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InspireHealth
INTEGRATED CANCER CARE

In this issue

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.

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Breast

Hwang, JH, H. J. Chang, Y. H. Shim, et al. **Effects of Supervised Exercise Therapy in Patients Receiving Radiotherapy for Breast Cancer.** *Yonsei Med J.* 2008 Jun 30; 493: 443-450.
PURPOSE: Postoperative radiotherapy for breast cancer has a number of associated complications. This study examined whether supervised moderate-intensity exercise could mitigate the complications that occur during radiotherapy. PATIENTS AND METHODS: Forty women were randomized before radiotherapy after various operations for breast cancer. Seventeen patients who were assigned to the exercise group performed supervised moderate-intensity exercise therapy for 50 min 3 times per week for 5 weeks. Twenty-three patients in the control group were asked to perform self-shoulder stretching exercise. The World Health Organization Quality of Life-BREF (WHOQOL-BREF), brief fatigue inventory (BFI), range of motion (ROM) of the shoulder, and pain score were assessed before and after radiotherapy. RESULTS: There were no significant differences noted at baseline between groups. In the exercise group, there was an increase in the WHOQOL-BREF and shoulder ROM and decrease in BFI and pain score after radiotherapy. On the other hand, patients in the control group showed decrease in the WHOQOL-BREF and shoulder ROM and increase in BFI and pain score after radiotherapy. There were statistically significant differences in the changes in the WHOQOL, BFI, shoulder ROM, and pain score between the groups. CONCLUSION: Patients receiving radiotherapy for breast cancer may benefit in physical and psychological aspects from supervised moderate-intensity exercise therapy.

Irwin, ML, A. W. Smith, A. McTiernan, et al. Influence of Pre- and Postdiagnosis **Physical Activity on Mortality in Breast Cancer Survivors: The Health, Eating, Activity, and Lifestyle Study**. *Journal of Clinical Oncology.* 2008 2624: 3958-3964.
Purpose: To investigate the association between pre- and postdiagnosis physical activity (as well as change in prediagnosis to postdiagnosis physical activity) and mortality among women with breast cancer. Patients and Methods: This was a prospective observational study of 933 women enrolled onto the Health, Eating, Activity, and Lifestyle Study who were diagnosed with local or regional breast cancer between 1995 and 1998 and observed until death or September 2004, whichever came first. The primary outcomes measured were total deaths and breast cancer deaths. The primary exposures were physical activity in the year before and 2 years after diagnosis and the pre- to postdiagnosis change in physical activity. Results: Compared with inactive women, the multivariable hazard ratios (HRs) for total deaths for women expending at least 9 metabolic equivalent hours per week (approximately 2 to 3 h/wk of brisk walking) were 0.69 (95% CI, 0.45 to 1.06; P = .045) for those active in the year before diagnosis and 0.33 (95% CI, 0.15 to 0.73; P = .046) for those active 2 years after diagnosis. Compared with women who were inactive both before and after diagnosis, women who increased physical activity after diagnosis had a 45% lower risk of death (HR = 0.55; 95% CI, 0.22 to 1.38), and women who decreased physical activity after diagnosis had a four-fold greater risk of death (HR = 3.95; 95% CI, 1.45 to 10.50). Conclusion: Moderate-intensity physical activity after a diagnosis of breast cancer may improve prognosis. copyright 2008 by American Society of Clinical Oncology.

Prostate

Saxe, GA, J. M. Major, L. Westerberg, S. Khandrika and T. M. Downs. **Biological Mediators of Effect of Diet and Stress Reduction on Prostate Cancer.** *Integrative Cancer Therapies.* 2008 Sep; 73: 130-138.
Background. A 6-month pilot intervention trial was conducted to determine whether adoption of a plant-based diet, reinforced by stress reduction, could reduce the rate of prostate-specific antigen (PSA) increase, a marker of disease progression, in asymptomatic, hormonally untreated patients experiencing consistently increasing PSA levels after surgery or radiation. Methods. A pre-post design was used to examine (1) the effect of intervention on potential mediators of disease progression, including body composition and weight-related biomarkers (sex steroid hormones and cytokines), and (2) whether changes in these variables were associated with change in rate of PSA increase. The baseline rate of PSA increase (from the time of posttreatment recurrence to the start of intervention) was

