RESOLUÇÃO CFM Nº 2.004/2012

(Publicada no D.O.U. 11 dez. 2012. Seção I, p.143)

Revoga a Resolução CFM nº 1.938/2010

Normatiza os procedimentos diagnósticos e terapêuticos da prática ortomolecular ou outros assemelhados, obedecendo aos postulados científicos oriundos de estudos clínico-epidemiológicos.

O **CONSELHO FEDERAL DE MEDICINA**, no uso das atribuições conferidas pela Lei n° 3.268, de 30 de setembro de 1957, regulamentada pelo Decreto n° 44.045, de 19 de julho de 1958, respectiva e posteriormente alterados pela Lei nº 11.000, de 15 de dezembro de 2004, e Decreto nº 6.821, de 14 de abril de 2009, e

CONSIDERANDO que o alvo de toda a atenção do médico é a saúde do ser humano, em benefício da qual deverá agir com o máximo de zelo e o melhor de sua capacidade profissional;

CONSIDERANDO que ao médico cabe zelar e trabalhar pelo perfeito desempenho ético da Medicina e pelo prestígio e bom conceito da profissão;

CONSIDERANDO que é dever do médico guardar absoluto respeito pela saúde e vida do ser humano, sendo-lhe vedado realizar atos não consagrados nos meios acadêmicos ou ainda não aceitos pela comunidade científica;

CONSIDERANDO que é vedado ao médico divulgar informação sobre assunto médico de forma sensacionalista, promocional ou de conteúdo inverídico;

CONSIDERANDO que é vedado ao médico usar experimentalmente qualquer tipo de terapêutica ainda não liberada para uso em nosso país, sem a devida autorização dos órgãos competentes e sem o consentimento do paciente ou de seu responsável legal, devidamente informados da situação e das possíveis consequências;

CONSIDERANDO a crescente divulgação, entre a população, de novos métodos terapêuticos baseados no emprego de substâncias com vistas ao equilíbrio celular, e a insuficiente comprovação científica de algumas dessas propostas;

CONSIDERANDO a existência de extensa literatura científica sobre radicais livres, substâncias antioxidantes e nutrição humana;

CONSIDERANDO a dificuldade da transposição de informações originadas de dados de experimentações realizadas em animais ou em sistemas, órgãos, tecidos e células isoladas para a prática clínica diária;

CONSIDERANDO os riscos potenciais de doses inadequadas de produtos terapêuticos, tais como algumas vitaminas e certos sais minerais;

CONSIDERANDO a necessidade de definir limites de emprego, indicações e critérios científicos para a aplicação de procedimentos associados à prática ortomolecular;

CONSIDERANDO o que preceituam as Resoluções nºs 196/96 e 251/97, do Conselho Nacional de Saúde, que, respectivamente, contém as diretrizes e normas regulamentadoras da pesquisa envolvendo seres humanos e dispõe sobre a pesquisa com novos fármacos, medicamentos, vacinas e testes diagnósticos;

CONSIDERANDO o teor das Portarias nºs 32/98 e 40/98 da Secretaria de Vigilância Sanitária/MS, e da Resolução RDC nº 269/2005, da Anvisa, que estabelecem normas para níveis de dosagens diárias de vitaminas e minerais em medicamentos e a utilização diária pelo usuário;

CONSIDERANDO o que preceitua a Resolução CFM nº 1.982/2012, que dispõe sobre os critérios de protocolo e avaliação para o reconhecimento de novos procedimentos e terapias médicas pelo Conselho Federal de Medicina;

CONSIDERANDO, finalmente, o decidido na sessão plenária de 8 de novembro de 2012,

RESOLVE:

Art. 1º Os termos prática ortomolecular, biomolecular ou outros assemelhados não caracterizam especialidade médica nem área de atuação, não podendo ser anunciados de acordo com as resoluções normativas sobre a matéria.

Art. 2º A avaliação de nutrientes, vitaminas, minerais, ácidos graxos ou aminoácidos que podem, eventualmente, estar em falta ou em excesso no organismo humano, faz parte da propedêutica médica.

§ 1º A identificação de alguma das deficiências ou excessos só poderá ser atribuída a erro nutricional ou distúrbio da função digestiva após terem sido investigadas e/ou tratadas as doenças de base concomitantes.

§ 2º Os tratamentos das eventuais deficiências ou excessos devem obedecer às comprovações embasadas por evidências clínico-epidemiológicas que indiquem efeito terapêutico benéfico.

Art. 3º A reposição medicamentosa em comprovadas deficiências de vitaminas, minerais, ácidos graxos ou aminoácidos será feita de acordo com a existência de nexo causal entre a reposição de nutrientes e a meta terapêutica ou preventiva.

Art. 4º Medidas higiênicas, dietéticas e de estilo de vida não podem ser substituídas por qualquer tratamento medicamentoso, suplementos de vitaminas, sais minerais, ácidos graxos ou aminoácidos.

Art. 5º A remoção de minerais, quando em excesso, ou de minerais tóxicos, agrotóxicos, pesticidas ou aditivos alimentares será feito de acordo com os seguintes princípios:

I - o excesso de cada substância tóxica deverá ser considerado isoladamente;

II - existência, na literatura médica, de fundamentação bioquímica e fisiológica sobre o efeito deletério do excesso da substância tóxica considerada, bem como de dados que comprovem a possibilidade de correção efetiva por meio da remoção proposta;

III - além da melhoria dos parâmetros laboratoriais, deverá haver comprovação científica de utilidade clínica;

IV - o valor terapêutico da remoção de determinada substância tóxica deverá ser avaliado para cada tipo de distúrbio.

