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## ABSTRACTS

## Tamoxifen and endometrial cancer

### ***Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14***

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J Natl Cancer Inst 1994 Apr 6;86(7):527-37*

Background: Tamoxifen is advantageous in treating all stages of breast cancer. However, studies have suggested that incidence and severity of endometrial cancer increase in women treated with tamoxifen. Purpose: We compared rates of endometrial and other cancers in tamoxifen- and non-tamoxifen-treated patients and described the pathologic characteristics of the endometrial cancers. Methods: Data were analyzed on 2843 patients with node-negative, estrogen receptor-positive, invasive breast cancer randomly assigned to placebo or tamoxifen (20 mg/d) and on 1220 tamoxifen-treated patients registered in NSABP B-14 subsequent to randomization. Average time on study is 8 years for randomly assigned patients and 5 years for registered patients. Results: The incidence rates of liver, gastrointestinal, urinary tract, and nonuterine genital tumors were not increased by tamoxifen treatment. Twenty-five endometrial cancers were originally reported, one of which was reclassified after subsequent review. Two cases occurred in the placebo group in patients whose medical status subsequent to random assignment had required tamoxifen treatment. Twenty-three occurred in the tamoxifen groups. Twenty-one of the 24 originally reported endometrial cancers were FIGO stage 1; 18 of 23 gradable cases were of good to moderate histologic grade. Four tamoxifen-treated women died of uterine cancer. The average annual hazard rate of endometrial cancer as a first event within the first 5 years of follow-up in the randomized, tamoxifen-treated group was 1.2/1000 patient-years; the cumulative hazard rate was 6.3/1000. Findings for the registered, tamoxifen-treated group were similar. Including all originally reported endometrial cancers, the annual hazard rate through all follow-up was 0.2/1000 in the placebo group and 1.6/1000 in the randomized, tamoxifen-treated group; the relative risk of endometrial cancer for the latter versus the former group was 7.5. Again for the latter group, using population-based rates of endometrial cancer from SEER data and information from another NSABP (B-06) trial, relative risks were 2.2 and 2.3, respectively. The 5-year cumulative hazard rate for disease-free survival in the randomized tamoxifen group was 38% less than that in the placebo group. Some data in this paper were provided by an investigator who submitted fraudulent data to the NSABP [see the "News" section]; therefore, the reader must read the entire text including Table 10 and the Editor's notes. In brief, data on 182 of the 2843 randomly assigned patients and 37 of the 1220 registered patients were provided by the investigator in question. After review, 24 of the 182 records showed falsification, all involving characteristics of patients prior to random assignment. Of the 37 registered-patient records, 8 showed falsification. Conclusions: Risk of endometrial cancer increases following tamoxifen therapy for invasive breast cancer; however, net benefit greatly outweighs risk. Endometrial cancers occurring after tamoxifen therapy do not appear to be of a different type with a worse prognosis than are such tumors in non-tamoxifen-treated patients. Implications: Tamoxifen treatment for breast cancer should continue. In addition, the relative risk of endometrial cancer observed in B-14 tamoxifen-treated patients is consistent with the twofold relative risk used in the initial risk-benefit computation for the NSABP breast cancer prevention trial.

## **Tamoxifen's effects on healthy women**

### **Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial**

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Lancet 1998 Jul 11;352(9122):98-101*