ascertained from medical records. Body composition and biomarkers were assessed at baseline (prior to intervention), during the intervention (3 months), and at the end of the intervention (6 months). Changes in body composition and biomarkers were determined and compared with rates of PSA increase over the corresponding time intervals. Results. There was a significant reduction in waist-to-hip ratio (P =.03) and increase in circulating sex hormone binding globulin (P =.04). The rate of PSA increase decreased from the preintervention period (PSA slope = 0.059) to the period from 0 to 3 months (PSA slope = 0.002, P <.01) and increased slightly, although not significantly, from 0 to 3 months to the period from 3 to 6 months (0.029, P =.43). Conclusions. Adoption of a plant-based diet and stress reduction may reduce central adiposity and improve the hormonal milieu in patients with recurrent PC. Changes in the rate of increase in PSA were in the same direction as changes in waist-to-hip ratio and opposite those of sex hormone binding globulin, raising the possibility that the effect of the intervention may have been mediated, in part, by these variables.

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

Bongaerts, BW, P. A. van den Brandt, R. A. Goldbohm, A. F. de Goeij and M. P. Weijenberg. **Alcohol Consumption, Type of Alcoholic Beverage and Risk of Colorectal Cancer at Specific Subsites.** *International Journal of Cancer.* 2008 Nov 15; 12310: 2411-2417.

Within the Netherlands Cohort Study on diet and cancer, we investigated associations between total alcohol consumption, specific alcoholic beverage consumption and risk of colorectal cancer (CRC) according to anatomical subsite. Hazard Ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models. Analyses were performed on 2,323 CRC cases, available after 13.3 years of follow-up. Compared to abstaining, alcohol consumption of >/=30.0 g/day (approximately 3 alcoholic drinks) was positively associated with the risk of CRC (HR: 1.32, 95% CI: 1.06-1.65). Analyses restricted to subjects who reported to have consumed equal amounts of alcohol 5 years before baseline compared to baseline, showed elevated risk estimates for consumers of >/=30.0 g of total alcohol per day as well (HR: 1.53, 95% CI: 1.16-2.01). Suggestive of a subsite-specific effect, cancer risk seemed to increase from proximal colon through rectum; HR: 1.29, 95% CI: 0.85-1.96 for proximal colon cancer, HR: 1.41, 95% CI: 0.94-2.11 for distal colon cancer, HR: 2.07, 95% CI: 1.03-4.18 for rectosigmoid cancer and HR: 1.69, 95% CI: 1.08-2.64 for rectal cancer. No associations were observed between consumption of alcoholic beverages and CRC risk when compared with the nondrinkers of the specific beverage and after adjustment for total alcohol intake. No evidence was found for sex-specific effects of alcohol and alcoholic beverages. In conclusion, our data showed a positive association between alcohol consumption and risk of CRC, which seemed to be mainly explained by the alcoholic content of alcoholic beverages, rather than other constituents. Also, cancer risk may vary according to anatomical subsite.

Howard, RA, D. M. Freedman, Y. Park, A. Hollenbeck, A. Schatzkin and M. F. Leitzmann. **Physical Activity, Sedentary Behavior, and the Risk of Colon and Rectal Cancer in the NIH-AARP Diet and Health Study.** *Cancer Causes and Control.* 2008 Nov; 199: 939-953.

Objective: In order to prospectively investigate physical activity at varying intensities and sedentary behavior in relation to colorectal cancer. Methods: We considered 488,720 participants of the NIH-AARP Diet and Health Study who were aged 50-71 years at baseline in 1995-1996. Through 31 December, 2003, we identified 3,240 and 1,482 colorectal cancers among men and women, respectively. We estimated multivariable relative risks (RR) and 95% confidence intervals (CI) of colorectal cancer using Cox regression. Results: Engaging in exercise/sports five or more times per week compared to never or rarely exercising was associated with a reduced risk of colon cancer among men (p = 0.001; RR = 0.79, 95% CI = 0.68-0.91) and a suggestive decrease in risk among women (p = 0.376; RR = 0.85, 95% CI = 0.70-1.04). Engaging in exercise/sports was also associated with a decreased risk of rectal cancer in men (P = 0.074; RR comparing extreme categories = 0.76, 95% CI = 0.61-0.94). In men, we observed inverse relations of both low intensity (p = 0.017; RR = 0.81, 95% CI = 0.65-1.00 for [greater-than or equal to]7 h/week) and moderate to vigorous intensity activity (p = 0.037; RR = 0.82, 95% CI = 0.67-0.99 for [greater-than or equal to]7 h/week) to colon cancer risk. In contrast, sedentary behavior (time spent watching television/videos) was positively associated with colon cancer (p < 0.001; RR = 1.61, 95% CI = 1.14-2.27 for [greater-than or equal to]9 h/day) among men. Similar, but less pronounced relations were observed in women. Conclusion: Engaging in physical activity of any intensity is associated with reductions in colon and rectal cancer risk. Conversely, time spent sedentary is associated with increased colon cancer risk.

