed with incident prostate cancer, 147 were diagnosed with advanced-stage prostate cancer, and 179 were diagnosed with fatal prostate cancer.[5] No association was observed between multivitamin use and incident or localized prostate cancer, but a significant 32% increase in advanced cancer and 98% increase in fatal prostate cancer were observed among men reporting excessive use of multivitamins ($>$ seven times per week) compared with never users. These associations were strongest in men who additionally took individual micronutrient supplements, including selenium, β-carotene, or zinc. In the Health Professionals Follow-Up Study, a two- to three-fold increased risk of advanced and fatal prostate cancer was observed in men who took high-dose calcium ($>$ 1,500 mg/d)[6] or zinc ($>$ 25 mg/d)[7] supplements. These data suggest that intake of one or more vitamins or minerals at levels exceeding a standard requirement dose may increase risk of advanced and fatal prostate cancer.

Antioxidant supplementation (β-carotene, vitamin E, and selenium) deserves specific consideration because antioxidants are given at substantially higher than standard requirement doses. One review and meta-analysis considered 12 eligible randomized clinical trials with 104,196 total participants. Antioxidant supplementation did not significantly reduce total cancer incidence or mortality. β-Carotene at high doses increased the risk of cancer incidence; the marginally increased cancer mortality was probably primarily a result of an increase in incidence. Selenium seemed to reduce cancer incidence and mortality in men; the decrease in mortality was probably a result of a decrease in incidence. However, recent results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized trial of selenium and vitamin E in 35,533 men followed for a median of 5.46 years, did not show any benefit of selenium or vitamin E on incident prostate cancer.[8] However, SELECT did not examine survival, and it is possible that vitamin E supplementation may reduce the risk of advanced and fatal prostate cancer and possibly improve cancer survival in smokers only.[9] An additional aspect of antioxidants is that high-dose antioxidant supplements might interfere with some radiation or chemotherapy regimens, which kill cells though oxidative mechanisms, although the evidence remains controversial.[10]

A vitamin of special interest is folate, which plays an essential role in one-carbon metabolism as a carrier of single-carbon units, including participation in DNA methylation and DNA biosynthesis.[11-13] Recently, some findings have suggested that, although folate intake may decrease the risk of early lesions of colorectal neoplasia, high intakes of folate after the neoplastic lesion develops may increase the risk of colorectal cancer.[14,15] This finding has raised concern that fortification of flour and uncooked cereal grains with synthetic folic acid may have increased incidence of colorectal cancer.[16,17] The role of antifolates in cancer treatment may also suggest that excessive folate in patients with cancer or survivors may provide an essential nutrient for tumor growth. Supplemental folic acid, as in multivitamins, combined with fortification may lead to high intakes in individuals. In a recently published study of a randomized controlled trial in Norway, individuals who had received folic acid plus vitamin B12 were 38% more likely to die from cancer than those who received placebo, especially from lung cancer.[18] Further study is warranted, but it is prudent for cancer survivors to avoid excessive folate intakes.

VITAMIN D

Vitamin D deserves special consideration for three reasons. First, in addition to vitamin D from diet or supplements, sun exposure is an important source. Unlike other vitamins, which generally are consumed adequately or even in excess in the United States, vitamin D status is generally deficient by most standards. Second, vitamin D acts more like a hormone that helps regulate gene transcription than as a conventional vitamin. Third, both mechanistic data and some human evidence suggest that vitamin D may have anticancer properties.

In 1980, it was hypothesized that inadequate vitamin D status resulting from lower solar ultraviolet B radiation exposure accounted for the association between higher latitudes and increased mortality of colon cancer,[19] breast cancer,[20] and ovarian cancer.[21] Thereafter, the proposed anticarcinogenic effects of vitamin D were extended to prostate cancer[22,23] and other malignancies.[24] In the past several decades, experimental studies have documented a number of anticarcinogenic properties of vitamin D, including inducing differentiation and inhibiting proliferation, invasiveness, angiogenesis, and metastatic potential. Although vitamin D may influence the risk of developing cancer, some of these biologic factors may relate to progression and survival. Late anticancer effects of vitamin D, such as reduction in metastases,

have been observed in numerous animal models. Some evidence from animal models suggests that vitamin D analogs may improve tumor control by radiation treatment, in part by promoting apoptosis.[25] In fact, some data suggest that vitamin D may be more strongly related to cancer progression than to incidence. For example, the geographical association between ultraviolet B exposure and cancer was stronger for mortality than for incidence for many cancers.[26] In addition, in some studies, patients diagnosed with cancer during the summer months, when vitamin D status is higher, had a better prognosis than those diagnosed and/or treated during the winter months.[27]