Art. 6º São destituídos de comprovação científica suficiente quanto ao benefício para o ser humano sadio ou doente, e por essa razão têm vedados o uso e divulgação no exercício da Medicina, os seguintes procedimentos, diagnósticos ou terapêuticos, que empregam:

I - para a prevenção primária e secundária, doses de vitaminas, proteínas, sais minerais e lipídios que não respeitem os limites de segurança (megadoses), de acordo com as normas nacionais e internacionais;

II - EDTA (ácido etilenodiaminotetracético) para remoção de metais tóxicos fora do contexto das intoxicações agudas e crônicas;

III - o EDTA e a procaína como terapia antienvelhecimento, anticâncer, antiarteriosclerose ou voltadas para doenças crônico-degenerativas;

IV - análise do tecido capilar fora do contexto do diagnóstico de contaminação e/ou intoxicação por metais tóxicos;

V - antioxidantes para melhorar o prognóstico de pacientes com doenças agudas;

VI - antioxidantes que interfiram no mecanismo de ação da quimioterapia e da radioterapia no tratamento de pacientes com câncer;

VII - quaisquer terapias antienvelhecimento, anticâncer, antiarteriosclerose ou voltadas para doenças crônico-degenerativas, exceto nas situações de deficiências diagnosticadas cuja reposição mostra evidências de benefícios cientificamente comprovados.

Art. 7º A indicação ou prescrição de medida terapêutica da prática ortomolecular, biomolecular ou outras assemelhadas é de exclusiva competência e responsabilidade do médico.

Art. 8º Revogam-se todas as disposições em contrário, em especial a Resolução CFM nº 1.938/2010, publicada no Diário Oficial da União, Seção I, p. 161, em 5 de fevereiro de 2010.

Art. 9º Esta resolução entra em vigor na data de sua publicação.

Brasília-DF, 8 de novembro de 2012

ROBERTO LUIZ D'AVILA
Presidente

HENRIQUE BATISTA E SILVA
Secretário-geral

EXPOSIÇÃO DE MOTIVOS DA RESOLUÇÃO CFM Nº 2.004/2012

Foi realizada criteriosa revisão da literatura de estudos de qualidade metodológica e clínico-epidemiológica sobre antioxidantes, vitaminas e suplementos. Nesta pesquisa se encontram claras evidências dos riscos e prejuízos à saúde, e nenhuma ou pouca evidência de benefícios dessas drogas para a capacidade funcional, qualidade de vida, cognição, bem como para prevenir doenças crônicas, retardar, modular e/ou reverter o processo de envelhecimento.

As prescrições de nutrientes, vitaminas, minerais, ácidos graxos ou aminoácidos devem ser restritas às deficiências comprovadas e ponderando-se seu custo-benefício, com revisão dos critérios de indicação, acompanhamento e suspensão.

Usar tais medicamentos com base em sintomatologia inespecífica e sem evidência laboratorial nenhuma é submeter o paciente a uma condição anormal de excesso de oferta.

A prescrição dos referidos medicamentos, vitaminas, hormônios e sais minerais precisa ser feita com base em evidências científicas comprovadas e somente trabalhos científicos realizados com metodologia adequada asseguram que determinado tratamento trará benefícios ao paciente.

Existem evidências de que o emprego de algumas vitaminas e antioxidantes sem que o organismo deles necessite, ao contrário do proposto pela chamada prática ortomolecular, pode causar vários e graves efeitos colaterais, inclusive o desencadeamento de certos tipos de câncer.

Finalmente, considerando a Resolução CFM nº 1.982/12, que dispõe sobre os critérios de protocolo e avaliação para o reconhecimento de novos procedimentos e terapias médicas pelo Conselho Federal de Medicina, é desnecessária a revisão periódica desta resolução. Se pesquisas forem realizadas, obedecidas as etapas pré-clínica, clínica restrita e clínica expandida, e validarem o uso de novos procedimentos na prática médica, os resultados serão encaminhados ao Conselho Federal de Medicina para as providências necessárias.

Brasília, 8 de novembro de 2012

GERSON ZAFALON MARTINS
Relator

HENRIQUE BATISTA E SILVA
Relator

BIBLIOGRAFIA UTILIZADA NA REVISÃO

Klein, EA, Thompson Jr IA, Tangen CM et al. ***Vitamin E and the risk of prostate cancer. The selenium and vitamin e cancer prevention trial (Select).*** *Jama 2011; 306(14): 1549-56.*

Conclusion: *Dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.*

Conclusão: *A suplementação com vitamina E aumenta significativamente o risco de câncer da próstata entre homens saudáveis.*

Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR. ***Dietary supplements and mortality rate in older women: the Iowa Women's Health Study.*** *Arch Intern Med. 2011; 171(18): 1625-33.*

Conclusions: *In older women, several commonly used dietary vitamin and mineral supplements may be associated with increased total mortality risk; this association is strongest with supplemental iron. In contrast to the findings of many studies, calcium is associated with decreased risk.*

Conclusões: *Em mulheres idosas, diversos suplementos vitamínicos e minerais utilizados frequentemente estão associados a um aumento do risco de mortalidade; esta associação é mais forte com ferro suplementar. Em contraste com os resultados de muitos estudos, o cálcio está associado com um risco diminuído.*

Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. ***Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials.*** *The Lancet - 14 June 2003 (Vol. 361, Issue 9374, Pages 2017-23).*

Interpretation: *The lack of a salutary effect was seen consistently for various doses of vitamins in diverse populations. Our results, combined with the lack of mechanistic data for efficacy of vitamin E, do not support the routine use of vitamin E.*

Interpretação: *Existe falta de um efeito saudável em várias doses de vitaminas em diversas populações. Nossos resultados, combinados com a falta de eficácia da vitamina E, contraindicam o uso rotineiro da vitamina E.*

Bjelakovic G, Nikolova D, Gluud L, Simonetti RG, Gluud C. ***Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis.*** *Jama. 2007; 297(8): 842-57.*

Conclusions: *Treatment with beta-carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.*

Conclusões: *O tratamento com betacaroteno, vitamina A e vitamina E aumentam a mortalidade. As funções potenciais da vitamina C e do selênio sobre a mortalidade precisam ser melhor estudadas.*

Lonn E et al. ***Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial.*** *Jama. 2005; 293(11): 1338-47.*

Conclusion: *In patients with vascular disease or diabetes mellitus, long-term vitamin E supplementation does not prevent cancer or major cardiovascular events and may increase the risk for heart failure.*

Conclusão: *Em pacientes com doença vascular ou* diabetes *mellitus, a suplementação a longo prazo com vitamina E não previne câncer ou eventos cardiovasculares maiores e aumenta o risco de insuficiência cardíaca.*

Hennekens CH et al. ***Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease.*** *N Engl J Med 1996; 334:1145-9.*

Conclusions: *In this trial among healthy men, 12 years of supplementation with beta-carotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes.*

