

LE Magazine June 1999

ABSTRACTS

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Carotenoids and curcumin

Chemopreventive effects of carotenoids and curcumin on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation

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Carcinogenesis 1998 Jan;19(1):81-5

The present study was carried out to examine the chemopreventive effects of carotenoids such as fucoxanthin, lycopene and lutein as well as curcumin and its derivative, tetrahydrocurcumin (THC), on development of putative preneoplastic aberrant crypt foci (ACF) in colons of mice initiated with 1,2-dimethylhydrazine dihydrochloride (DMH). Influence on proliferation of colonic crypt epithelial cells was also assessed in terms of 5-bromo-2'-deoxyuridine (BrdU) incorporation. Five-week-old B6C3F1 male mice were divided into three groups, groups 1 and 2 being given DMH (20 mg/kg body wt, s.c.) twice a week for 3 weeks. Animals of group 1 were then treated with one of the test compounds, lycopene (0.005% and 0.0025%) or fucoxanthin (0.01%) in the drinking water and lutein (0.05%), curcumin (0.5%) or THC (0.5% and 0.2%) in the diet from weeks 5-12. Group 2 served as a carcinogen alone control and group 3 mice were given test compounds alone. All animals were killed at week 12. Numbers of ACF/mouse in the group 1 treated with fucoxanthin (47.1 +/- 13.7), lutein (42.6 +/- 19.6) or 0.5% THC (46.6 +/- 17.7) were significantly decreased as compared to the control group 2 value (63.3 +/- 19.4) ($P < 0.01$). Numbers of aberrant crypts (ACs)/mouse were also significantly lower after treatment with lutein (79.9 +/- 34.7) or 0.5% THC (81.8 +/- 32.5) than in the control group (115.1 +/- 37.1) ($P < 0.01$). BrdU labeling indices (LI) in mice treated with lutein and 0.5% THC were significantly decreased in both upper and lower half compartments of colonic crypts as compared to the controls ($P < 0.05$ and 0.01, respectively), especially the upper half data corresponding to reduction of ACs/mouse. The results thus suggest that fucoxanthin, lutein, and THC may have potential as chemopreventive agents against colon carcinogenesis.

Green tea and cancer incidence

Cancer-preventive effects of drinking green tea among a Japanese population

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Prev Med 1997 Nov-Dec;26(6):769-75

BACKGROUND: Laboratory studies have revealed the cancer preventive effects of green tea, so the association between green tea consumption and cancer was examined in a human population. **METHODS:** The association between green tea consumption and cancer incidence was studied in our prospective cohort study of a Japanese population. We surveyed 8,552 individuals over 40 years of age living in a town in Saitama prefecture on their living habits, including daily consumption of green tea. During the 9 years of follow-up study (71,248.5 person-years), we identified a total of 384 cases of cancer in all sites. **RESULTS:** We found a negative association between green tea consumption and cancer incidence, especially among females drinking more than 10 cups a day. The slowdown in increase of cancer incidence with age observed among females who consumed more than 10 cups a day is consistent with the finding that increased consumption of green tea is associated with later onset of cancer. Age-standardized average annual incidence rate was significantly lower among females who consumed large amounts of green tea. Relative risk (RR) of cancer incidence was also lower among both females (RR = 0.57, 95% CI = 0.33-0.98) and males (RR = 0.68, 95% CI = 0.39-1.21) in groups with the highest consumption, although the preventive effects did not achieve statistical significance among males, even when stratified by smoking and adjusted for alcohol and dietary variables. **CONCLUSION:** Our epidemiological study showed that green tea has a potentially preventive effect against cancer among humans.

Chemo-preventive effects of genistein

Genistein inhibits proliferation similarly in estrogen receptor-positive and negative human breast carcinoma cell lines characterized by P21WAF1/CIP1 induction, G2/M arrest, and apoptosis

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J Cell Biochem 1998 Apr 1;69(1):44-54

Genistein has been proposed to be responsible for lowering the rate of breast cancer in Asian women but the mechanism for this chemopreventive effect in vivo is unknown. In this study, we present in vitro evidence that genistein inhibits cell proliferation similarly in ER-positive and ER-negative human breast carcinoma cell lines. This inhibition is associated with specific G2/M arrest and induction of p21WAF1/CIP1 expression. Genistein results in a five- to six-fold increase in p21WAF1/CIP1 mRNA levels and a three- to four-fold increase in protein levels, only a 1.5-fold increase in 1WAF1/CIP1 transcription but a three- to six-fold increase in p21WAF1/CIP1 mRNA stability. The increase in p21WAF1/CIP1 is followed by increased apoptosis. The similar effects of genistein on a number of breast carcinoma cell lines with different ER and p53 status suggest that the actions of genistein reported here are mediated through ER and p53 independent mechanisms. The chemopreventive effects of genistein in vivo could be mediated along an identical or similar anti-proliferative pathway.