Stronger evidence for an effect of vitamin D status on cancer progression is based on studies showing that measures of vitamin D status assessed prediagnostically or at the time of diagnosis/treatment have been associated with better survival. In one study of 447 patients with early-stage non–small-cell lung cancer, after adjusting for age, sex, stage, smoking, and treatment, a 26% borderline significant better overall survival was observed for patients in the highest versus lowest quartile of circulating 25-hydroxyvitamin D levels. Stratified by stage, a 55% significant reduction was observed among patients with stages IB to IIB.[28,29] No association was observed for advanced-stage disease. In one study conducted in Norway, cod liver oil, an important source of vitamin D, was associated with improved survival for total solid tumors and especially for lung cancer among those who developed cancer.[30] However, other supplements also were associated with improved survival, and cod liver oil has other components than vitamin D. For breast cancer, in one cohort of 512 women with early breast cancer diagnosed from 1989 to 1996, 25-hydroxyvitamin D levels were measured in stored blood. Mean follow-up time was 11.6 years; 116 women experienced distant recurrences, and 106 women died. Women with deficient vitamin D levels had a 94% increased risk of distant recurrence and a 73% increased risk of death compared with those with sufficient levels. The association remained after individual adjustment for key tumor- and treatment-related factors but was slightly attenuated in multivariate analyses for distant recurrence and for death.[31]

Although the results from studies in which 25-hydroxyvitamin D is measured in cancer patients are provocative, there are two potential limitations inherent in this design. First, it is possible that sicker patients with a worse prognosis may have lower vitamin D levels (for example, because of less sun exposure), even after adjustment for other prognostic indicators or limiting analyses to patients with early-stage disease. Second, the level of vitamin D, although taken from a postdiagnostic blood sample, could correlate with prediagnostic levels; thus, we cannot definitively determine the timing of the association. One study attempted to address these issues. Prediagnostic 25-hydroxyvitamin D levels were examined in relation to mortality among 304 participants in the Nurses' Health Study and the Health Professionals Follow-Up Study who were diagnosed with colorectal cancer from 1991 to 2002 and followed until 2005.[28] In multivariate analyses, compared with those in the lowest quartile, participants in the highest quartile had a multivariate adjusted 48% reduced hazard ratio for overall mortality and a nonsignificant 49% reduced hazard ratio for colorectal cancer–specific mortality. The results persisted after excluding patients diagnosed within 5 years of blood collection. Furthermore, predicted 25-hydroxyvitamin D level was examined in relation to mortality among 1,017 participants in these same cohorts who were diagnosed with colorectal cancer from 1986 to 2004.[32] Higher predicted 25-hydroxyvitamin D levels (based on a quantification of six factors that influence vitamin D status) were associated with a 50% significant reduction in colorectal cancer–specific mortality and a 38% reduction in overall mortality compared with lower levels. These associations persisted even after adjusting for prediagnostic predicted 25-hydroxyvitamin D level. These observational data suggest the intriguing possibility that improving vitamin D status at the time of and after diagnosis could potentially prolong survival.

Currently, interventional studies that administer vitamin D versus placebo in patients with cancer are lacking. Such trials should be a high priority because of the hypothesized benefits and low risk of vitamin D, because many cancer patients are vitamin D deficient, and because such interventions can be feasibly completed within a relatively short time period. Because any effect of vitamin D could differ by tumor type, studies need to be conducted separately for various cancers because the results for one cancer may not necessarily be generalized to another.

ASPIRIN AND COX-2 INHIBITION

A compelling body of evidence from epidemiologic studies[33,34] and randomized trials[35-38] demonstrates that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of colorectal adenoma and cancer, presumably through inhibition of COX-2. COX is the rate-limiting enzyme for the metabolic conversion of arachidonic acid to prostaglandins and related eicosanoids. The COX-2 isoenzyme is induced by growth factors, oncogenes, tumor promoters, and inflammatory cytokines.[39,40] Despite the likely benefit of aspirin in lowering colorectal cancer risk, concern about aspirin's adverse effect profile has engendered limited enthusiasm about recommending widespread, long-term aspirin use for colorectal cancer prevention in the general population. The US Preventative Task Force recently recommended against the routine use of aspirin for chemoprevention but did suggest the possibility that aspirin may be appropriate for specific subgroups of high-risk individuals.[41]