Background: Tamoxifen, a drug with antioestrogenic effects, is predicted to prevent the occurrence of breast cancer. We have undertaken a trial of tamoxifen in healthy women who are at increased risk of breast cancer because of family history. We report a planned interim analysis. Methods: Between October, 1986, and April, 1996, we accrued 2494 healthy women aged between 30 and 70 with a family history of breast cancer. They have been randomised (double blind) to receive tamoxifen 20 mg per day orally or placebo for up to 8 years. Follow-up included clinical assessment, annual mammography, and assessment of toxicity and compliance. The primary endpoint was the occurrence of breast cancer, which was analysed on an intention-to-treat basis with a survival curve. Findings: With a median follow-up of 70 months, 2471 women (tamoxifen 1238, placebo 1233) were suitable for analysis. The groups were evenly matched at baseline, and compliance was good. The overall frequency of breast cancer is the same for women on tamoxifen or placebo (tamoxifen 34, placebo 36, relative risk 1.06 [95% CI 0.7-1.7],  $p=0.8$ ). Participants who were already on hormone-replacement therapy when they entered the study had an increased risk of breast cancer compared with non-users. Those participants who started such therapy while on trial had a significantly reduced risk. The safety profile of tamoxifen was as expected. Interpretation: We have been unable to show any effect of tamoxifen on breast-cancer incidence in healthy women, contrary to the report from the NSABP-P1 study showing a 45% reduction in healthy women given tamoxifen versus placebo. Differences in the study populations for the two trials may underlie these conflicting findings: eligibility in our trial was based predominantly on a strong family history of breast cancer whereas in the NSABP trial was mostly based on non-genetic risk factors. The importance of oestrogen promotion may vary between such populations.

## Tamoxifen and hysterectomized women

### ***Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomized women. Italian Tamoxifen Prevention Study.***

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Lancet, 1998, Vol 352, Iss 9122, pp 93-97*

Background: Tamoxifen is a candidate chemopreventive agent in breast cancer, although the drug may be associated with the development of endometrial cancer. Therefore we did a trial in hysterectomized women of tamoxifen as a chemopreventive.

Methods In October, 1992, we started a double-blind placebo-controlled, randomised trial of tamoxifen in women (mainly in Italy) who did not have breast cancer and who had had a hysterectomy. Women were randomised to receive tamoxifen 20 mg per day or placebo, both orally for 5 years. The original plan was to follow the intervention phase by 5 years' follow-up. In June, 1997, the trialists and the data-monitoring committee decided to end recruitment primarily because of the number of women dropping out of the study. Recruitment ended on July 11, 1997, and the study will continue as planned. The primary endpoints are the occurrence of and deaths from breast cancer, This preliminary interim analysis is based on intention-to-treat. Findings 5408 women were randomised; participating women have a median follow-up of 46 months for major endpoints. 41 cases of breast cancer occurred so far; there have been no deaths from breast cancer, There is no difference in breast-cancer frequency between the placebo (22 cases) and tamoxifen (19) arms, There is a statistically significant reduction of breast cancer among women receiving tamoxifen who also used hormone-replacement therapy during the trial: among 390 women on such therapy and allocated to placebo, we found eight cases of breast cancer compared with one case among 362 women allocated to tamoxifen. Compared with the placebo group, there was a significantly increased risk of vascular events and hypertriglyceridaemia among women on tamoxifen.

Interpretation Although this preliminary analysis has low power, in this cohort of women at low-to-normal risk of breast cancer, the postulated protective effects of tamoxifen are not yet apparent. Women using hormone replacement therapy appear to have benefitted from use of tamoxifen, There were no deaths from breast cancer recorded in women in the study. It is essential to continue follow-up to quantify the long-term risks and benefits of tamoxifen therapy.

# The NSABP P-1 study report

## ***Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study***

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*J Natl Cancer Inst 1998 Sep 16;90(18):1371-88*

Background: The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention. To test this hypothesis, the National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992. Methods: Women (N=13388) at increased risk for breast cancer because they 1) were 60 years of age or older, 2) were 35-59 years of age with a 5-year predicted risk for breast cancer of at least 1.66%, or 3) had a history of lobular carcinoma in situ were randomly assigned to receive placebo (n=6707) or 20 mg/day tamoxifen (n=6681) for 5 years. Gail's algorithm, based on a multivariate logistic regression model using combinations of risk factors, was used to estimate the probability (risk) of occurrence of breast cancer over time. Results: Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided  $P < .00001$ ), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50-59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided  $P < .002$ ). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Colles'), and spine fractures was observed. The rate of endometrial cancer was increased in the tamoxifen group (risk ratio = 2.53; 95% confidence interval = 1.35-4.97); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older. Conclusions: Tamoxifen decreases the incidence of invasive and noninvasive breast cancer. Despite side effects resulting from administration of tamoxifen, its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease.