Breast cancer prevention

Case-control study of phyto-oestrogens and breast cancer

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Lancet 1997 Oct 4;350(9083):990-4

BACKGROUND: Phyto-oestrogens are a group of naturally occurring chemicals derived from plants; they have a structure similar to oestrogen, and form part of our diet. They also have potentially anticarcinogenic biological activity. We did a case-control study to assess the association between phyto-oestrogen intake (as measured by urinary excretion) and the risk of breast cancer.

METHODS: Women with newly diagnosed early breast cancer were interviewed by means of questionnaires, and a 72 h urine collection and blood sample were taken before any treatment started. Controls were randomly selected from the electoral roll after matching for age and area of residence. 144 pairs were included for analysis. The urine samples were assayed for the isoflavonic phyto-oestrogens daidzein, genistein, and equol, and the lignans enterodiol, enterolactone, and matairesinol. **FINDINGS:** After adjustment for age at menarche, parity, alcohol intake, and total fat intake, high excretion of both equol and enterolactone was associated with a substantial reduction in breast-cancer risk, with significant trends through the quartiles: equol odds ratios were 1.00, 0.45 (95% CI 0.20, 1.02), 0.52 (0.23, 1.17), and 0.27 (0.10, 0.69)-trend $p = 0.009$ -and enterolactone odds ratios were 1.00, 0.91 (0.41, 1.98), 0.65 (0.29, 1.44), 0.36 (0.15, 0.86)--trend $p = 0.013$. For most other phytoestrogens there was a reduction in risk, but it did not reach significance. Difficulties with the genistein assay precluded analysis of that substance. **INTERPRETATION:** There is a substantial reduction in breast-cancer risk among women with a high intake (as measured by excretion) of phyto-oestrogens-particularly the isoflavonic phyto-oestrogen equol and the lignan enterolactone. These findings could be important in the prevention of breast cancer.

CHD and estrogen

Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women - Heart and Estrogen/progestin Replacement Study (HERS) Research Group

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JAMA 1998 Aug 19;280(7):605-13

CONTEXT: Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials. OBJECTIVE: To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease. DESIGN: Randomized, blinded, placebo-controlled secondary prevention trial. SETTING: Outpatient and community settings at 20 US clinical centers. PARTICIPANTS: A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years. INTERVENTION: Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years. MAIN OUTCOME MEASURES: The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered. RESULTS: Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P < .001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38). CONCLUSIONS: During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

Hormone therapy and cancer

Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials

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BMJ 1997 Jul 19;315(7101):149-53

OBJECTIVE: To examine the incidence of cardiovascular diseases and cancer from published clinical trials that studied other outcomes of postmenopausal hormone therapy as some surveys have suggested that it may decrease the incidence of cardiovascular diseases and increase the incidence of hormone dependent cancers. **DESIGN:** Trials that compared hormone therapy with placebo, no therapy, or vitamins and minerals in comparable groups of postmenopausal women and reported cardiovascular or cancer outcomes were searched from the literature. **SUBJECTS:** 22 trials with 4124 women were identified. In each group, the numbers of women with cardiovascular and cancer events were summed and divided by the numbers of women originally allocated to the groups. **RESULTS:** Data on cardiovascular events and cancer were usually given incidentally, either as a reason for dropping out of a study or in a list of adverse effects. The calculated odds ratios for men taking hormones versus those not taking hormones was 1.39 (95% confidence interval 0.48 to 3.95) for cardiovascular events without pulmonary embolus and deep vein thrombosis and 1.64 (0.55 to 4.18) with them. It is unlikely that such results would have occurred if the true odds ratio were 0.7 or less. For cancers, the numbers of reported events were too low for a useful conclusion. **CONCLUSIONS:** The results of these pooled data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events.