Such a subgroup would likely include patients with established colorectal cancer, including those with nonmetastatic disease who have undergone a resection for curative intent. Such patients would stand to benefit considerably if aspirin therapy could lower the risk of recurrence and improve the odds of survival. In animal models, aspirin or other NSAIDs have been shown to inhibit tumor growth and metastases, as well as prolong survival.[42,43] A randomized trial of standard-dose aspirin (325 mg) in patients with prior Dukes' stage A or B1 colon or rectal cancer who had undergone curative resection of their primary tumor demonstrated a 35% reduction in risk of colorectal adenoma after a median of 30 months of treatment.[36]

To investigate whether aspirin use can influence the prognosis of patients with established colorectal cancer, an analysis of 1,279 patients with established stage I, II, or III colorectal cancer enrolled onto two large, ongoing prospective cohort studies (the Nurses' Health Study and the Health Professionals Follow-Up Study) was conducted.[44] Use of aspirin after diagnosis of nonmetastatic colorectal cancer was associated with a 29% reduction in colorectal cancer death and a 21% reduction in overall death (12-year median follow-up). Regular aspirin use after diagnosis was associated with a particularly lower risk of colorectal cancer–specific mortality

among participants in whom primary tumors overexpressed COX-2.[44,45] A recent study also observed an association between improved colorectal cancer–specific survival and prolonged NSAID use before diagnosis.[47] Although data supporting a role for aspirin or NSAIDs in lung cancer prevention are conflicting,[46] there are also promising results suggesting a role for COX-2 expression in tailoring lung cancer treatment. In a phase II trial of patients with advanced non–small-cell lung cancer treated with chemotherapy, random assignment to the COX-2–selective inhibitor celecoxib did not improve survival compared with patients who did not receive the drug. However, patients with increased COX-2 expression receiving celecoxib had better survival than patients with increased COX-2 expression not receiving the drug.[48] Similarly, a recent prospective, observational study of 4,164 women with stage I, II, or III breast cancer found that use of aspirin after diagnosis (6 to 7 days per week) was associated with a decrease in risk of breast cancer death (multivariate relative risk = 0.36; 95% CI, 0.24 to 0.54) compared with nonusers.[49]

These results suggest that aspirin may not only prevent certain cancers, but also influence the biology of established disease. Moreover, these data underscore the potential for using COX-2 or related markers to tailor aspirin use among patients with newly diagnosed cancer. If confirmed in other prospective studies, testing tumors for COX-2 status could be used as a means of identifying patients who are relatively sensitive to the anticancer effect of aspirin and should be considered more strongly for treatment. In contrast, patients with COX-2–negative tumors may be relatively aspirin resistant and could be spared unnecessary exposure to aspirin's potential adverse effects. Randomized trials are needed to confirm these results before routine clinical recommendations can be implemented. Recently, a large, placebo-controlled trial examining the use of 200 mg of daily aspirin has begun enrolling patients with stage III colorectal cancer in several centers in Southeast Asia and India. This trial will hopefully offer results by 2015.

SUMMARY

Vitamin and mineral supplements are widely consumed in general and by cancer patients and survivors. In individuals with developing but yet undiagnosed cancers, patients with cancer receiving treatment, and cancer survivors, these supplements could have unique effects, either beneficial or adverse, because of the presence of the tumor. Thus, patients with cancer need to be considered distinctly from those without cancer because it is plausible, for example, that a supplement has anticancer benefits before tumor development but could potentially accelerate tumor growth. In fact, some evidence suggests that folate or folic acid could potentially act in this manner. Thus, it is currently prudent that patients with cancer and survivors avoid high consumption of folic acid. For prostate cancer, there is suggestive evidence that excess consumption of one or a combination of components in a multivitamin/multimineral may accelerate cancer progression and increase fatality, although studies specifically in survivors have not been reported to date. Smoking may be an important modifying factor, and for some cancers that are associated with smoking, survivors will be enriched with smokers. High-dose β-carotene seems to increase risk of developing some cancers in smokers, although it is unclear whether it influences prognosis. Antioxidant supplements do not seem to have broad anticancer or harmful effects (except for high-dose β-carotene in smokers) but may possibly be beneficial for specific cancers in some specific high-risk groups (eg, vitamin E for prostate cancer in smokers).