## Cancers associated with tamoxifen

### *Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies*

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*J Natl Cancer Inst* 1995 May 3;87(9):645-51

Background: Tamoxifen is being increasingly used for the treatment of breast cancer and is undergoing study for the primary prevention of breast cancer. However, concerns have been raised that the drug may increase the incidence of new primary malignancies, such as endometrial, liver, and colorectal cancers. Purpose: Our goal was to assess the carcinogenic risks associated with long-term use of tamoxifen in women with early stage breast cancer. Methods: The incidence of new primary cancers among 2729 women participants of the Stockholm Trial was determined at a median follow-up of 9 years. In this trial, after primary surgery, postmenopausal patients aged less than 71 years with unilateral invasive breast cancer were randomly allocated to receive either 2 years of adjuvant tamoxifen (40 mg daily) or no adjuvant endocrine therapy. Information on second cancers was obtained by retrospective linkage to the Swedish Cancer Registry. To increase statistical power, a joint analysis of the incidence of endometrial and gastrointestinal cancers was performed in the following three major studies in Scandinavia evaluating adjuvant tamoxifen therapy: the Stockholm Trial, the Danish Breast Cancer Group Trial, and the South-Swedish Trial. These studies included a total of 4914 patients with a median follow-up of 8-9 years. All P values were calculated from two-tailed tests of statistical significance. Results: In the Stockholm Trial, there was a statistically significant ( $P = .008$ ) reduction in the incidence of second primary cancers in the contralateral breast among the tamoxifen-treated patients. However, there was a nearly sixfold increase in endometrial cancers ( $P < .001$ ) and a threefold increase in gastrointestinal cancers in the tamoxifen-treated patients. The results of the joint studies showed a statistically significant increase in endometrial cancers among the tamoxifen-treated patients (relative risk [RR] = 4.1; 95% confidence interval [CI] = 1.9-8.9). There was also an excess of gastrointestinal cancers associated with tamoxifen. Most of this excess involved colorectal cancers (RR = 1.9; 95% CI = 1.1-3.3) and stomach cancer (RR = 3.2; 95% CI = 0.9-11.7). There was no substantial increase in any other type of gastrointestinal cancer (e.g., liver cancer) among the tamoxifen-treated patients. Conclusion: The endometrium and gastrointestinal organs may be target sites for tamoxifen-induced carcinogenesis in humans. Implications: The increased incidence of colorectal and stomach cancers reported here should be regarded as tentative until supported by long-term data from a larger number of tamoxifen trials. Also, appropriate surveillance of cancer incidence is warranted for the protection of participants enrolled in current tamoxifen chemoprevention trials.

## Tamoxifen side effects

### *Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial*

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*Lancet 1994 May 28;343(8909):1318-21*

Randomised, double-blind controlled trials have been started to determine whether tamoxifen can prevent or delay development of breast cancer in healthy women with a family history of the disease. We recruited a randomised cohort of 111 postmenopausal women (aged 46-71 years) from the Pilot Breast Cancer Prevention Trial at the Royal Marsden Hospital to study the effect of tamoxifen on the uterus and ovaries. The main outcome measures were obtained by transvaginal ultrasonography with colour doppler imaging and microscopic examination of endometrial biopsies removed at the time of the scan. There was no significant difference between tamoxifen (20 mg/day) and placebo groups in the age of the women, or the time of the scan (and sampling) after randomisation. Women taking tamoxifen had a significantly larger uterus and a lower impedance to blood flow in the uterine arteries. 39% of women taking tamoxifen had histological evidence of an abnormal endometrium compared with 10% in the control group. 10 patients in the tamoxifen group (16%) had atypical hyperplasia and another 5 (8%) had a polyp. Women with a histological abnormality had a significantly thicker endometrium and a decreased impedance to blood flow in the uterine arteries. There was no correlation between the presence of uterine abnormalities and the age of the women, or the concentrations of tamoxifen or desmethyl tamoxifen in the peripheral blood. These findings confirm that tamoxifen can cause potentially malignant changes in the endometrium of postmenopausal women. Transvaginal ultrasonography can be used to identify those women who should have endometrial samples removed for microscopic analysis.