Estrogen's effects on breast cancer risk

Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women

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JAMA 1990 Nov 28;264(20):2648-53

We prospectively examined the use of estrogen replacement therapy in relation to breast cancer incidence in a cohort of women 30 to 55 years of age in 1976. During 367 187 person-years of follow-up among postmenopausal women, 722 incident cases of breast cancer were documented. Overall, past users of replacement estrogen were not at increased risk (relative risk, 0.98; 95% confidence interval, 0.81 to 1.18), including even those with more than 10 years since last [corrected] use (relative risk after adjustment for established risk factors, 0.70; 95% confidence interval, 0.45 to 1.10). However, the risk of breast cancer was significantly elevated among current users (relative risk, 1.36; 95% confidence interval, 1.11 to 1.67). Among current users, a stronger relationship was observed with increasing age but not with increasing duration of use. These data suggest that long-term past use of estrogen replacement therapy is not related to risk of breast cancer but that current use may modestly increase risk.

Flavonoids and heart disease

Dietary antioxidant flavonoids and risk of coronary heart disease the Zutphen Elderly Study

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Lancet 1993 Oct 23;342(8878):1007-11

Flavonoids are polyphenolic antioxidants naturally present in vegetables, fruits, and beverages such as tea and wine. In vitro, flavonoids inhibit oxidation of low-density lipoprotein and reduce thrombotic tendency, but their effects on atherosclerotic complications in human beings are unknown. We measured the content in various foods of the flavonoids quercetin, kaempferol, myricetin, apigenin, and luteolin. We then assessed the flavonoid intake of 805 men aged 65-84 years in 1985 by a cross-check dietary history; the men were then followed up for 5 years. Mean baseline flavonoid intake was 25.9 mg daily. The major sources of intake were tea (61%), onions (13%), and apples (10%). Between 1985 and 1990, 43 men died of coronary heart disease. Fatal or nonfatal myocardial infarction occurred in 38 of 693 men with no history of myocardial infarction at baseline. Flavonoid intake (analysed in tertiles) was significantly inversely associated with mortality from coronary heart disease (p for trend = 0.015) and showed an inverse relation with incidence of myocardial infarction, which was of borderline significance (p for trend = 0.08). The relative risk of coronary heart disease mortality in the highest versus the lowest tertile of flavonoid intake was 0.42 (95% CI 0.20-0.88). After adjustment for age, body-mass index, smoking, serum total and high-density-lipoprotein cholesterol, blood pressure, physical activity, coffee consumption, and intake of energy, vitamin C, vitamin E, beta-carotene, and dietary fibre, the risk was still significant (0.32 [0.15-0.71]). Intakes of tea, onions, and apples were also inversely related to coronary heart disease mortality, but these associations were weaker. Flavonoids in regularly consumed foods may reduce the risk of death from coronary heart disease in elderly men.

GTE and chemotherapy

Green tea extract inhibits nucleoside transport and potentiates the antitumor effect of antimetabolites

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Chin Med Sci J 1991 Mar;6(1):1-5

The present study provides evidence that green tea extract (GTE), consisting of polyphenol components, is a highly active nucleoside transport inhibitor. GTE markedly inhibited radiolabeled thymidine and uridine transport in mouse leukemia L1210 cells, with IC₅₀ values of 3.2 and 8.0 $\mu\text{mol/L}$, respectively. GTE blocked the rescue effect of exogenous nucleosides and enhanced the cytotoxicity of AraC and MTX to L1210 cells and human hepatoma BEL-7402 cells. GTE markedly potentiated the inhibitory effect of AraC on leukemia L1210 and P388 in mice. These results indicate that GTE is potentially useful when combined with antimetabolites in cancer chemotherapy.

Green tea, cardiovascular disease and the liver

Cross sectional study of effects of drinking green tea on cardiovascular and liver diseases

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BMJ 1995 Mar 18;310(6981):693-6

OBJECTIVE: To investigate the association between consumption of green tea and various serum markers in a Japanese population, with special reference to preventive effects of green tea against cardiovascular disease and disorders of the liver. **DESIGN:** Cross sectional study. **SETTING:** Yoshimi, Japan. **SUBJECTS:** 1371 men aged over 40 years resident in Yoshimi and surveyed on their living habits including daily consumption of green tea. Their peripheral blood samples were subjected to several biochemical assays. **RESULTS:** Increased consumption of green tea was associated with decreased serum concentrations of total cholesterol (P for trend < 0.001) and triglyceride (P for trend = 0.02) and an increased proportion of high density lipoprotein cholesterol together with a decreased proportion of low and very low lipoprotein cholesterols (P for trend = 0.02), which resulted in a decreased atherogenic index (P for trend = 0.02). Moreover, increased consumption of green tea, especially more than 10 cups a day, was related to decreased concentrations of hepatological markers in serum, aspartate aminotransferase (P for trend = 0.06), alanine transferase (P for trend = 0.07), and ferritin (P for trend = 0.02). **CONCLUSION--**The inverse association between consumption of green tea and various serum markers shows that green tea may act protectively against cardiovascular disease and disorders of the liver.

