



# RESEARCH UPDATES

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October 2009



## Breast

Hervik, J and O. Mjaland. **Acupuncture for the Treatment of Hot Flashes in Breast Cancer Patients, a Randomized, Controlled Trial.** *Breast Cancer Res Treat.* 2009 July; 1162: 311-316.

Acupuncture has been used to treat the problem of hot flashes in healthy postmenopausal women. The object of this study was to investigate the efficacy of acupuncture in women with breast cancer suffering from hot flashes as a result of anti-oestrogen medication. In a prospective, controlled trial, 59 women suffering from hot flashes following breast cancer surgery and adjuvant oestrogen-antagonist treatment (Tamoxifen) were randomized to either 10 weeks of traditional Chinese acupuncture or sham acupuncture (SA). Mean number of hot flashes at day and night were recorded prior to treatment, during the treatment period as well as during the 12 weeks following treatment. A validated health score (Kupperman index) was conducted at baseline, at the end of the treatment period and at 12 weeks following treatment. During the treatment period mean number of hot flashes at day and night was significantly reduced by 50 and almost 60%, respectively from baseline in the acupuncture group, and was further reduced by 30% both at day and night during the next 12 weeks. In the sham acupuncture group a significant reduction of 25% in hot flashes at day was seen during treatment, but was reversed during the following 12 weeks. No reduction was seen in hot flashes at night. Kupperman index was reduced by 44% from baseline to the end of the treatment period in the acupuncture group, and largely maintained 12 weeks after treatment ended. No corresponding changes were seen in the sham acupuncture group. Acupuncture seems to provide effective relief from hot flashes both day and night in women operated for breast cancer, treated with Tamoxifen. This treatment effect seems to coincide with a general health improvement measured with the validated Kupperman index.

Iwasaki, M, G. S. Hamada, I. N. Nishimoto, et al. **Dietary Isoflavone Intake and Breast Cancer Risk in Case-Control Studies in Japanese, Japanese Brazilians, and Non-Japanese Brazilians.** *Breast Cancer Res Treat.* 2009 July; 1162: 401-411.

Although epidemiologic studies have shown an

inverse association between isoflavones and breast cancer risk, little evidence for a dose-response relation is available. We conducted hospital-based case-control studies of patients aged 20-74 years with primary, incident, histologically confirmed invasive breast cancer, and matched controls from medical checkup examinees in Nagano, Japan and from cancer-free patients in Sao Paulo, Brazil. A total of 850 pairs (390 Japanese, 81 Japanese Brazilians and 379 non-Japanese Brazilians) completed validated food frequency questionnaires. The odds ratio of breast cancer according to isoflavone intake was estimated using a conditional logistic regression model. We found a statistically significant inverse association between isoflavone intake and the risk of breast cancer for Japanese Brazilians and non-Japanese Brazilians. For Japanese, a non-significant inverse association was limited to postmenopausal women. In the three populations combined, breast cancer risk linearly decreased from 'no' to 'moderate' isoflavone intake and thereafter leveled off. Compared to non-consumers, adjusted odds ratios (95% confidence interval) for consumers in increasing quintile intake categories (median intake in each category: 8.7, 23.1, 33.8, 45.7, and 71.3 mg/day) were 0.69 (0.44-1.09), 0.54 (0.31-0.94), 0.45 (0.26-0.77), 0.34 (0.19-0.62), and 0.43 (0.24-0.76), respectively. Overall, we found an inverse association between dietary isoflavone intake and risk of breast cancer. Our finding suggests a risk-reducing rather than risk-enhancing effect of isoflavones on breast cancer within the range achievable from dietary intake alone. In addition, women may benefit from risk reduction if they consume at least moderate amounts of isoflavones.

## Lycopene

Karppi, J, S. Kurl, T. Nurmi, T. H. Rissanen, E. Pukkala and K. Nyyssonen. **Serum Lycopene and the Risk of Cancer: The Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study.** *Ann Epidemiol.* 2009 July; 197: 512-518.