Leung, EY, J. E. Crozier, D. Talwar, et al. **Vitamin Antioxidants, Lipid Peroxidation, Tumour Stage, the Systemic Inflammatory Response and Survival in Patients with Colorectal Cancer**. *International Journal of Cancer.* 2008 Nov 15; 12310: 2460-2464.

Both the tumour growth and progression and the systemic inflammatory response have the potential to increase oxidative stress. We therefore examined the relationship between lipid-soluble antioxidant vitamins, lipid peroxidation, the systemic inflammatory response and survival in patients with primary operable (n = 53) and advanced inoperable (n = 53) colorectal cancer. Compared with those patients with primary operable colorectal cancer, patients with unresectable liver disease had significantly lower median concentrations of alpha-tocopherol (p < 0.001), lutein (p < 0.001), lycopene (p < 0.001), alpha-carotene (p < 0.01) and beta-carotene (p < 0.001) and higher malondialdehyde concentrations. An elevated systemic inflammatory response (Glasgow prognostic score, mGPS) was associated with a greater proportion of females (p < 0.05) and more advanced tumour stage (p < 0.05), lower circulating levels of retinol (p < 0.01), lutein (p < 0.01), lycopene (p < 0.01) and alpha- (p < 0.01) and beta-carotene but not MDA (p = 0.633). In the liver metastases group 41 patients died of their cancer and a further 1 patient died of intercurrent disease on follow-up. On univariate survival analysis, mGPS (p < 0.01), retinol (p < 0.001), alpha-tocopherol (p < 0.05) and alpha-carotene (p < 0.05) were associated significantly with cancer-specific survival. On multivariate survival analysis of these significant variables, only mGPS (p < 0.01) and retinol (p < 0.001) were independently associated with cancer-specific survival. The results of the present study showed that the systemic inflammatory response was associated with a reduction of lipid-soluble antioxidant vitamins, whereas advanced tumour stage was associated with increased lipid peroxidation in patients with colorectal cancer. Of the antioxidant vitamins measured, only retinol was independently associated with cancer-specific survival.

Lymphoma

Eriksson, M, L. Hardell, M. Carlberg and M. Akerman. **Pesticide Exposure as Risk Factor for Non-Hodgkin Lymphoma Including Histopathological Subgroup Analysis.** *International Journal of Cancer.* 2008 01 Oct; 1237: 1657-1663.

We report a population based case-control study of exposure to

pesticides as risk factor for non-Hodgkin lymphoma (NHL). Male and female subjects aged 18-74 years living in Sweden were included during December 1, 1999, to April 30, 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total 910 (91%) cases and 1016 (92%) controls participated. Exposure to herbicides gave odds ratio (OR) 1.72, 95% confidence interval (CI) 1.18-2.51. Regarding phenoxyacetic acids highest risk was calculated for MCPA; OR 2.81, 95% CI 1.27-6.22, all these cases had a latency period >10 years. Exposure to glyphosate gave OR 2.02, 95% CI 1.10-3.71 and with >10 years latency period OR 2.26, 95% CI 1.16-4.40. Insecticides overall gave OR 1.28, 95% CI 0.96-1.72 and impregnating agents OR 1.57, 95% CI 1.07-2.30. Results are also presented for different entities of NHL. In conclusion our study confirmed an association between exposure to phenoxyacetic acids and NHL and the association with glyphosate was considerably strengthened. copyright 2008 Wiley-Liss, Inc.

