



RESEARCH UPDATES

For the latest in worldwide integrated cancer care

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InspireHealth
INTEGRATED CANCER CARE

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Research Updates is produced once a month by InspireHealth to inform those interested of newly published articles in integrative cancer care. Authoritative articles are selected based on their evidence and their relevance to this area of medicine.

Thank you to **The Canadian Breast Cancer Foundation BC/Yukon Chapter** for their generous support.



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Breast

Kallianpur, AR, S. -A Lee, Y. -T Gao, et al. **Dietary Animal-Derived Iron and Fat Intake and Breast Cancer Risk in the Shanghai Breast Cancer Study.** *Breast Cancer Res Treat.* 2008 Jan; 107(1): 123-132. Background: Dietary fats and other constituents have been studied extensively in relation to breast cancer risk. Iron, an essential micronutrient with pro-oxidant properties, has received little attention, and specific fats may augment its toxicity. We investigated the effects of iron and fats from various food sources on the risk of breast cancer. Methods: Participants in a population-based case-control study, 3,452 breast cancer cases, and 3,474 age-frequency-matched controls, completed in-person interviews, including a detailed food-frequency questionnaire. Plant- and animal-derived iron and fat intakes were derived from dietary intake data and food composition tables. Unconditional logistic regression models were used to study the independent and interactive effects of different forms of iron and fats on breast cancer risk. Results: Animal-derived (largely heme) iron intake was positively associated with breast cancer risk ($P_{\text{trend}} < 0.01$; OR = 1.49 in the highest vs. lowest quartile, 95% confidence interval [CI] 1.25-1.78) after adjustment for known risk factors, antioxidant vitamin and isoflavone intake, and vitamin supplement use. The effect of animal-derived iron was similar in pre- and postmenopausal women. Intake of animal-derived fats was also associated with increased risk (adjusted OR = 1.34, 95% CI 1.14-1.58), particularly after menopause. A significant interaction between iron and fat from animal sources was observed ($P < 0.01$). Conclusions: A high intake of animal-derived (heme) iron may be associated with an increased risk of primary breast cancer in Chinese women, and saturated and mono-unsaturated fats that are also derived from animal sources may augment this effect. Combined reductions in animal-derived iron and fat consumption have the potential to reduce breast cancer risk.

Fink, BN, S. E. Steck, M. S. Wolff, et al. **Dietary Flavonoid Intake and Breast Cancer Survival among Women on Long Island.** *Cancer Epidemiology Biomarkers and Prevention.* 2007 01 Nov; 16(11): 2285-2292. Background: Laboratory research and a

growing number of epidemiologic studies have provided evidence for a reduced risk of breast cancer associated with dietary intake of certain classes of flavonoids. However, the effects of flavonoids on survival are not known. In a population-based cohort of breast cancer patients, we investigated whether dietary flavonoid intake before diagnosis is associated with subsequent survival. Methods: Women ages 25 to 98 years who were newly diagnosed with a first primary invasive breast cancer between August 1, 1996, and July 31, 1997, and participated in a population-based, case-control study ($n = 1,210$) were followed for vital status through December 31, 2002. At the case-control interview conducted shortly after diagnosis, respondents completed a FFQ that assessed dietary intake in the previous 12 months. All-cause mortality ($n = 173$ deaths) and breast cancer-specific mortality ($n = 113$ deaths) were determined through the National Death Index. Results: Reduced hazard ratios [age- and energy-adjusted hazard ratio (95% confidence interval)] for all-cause mortality were observed among premenopausal and postmenopausal women for the highest quintile of intake, compared with the lowest, for flavones [0.63 (0.41-0.96)], isoflavones [0.52 (0.33-0.82)], and anthocyanidins [0.64 (0.42-0.98)]. No significant trends in risk were observed. Results were similar for breast cancer-specific mortality only. Conclusion: Mortality may be reduced in association with high levels of dietary flavones and isoflavones among postmenopausal U.S. breast cancer patients. Larger studies are needed to confirm our findings.