Conclusões: *Neste estudo com homens saudáveis, a suplementação com betacaroteno durante 12 anos não causou benefício ou malefício em termos de incidência de neoplasias malignas, doença cardiovascular ou morte.*

The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta carotene Cancer Prevention Study Group. *N Engl J Med. 1994 Apr 14;330(15):1029-35.*

Conclusions: *We found no reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or beta-carotene. In fact, this trial raises the possibility that these supplements may actually have harmful as well as beneficial effects.*

Conclusões: *Não houve redução na incidência de câncer do pulmão entre homens fumantes após 5 a 8 anos de suplementação com vitamina E ou betacaroteno. O presente estudo aumenta as possibilidades de que estes suplementos vitamínicos possuem efeitos que causam mais danos que benefícios.*

*Omenn GS et al****. Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease.*** *N Engl J Med. 1996 May 2;334(18):1150-5.*

Conclusions: *After an average of four years of supplementation, the combination of beta- carotene and vitamin A had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer, cardiovascular disease, and any cause in smokers and workers exposed to asbestos.*

Conclusões: *Após quatro anos de suplementação com a combinação de betacaroteno e vitamina A não houve benefícios, e possivelmente ocorreram efeitos adversos na incidência de câncer do pulmão e no risco de morte por câncer do pulmão, doença cardiovascular em fumantes, e trabalhadores expostos ao asbesto.*

Neuhouser ML, Wassertheil-Smoller S, Thomson C et al. ***Multivitamin use and risk of cancer and cardiovascular disease in the women's health initiative cohorts.*** *Arch Intern Med. 2009; 169(3): 294-304.*

Conclusion: *After a median follow-up of 8.0 and 7.9 years in the clinical trial and observational study cohorts, respectively, the Women's Health Initiative study provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women.*

Conclusão: *Após um seguimento de 8 e 7,9 anos no ensaio clínico e estudo coorte observacional, respectivamente, o estudo WHI demonstra evidência convincente de que o uso de polivitamínicos tem pouca ou nenhuma influência no risco de cânceres comuns, doenças cardiovasculares ou mortalidade total das mulheres pós-menopausadas.*

Isaac MGEKN, Quinn R, Tabet N. ***Vitamin E for Alzheimer's disease and mild cognitive impairment.*** *Cochrane Database of Systematic Reviews 2008, Issue 3.*

Authors' conclusions: *There is no evidence of efficacy of Vitamin E in the prevention or treatment of people with AD or MCI. More research is needed to identify the role of Vitamin E, if any, in the management of cognitive impairment.*

Conclusões dos autores: *Não existem evidências quanto a eficácia da vitamina E na prevenção e tratamento de portadores de doença de Alzheimer ou comprometimento cognitivo leve. Mais pesquisas são necessárias para identificar a função da vitamina E, se houver alguma, no manejo do comprometimento cognitivo.*

Evans JR, Henshaw KS. ***Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration.*** *Cochrane Database of Systematic Reviews 2008, Issue 1.*

Authors' conclusions: *There is no evidence to date that the general population should take antioxidant vitamin and mineral supplements to prevent or delay the onset of AMD. There are several large ongoing trials.*

Conclusões dos autores: *Não existem evidências para que a população geral deva tomar suplementos minerais e vitamínicos antioxidantes para prevenir ou retardar o início da degeneração macular senil. Existem ainda grandes estudos em evolução.*

*Caraballoso M, Sacristan M, Serra C, Bonfill Cosp X****. Drugs for preventing lung cancer in healthy people.*** *Cochrane Database of Systematic Reviews 2003, Issue 2.*

Authors' conclusions: *There is currently no evidence to support recommending vitamins such as alpha-tocopherol, beta-carotene or retinol, alone or in combination, to prevent lung cancer.*

Conclusões dos autores: *Não existem evidências para se recomendar a indicação de vitaminas como betacaroteno, retinol, vitamina E, isoladas ou em combinação, para prevenir o câncer de pulmão.*

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. ***Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases.*** *Cochrane Database of Systematic Reviews 2012, Issue 3.*

Authors' conclusions: *We found no evidence to support antioxidant supplements for primary or secondary prevention. Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A. Antioxidant supplements need to be considered as medicinal products and should undergo sufficient evaluation before marketing.*

Conclusões dos autores: *Não existem evidências que deem suporte ao uso de polivitamínicos antioxidantes na prevenção primária e secundária. Betacaroteno e vitamina E podem aumentar a mortalidade, bem como altas doses de vitamina A. Os polivitamínicos antioxidantes necessitam ser considerados como medicamentos, e devem passar por suficientes avaliações antes da comercialização.*

VITAMINAS – OXIDANTES E MORTALIDADE

Effect on mortality:

- **antioxidant supplements do not reduce mortality risk (**level 1 [likely reliable] evidence**)**
  - based on Cochrane review
  - systematic review of 78 randomized trials with 296,707 adults comparing antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) to placebo or no intervention for primary or secondary prevention of any condition
  - 56 trials (72%) were high quality based on adequate randomization, allocation concealment, blinding and follow-up; 52 trials (80,807 adults) evaluated antioxidants for secondary disease prevention

- no significant difference in mortality in overall analysis
- no significant difference in mortality in overall analysis stratified by specific supplement, except trend toward reduction in mortality with selenium (risk ratio [RR] 0.96, 95% CI 0.91-1.01) in analysis of 24 trials with 86,150 adults
- in analyses limited to high-quality trials

- unstratified analysis found antioxidants associated with increased risk of mortality (RR 1.04, 95% CI 1.01-1.07)
- specific antioxidants associated with increased mortality were beta-carotene (RR 1.05, 95% CI 1.01-1.09) and vitamin E (RR 1.03, 95% CI 1-1.05)
  - analyses of lower-quality trials suggested decreased mortality
  - Reference - Cochrane Database Syst Rev 2012 Mar 14;(3):CD007176, commentary on earlier version can be found in ACP J Club 2008 Sep 16;149(3):9 EBSCO*host* Full Text, Am Fam Physician 2008 Nov 1;78(9):1079 EBSCO*host* Full Text full-text, earlier version published in JAMA 2007 Feb 28;297(8):842 full-text, correction can be found in JAMA 2008 Feb 20;299(7):765, commentary can be found in ACP J Club 2007 Jul-Aug;147(1):4 EBSCO*host* Full Text, JAMA 2007 Jul 25;298(4):400