Purpose: Lycopene is thought to decrease the risk of cancers, although previous epidemiologic studies have produced inconsistent results. The aim of the present study was to evaluate the protective effect of lycopene against the risk of cancer. Methods: The study population consisted of 997 middle-aged Finnish men in the Kuopio Ischaemic

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### CAM of the Month

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Heart Disease Risk Factor (KIHD) cohort. During the mean follow-up time of 12.6 years, a total of 141 cancer cases appeared, of which 55 were prostate cancers. The association between the serum concentrations of lycopene and the risk of cancer was studied using the Cox proportional hazard models. Results: An inverse association was observed between serum lycopene and overall cancer incidence. The adjusted risk ratio (RR) in the highest tertile of serum lycopene was 0.55 (95% confidence interval [CI], 0.34-0.89;  $p = 0.015$ ) compared with the lowest serum lycopene group. No association was observed between the lycopene concentrations and a prostate cancer risk. RR for other cancers was 0.43 (95% CI, 0.23-0.79;  $p = 0.007$ ). Conclusions: These findings suggest that in middle-aged men, the higher circulating concentrations of lycopene may contribute to the lower risk of cancer, with the exception of prostate cancer.

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## Esophageal

Chen, Y-, C. -H Lee, I. -C Wu, et al. **Food Intake and the Occurrence of Squamous Cell Carcinoma in Different Sections of the Esophagus in Taiwanese Men.** *Nutrition.* 2009 July 2009/August; 257-8: 753-761.

Objective: The main objective of this study was to further elucidate the effect of consuming various foods on the development of squamous cell carcinoma (SCC) in three different sections of the esophagus. Methods: A total of 343 patients with SCC of the esophagus and 755 cancer-free control subjects were recruited for this study from 1996 to 2005. Results: We found that intake of vegetables, raw onions/garlic, and fruits are significantly protective against esophageal SCC risk, whereas intake of hot foods can significantly increase its risk. There was a significant inverse relation between the frequency of tea consumption and esophageal SCC risk ( $P$  for trend = 0.005), with a 0.5-fold lower risk associated with the intake of unfermented tea (green tea, oolong tea, or jasmine tea). The effects of dietary factors on esophageal SCC were similar in all subsites, with the exception of consumption of coffee. Coffee consumption was more pronounced in having a protective effect in the middle third section compared with the lower third section of the esophagus (adjusted odds ratio 0.4, 95% confidence interval 0.2-0.9), although this protective effect was marginally significant (adjusted odds ratio 0.6, 95% confidence interval 0.4-1.0) against esophageal SCC in all subsites. Our data also suggest that discomfort when eating hot foods may exert a carcinogenic effect by direct contact with the esophageal mucosa and tend to have more harmful effects in the upper than in the lower esophagus. In contrast, vegetables, fruits, and tea with components that are thought to inhibit carcinogenesis by absorbed components affected all subsites similarly. Conclusion: Our results add additional information that certain dietary components may affect carcinogenesis locally and systemically.

Islami, F, P. Boffetta, J. S. Ren, L. Pedoeim, D. Khatib and F. Kamangar. **High-Temperature Beverages and Foods and Esophageal Cancer Risk--a Systematic Review** *International Journal of Cancer.* 2009 Aug 1; 1253: 491-524.

Coffee, tea and mate may cause esophageal cancer (EC) by causing thermal injury to the esophageal mucosa. If so, the risk of EC attributable to thermal injury could be large in populations in which these beverages are commonly consumed. In addition, these drinks may cause or prevent EC via their chemical constituents. Therefore, a large number of epidemiologic studies have investigated the association of an indicator of amount or temperature of use of these drinks or other hot foods and beverages with risk of EC. We conducted a systematic review of

these studies and report the results for amount and temperature of use separately. By searching PubMed and the ISI, we found 59 eligible studies. For coffee and tea, there was little evidence for an association between amount of use and EC risk; however, the majority of studies showed an increased risk of EC associated with higher drinking temperature which was statistically significant in most of them. For mate drinking, the number of studies was limited, but they consistently showed that EC risk increased with both amount consumed and temperature, and these 2 were independent risk factors. For other hot foods and drinks, over half of the studies showed statistically significant increased risks of EC associated with higher temperature of intake. Overall, the available results strongly suggest that high-temperature beverage drinking increases the risk of EC. Future studies will require standardized strategies that allow for combining data and results should be reported by histological subtypes of EC

## Pancreatic

Andreotti, G, L. E. B. Freeman, L. Hou, et al. **Agricultural Pesticide use and Pancreatic Cancer Risk in the Agricultural Health Study Cohort.** *International Journal of Cancer.* 2009 15 May; 12410: 2495-2500.