Prostate

Chavarro, JE, M. J. Stampfer, H. Campos, T. Kurth, W. C. Willett and J. Ma. **A Prospective Study of Trans-Fatty Acid Levels in Blood and Risk of Prostate Cancer.** *Cancer Epidemiology Biomarkers and Prevention.* 2008 01 Jan; 17(1): 95-101. Background: Previous studies suggest a positive association between markers of trans-fatty acid intake and prostate cancer. We therefore prospectively evaluated the association between blood trans-fatty acid levels and risk of prostate cancer. Methods: We conducted a nested case-control study among 14,916 apparently healthy men who provided blood samples in 1982. Blood fatty acid levels

were determined for 476 men diagnosed with prostate cancer during a 13-year follow-up and their matched controls. Controls were individually matched to cases according to age and smoking status at baseline. Conditional logistic regression was used to estimate the relative risk and 95% confidence interval of total, nonaggressive (stage A/B and low grade), and aggressive (stage C/D, high grade, subsequent distant metastasis or death) prostate cancer associated with blood levels of specific trans-fatty acids. Results: Blood levels of all the trans-fatty acids examined were unrelated to total prostate cancer risk. When results were divided according to tumor aggressiveness, blood levels of 18:1n-9t, all the 18:2t examined, and total trans-fatty acids were positively associated to nonaggressive tumors. The relative risks (95% confidence intervals; P trend) comparing top with bottom quintile trans-fatty acid levels were 2.16 (1.12-4.17; 0.11) for 18:1n-9t, 1.97 (1.03-3.75; 0.01) for total 18:2 t, and 2.21 (1.14-4.29; 0.06) for total trans-fatty acids. None of the trans fats examined was associated with aggressive prostate tumors. Conclusion: Blood levels of trans isomers of oleic and linoleic acids are associated with an increased risk of nonaggressive prostate tumors. As this type of tumors represents a large proportion of prostate cancer detected using prostate-specific antigen screening, these findings may have implications for the prevention of prostate cancer.

Koutros, S, A. J. Cross, D. P. Sandler, et al. **Meat and Meat Mutagens and Risk of Prostate Cancer in the Agricultural Health Study.** *Cancer Epidemiology Biomarkers and Prevention.* 2008 01 Jan; 171: 80-87. Meats cooked at high temperatures, such as pan-frying or grilling, are a source of carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons. We prospectively examined the association between meat types, meat cooking methods, meat doneness, and meat mutagens and the risk for prostate cancer in the Agricultural Health Study. We estimated relative risks and 95% confidence intervals (95% CI) for prostate cancer using Cox proportional hazards regression using age as the underlying time metric and adjusting for state of residence, race, smoking status, and family history of prostate cancer. During 197,017 person-years of follow-up, we observed 668 incident prostate cancer cases (613 of these were diagnosed after the first year of follow-up and 140 were advanced cases) among 23,080 men with complete dietary data. We found no association between meat type or specific cooking method and prostate cancer risk. However, intake of well or very well done total meat was associated with a 1.26-fold increased risk of incident prostate cancer (95% CI, 1.02-1.54) and a 1.97-fold increased risk of advanced disease (95% CI, 1.26-3.08) when the highest tertile was compared with the lowest. Risks for the two heterocyclic amines 2-amino-3,4,8-trimethylimidazo-[4,5-f]quinoxaline and 2-amino-3,8- dimethylimidazo-[4,5-b]quinoxaline were of borderline significance for incident disease [1.24 (95% CI, 0.96-1.59) and 1.20 (95% CI, 0.93-1.55), respectively] when the highest quintile was compared with the lowest. In conclusion, well and very well done meat was associated with an increased risk for prostate cancer in this cohort.

vitamins and minerals and risk of neoplastic progression of Barrett's esophagus and EA. The Seattle Barrett's Esophagus Program is a prospective study based on 339 men and women with histologically confirmed Barrett's esophagus. Participants underwent baseline and periodic follow-up exams, which included endoscopy and self-administered questionnaires on diet, supplement use, and lifestyle characteristics. Use of multivitamins and 4 individual supplements was calculated using time-weighted averages of reported use over the observational period. Cox proportional-hazards models were used to calculate hazard ratios (HR) for each endpoint: EA, tetraploidy, and aneuploidy. During a mean follow-up of 5 yr, there were 37 cases of EA, 42 cases of tetraploidy, and 34 cases of aneuploidy. After controlling for multiple covariates including diet, nonsteroidal anti-inflammatory drug use, obesity, and smoking, participants who took 1 or more multivitamin pills/day had a significantly decreased risk of tetraploidy [HR = 0.19; 95% confidence interval (CI) = 0.08-0.47] and EA (HR = 0.38; 95% CI = 0.15-0.99) compared to those not taking multivitamins. Significant inverse associations were also observed between risk of EA and supplemental vitamin C ([greater-than or equal to]250 mg vs. none: HR = 0.25; 95% CI = 0.11-0.58) and vitamin E ([greater-than or equal to]180 mg vs. none: HR = 0.25; 95% CI = 0.10-0.60). In this cohort study, use of multivitamins and single antioxidant supplements was associated with a significantly reduced risk of EA and markers of neoplastic progression among individuals with Barrett's esophagus.