VITAMINAS, ANTIOXIDANTES – CÂNCER

General cancer prevention:

- **antioxidant supplements do not reduce mortality risk (**level 1 [likely reliable] evidence**)**
  - based on Cochrane review
  - systematic review of 78 randomized trials with 296,707 adults comparing antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) to placebo or no intervention for primary or secondary prevention of any condition
  - 56 trials (72%) were high quality based on adequate randomization, allocation concealment, blinding and follow-up; 52 trials (80,807 adults) evaluated antioxidants for secondary disease prevention
  - no significant difference in mortality in overall analysis
  - no significant difference in mortality in overall analysis stratified by specific supplement, except trend toward reduction in mortality with selenium (risk ratio [RR] 0.96, 95% CI 0.91-1.01) in analysis of 24 trials with 86,150 adults
  - in analyses limited to high-quality trials
- unstratified analysis found antioxidants associated with increased risk of mortality (RR 1.04, 95% CI 1.01-1.07)
- specific antioxidants associated with increased mortality were beta-carotene (RR 1.05, 95% CI 1.01-1.09) and vitamin E (RR 1.03, 95% CI 1-1.05)
  - analyses of lower-quality trials suggested decreased mortality

- Reference - Cochrane Database Syst Rev 2012 Mar 14;(3):CD007176, commentary on earlier version can be found in ACP J Club 2008 Sep 16;149(3):9 EBSCO*host* Full Text, Am Fam Physician 2008 Nov 1;78(9):1079 EBSCO*host* Full Text full-text, earlier version published in Jama 2007 Feb 28;297(8):842 full-text, correction can be found in Jama 2008 Feb 20;299(7):765, commentary can be found in ACP J Club 2007 Jul-Aug;147(1):4 EBSCO*host* Full Text, Jama 2007 Jul 25;298(4):400

- **antioxidant supplementation not associated with reduced risk of cancer**
  - based on systematic review
  - systematic review of 22 trials evaluating antioxidant supplements for primary and secondary prevention of cancer in 161,045 persons (compared to placebo or no intervention)
  - antioxidants not associated with reduced risk of cancer
    - overall in 22 trials
    - primary prevention in 12 trials
    - secondary prevention in 9 trials
  - similar results in analyses organized by antioxidant type or study quality
  - type of cancer did not change result except for INCREASED risk of bladder cancer (relative risk 1.52, 95% CI 1.06-2.17) in analysis of 4 trials
  - Reference - Ann Oncol 2010 Jan;21(1):166

- **Beta-carotene supplementation may increase cancer incidence among smokers, selenium associated with decreased cancer mortality and vitamin E supplementation may have no effect**
  - based on systematic review of 12 trials that compared antioxidants vs. placebo and effect on cancer incidence and cancer mortality
  - antioxidant supplementation did not reduce total cancer incidence or mortality
  - beta carotene supplementation associated with increased incidence of cancer among smokers and trend toward increased cancer mortality (relative risk 1.16, 95% CI 0.98-1.37)
  - selenium associated with reduced cancer incidence in men but not women ($p < 0.001$) and with reduced cancer mortality
  - vitamin E supplementation had no effect on overall cancer incidence or cancer mortality
  - Reference - Mayo Clin Proc 2008 Jan;83(1):23 EBSCO*host* Full Text

- **vitamin C, vitamin E and beta-carotene supplementation not associated with reduced risk of cancer in women with cardiovascular disease risk**
  - based on secondary analysis of randomized trial
  - 7,627 women (mean age 60.4 years) without history of cancer who had cardiovascular disease (or ≥ 3 risk factors for cardiovascular disease) had 3 separate randomizations
    - vitamin C 500 mg vs. placebo daily
    - vitamin E 600 units vs. placebo every other day
    - beta-carotene 50 mg vs. placebo every other day
  - compliance (taking ≥ 2/3 capsules) was 76% at 4 years and 68% at 8 years for each antioxidant

- no significant effect of vitamin C, vitamin E or beta-carotene on incidence of any cancer
- vitamin C associated with increased risk of lung cancer (relative risk 1.84, 95% CI 1.14-2.97) but study not powered to detect differences in specific cancer types
- Reference - Women's Antioxidant Cardiovascular Study (Wacs) (J Natl Cancer Inst 2009 Jan 7;101(1):14)

- **beta-carotene supplementation may increase risk of lung and stomach cancers but appears to have no effect on cancer risk overall**
  - based on systematic review of 9 randomized trials of beta-carotene supplementation and cancer risk
  - no significant effect of beta-carotene on incidence of
- any cancer
- pancreatic cancer
- colorectal cancer
- prostate cancer
- breast cancer
- melanoma
- non-melanoma skin cancer
  - beta-carotene supplementation 20-30 mg per day significantly associated with increased risk of
- lung cancer (relative risk [RR] 1.16, 95% CI 1.06-1.27)
- stomach cancer (RR 1.34, 95% CI 1.06-1.7)
  - subgroups including smokers and asbestos workers supplemented with beta-carotene reported to be at increased risk
  - Reference - Int J Cancer 2010 Jul 1;127(1):172

Colorectal cancer prevention:

- **most antioxidant supplements (beta-carotene and vitamins A, C and E) do not prevent gastrointestinal (GI) cancers (**level 1 [likely reliable] evidence**)**
  - based on Cochrane review
  - systematic review of 14 randomized placebo-controlled trials with 170,525 patients
  - no significant effects on esophageal, gastric, colorectal, pancreatic or liver cancer incidences with supplementation of beta carotene, vitamin A, vitamin C, vitamin E or selenium (alone or in combination)
  - antioxidant supplementation may increase mortality
- based on findings from 7 high-quality trials with 131,727 patients, statistical significance varied with meta-analytic technique
- increase in mortality attributable to beta-carotene, alone or combined with vitamin A or vitamin E
  - selenium showed possible reduced incidence of GI cancer, based on 4 trials (but 3 had unclear or inadequate methodology)

