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# Antioxidant Supplements for Prevention of Gastrointestinal Cancers: A Systematic Review and Meta-Analysis

**Source:** Bjelakovic et al. *Lancet*. 2004;364:1219-1228.

Clinicians and patients have hoped that antioxidants might prevent cancer. Since oxidant stress may be one of the culprits in gene mutation that leads to carcinogenesis, it was logical to entertain the therapeutic potential of antioxidant supplements. Observational studies have been generally supportive of potential benefits from antioxidants, but of course randomized interventional trials trump observational data as an evidence source.

This meta-analysis reviewed trials of antioxidants for prevention of GI cancer. Inclusion criteria required that the trials be randomized and placebo controlled. Trial quality was ranked overall as high (n = 14 trials, study subjects = 170,525). Antioxidants addressed included beta-carotene, selenium, and vitamins A, C, and E.

In the overall analysis, none of the nutrients favorably impacted cancer incidence, although in 4 trials (3 of which are quoted as having unclear or inadequate methodology), selenium favorably affected GI cancer. Disturbingly, there were several trials that showed either increases of cancer, mortality or both. Despite our common-sense attraction to use antioxidants, convincing beneficial effects remain to be demonstrated. ■

# Imiquimod 5% Cream for the Treatment of Actinic Keratosis

**Source:** Saeimies RM, et al. *J am Acad Dermatol*. 2004;51:547-555.

Recent changes in dermatologic nomenclature classify actinic keratosis (AK) as keratinocytic intraepidermal neoplasia, or carcinoma in situ. A variety of treatments provide destruction and resolution of AK. Most of the time, biopsy is not performed, but rather, topicals like 5-fluorouracil are applied until a typical inflammatory cutaneous response exfoliates the lesions. Because the adverse effects of traditional treatments may be problematic, and the efficacy of standard therapies is imperfect, additional modalities are welcome.

Imiquimod 5% (Aldara™) is a commonly used topical immunomodulator for treatment of genital warts. It is also no approved for the treatment of AK. This investigation studied the efficacy of imiquimod (compared to placebo vehicle cream) applied 3 times weekly for 16 weeks to biopsy-proven AK in 286 patients.

Complete clearance of AK was seen in 57.1% of imiquimod patients, vs 2.2% of the placebo group. The most common adverse events associated with treatment were local cutaneous reactions of burning, erythema, itching, pain, and soreness. One or more of these adverse events were seen in the majority of patients, and essentially all patients experienced erythema. No serious adverse effects were attributed to imiquimod. Imiquimod may be considered a reasonable topical treatment for patients in primary care settings presenting with AK. ■

# Two 8-month Regimens of Chemotherapy for Treatment of Newly Diagnosed Pulmonary Tuberculosis

**Source:** Jindani A, et al. *Lancet*. 2004;364:1244-1251.

The epidemiologic presence of tuberculosis has grown greater to some degree because of the sustained and evolving population of HIV-infected individuals worldwide. Standard therapy (as per the World Health Organization) for newly diagnosed smear positive tuberculosis has been a 6-month course of isoniazid (I) and rifampicin (R). Short course regimens are usually structured to include a 2 month intensive phase during which 4 drugs are given [ethambutol (E), isoniazid (I), rifampicin (R), and pyrazinamide (P)], followed by a 4-6 month 2 drug phase (I + R) .

This trial compared an 8-month regimen based upon ethambutol (E) and isoniazid with standard 6 month therapy. Two different 8-month regimens were used: Daily E+I+R+P for 2 months followed by E + I, or thrice weekly E+I+R+P for 2 months followed by E + I. The outcome of culture negativity was monitored at 2 months and 12 months.