Colon

Logan, RF, M. J. Grainge, V. C. Shepherd, N. C. Armitage, K. R. Muir and Group ukCAP Trial. **Aspirin and Folic Acid for the Prevention of Recurrent Colorectal Adenomas** *Gastroenterology.* 2008 Jan; 134: 29-38. BACKGROUND & AIMS: Although observational studies have found regular aspirin use to be associated with a reduced risk of colorectal neoplasia, results from randomized trials using aspirin have been inconsistent. Dietary folate intake also has been found to be associated with a reduced risk of colorectal neoplasms in observational studies. METHODS: A multicenter, randomized, double-blind trial of aspirin (300 mg/day) and folate supplements (0.5 mg/day) to prevent colorectal adenoma recurrence was performed using a 2 x 2 factorial design. All patients had an adenoma (≥ 0.5 cm) removed in the 6 months before recruitment and were followed-up at 4-month intervals with a second colonoscopy after approximately 3 years. The primary outcome measure was a colorectal adenoma diagnosed after baseline. RESULTS: A total of 945 patients were recruited into the study, of whom 853 (90.3%) underwent a second colonoscopy. In total, 99 (22.8%) of 434 patients receiving aspirin had a recurrent adenoma compared with 121 (28.9%) of 419 patients receiving placebo (relative risk, 0.79; 95% confidence interval [CI], 0.63-0.99). A total of 104 patients developed an advanced colorectal adenoma; 41 (9.4%) of these were in the aspirin group and 63 (15.0%) were in the placebo group (relative risk, 0.63; 95% CI, 0.43-0.91). Folate supplementation was found to have no effect on adenoma recurrence (relative risk, 1.07; 95% CI, 0.85-1.34). CONCLUSIONS: Aspirin (300 mg/day) but not folate (0.5 mg/day) use was found to reduce the risk of colorectal adenoma recurrence, with evidence that aspirin could have a significant role in preventing the development of advanced lesions.

Endometrial

McCullough, ML, A. V. Patel, R. Patel, et al. **Body Mass and Endometrial Cancer Risk by Hormone Replacement Therapy and Cancer Subtype.** *Cancer Epidemiology Biomarkers and Prevention.* 2008 01 Jan; 171: 73-79. Epidemiologic studies unequivocally show that greater body mass increases the risk of endometrial cancer, but whether risk varies by

 Thank you to the **BC Foundation for Prostate Disease** for their generous support.
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Esophageal

Dong, LM, A. R. Kristal, U. Peters, et al. **Dietary Supplement use and Risk of Neoplastic Progression in Esophageal Adenocarcinoma: A Prospective Study.** *Nutr Cancer.* 2008 Jan; 60: 39-48. The incidence of esophageal adenocarcinoma (EA) and its precursor condition, Barrett's esophagus, has risen rapidly in the United States for reasons that are not fully understood. Therefore, we evaluated the association between use of supplemental