- Reference - systematic review last updated 2004 Aug 24 (Cochrane Library 2004 Issue 4:CD004183), commentary can be found in Am Fam Physician 2005 Feb 1;71(3):465 full-text
- also published in Lancet 2004 Oct 2;364(9441):1219 EBSCO*host* Full Text**,** editorial can be found in Lancet 2004 Oct 2-8;364(9441):1193 EBSCO*host* Full Text, commentary can be found in ACP J Club 2005 Jan-Feb;142(1):20 EBSCO*host* Full Text, Lancet 2005 Feb 5-11;365(9458):470 EBSCO*host* Full Text

○ vitamin C **and** vitamin E **intake not associated with reduced colorectal cancer mortality (**level 2 [mid-level] evidence**)**

- based on cohort study of 711,891 men and women in American Cancer Society's Cancer Prevention Study II
- Reference - Cancer Epidemiol Biomarkers Prev 2001 Jan;10(1):17 full-text

Effect on mortality:

○ **antioxidant supplements do not reduce mortality risk (**level 1 [likely reliable] evidence**)**

- based on Cochrane review
- systematic review of 78 randomized trials with 296,707 adults comparing antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) to placebo or no intervention for primary or secondary prevention of any condition
- 56 trials (72%) were high quality based on adequate randomization, allocation concealment, blinding and follow-up; 52 trials (80,807 adults) evaluated antioxidants for secondary disease prevention
- no significant difference in mortality in overall analysis
- no significant difference in mortality in overall analysis stratified by specific supplement, except trend toward reduction in mortality with selenium (risk ratio [RR] 0.96, 95% CI 0.91-1.01) in analysis of 24 trials with 86,150 adults
- in analyses limited to high-quality trials

○ unstratified analysis found antioxidants associated with increased risk of mortality (RR 1.04, 95% CI 1.01-1.07)

○ specific antioxidants associated with increased mortality were beta-carotene (RR 1.05, 95% CI 1.01-1.09) and vitamin E (RR 1.03, 95% CI 1-1.05)

- analyses of lower-quality trials suggested decreased mortality
- Reference - Cochrane Database Syst Rev 2012 Mar 14;(3):CD007176, commentary on earlier version can be found in ACP J Club 2008 Sep 16;149(3):9 EBSCO*host* Full Text, Am Fam Physician 2008 Nov 1;78(9):1079 EBSCO*host* Full Text full-text, earlier version published in JAMA 2007 Feb 28;297(8):842 full-text, correction can be found in JAMA 2008 Feb 20;299(7):765, commentary can be found in ACP J Club 2007 Jul-Aug;147(1):4 EBSCO*host* Full Text, JAMA 2007 Jul 25;298(4):400

Effect on cardiovascular disease:

- available randomized trial evidence does not generally support cardiovascular benefit from antioxidant vitamin supplementation
  - based on systematic review (AHRQ Evidence Report 2003 Jun:83)
  - vitamin E not effective for treating or preventing cardiovascular disease, evidence does not support vitamin C, insufficient evidence to support or refute use of coenzyme Q10 (ACP J Club 2004 May-Jun;140(3):73 EBSCO*host* Full Text)
  - summary can be found in Am Fam Physician 2004 Jun 1;69(11):2716
- evidence-based review of vitamin supplements for prevention of coronary disease and stroke found observational studies supporting for vitamin E and inconsistent for vitamin C and folate, but randomized trials have not confirmed results and do not support use of vitamin supplements, beta-carotene supplements may be harmful and should not be used (Am Fam Physician 2000 Sep 15;62(6):1359 EBSCO*host* Full Text full-text), editorial can be found in Am Fam Physician 2000 Sep 15;62(6):1276 EBSCO*host* Full Text full-text
- **evidence-based review of multivitamin/mineral supplements for prevention of chronic disease**
  - no benefit in preventing cardiovascular disease
  - no benefit in preventing cataract
  - no consistent adverse effects except skin yellowing with beta-carotene, but limited evidence for safety
  - multivitamin/mineral supplements may reduce risk for advanced age-related macular degeneration in high-risk persons
  - some evidence for reduction in cancer risk in persons with suboptimal nutritional status
- combined beta-carotene, vitamin E and selenium reduce gastric cancer incidence and mortality, and overall cancer mortality, in 1 trial in poorly nourished Chinese persons
- combined vitamin C, vitamin E, beta-carotene, selenium and zinc reduce cancer risk in men but not in women in 1 French trial
- beta-carotene increased lung cancer risk in smokers and persons exposed to asbestos
  - Reference - AHRQ Evidence Report on Multivitamin/Mineral Supplements and Prevention of Chronic Disease 2006 May:139, National Institutes of Health (NIH) Consensus Conference 2006 May 15-17 on multivitamin/mineral supplements and chronic disease prevention (NIH Consens State Sci Statements 2006 May 15-17;23(2):1 full-text)
- **neither antioxidants nor B vitamin supplements protect against progression of atherosclerosis (**level 3 [lacking direct] evidence**)**
  - based on meta-analyses with 16 randomized trials
  - Reference - Am J Clin Nutr 2006 Oct;84(4):880 full-text

Recommendations:

- United States Preventive Services Task Force (USPSTF) recommendations
  - USPSTF recommends AGAINST using beta-carotene supplements (USPSTF Grade D)
  - USPSTF finds insufficient evidence to recommend for or against use of vitamins A, C or E, multivitamins with folic acid, or antioxidant combinations for prevention of cancer or cardiovascular disease (USPSTF Grade I)
  - Reference - USPSTF Task Force 2003 recommendations in Ann Intern Med 2003 Jul 1;139(1):51 EBSCO*host* Full Text full-text, commentary can be found in Ann Intern Med 2003 Jul 1;139(1):I EBSCO*host* Full Text full-text, supporting evidence-based review can be found in Ann Intern Med 2003 Jul 1;139(1):56 EBSCO*host* Full Text full-text, summary can be found in Am Fam Physician 2003 Dec 15;68(12):2422
- American Heart Association concludes scientific data do not justify use of antioxidant vitamin supplements for cardiovascular disease risk reduction (Circulation 2004 Aug 3;110(5):637 full-text), summary can be found in Am Fam Physician 2005 Apr 1;71(7):1433

Expert advises against high doses of supplements

5 may 2012-- That vitamin D and calcium you're taking could be causing more harm than good, a new article in the *Journal of the National Cancer Institute* says.