Pancreatic cancer is a rapidly fatal disease that has been linked with pesticide use. Previous studies have reported excess risks of pancreatic cancer with organochlorines such as DDT, however, many other commonly used pesticides have not been examined. To further examine the potential associations between the use of a number of pesticides and pancreatic cancer, we conducted a case-control analysis in the Agricultural Health Study, one of the largest prospective cohorts with over 89,000 participants including pesticide applicators and their spouses in Iowa and North Carolina. This analysis included 93 incident pancreatic cancer cases (64 applicators, 29 spouses) and 82,503 cancer-free controls who completed an enrollment questionnaire providing detailed pesticide use, demographic and lifestyle information. Ever use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) x (exposure intensity score)] of 13 pesticides was assessed. Risk estimates were calculated using unconditional logistic regression controlling for age, smoking, and diabetes. Among pesticide applicators, 2 herbicides (EPTC and pendimethalin) of the 13 pesticides examined for intensity-weighted lifetime use showed a statistically significant exposure-response association with pancreatic cancer. Applicators in the top half of lifetime pendimethalin use had a 3.0-fold (95% CI 1.3-7.2,  $p$ -trend = 0.01) risk compared with never users, and those in the top half of lifetime EPTC use had a 2.56-fold (95% CI = 1.1-5.4,  $p$ -trend = 0.01) risk compared with never users. Organochlorines were not associated with an excess risk of pancreatic cancer in this study. These findings suggest that herbicides, particularly pendimethalin and EPTC, may be associated with pancreatic cancer.

Thiebaut, AC, L. Jiao, D. T. Silverman, et al. **Dietary Fatty Acids and Pancreatic Cancer in the NIH-AARP Diet and Health Study** *J Natl Cancer Inst.* 2009 Jul 15; 10114: 1001-1011.

BACKGROUND: Previous research relating dietary fat, a modifiable risk factor, to pancreatic cancer has been inconclusive. METHODS: We prospectively analyzed the association between intakes of fat, fat subtypes, and fat food sources and exocrine pancreatic cancer in the National Institutes of Health-AARP Diet and Health Study, a US cohort of 308 736 men and 216 737 women who completed a 124-item food frequency questionnaire in 1995-1996. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models, with adjustment for energy intake, smoking history, body mass index, and diabetes. Statistical tests were two-sided. RESULTS: Over an average follow-up of 6.3 years, 865 men and 472 women were diagnosed with exocrine pancreatic cancer (45.0 and 34.5 cases per 100 000 person-years, respectively). After

multivariable adjustment and combination of data for men and women, pancreatic cancer risk was directly related to the intakes of total fat (highest vs lowest quintile, 46.8 vs 33.2 cases per 100 000 person-years, HR = 1.23, 95% CI = 1.03 to 1.46; P(trend) = .03), saturated fat (51.5 vs 33.1 cases per 100 000 person-years, HR = 1.36, 95% CI = 1.14 to 1.62; P(trend) < .001), and monounsaturated fat (46.2 vs 32.9 cases per 100 000 person-years, HR = 1.22, 95% CI = 1.02 to 1.46; P(trend) = .05) but not polyunsaturated fat. The associations were strongest for saturated fat from animal food sources (52.0 vs 32.2 cases per 100 000 person-years, HR = 1.43, 95% CI = 1.20 to 1.70; P(trend) < .001); specifically, intakes from red meat and dairy products were both statistically significantly associated with increased pancreatic cancer risk (HR = 1.27 and 1.19, respectively). **CONCLUSION:** In this large prospective cohort with a wide range of intakes, dietary fat of animal origin was associated with increased pancreatic cancer risk.

Chan, JM, F. Wang and E. A. Holly. **Sweets, Sweetened Beverages, and Risk of Pancreatic Cancer in a Large Population-Based Case-Control Study.** *Cancer Causes & Control.* 2009 Aug; 206: 835-846.