Promising areas include the potential roles of vitamin D for multiple cancers and aspirin for colorectal cancer survivors. Although vitamin D can be considered as a vitamin supplement, much, if not most, of vitamin D currently is attained through sun exposure. In fact, the standard doses (200 to 600 IU/d) may be inadequate to achieve optimal levels. Attaining 25-hydroxyvitamin D levels of at least 30 ng/mL, which may be optimal according to some studies, may require 1,000 to 2,000 U/d for most individuals, although those with minimal sun exposure over prolonged periods may require even higher doses.[50] Although the anticancer benefits of vitamin D are not definitively proven in interventions, achieving these intakes and levels in patients with cancer, who often are severely deficient in vitamin D, is prudent given the general health benefits of adequate vitamin D status.[50] Aspirin is proven to lower risk of colorectal cancer, although it is not typically used in a primary prevention setting because of its associated adverse effect profile; if aspirin is confirmed to improve survival, particularly among those with COX-2–positive tumors, it may serve as a useful adjunct to treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Velicer CM, Ulrich CM: Vitamin and mineral supplement use among US adults after cancer diagnosis: A systematic review. J Clin Oncol 26:665-673, 2008
2. World Cancer Research Fund: Food, nutrition, physical activity, and the prevention of cancer: A global perspective. Washington, DC, World Cancer Research Fund/American Institute for Cancer Research, 2007
3. Doyle C, Kushi LH, Byers T, et al: Nutrition and physical activity during and after cancer treatment: An American Cancer Society guide for informed choices. CA Cancer J Clin 56:323-353, 2006
4. Stevens VL, McCullough ML, Diver WR, et al: Use of multivitamins and prostate cancer mortality in a large cohort of US men. Cancer Causes Control 16:643-650, 2005
5. Lawson KA, Wright ME, Subar A, et al: Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. J Natl Cancer Inst 99:754-764, 2007
6. Giovannucci E, Liu Y, Stampfer MJ, et al: A prospective study of calcium intake and incident and fatal prostate cancer. Cancer Epidemiol Biomarkers Prev 15:203-210, 2006
7. Leitzmann MF, Stampfer MJ, Wu K, et al: Zinc supplement use and risk of prostate cancer. J Natl Cancer Inst 95:1004-1007, 2003
8. Lippman SM, Klein EA, Goodman PJ, et al: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 301:39-51, 2009

9. Watters JL, Gail MH, Weinstein SJ, et al: Associations between alpha-tocopherol, beta-carotene, and retinol and prostate cancer survival. Cancer Res 69:3833-3841, 2009

10. Lawenda BD, Kelly KM, Ladas EJ, et al: Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J Natl Cancer Inst 100:773-783, 2008

11. Lucock M: Folic acid: Nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab 71:121-138, 2000

12. Van den Veyver IB: Genetic effects of methylation diets. Annu Rev Nutr 22:255-282, 2002

13. Lamprecht SA, Lipkin M: Chemoprevention of colon cancer by calcium, vitamin D and folate: Molecular mechanisms. Nat Rev Cancer 3:601-614, 2003

14. Song J, Sohn KJ, Medline A, et al: Chemopreventive effects of dietary folate on intestinal polyps in Apc+/- Msh2-/- mice. Cancer Res 60:3191-3199, 2000

15. Song J, Medline A, Mason JB, et al: Effects of dietary folate on intestinal tumorigenesis in the Apc^{Min} mouse. Cancer Res 60:5434-5440, 2000

16. Mason JB, Dickstein A, Jacques PF, et al: A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis. Cancer Epidemiol Biomarkers Prev 16: 1325-1339, 2007

17. Hirsch S, Sanchez H, Albala C, et al: Colon cancer in Chile before and after the start of the flour fortification program with folic acid. Eur J Gastroenterol Hepatol 21:436-439, 2009

18. Ebbing M, Bonaa KH, Nygard O, et al: Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA 302:2119-2126, 2009

19. Garland CF, Garland FC: Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 9:227-231, 1980

20. Garland FC, Garland CF, Gorham ED, et al: Geographic variation in breast cancer mortality in the United States: A hypothesis involving exposure to solar radiation. Prev Med 19:614-622, 1990

21. Lefkowitz ES, Garland CF: Sunlight, vitamin D, and ovarian cancer mortality rates in US women. Int J Epidemiol 23:1133-1136, 1994