use of postmenopausal hormone therapy (HT), location of fat deposition, or cancer sub-type is still unclear. We examined these associations among 33,436 postmenopausal women in the Cancer Prevention Study II Nutrition Cohort, who completed questionnaires on diet, lifestyle, and medical history at baseline in 1992. A total of 318 cases were eligible through June 2003. Cox-proportional hazards analyses were used to estimate multivariate-adjusted rate ratios (RR). As expected, adult body mass index (BMI) was a strong predictor of risk [RR, 4.70; 95% confidence interval (CI), 3.12-7.07 for BMI 35+ versus 22.5-25.0, P trend < 0.0001]. Use of estrogen plus progestin post-menopausal HT modified the association. Among never-users, risk was significantly linear across the entire range of BMI examined (RR, 0.51; 95% CI, 0.29-0.92 for <22.5 versus 22.5-25.0; RR, 4.41; 95% CI, 2.70-7.20 for [greater-than or equal to]35 versus 22.5-25.0, P trend < 0.0001), but among ever estrogen plus progestin users, the association was not significant (P trend = 1.0; P interaction < 0.0001). We observed no difference in risk according to tendency for central versus peripheral fat deposition. Greater BMI ([greater-than or equal to]30 versus <25.0) increased risk of both "type I" (classic estrogen pathway, RR, 4.22; 95% CI, 3.07-5.81) and "type II" (serous, clear cell, and all other high grade) cancers (RR, 2.87; 95% CI, 1.59-5.16). The increased risk of endometrial cancer across the range of BMI in women who never used postmenopausal HT stresses the need to prevent both overweight and obesity in women.

Psychosocial

Sigal, JJ, M. Claude Ouimet, R. Margolese, L. Panarello, V. Stibernik and S. Bescec. **How Patients with Less-Advanced and More-Advanced Cancer Deal with Three Death-Related Fears: An Exploratory Study.** *J Psychosoc Oncol.* 2008 261: 53-68. The means used by cancer patients to cope with each of three death anxieties (i.e., fear of pain and suffering, loneliness, and the unknown) that contribute to their psychological distress have rarely been examined. Differences between cancer patients with Stage I or II disease (Group 1) and Stage III or IV disease (Group 2) were explored. T-tests revealed no difference between the groups. Age-controlled Pearson correlations were used to determine the relationship between all three death anxieties, and some recognized coping devices used by cancer patients, namely, coping styles, optimism, and religiosity/spirituality. Results showed that, for Group 1, avoidant coping correlated positively with fear of the unknown, and social diversion correlated positively with fear of pain and suffering. As for similarities between groups, with the exception of fear of pain and suffering for Group 2, emotion-focused coping correlated positively with all three death anxieties, and optimism correlated negatively with fear of the unknown. The advantage for researchers and clinicians of including measures or evaluation of the death anxieties in their considerations of the psychological distress of cancer patients is discussed.

Acupressure

Gardani, G, R. Cerrone, C. Biella, et al. **A Progress Study of 100 Cancer Patients Treated by Acupressure for Chemotherapy-Induced Vomiting After Failure with the Pharmacological Approach.** *Minerva Med.* 2007 Dec; 986: 665-668. Aim. The recent rediscovery of the natural traditional medical sciences has contributed to improve the treatment of the human diseases and, in particular, it has been shown that the pharmacological approach is not the only possible strategy in the treatment of nausea and vomiting, since bioenergetic approaches, such as acupressure and acupuncture, may also counteract the onset of vomiting due to different causes. Previous preliminary clinical studies had already suggested a possible efficacy of acupressure also in the treatment of chemotherapy-induced vomiting resistant to the classical antiemetic drugs. The aim of this study was to confirm these preliminary data. Methods. The study

was performed in 100 consecutive metastatic solid tumour patients, who underwent chemotherapy for their advanced neoplastic disease, and who had no benefit from the standard antiemetic agents, including corticosteroids, antidopaminergics and 5-HT 3R-antagonists. Acupressure was made by a stimulation of PC6 acupoint. Results. The emetic symptomatology was reduced by acupressure in 68/100 (68%) patients, without significant differences in relation to tumour histotype. The lowest efficacy was observed in patients treated by anthracycline-containing regimens, without, however, statistically significant differences with respect to the other chemotherapeutic combinations. Conclusion. This study confirms previous preliminary clinical results, which had already suggested the potential efficacy of acupressure in the treatment of vomiting due to cancer chemotherapy. Therefore, acupressure may be successfully included within the therapeutic strategies of cancer chemotherapy-induced vomiting.