Neither of the 8-month regimens provided superior outcomes to the traditional 6 month regimen. Thrice weekly multi-drug administration was less efficacious than daily. The standard 6-month regimen should remain preferred. ■

# Self-Measured Home Blood Pressure in Predicting Ambulatory Hypertension

**Source:** Mansoor GA, et al. *Am J Hypertens*. 2004;17:1017-1022.

Ambulatory blood pressure monitoring (ABPM) provides the best metric of overall blood pressure burden. Several factors have compromised use of ABPM as a primary metric in managing hypertension (HTN): its cost, inconvenience, relative lesser availability, and less frequent incorporation in major clinical trials than simple office blood pressure. Home blood pressure (HBP) is increasingly recognized as a valued measurement, especially when OBP is suspected of reflecting white coat hypertension, or when ABPM is not available.

This study evaluated the threshold of HBP that would capture 80% of persons who, as demonstrated by ABPM BP >135/85, have borderline or stage 1 HTN. Subjects (n = 48) who had demonstrated at least 2 elevated BP readings in an office setting underwent ABPM and HBP.

As has been repeatedly demonstrated in other trials, HBP correlated better with ABPM than OBP. The threshold of HBP, at which 80% of persons with HTN (as defined by ABPM >135/85) would be detected, was determined to be 125/76. Persons with HBP > 135/85 are designated as hypertensive. Those with HBP < 125/76 are considered normotensive (regardless of OBP measurement), and those between 125/76-135/85, being indeterminate, merit consideration of ABPM to further refine their burden of blood pressure. ■

# Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

**Source:** Gussekloo J, et al. *JAMA*. 2004;292:2591-2599.

There is little disagreement about the merit of treating frank hypothyroidism. Because of conflicting data, much less consensus exists about whether subclinical hypothyroidism (ie, elevated TSH levels with normal T4) should be treated. Since thyroid disorders increase with age, a population of advanced years is an appropriate group in which to evaluate this issue further.

The Leiden 85-Plus Study is a prospective study of all individuals born in 1912-1914 living in Leiden, the Netherlands. Data was prospectively obtained from the entire population who agreed to be enrolled, without exclusions (n = 599), and these subjects were followed from age 85-89.

Outcome measures included cognitive function, degree of disability, depression, and overall mortality, each of which was assessed in relation to baseline and follow-up TSH and T4. The investigation uncovered 39 participants with previously undiagnosed overt hypothyroidism and 30 with undetected subclinical hypothyroidism. There were 2 new diagnoses of hyperthyroidism and 17 new diagnoses of subclinical hyperthyroidism (ie, decreased TSH with normal T4).

Thyroid status was not related to disability, depression, or cognitive function. However, the highest mortality was seen in those with a suppressed TSH level at baseline (subclinical hyperthyroidism). Somewhat surprisingly, subjects with elevations in TSH had the lowest mortality. Based upon these data, Gussekloo et al posit that thyroid replacement in subclinical hypothyroidism is unlikely to be beneficial; indeed, it could even be harmful. ■

# Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women

**Source:** Pai JK, et al *N Engl J Med*. 2004;351:2599-2610.

Inflammatory markers have been consistently associated with coronary artery disease (CAD), the most thoroughly studied of which has been C-reactive protein (CRP). Since interleukin-6 (IL6) and tumor necrosis factor alpha (TNFa) are cytokines which induce CRP secretion, their status might also reflect CAD risk. TNFa is not as readily measurable as are its primary receptors, sTNF-R1 and sTNF-R2.

The Nurses Health Study (n = 121,700) and the Health Professionals Follow-up Study (n = 51,529) provided subjects who gave baseline blood samples, all of whom were free of known CAD at the time. Over approximately 8 years of follow-up, data from 515 men and women who had suffered an MI were compared with controls matched for age and smoking status.

Initial analysis indicated that increased levels of sTNF-R1 and sTNF-R2 were associated with CAD in women, but not men. However, after adjustment for other risk factors, only CRP remained a significant predictor of CAD. For instance, lower HDL levels were also associated with higher levels of inflammatory markers, and mitigated some of the predictive value of inflammatory markers. CRP remains a consistent predictor of CAD risk. ■

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