**OBJECTIVE:** We examined the associations between sweets, sweetened and unsweetened beverages, and sugars and pancreatic cancer risk. **METHODS:** We conducted a population-based case-control study (532 cases, 1,701 controls) and used multivariate logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI). Because associations were often different by sex, we present results for men and women combined and separately. **RESULTS:** Among men, greater intakes of total and specific sweets were associated with pancreatic cancer risk (total sweets: OR = 1.9, 95% CI: 1.0, 3.6; sweet condiments: OR = 1.9, 95% CI: 1.2, 3.1; chocolate candy: OR = 2.4, 95% CI: 1.1, 5.0; other mixed candy bars: OR = 3.3, 95% CI: 1.5, 7.3 for 1 + servings/day versus none/rarely). Sweets were not consistently associated with risk among women. Sweetened beverages were not associated with increased pancreatic cancer risk. In contrast, low-calorie soft drinks were associated with increased risk among men only; while other low-/non-caloric beverages (e.g., coffee, tea, and water) were unassociated with risk. Of the three sugars assessed (lactose, fructose, and sucrose), only the milk sugar lactose was associated with pancreatic cancer risk (OR = 2.0, 95% CI: 1.5, 2.7 comparing extreme quartiles). **CONCLUSION:** These results provide limited support for the hypothesis that sweets or sugars increase pancreatic cancer risk.

## Colorectal

Fedirko, V, R. M. Bostick, W. D. Flanders, et al. **Effects of Vitamin D and Calcium Supplementation on Markers of Apoptosis in Normal Colon Mucosa: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial** *Cancer Prevention Research.* 2009 Mar; 23: 213-223.

To further clarify and/or develop calcium and vitamin D as chemopreventive agents against colorectal cancer in humans, understand the mechanisms by which these agents reduce risk for the disease, and develop "treatable" biomarkers of risk for colorectal cancer, we conducted a pilot, randomized, double-blind, placebo-controlled, 2 x 2 factorial clinical trial to test the effects of calcium and vitamin D3, alone and in combination on markers of apoptosis, in the normal colorectal mucosa. Ninety-two men and women with at least one pathology-confirmed colorectal adenoma were treated with 2.0 g/d calcium or 800 IU/d vitamin D3, alone or in combination, versus placebo over 6 months. Overall expression and colorectal crypt distributions of Bcl-2 (an apoptosis inhibitor) and Bax (an apoptosis promoter) in biopsies of normal-appearing rectal mucosa were detected by automated immunohistochemistry and quantified by image analysis. After 6 months of treatment, Bax expression along the full lengths of crypts increased 56% (P =

0.02) in the vitamin D group and 33% in both the calcium (P = 0.31) and calcium plus vitamin D (P = 0.36) groups relative to the placebo group. The vitamin D treatment effect was more pronounced in the upper 40%, or differentiation zone, of crypts (80%; P = 0.01). There were no statistically significant treatment effects on Bcl-2 expression. Overall, these preliminary results suggest that calcium and vitamin D, individually or together, may enhance apoptosis in the normal human colorectal epithelium, and the strongest treatment effects may be vitamin D related and in the upper sections of the colorectal crypts.

## Exercise

Katzmarzyk, PT, T. S. Church, C. L. Craig and C. Bouchard. **Sitting Time and Mortality from all Causes, Cardiovascular Disease, and Cancer.** *Med Sci Sports Exerc.* 2009 May; 415: 998-1005.

**Purpose:** Although moderate-to-vigorous physical activity is related to premature mortality, the relationship between sedentary behaviors and mortality has not been fully explored and may represent a different paradigm than that associated with lack of exercise. We prospectively examined sitting time and mortality in a representative sample of 17,013 Canadians 18-90 yr of age. **Methods:** Evaluation of daily sitting time (almost none of the time, one fourth of the time, half of the time, three fourths of the time, almost all of the time), leisure time physical activity, smoking status, and alcohol consumption was conducted at baseline. Participants were followed prospectively for an average of 12.0 yr for the ascertainment of mortality status. **Results:** There were 1832 deaths (759 of cardiovascular disease (CVD) and 547 of cancer) during 204,732 person-yr of follow-up. After adjustment for potential confounders, there was a progressively higher risk of mortality across higher levels of sitting time from all causes (hazard ratios (HR): 1.00, 1.00, 1.11, 1.36, 1.54; P for trend <0.0001) and CVD (HR: 1.00, 1.01, 1.22, 1.47, 1.54; P for trend <0.0001) but not cancer. Similar results were obtained when stratified by sex, age, smoking status, and body mass index. Age-adjusted all-cause mortality rates per 10,000 person-yr of follow-up were 87, 86, 105, 130, and 161 (P for trend <0.0001) in physically inactive participants and 75, 69, 76, 98, 105 (P for trend = 0.008) in active participants across sitting time categories. **Conclusions:** These data demonstrate a dose-response association between sitting time and mortality from all causes and CVD, independent of leisure time physical activity. In addition to the promotion of moderate-to-vigorous physical activity and a healthy weight, physicians should discourage sitting for extended periods.