Antioxidants

Phytochemicals Stevenson, DE and R. D. Hurst. **Polyphenolic -- just Antioxidants Or Much More?** *Cellular & Molecular Life Sciences.* 2007 Nov; 6422: 2900-2916. Polyphenolic phytochemicals are ubiquitous in plants, in which they function in various protective roles. A 'recommended' human diet contains significant quantities of polyphenolics, as they have long been assumed to be 'antioxidants' that scavenge excessive, damaging, free radicals arising from normal metabolic processes. There is recent evidence that polyphenolics also have 'indirect' antioxidant effects through induction of endogenous protective enzymes. There is also increasing evidence for many potential benefits through polyphenolic-mediated regulation of cellular processes such as inflammation. Inductive or signalling effects may occur at concentrations much lower than required for effective radical scavenging. Over the last 2-3 years, there have been many exciting new developments in the elucidation of the in vivo mechanisms of the health benefits of polyphenolics. We summarise the current knowledge of the intake, bio-availability and metabolism of polyphenolics, their antioxidant effects, regulatory effects on signalling pathways, neuro-protective effects and regulatory effects on energy metabolism and gut health.

Herbal Supplements

Seely, D, D. A. Kennedy, S. P. Myers, et al. **In Vitro Analysis of the Herbal Compound Essiac.** *Anticancer Res.* 2007 Nov-Dec; 276B: 3875-3882. BACKGROUND: Despite the recommendation of the Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative, little research has been published on the widely used herbal compound Essiac. We aimed to address this deficiency by conducting a series of assays to determine some of the purported activities of Essiac in vitro. MATERIALS AND METHODS: The activity of Essiac was measured using established assays to assess anti-oxidant, fibrinolytic, anti-microbial, anti-inflammatory, immune modulation, cell-specific cytotoxicity, and impact on cytochrome P450 (CYP450) enzyme pathways. RESULTS: Essiac exhibited significant antioxidant activity in the ABTS assay. A 20-fold dilution of Essiac also exhibited significant immunomodulatory effects, specifically through stimulation of granulocyte phagocytosis, increases in CD8+ cell activation, and moderately inhibiting inflammatory pathways. Essiac exhibited significant cell-specific cytotoxicity towards ovarian epithelial carcinoma cells (A2780). Importantly, a 20-fold dilution of Essiac showed significant inhibition of several CYP450 enzymes, most notably CYP1A2 (37%) and CYP2C19 (24%). Essiac demonstrated dose-dependent inhibition of clot fibrinolysis. CONCLUSION: In vitro analysis of Essiac indicates significant antioxidant and immunomodulatory properties, as well as neoplastic cell specific cytotoxicity consistent with the historical properties ascribed to this compound.

Importantly, significant CYP450 and fibrinolysis inhibition were also observed. This is the first comprehensive investigation of the in vitro effects of Essiac.

Sun Exposure

Kricker, A, B. K. Armstrong, A. M. Hughes, et al. **Personal Sun Exposure and Risk of Non Hodgkin Lymphoma: A Pooled Analysis from the Interlymph Consortium.** *International Journal of Cancer.* 2008 01 Jan; 1221: 144-154. In 2004-2007 4 independent case-control studies reported evidence that sun exposure might protect against NHL; a fifth, in women only, found increased risks of NHL associated with a range of sun exposure measurements. These 5 studies are the first to examine the association between personal sun exposure and NHL. We report here on the relationship between sun exposure and NHL in a pooled analysis of 10 studies participating in the International Lymphoma Epidemiology Consortium (InterLymph), including the 5 published studies. Ten case-control studies covering 8,243 cases and 9,697 controls in the USA, Europe and Australia contributed original data for participants of European origin to the pooled analysis. Four kinds of measures of self-reported personal sun exposure were assessed at interview. A two-stage estimation method was used in which study-specific odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for potential confounders including smoking and alcohol use, were obtained from unconditional logistic regression models and combined in random-effects models to obtain the pooled estimates. Risk of NHL fell significantly with the composite measure of increasing recreational sun exposure, pooled OR = 0.76 (95% CI 0.63-0.91) for the highest exposure category (p for trend 0.01). A downtrend in risk with increasing total sun exposure was not statistically significant. The protective effect of recreational sun exposure was statistically significant at 18-40 years of age and in the 10 years before diagnosis, and for B cell, but not T cell, lymphomas. Increased recreational sun exposure may protect against NHL.