22. Schwartz GG, Hulka BS: Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). Anticancer Res 10:1307-1311, 1990

23. Hanchette CL, Schwartz GG: Geographic patterns of prostate cancer mortality. Cancer 70:2861-2869, 1992

24. Grant WB: An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 94:1867-1875, 2002

25. Sundaram S, Sea A, Feldman S, et al: The combination of a potent vitamin D3 analog, EB 1089, with ionizing radiation reduces tumor growth and induces apoptosis of MCF-7 breast tumor xenografts in nude mice. Clin Cancer Res 9:2350-2356, 2003

26. Boscoe FP, Schymura MJ: Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2002. BMC Cancer 6:264, 2006

27. Porojnicu A, Robsahm TE, Berg JP, et al: Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: A possible role of sun-induced vitamin D. J Steroid Biochem Mol Biol 103:675-678, 2007

28. Ng K, Meyerhardt JA, Wu K, et al: Circulating 25-hydroxyvitamin D levels and survival in patients with colorectal cancer. J Clin Oncol 26:2984-2991, 2008

29. Zhou W, Heist RS, Liu G, et al: Circulating 25-hydroxyvitamin D levels predict survival in early-stage non–small-cell lung cancer patients. J Clin Oncol 25:479-485, 2007

30. Skeie G, Braaten T, Hjartaker A, et al: Cod liver oil, other dietary supplements and survival among cancer patients with solid tumours. Int J Cancer 125:1155-1160, 2009

31. Goodwin PJ, Ennis M, Pritchard KI, et al: Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. J Clin Oncol 27:3757-3763, 2009

32. Ng K, Wolpin BM, Meyerhardt JA, et al: Prospective study of predictors of vitamin D status and survival in patients with colorectal cancer. Br J Cancer 101:916-923, 2009

33. Serhan CN: Resolution phases of inflammation: Novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. Annu Rev Immunol 25:101-137, 2007

34. Chan AT: Aspirin, non-steroidal anti-inflammatory drugs, and colorectal neoplasia: Future challenges in chemoprevention. Cancer Causes Control 14:413-418, 2003

35. Baron JA, Cole BF, Sandler RS, et al: A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 348:891-899, 2003

36. Sandler RS, Halabi S, Baron JA, et al: A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 348:883-890, 2003

37. Benamouzig R, Deyra J, Martin A, et al: Daily soluble aspirin and prevention of colorectal adenoma recurrence: One-year results of the APACC trial. Gastroenterology 125:328-336, 2003

38. Logan RF, Grainge MJ, Shepherd VC, et al: Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology 134:29-38, 2008

39. Brown JR, DuBois RN: COX-2: A molecular target for colorectal cancer prevention. J Clin Oncol 23:2840-2855, 2005

40. Dannenberg AJ, Lippman SM, Mann JR, et al: Cyclooxygenase-2 and epidermal growth factor receptor: Pharmacologic targets for chemoprevention. J Clin Oncol 23:254-266, 2005

41. Dube C, Rostom A, Lewin G, et al: The use of aspirin for primary prevention of colorectal cancer: A systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med 146:365-375, 2007

42. Yao M, Zhou W, Sangha S, et al: Effects of nonselective cyclooxygenase inhibition with low-dose ibuprofen on tumor growth, angiogenesis, metastasis, and survival in a mouse model of colorectal cancer. Clin Cancer Res 11:1618-1628, 2005

43. Lundholm K, Gelin J, Hyltander A, et al: Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. Cancer Res 54:5602-5606, 1994

44. Chan AT, Ogino S, Fuchs CS: Aspirin use and survival after diagnosis of colorectal cancer. JAMA 302:649-658, 2009

45. Chan AT, Ogino S, Fuchs CS: Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 356:2131-2142, 2007

46. Feskanich D, Bain C, Chan AT, et al: Aspirin and lung cancer risk in a cohort study of women: Dosage, duration and latency. Br J Cancer 97:1295-1299, 2007

47. Zell JA, Ziogas A, Bernstein L, et al: Nonsteroidal anti-inflammatory drugs: Effects on mortality after colorectal cancer diagnosis. Cancer 115:5662-5671, 2009

48. Edelman MJ, Watson D, Wang X, et al: Eicosanoid modulation in advanced lung cancer: Cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy—Cancer and Leukemia Group B Trial 30203. J Clin Oncol 26:848-855, 2008

49. Holmes MD, Chen WY, Li L, et al: Aspirin intake and survival after breast cancer. J Clin Oncol 28:1467-1472, 2010

50. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al: Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 84:18-28, 2006