EGCG and cancer cells

Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts

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Cancer Lett 1998 Jul 17;129(2):173-9

(-)-Epigallocatechin gallate (EGCG), a catechin polyphenol compound, represents the main ingredient of green tea extract. Although EGCG has been shown to be growth inhibitory in a number of tumor cell lines, it is not clear whether the effect is cancer-specific. In this study we compared the effect of EGCG on the growth of SV40 virally transformed WI38 human fibroblasts (WI38VA) with that of normal WI38 cells. The IC₅₀ value of EGCG was estimated to be 120 and 10 microM for WI38 and WI38VA cells, respectively. Thus, EGCG at 40 microM completely inhibited the growth of WI38VA cells, but had little or no inhibitory effect on the growth of WI38 cells. Similar differential growth inhibition was also observed between a human colorectal cancer cell line (Caco-2), a breast cancer cell line (Hs578T) and their respective normal counterparts. EGCG at a concentration range of 40-200 microM induced a significant amount of apoptosis in WI38VA cultures, but not in WI38 cultures, as determined by terminal deoxynucleotidyl transferase assay. After exposure to EGCG at 200 microM for 8 h, more than 50% of WI38VA cells in a confluent culture became apoptotic. In contrast, less than 1% of WI38 cells displayed apoptotic labeling under the same condition. EGCG did not affect the serum-induced expression of c-fos and c-myc genes in normal WI38 cells. However, it significantly enhanced their expression in transformed WI38VA cells. It is possible that differential modulation of certain genes, such as c-fos and c-myc, may cause differential effects of EGCG on the growth and death of cancer cells.

Stroke prevention and green tea

Possible contribution of green tea drinking habits to the prevention of stroke

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Tohoku J Exp Med 1989 Apr;157(4):337-43*

Among 5910 nondrinking and nonsmoking women (of greater than or equal to 40 years of age) in a prefectural city of Sendai, and two villages of Taijiri and Wakuya in Miyagi prefecture, Japan, medical history of stroke was less frequently observed among those who took more green tea in daily life. No relation with tea drinking was observed for hypertension history. The uneven distribution of stroke history was detectable even after the effects of age, location of residence, and high salt intake were ruled out. The incidence of stroke and cerebral hemorrhage during a 4-year follow-up of the study population was twice or more times higher in those who took less green tea (less than 5 cups a day) than in those who took more (greater than or equal to 5 cups daily).

Fish longevity

Age determination and longevity in fishes

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Gerontology 1994;40(2-4):70-96

It is possible to determine the age of fishes with reasonable accuracy by reading the 'growth rings' (annuli) in hard parts (scale, otolith, opercular bone, vertebra and cross-section of dorsal or pectoral spine and fin rays). Primary growth increments in 'otoliths' can also be used as an alternative method of age determination. The traditional methods could be supplemented with more reliable fluorochrome and microradiographic techniques. The suitability of the use of hard parts and the techniques may vary among the species. It is essential that the 'true rings' be distinguished from other types of rings, such as false rings, larval rings and spawning rings through repeated examination of samples to avoid confusion and inaccuracy in age determination. The causes and the periodicity of ring formation may vary from species to species. The growth history of fishes could be traced by back calculation of length attained at different ages. Among the different types of growth equations, the Von Bertalanffy's model appears to be the most suitable for fishes of both temperate and tropical regions. With slight modification, the same model may also serve to estimate the maximum theoretical calculated age (longevity) of fishes. The longevity of fishes show wide variations. The life-span may be short, intermediate and long. Whereas the lowest range of life-span (1-2 years) is exhibited by some species of lampreys and teleosts, there are species of dogfishes, sturgeons, paddle fishes, rockfishes and eels which have the life-span (70-152 years) in the highest range. A number of factors (size, sex, temperature, diet, reproduction, age at maturity and genetic composition) are believed to influence the longevity of fishes.

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