Yun, YH, M. K. Lim, Y. J. Won, et al. **Dietary Preference, Physical Activity, and Cancer Risk in Men: National Health Insurance Corporation Study.** *BMC Cancer.* 2008 8366.

**BACKGROUND:** The effects of vegetable preference and leisure-time physical activity (LPA) on cancer have been inconsistent. We examined the effects of dietary preference and physical activity, as well as their combined effect on cancer risk. **METHODS:** This prospective cohort study included 444,963 men, older than 40 years, who participated in a national health examination program begun in 1996. Based on the answer to the question "What kind of dietary preference do you have?" we categorized dietary preference as (1) vegetables, (2) mixture of vegetables and meat, and (3) meats. We categorized LPA as low ( = 30 min/session or > or = 5 times/wk, or = 5 times/wk, > or = 30 min/session). We obtained cancer incidence data for 1996 through 2002 from the Korean Central Cancer Registry. We used a standard Poisson regression model with a log link function and person-time offset to estimate incidence and relative risk. **RESULTS:** During the 6-year follow-up period, we identified 14,109 cancer cases. Multivariate analysis revealed that a preference for vegetables or a mixture of vegetables and meat as opposed to a preference for meat played a significant protective role against lung cancer incidence (aRR, 0.81;

95% confidence interval [CI], 0.68-0.98). Compared with the low LPA group, subjects with moderate-high LPA had a significantly lower risk for stomach (aRR, 0.91; 95%CI, 0.86-0.98), lung (aRR, 0.83; 95%CI, 0.75-0.92), and liver (aRR, 0.88; 95%CI, 0.81-0.95) cancer. Among current smokers, the combined moderate-high LPA and vegetable or mixture of vegetables and meat preference group showed a 40% reduced risk of lung cancer (aRR, 0.60; 95%CI, 0.47-0.76) compared with the combined low LPA and meat preference group. Among never/former smokers, subjects with moderate-high LPA and a preference for vegetables or a mixture of vegetables and meat showed reduced stomach cancer risk (aRR, 0.72; 95%CI, 0.54-0.95). **CONCLUSION:** Our findings add to the evidence of the beneficial effects of vegetable preference on lung cancer risk and of physical activity on lung, stomach, and liver cancer risk. Additionally, vegetable preference combined with LPA might significantly reduce lung and stomach cancer risk.

### Gastric

Hernandez-Ramirez, RU, M. V. Galvan-Portillo, M. H. Ward, et al. **Dietary Intake of Polyphenols, Nitrate and Nitrite and Gastric Cancer Risk in Mexico City.** *International Journal of Cancer.* 2009 Sep 15; 1256: 1424-1430.

N-nitroso compounds (NOC) are potent animal carcinogens and potential human carcinogens. The primary source of exposure for most individuals may be endogenous formation, a process that can be inhibited by dietary polyphenols. To estimate the risk of gastric cancer (GC) in relation to the individual and combined consumption of polyphenols and NOC precursors (nitrate and nitrite), a population-based case-control study was carried out in Mexico City from 2004 to 2005 including 257 histologically confirmed GC cases and 478 controls. Intake of polyphenols, nitrate and nitrite were estimated using a food frequency questionnaire. High intakes of cinnamic acids, secoisolariciresinol and coumestrol were associated with an approximately 50% reduction in GC risk. A high intake of total nitrite as well as nitrate and nitrite from animal sources doubled the GC risk. Odds ratios around 2-fold were observed among individuals with both low intake of cinnamic acids, secoisolariciresinol or coumestrol and high intake of animal-derived nitrate or nitrite, compared to high intake of the polyphenols and low animal nitrate or nitrite intake, respectively. Results were similar for both the intestinal and diffuse types of GC. Our results show, for the first time, a protective effect for GC because of higher intake of cinnamic acids, secoisolariciresinol and coumestrol, and suggest that these polyphenols reduce GC risk through inhibition of endogenous nitrosation. The main sources of these polyphenols were pears, mangos and beans for cinnamic acids; beans, carrots and squash for secoisolariciresinol and legumes for coumestrol.