Moan, J, A. C. Porojnicu, A. Dahlback and R. B. Setlow. **Addressing the Health Benefits and Risks, Involving Vitamin D Or Skin Cancer, of Increased Sun Exposure.** *Proc Natl Acad Sci U S A.* 2008 Jan 15; 1052: 668-673. Solar radiation is the main cause of skin cancers. However, it also is a main source of vitamin D for humans. Because the optimal status of vitamin D protects against internal cancers and a number of other diseases, a controversy exists: Will increased sun exposure lead to net health benefits or risks? We calculated the relative yield of vitamin D photosynthesis as a function of latitude with a radiative transfer model and cylinder geometry for the human skin surface. The annual yield of vitamin D is 3.4 and 4.8 times larger below the equator than in the U.K. and Scandinavia, respectively. In populations with similar skin types, there are clear latitude gradients of all major forms of skin cancer, indicating a north-south gradient in real sun exposure. Surprisingly, the incidence rates of major internal cancers also increase from north to south. However, the survival prognosis also improves significantly from north to south. Reasons for these findings are discussed in view of the role of vitamin D. In Norway, melanoma rates increased by a factor of 6 from 1960 to 1990, while the prognosis improved in the same period. After 1990, melanoma rates have remained constant or even decreased in age groups <50 years, whereas the prognosis has not improved further. These data, together with those for internal cancers and the beneficial effects of an optimal vitamin D status, indicate that increased sun exposure may lead to improved cancer prognosis and, possibly, give more positive than adverse health effects.

CAM of the Month

Irigaray, P, J. A. Newby, R. Clapp, et al. **Lifestyle-Related Factors and Environmental Agents Causing Cancer: An Overview** *Biomedicine & Pharmacotherapy.* 2007 Dec; 6110: 640-658. The increasing incidence of a variety of cancers after the Second World War confronts scientists with the question of their origin. In Western countries, expansion and ageing of the population as well as progress in cancer detection using new diagnostic and screening tests cannot fully account for the observed growing incidence of cancer. Our hypothesis is that environmental factors play a more important role in cancer genesis than it is usually agreed. (1) Over the last 2-3 decades, alcohol consumption and tobacco smoking in men have significantly decreased in Western Europe and North America. (2) Obesity is increasing in many countries, but the growing incidence of cancer also concerns cancers not related to obesity nor to other known lifestyle-related factors. (3) There is evidence that the environment has changed over the time period preceding the recent rise in cancer incidence, and that this change, still continuing, included the accumulation of many new carcinogenic factors in the environment. (4) Genetic susceptibility to cancer due to genetic polymorphism cannot have changed over one generation and actually favours the role of exogenous factors through gene-environment interactions. (5) Age is not the unique factor to be considered since the rising incidence of cancers is seen across all age categories, including children, and adolescents. (6) The fetus is specifically vulnerable to exogenous factors. A fetal exposure during a critical time window may explain why current epidemiological studies may still be negative in adults. We therefore propose that the involuntary exposure to many carcinogens in the environment, including microorganisms (viruses, bacteria and parasites), radiations (radioactivity, UV and pulsed electromagnetic fields) and many xenochemicals, may account for the recent growing incidence of cancer and therefore that the risk attributable to environmental carcinogen may be far higher than it is usually agreed. Of major concern are: outdoor air pollution by carbon particles associated with polycyclic aromatic hydrocarbons; indoor air pollution by environmental tobacco smoke, formaldehyde and volatile organic compounds such as benzene and 1,3 butadiene, which may particularly affect children and food contamination by food additives and by carcinogenic contaminants such as nitrates, pesticides, dioxins and other organochlorines. In addition, carcinogenic metals and metalloids, pharmaceutical medicines and some ingredients and contaminants in cosmetics may be involved. Although the risk fraction attributable to environmental factors is still unknown, this long list of carcinogenic and especially mutagenic factors supports our working hypothesis according to which numerous cancers may in fact be caused by the recent modification of our environment.

InspireHealth provides an integrated whole person approach to health for individuals living with cancer. Our medical doctors guide patients to explore and learn about a variety of wellness approaches to health and healing in addition to conventional cancer treatment. This integrated medical model, which engages people in their own care, improves quality of life and reduces the likelihood of cancer recurrence. The editorial board includes: Dr. Hal Gunn, CEO and Co-founder, Dr. Janice Wright, Dr. Teresa Clarke and Dr. Ron Puhky.

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