The paper, co-authored by a professor at the University of Arizona's Mel and Enid Zuckerman College of Public Health, cites evidence that high doses of some supplements increase cancer risk.
"You may not need to take supplements if you have a healthy diet," said article co-author Elizabeth Jacobs, a UA associate professor of epidemiology and a researcher at the Arizona Cancer Center. She cited an old phrase: "The dose makes the poison."
"If you are deficient in nutrients, taking a supplement is probably not going to cause any harm, but if you are already adequate in nutrients, then taking a supplement at a minimum has no benefit and in some cases has been shown to cause harm," Jacobs said.
Jacobs said the authors are not trying to say people who take supplements will get cancer. But she cautions about taking megadoses like 10,000 I.U.s of vitamin D per day, for example.
Labels: Calcium, d vitamin, Supplements

VITAMINAS – OXIDANTES – DOENÇA CARDIOVASCULAR

Multivitamins do not prevent cardiovascular disease:

- **low-dose multiple antioxidant vitamin supplementation does not prevent cardiovascular disease (**level 1 [likely reliable] evidence**)**

- 13,017 French adults (men aged 45-60 years and women aged 35-60 years) randomized to low-dose multivitamin (ascorbic acid 120 mg, vitamin E 30 mg, beta-carotene 6 mg, selenium 100 mcg, and zinc 20 mg) vs. placebo once daily for median 7.5 years; known as SU.VI.MAX trial
- no significant differences in rates of ischemic cardiovascular disease (2.1% vs. 2.1%), total cancer incidence (4.1% vs. 4.5%) or all-cause mortality (1.2% vs. 1.5%)
- no significant differences in any of these outcomes in women
- in men, no significant difference in ischemic cardiovascular disease (4.2% vs. 4.6%) but low-dose multivitamin supplementation reduced total cancer incidence (3.5% vs. 4.9%, p = 0.008, NNT 72) and all-cause mortality (1.6% vs. 2.5%, p = 0.02, NNT 111)
- Reference - Arch Intern Med 2004 Nov 22;164(21):2335 full-text, correction can be found in Arch Intern Med 2005 Feb 14;165(3):286

○ **multivitamin use may not reduce risk of cardiovascular disease, cancer or mortality in postmenopausal women (**level 2 [mid-level] evidence**)**

- based on cohort of 161,808 postmenopausal women from Women's Health Initiative randomized trials and observational study
- 41.5% used multivitamins
- no differences in rates of any cancer or cardiovascular outcomes or mortality comparing women who did vs. did not use multivitamins in median follow-up 8 years
- Reference - Arch Intern Med 2009 Feb 9;169(3):294

○ **antioxidant vitamins is not effective for cardiovascular disease prevention in high-risk patients (**level 1 [likely reliable] evidence**)**

- based on randomized trial
- trial included patients with non-fasting total cholesterol > 135 mg/dL (3.5 mmol/L) and coronary artery disease, diabetes, occlusive disease of non-coronary arteries or men > 65 years old with treated hypertension
- trial excluded patients with liver disease, renal disease, muscle disease, severe heart failure, conditions that might interfere with compliance and severe non-vascular disease
- 32,145 patients started with run-in phase of placebo for 4 weeks then simvastatin (Zocor) 40 mg daily for 4-6 weeks with evaluation of cholesterol to determine "LDL responsiveness", patients whose physicians considered them clearly indicated or contraindicated to take simvastatin were not randomized; 36% were not randomized due to patient choice or low likelihood of compliance for 5 years (26%), clear indication (or rarely contraindication) to statin (5%), elevated liver enzyme, creatinine or CK levels on pretreatment tests (3%), myopathy (0.01%) or other problems (3.3%)
- 20,536 patients were randomized to simvastatin 40 mg vs. antioxidants (vitamin E 600 mg, vitamin C 250 mg, beta-carotene 20 mg) vs. both vs. double placebo daily for mean 5 years; patients were encouraged to take nonstudy statin if deemed appropriate by their physician
- antioxidant vitamins used in the study were not effective

- Reference - Heart Protection Study (Lancet 2002 Jul 6;360(9326):23 EBSCO*host* Full Text), commentary can be found in J Fam Pract 2002 Oct;51(10):810 EBSCO*host* Full Text, ACP J Club 2003 Jan-Feb;138(1):3 EBSCO*host* Full Text

- **antioxidants not effective in patients with coronary disease and may reduce clinical efficacy of lipid-lowering agents**
  - 160 patients < 70 years old with clinical coronary disease (prior myocardial infarction, coronary intervention or angina), angiographic coronary stenoses, low HDL cholesterol, normal LDL cholesterol and normal triglyceride levels randomized to lipid-lowering therapy (simvastatin 10-20 mg/day then titrated plus slow-release niacin up to 4 g/day) vs. antioxidants (vitamin E 400 units, vitamin C 500 mg, beta-carotene 12.5 mg and selenium 50 mcg twice daily) vs. both vs. placebos for 3 years
  - risk of cardiovascular event (death, myocardial infarction, stroke or revascularization) was 3% with lipid-lowering therapy vs. 21% with antioxidants vs. 14% with both vs. 24% with placebos; antioxidants lowered clinical efficacy and attenuated increased in HDL cholesterol with lipid-lowering agents
  - Reference - N Engl J Med 2001 Nov 29;345(22):1583 EBSCO*host* Full Text full-text, editorial can be found in N Engl J Med 2001 Nov 29;345(22):1636 EBSCO*host* Full Text, commentary can be found inN Engl J Med 2002 Apr 4;346(14):1092 EBSCO*host* Full Text, Rev Cardiovasc Med 2002 Fall;3(4):205
- self-selected supplementation with vitamin E, vitamin C or multivitamins NOT associated with significantly decreased coronary mortality or cardiovascular mortality in prospective cohort study of 83,639 male physicians in United States followed for mean 5.5 years (Arch Intern Med 2002 Jul 8;162(13):1472 full-text), commentary can be found in Arch Intern Med 2002 Dec 9/23;162(22):2630

Effect on cardiovascular disease:

- available randomized trial evidence does not generally support cardiovascular benefit from antioxidant vitamin supplementation
  - based on systematic review (AHRQ Evidence Report 2003 Jun:83)
  - vitamin E not effective for treating or preventing cardiovascular disease, evidence does not support vitamin C, insufficient evidence to support or refute use of coenzyme Q10 (ACP J Club 2004 May-Jun;140(3):73 EBSCO*host* Full Text)
  - summary can be found in Am Fam Physician 2004 Jun 1;69(11):2716
- evidence-based review of vitamin supplements for prevention of coronary disease and stroke found observational studies supporting for vitamin E and inconsistent for vitamin C and folate, but randomized trials have not confirmed results and do not support use of vitamin supplements, beta-carotene supplements may be harmful and should not be used (Am Fam Physician 2000 Sep 15;62(6):1359 EBSCO*host* Full Text full-text), editorial can be found in Am Fam Physician 2000 Sep 15;62(6):1276 EBSCO*host* Full Text full-text

- **evidence-based review of multivitamin/mineral supplements for prevention of chronic disease**
  - no benefit in preventing cardiovascular disease
  - no benefit in preventing cataract
  - no consistent adverse effects except skin yellowing with beta-carotene, but limited evidence for safety
  - multivitamin/mineral supplements may reduce risk for advanced age-related macular degeneration in high-risk persons
  - some evidence for reduction in cancer risk in persons with suboptimal nutritional status
- combined beta-carotene, vitamin E and selenium reduce gastric cancer incidence and mortality, and overall cancer mortality, in 1 trial in poorly nourished Chinese persons
- combined vitamin C, vitamin E, beta-carotene, selenium and zinc reduce cancer risk in men but not in women in 1 French trial
- beta-carotene increased lung cancer risk in smokers and persons exposed to asbestos
  - Reference - AHRQ Evidence Report on Multivitamin/Mineral Supplements and Prevention of Chronic Disease 2006 May:139, National Institutes of Health (NIH) Consensus Conference 2006 May 15-17 on multivitamin/mineral supplements and chronic disease prevention (NIH Consens State Sci Statements 2006 May 15-17;23(2):1 full-text)
- **neither antioxidants nor B vitamin supplements protect against progression of atherosclerosis (**level 3 [lacking direct] evidence**)**
  - based on meta-analyses with 16 randomized trials
  - Reference - Am J Clin Nutr 2006 Oct;84(4):880 full-text

Recommendations:

- United States Preventive Services Task Force (USPSTF) recommendations
  - USPSTF recommends AGAINST using beta-carotene supplements (USPSTF Grade D)
  - USPSTF finds insufficient evidence to recommend for or against use of vitamins A, C or E, multivitamins with folic acid, or antioxidant combinations for prevention of cancer or cardiovascular disease (USPSTF Grade I)
  - Reference - USPSTF Task Force 2003 recommendations in Ann Intern Med 2003 Jul 1;139(1):51 EBSCO*host* Full Text full-text, commentary can be found in Ann Intern Med 2003 Jul 1;139(1):I EBSCO*host* Full Text full-text, supporting evidence-based review can be found in Ann Intern Med 2003 Jul 1;139(1):56 EBSCO*host* Full Text full-text, summary can be found in Am Fam Physician 2003 Dec 15;68(12):2422
- American Heart Association concludes scientific data do not justify use of antioxidant vitamin supplements for cardiovascular disease risk reduction (Circulation 2004 Aug 3;110(5):637 full-text), summary can be found in Am Fam Physician 2005 Apr 1;71(7):1433

VITAMINAS, ANTIOXIDANTES – DOENÇA DE ALZHEIMER

Vitamins

- **insufficient evidence to recommend vitamin E in patients with Alzheimer disease or MCI**
  - based on Cochrane review
  - systematic review of 1 unconfounded, blinded randomized trials evaluating vitamin E 2000 units orally per day alone or with selegiline 5 mg twice daily vs. placebo in 341 patients with moderate to severe dementia followed for 2 years
  - patients were followed to 1 or 4 end points, mortality, institutionalization, loss of 2 of 3 activities of daily living or decline of Clinical Dementia Rating score from 2 to 3
  - baseline differences in mean Mini Mental State Examination (MMSE) scores favoring vitamin E 11.3 vs. placebo 13.3 (RR 0.47, p = 0.001)
  - vitamin E associated with
    - fewer reaching end points (odds ratio [OR] 0.49, CI 0.25-0.96, NNT 4-141 assuming 78% to endpoint in controls)
    - increased falls (OR 3.09, 95% CI 1.07-8.62, NNH 4-302, assuming 5% falls in controls)
  - Reference - systematic review last updated 200 7 Jan 15 (Cochrane Library 2000 Issue 4:CD002854)
- **vitamin E does not prevent Alzheimer disease (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 790 subjects aged 55-90 years in United States and Canada with amnestic MCI, impaired memory and MMSE score 24-30 were randomized to vitamin E 1,000 units twice daily (1,000 units daily for first 6 weeks) vs. donepezil 10 mg daily (5 mg for first 6 weeks) vs. neither for 3 years
  - all patients received multivitamin with vitamin E 15 units daily and placebos for vitamin E and/or donepezil to maintain blinding
  - 769 patients completed baseline assessment
  - 212 patients (28%) developed possible or probable Alzheimer disease at rate of 16% per year
  - no significant differences between vitamin E and placebo in primary outcome at any time during the trial and few differences in some cognitive measures limited to first 18 months
  - no significant differences comparing vitamin E vs. placebo in subgroup of APOE-e4 carriers (55% of cohort)
  - Reference - N Engl J Med 2005 Jun 9:352(23):2379 **EBSCO*host* Full Text** full-text, editorial can be found in N Engl J Med 2005 Jun 9;352(23):2439 **EBSCO*host* Full Text**, commentary can be found in N Engl J Med 2005 Sep 1;353(9):951 **EBSCO*host* Full Text**, commentary can be found in BMJ 2005 Sep 3;331(7515):464
- **insufficient evidence to evaluate effect of folic acid supplementation on cognitive function in elderly patients (level 2 [mid-level] evidence)**
  - based on Cochrane review with clinical heterogeneity
  - systematic review of 8 randomized placebo-controlled trials evaluating folic acid supplements with or without vitamin B12 in elderly persons