### Palliative Care

Takahashi, H **Effects of Acupuncture on Terminal Cancer Patients in the Home Care Setting.** *Medical Acupuncture.* 2009 01 May; 212: 123-129.

**Background:** In the field of palliative care medicine, acupuncture is gaining popularity and has been validated with some scientific evidence. However, given the many treatment modalities associated with acupuncture, the optimal approach has not yet been determined. **Objective:** To evaluate the efficacy of acupuncture on various symptoms in terminal cancer patients. **Design, Setting, and Patients:** Between September 2005 and February 2008, acupuncture was performed on 12 terminal cancer patients (aged 56-83 years) receiving home care who had been evaluated to live less than 1 month at the time of discharge from hospital. The patients presented with a variety of symptoms, including pain, nausea, vomiting, dyspnea, and general fatigue, and were considered to be deficient in Qi and as having less Yin compared with Yang. **Intervention:** Acupuncture treatments included the N[right arrow]N+1 treatment along the corresponding energy axes, use of Shu-Mu subsystems, distinct

meridian systems, and local acupoints specifically associated with each condition. Treatments were repeated weekly until death of the patient. **Main Outcome Measures:** Change in symptoms, need for hospitalization, and patient self-report of quality of life. **Results:** All patients survived at least 1 month after the initiation of the acupuncture treatment at home (mean [SD] length of stay at home, 133 [75] days). There was a moderate to significant reduction in the severity of constipation, dyspnea, and general fatigue, although the effects on pain and nausea were variable. No patient required hospitalization for the palliation of symptoms, nor did any patients experience anxiety or other psychological problems that needed further medical attention. All patients were able to remain home until death. **Conclusion:** Acupuncture appeared to significantly contribute to the palliation of symptoms experienced by terminal cancer patients.

### CAM of the Month

Block, KI, C. Gyllenhaal, D. Tripathy, et al. **Survival Impact of Integrative Cancer Care in Advanced Metastatic Breast Cancer.** *Breast J.* 2009 July-August; 154: 357-366.

Integrative cancer treatment is of substantial interest to many cancer patients. Research is needed to evaluate the effects of integrative treatment on patient outcomes. We report survival data for a consecutive case series of advanced metastatic breast cancer patients who received a comprehensive clinical program combining conventional treatments with nutrition and supplementation, fitness and mind-spirit instruction at the Block Center for Integrative Cancer Treatment. Treatment outcomes using integrative care for this disease have not previously been documented; survival data will thus contribute to decisions concerning future research directions and design. Ninety consecutive patients with metastatic breast cancer diagnosed during 1984-1997 who received chemotherapy at the integrative cancer center were included. Prognostic factors, treatments and survival from onset of metastases were determined from analysis of scans, labs, pathology and medical records. The log-rank test and Cox proportional hazards analyses were used, and a Kaplan-Meier curve was calculated. All patients had metastatic disease at baseline, 96% were relapsed and 52% had received prior chemotherapy for metastatic disease. Median age at onset of metastasis was 46 years. Median survival was 38 months (95% CI 27,48). Published literature on populations with somewhat more favorable prognostic factors treated in conventional clinics showed median survivals of 20 to 23 months. Through the 1990s, median survival reported in metastatic breast cancer trials or observations generally ranged from 12 to 24 months. Five-year survival was 27% for Center versus 17% for comparison patients. Despite a higher proportion of younger and relapsed patients, survival of metastatic breast cancer patients at the Center was approximately double that of comparison populations and possibly even higher compared to trials published during this period. Explanations for the advantage relative to conventional treatment alone may include the nutritional, nutraceutical, exercise and psychosocial interventions, individually or in combination; self-selection of patients cannot be ruled out. Further research to evaluate the impact of integrative breast cancer treatment on survival is warranted.

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