## Protein intake

### ***Exogenous amino acids stimulate net muscle protein synthesis in the elderly***

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*Journal of Clinical Investigation, 1998, Vol 101, Iss 9, pp 2000-2007*

We have investigated the response of amino acid transport and protein synthesis in healthy elderly individuals (age 71+/-2 yr) to the stimulatory effect of increased amino acid availability. Muscle protein synthesis and breakdown, and amino acid transport were measured in the postabsorptive state and during the intravenous infusion of an amino acid mixture. Muscle-free amino acid kinetics were calculated by means of a three compartment model using data obtained by femoral arterio-venous catheterization and muscle biopsies from the vastus lateralis during the infusion of stable isotope tracers of amino acids. In addition, muscle protein fractional synthetic rate (FSR) was measured. Peripheral amino acid infusion significantly increased amino acid delivery to the leg, amino acid transport, and muscle protein synthesis when measured either with the three compartment model ( $P < 0.05$ ) or with the traditional precursor-product approach (FSR increased from 0.0474+/-0.0054 to 0.0940+/-0.0143%/h,  $P < 0.05$ ). Because protein breakdown did not change during amino acid infusion, a positive net balance of amino acids across the muscle was achieved. We conclude that, although muscle mass is decreased in the elderly, muscle protein anabolism can nonetheless be stimulated by increased amino acid availability. We thus hypothesize that muscle mass could be better maintained with an increased intake of protein or amino acids.

## Vitamin C and AMI

### *Antioxidative defense in human myocardial reperfusion injury*

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J Environ Pathol Toxicol Oncol 1998;17(3-4):281-4*

The activity of glutathione peroxidase (GSH-Px) as well as the activities of other antioxidative enzymes such as CuZn superoxide dismutase (CuZn SOD), catalase (CAT), glutathione reductase (GR) in erythrocytes, the plasma activity of glutathione-S-transferase (GST), and the plasma levels of vitamin E and vitamin C were evaluated in nine patients with acute myocardial infarction (AMI). Blood samples were taken before and 1, 3, 6, and 24 hours after the institution of thrombolytic therapy. The results were compared with those in 30 healthy volunteers. A significant decrease in catalase (CAT) activity and vitamin E content in patients before and after thrombolytic therapy as compared with controls was recorded. Our results confirmed that a disturbed oxidative/antioxidative balance is present after AMI and after thrombolytic therapy.

## Antioxidant effects on the heart

### ***Vitamin C attenuates abnormal vasomotor reactivity in spasm coronary arteries in patients with coronary spastic angina***

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**Objectives:** This study sought to examine the effect of vitamin C, an antioxidant, on the abnormal vasomotor reactivity in spasm coronary arteries. **Background:** Oxygen free radicals generated in the arterial walls have been shown to cause endothelial vasomotor dysfunction. **Methods:** Responses of the epicardial arterial diameters of the left coronary arteries to the intracoronary infusion of acetylcholine (ACh) (10 and 50 microg/min) were measured by quantitative coronary angiography before and during combined intracoronary infusion of vitamin C (10 mg/min) or saline as a placebo in 32 patients with coronary spastic angina and in 34 control subjects. **Results:** Vitamin C infusion suppressed the constrictor response of the epicardial diameter to ACh in spasm coronary arteries but had no significant effect in the control coronary arteries (percent change in distal diameter in response to 10 microg/min of ACh [constriction (-), dilation (+), mean +/- SEM] before vitamin C: -8.2 +/- 2.9% in spasm arteries, +8.4 +/- 2.9% in control arteries; during vitamin C: +0.2 +/- 3.8% in spasm arteries, +7.2 +/- 1.3% in control arteries [ $p < 0.01$  vs. spasm arteries before vitamin C]). The coronary sinus-arterial difference in plasma thiobarbituric acid reactive substances during ACh infusion, an indicator of lipid peroxidation in coronary circulation, was higher in patients with coronary spastic angina than in control subjects ( $p < 0.01$ ) but was suppressed in patients with coronary spastic angina to comparable levels in control subjects by combined infusion of vitamin C. Saline infusion had no effect. **Conclusions:** The results indicate that vitamin C attenuates vasomotor dysfunction in epicardial coronary arteries in patients with coronary spastic angina. Oxygen free radicals may at least in part play a role in the abnormal coronary vasomotor reactivity in response to ACh in spasm coronary arteries.