- 4 trials included healthy elderly persons, 4 trials included patients with mild to moderate cognitive impairment or dementia
- meta-analysis not possible due to differences in patient populations, outcomes, duration, and supplement dose
- in 1 trial with 41 patients with Alzheimer disease, folic acid 1 mg/day associated with (at 6 months)
  - improved response to cholinesterase inhibitors (p = 0.02)
  - significant improvement in scores on Instrumental Activities of Daily Living (p = 0.02)
  - significant improvement in scores on Social Behavior subscale of Nurse's Observation Scale for Geriatric Patients (p = 0.02)
- in 1 trial with 818 healthy elderly people with high homocysteine levels, folic acid 800 mcg/day associated with improved global cognitive function, memory, and information processing at 3-year follow-up
- Reference - Cochrane Database Syst Rev 2008 Oct 8;(4):CD004514

- **no randomized trials identified evaluating vitamin B6 in patients with cognitive impairment or dementia**
- based on Cochrane review
- 2 randomized placebo-controlled trials in 109 healthy older persons found no significant difference in cognition or mood with daily vitamin B supplementation, follow-up ranged from 5-12 weeks
- Reference - Cochrane Database Syst Rev 2008 Jul 16;(3):CD004393

- **vitamins B6, B12 and folic acid may slow rate of brain atrophy in older adults with MCI (level 3 [lacking direct] evidence)**
- based on randomized trial without clinical outcomes
- 271 patients > 70 years old with MCI randomized to combination folic acid 0.8 mg, vitamin B12 0.5 mg and vitamin B6 20 mg daily vs. placebo for 24 months
- 69% had brain atrophy measured with magnetic resonance imaging
- vitamins associated with slower rate of brain atrophy per year vs. placebo (p = 0.001, NNT 4)
- Reference - PLoS One 2010 Sep 8;5(9):e12244 **EBSCO*host* Full Text** full-text

- **daily vitamin B12, B6, and folic acid do not appear to improve cognition or reduce risk of cognitive decline**
- based on randomized trial of 299 men ≥ 75 years old with hypertension followed for 8 years
- Reference - Neurology 2010 Oct 26;75(17):1540 full-text

Antioxidants:

- **vitamin E does not prevent Alzheimer disease (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 790 subjects aged 55-90 years in United States and Canada with amnestic mild cognitive impairment of insidious onset and gradual progression, impaired memory and mini-Mental Status Exam score 24-30 were randomized to vitamin E 1,000 units twice daily (1,000 units daily for first 6 weeks) vs. donepezil 10 mg daily (5 mg for first 6 weeks) vs. neither for 3 years

- all patients received multivitamin with vitamin E 15 units daily and placebos for vitamin E and/or donepezil to maintain blinding
- 769 patients completed baseline assessment
- 212 patients (28%) developed possible or probable Alzheimer disease at rate of 16%/year
- no significant differences between vitamin E and placebo in primary outcome at any time during the trial and few differences in some cognitive measures limited to first 18 months
- no significant differences comparing vitamin E vs. placebo in subgroup of APOE e4 carriers (55% of cohort)
- Reference - N Engl J Med 2005 Jun 9:352(23):2379 **EBSCO*host* Full Text** full-text, editorial can be found in N Engl J Med 2005 Jun 9;352(23):2439 **EBSCO*host* Full Text**, commentary can be found in N Engl J Med 2005 Sep 1;353(9):951 **EBSCO*host* Full Text**, commentary can be found in BMJ 2005 Sep 3;331(7515):464

- use of antioxidant supplements and dietary intake of antioxidants have mixed findings in cohort studies evaluating vitamin C and vitamin E
  - **combined use of vitamin C and vitamin E supplements associated with reduced risk of Alzheimer disease (level 2 [mid-level] evidence)**
    - based on cross-sectional study
    - 4,740 persons > 65 years in Utah, 200 prevalent cases of Alzheimer disease (AD)
    - combined supplement use had adjusted odds ratio 0.22
    - 3,227 survivors without AD followed up 1-6 years later, 104 incident cases of AD, combined supplement use had adjusted hazard ratio 0.36
    - no protective effect demonstrated for either vitamin alone
    - Reference - Arch Neurol 2004 Jan;61(1):82 full-text
  - **combined use of vitamin C and vitamin E supplements associated with reduced risk of vascular dementia but not risk of Alzheimer dementia (level 2 [mid-level] evidence)** in cohort of 3,385 Japanese American men aged 71-93 years living in Hawaii (Neurology 2000 Mar 28;54(6):1265)
  - **high dietary intake of vitamin C and vitamin E associated with lower risk for Alzheimer disease in cohort studies (level 2 [mid-level] evidence)**
    - high dietary intake of vitamin C and vitamin E associated with lower risk for Alzheimer disease, based on mean 6-year follow-up of 5,395 persons > 55 years old, 197 developed dementia during follow-up (JAMA 2002 Jun 26;287(24):3223 full-text), editorial can be found in JAMA 2002 Jun 26;287(24):3261, commentary can be found in JAMA 2002 Nov 13;288(18):2265
    - **high dietary intake of vitamin E from food (but not other antioxidants or vitamin E from supplements) associated with reduced risk for Alzheimer disease (level 2 [mid-level] evidence)**, based on mean 4-year follow-up of 815 persons > 65 years old, 131 developed dementia during follow-up (JAMA 2002 Jun 26;287(24):3230 full-text), editorial can be found in JAMA 2002 Jun 26;287(24):3261, commentary can be found in JAMA 2002 Nov 13;288(18):2265

- **vitamin C and E use NOT associated with reduced risk for incident dementia**
  - based on 3 cohort studies
  - **antioxidant vitamin intake NOT associated with risk of Alzheimer disease (level 2 [mid-level] evidence)** in study of 980 persons > 65 years old followed for mean 4 years; 242 (25%) developed Alzheimer disease; no significant decreased risk with intake of carotenes, vitamin C or vitamin E in supplemental or dietary forms (Arch Neurol 2003 Feb;60(2):203 full-text), commentary can be found in BMJ 2003 May 31;326(7400)
  - 3,734 Japanese American men followed for mean 5.2 years (JAMA 2002 Nov 13;288(18):2266)
  - 2,969 persons > 65 years old in Seattle, Washington followed for mean 5.5 years (J Am Geriatr Soc 2008 Feb;56(2):291