## Vitamin C and hypertension

### *Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients*

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*Circulation* 1997 Sep 2;96(5):1513-9

Background: There is evidence for increased formation of free radicals in patients with hypertension, raising the possibility that NO is inactivated by free radicals, which impairs coronary endothelial function. Therefore, we tested the hypothesis that the antioxidant vitamin C could improve abnormal endothelial function of coronary arteries in patients with hypertension. Methods and results: In 22 hypertensive patients without relevant coronary artery stenoses, endothelium-dependent vascular responses of the left anterior descending coronary artery (LAD) to acetylcholine (0.01, 0.1, and 1.0 micromol/L) were determined before and immediately after intravenous infusion of 3 g vitamin C (17 patients) or placebo (5 patients). In a subgroup of 10 patients, papaverine-induced flow-dependent vasodilation (FDD) was measured before and after vitamin C (5 patients) or placebo (5 patients) infusion. Segmental responses of the coronary artery luminal area were analyzed with quantitative coronary angiography. Before vitamin C infusion, the mean changes of LAD luminal areas at increasing doses of acetylcholine were  $-6.1 \pm 2.2\%$ ,  $-15.2 \pm 4.9\%$ , and  $-33.9 \pm 8.1\%$  (negative numbers symbolize vasoconstriction) and during FDD,  $5.4 \pm 1.0\%$ . The vasoconstrictor response during acetylcholine was reduced and FDD was augmented by vitamin C. After vitamin C infusion, LAD luminal areas changed by  $-3.2 \pm 2.3\%$ ,  $-5.8 \pm 3.6\%$ , and  $-10.2 \pm 5.6\%$  ( $P < .05$ , acetylcholine) and  $17.8 \pm 2.8\%$  ( $P < .05$ , FDD). Doppler flow velocity (during baseline, acetylcholine, and FDD) was not significantly affected by vitamin C. Conclusions: Vitamin C improves the endothelium-dependent vasomotor capacity of coronary arteries in patients with hypertension and patent coronary arteries. These findings suggest that increased oxidative stress contributes to endothelial dysfunction in hypertensive patients.

## Diabetes and vitamin C

### *Vitamin C improves endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus*

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*J Am Coll Cardiol* 1998 Mar 1;31(3):552-7

**Objectives:** We sought to determine whether the antioxidant vitamin C improves endothelium-dependent vasodilation of forearm resistance vessels in patients with insulin-dependent diabetes mellitus. **Background:** Endothelium-dependent vasodilation is impaired in patients with diabetes mellitus. Oxidatively mediated degradation of endothelium-derived nitric oxide contributes to abnormal endothelium-dependent vasodilation in animal models of diabetes mellitus. **Methods:** The study group included 10 patients with insulin-dependent diabetes mellitus and 10 age-matched control subjects. Forearm blood flow was determined by venous occlusion plethysmography. Endothelium-dependent vasodilation was assessed by intraarterial infusion of methacholine (0.3 to 10 microg/min). Endothelium-independent vasodilation was assessed by intraarterial infusion of nitroprusside (0.3 to 10 microg/min). Forearm blood flow dose-response curves were determined for each drug infusion before and during concomitant infusion of vitamin C (24 mg/min). **Results:** In diabetic subjects, endothelium-dependent vasodilation was augmented by the concomitant infusion of vitamin C ( $p = 0.001$ ). Endothelium-independent vasodilation was not affected by the concomitant infusion of vitamin C ( $p = \text{NS}$ ). In control subjects, vitamin C infusion did not affect endothelium-dependent vasodilation ( $p = \text{NS}$ ). **CONCLUSIONS:** Vitamin C selectively restores the impaired endothelium-dependent vasodilation in the forearm resistance vessels of patients with insulin-dependent diabetes mellitus. These findings indicate that nitric oxide degradation by oxygen-derived free radicals contributes to abnormal vascular reactivity in humans with insulin-dependent diabetes mellitus.

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