Skin

Demidov, LV, L. V. Manziuk, G. Y. Kharkevitch, N. A. Pirogova and E. V. Artamonova. **Adjuvant Fermented Wheat Germ Extract (Avemar[Trademark]) Nutraceutical Improves Survival of High-Risk Skin Melanoma Patients: A Randomized, Pilot, Phase II Clinical Study with a 7-Year Follow-Up**. *Cancer Biotherapy and Radiopharmaceuticals.* 2008 01 Aug; 234: 477-482. Objective: The fermented wheat germ extract (FWGE) nutraceutical (Avemar[trademark]), manufactured under "good manufacturing practice" conditions and, fulfilling the self-affirmed "generally recognized as safe" status in the United States, has been approved as a "dietary food for special medical purposes for cancer patients" in Europe. In this paper, we report the adjuvant use of this nutraceutical in the treatment of high-risk skin melanoma patients. Methods: In a randomized, pilot, phase II clinical trial, the efficacy of dacarbazine (DTIC)-based adjuvant chemotherapy on survival parameters of melanoma patients was compared to that of the same treatment supplemented with a 1-year long administration of FWGE. Results: At the end of an additional 7-year-long follow-up period, log-rank analyses (Kaplan-Meier estimates) showed significant differences in both progression-free (PFS) and overall survival (OS) in favor of the FWGE group. Mean PFS: 55.8 months (FWGE group) versus 29.9 months (control group), p = 0.0137. Mean OS: 66.2 months (FWGE group) versus 44.7 months (control group), p = 0.0298. Conclusions: The inclusion of Avemar into the adjuvant protocols of high-risk skin melanoma patients is highly recommended. copyright Mary Ann Liebert, Inc. 2008.

Gastric

Li, J, G. Z. Sun, H. S. Lin, et al**. The Herb Medicine Formula "Yang Wei Kang Liu" Improves the Survival of Late Stage Gastric Cancer Patients and Induces the Apoptosis of Human Gastric Cancer Cell Line through Fas/Fas Ligand and Bax/Bcl-2 Pathways**. *Int Immunopharmacol.* 2008 Sep; 89: 1196-1206. The herb medicine formula "Yang Wei Kang Liu" (YWKLF) has been used to inhibit the metastasis of human gastric cancer to prolong patient survival. In this study, we evaluated the effect of combination of chemotherapy with YWKLF on the survival of stage IV gastric cancer patients and the potential mechanisms of YWKLF by focusing on its capacity to activate apoptotic pathways in human gastric cancer cell line MGC-803. We found that combination of chemotherapy with oral administration of YWKLF significantly increased the survival of stage IV gastric cancer patients. In an approach of "serum pharmacology" in which sera were collected from rabbits orally administered with YWKLF and examined for their anti-tumor cell activity in vitro, we observed that sera from rabbits administered with YWKLF induced the apoptosis of MGC-803 cells by causing the loss of mitochondrial membrane potential, increasing the expression of Fas protein and Bax mRNA, as well as down-regulating Fas-L mRNA. Our results suggest that activation of major pro-apoptotic pathways may account for the anti-gastric cancer activity of YWKLF, which may provide a basis for isolation and identification of more highly effective anti-cancer components.

Endometrial

Patel, AV, H. S. Feigelson, J. T. Talbot, et al. **The Role of Body Weight in the Relationship between Physical Activity and Endometrial Cancer: Results from a Large Cohort of US Women**. *International Journal of Cancer.* 2008 15 Oct; 1238: 1877-1882.
Factors influencing circulating estrogen levels, insulin-mediated pathways or energy balance through obesity-related mechanisms, such as physical activity, have been proposed as potential risk factors for endometrial cancer. We examined measures of physical activity in relation to endometrial cancer risk in the American Cancer Society Cancer Prevention Study II Nutrition Cohort, a prospective study of cancer incidence and mortality, using information obtained at baseline in 1992. From 1992 to 2003, 466 incident endometrial cancers were identified among 42,672 postmenopausal women with intact uteri who were cancer-free at enrollment. Cox proportional hazards modeling was used to compute hazard rate ratios (RR) while adjusting for potential confounders. To assess the role of body mass index (BMI) in this relationship, we computed multivariate RR with and without adjustment for BMI and stratifying by BMI. All measures of physical activity and the avoidance of sedentary behavior were associated with lower endometrial cancer risk. Baseline recreational physical activity was associated with 33% lower risk (RR = 0.67, 95% CI 0.44-1.03 for 31.5+ vs. <7 MET-hr/week, trend p = 0.007) in the multivariate model without BMI. However, the trend was attenuated after further adjustment for BMI (trend p = 0.18). BMI significantly modified the association between physical activity and endometrial cancer risk (heterogeneity of trends p = 0.01). The inverse relationship was seen only among overweight or obese women (trend p = 0.003) and not in normal weight women (trend p = 0.51). In summary, light and moderate physical activity including daily life activities were associated with lower endometrial cancer risk in our study, especially among women who are overweight or obese. copyright 2008 Wiley-Liss, Inc.

Nutrition

Heber, D **Multitargeted Therapy of Cancer by Ellagitannins** *Cancer Lett.* 2008 Oct 8; 2692: 262-268. Ellagitannins are bioactive polyphenols that have antioxidant and anti-inflammatory bioactivities. Pomegranate juice has the highest concentration of ellagitannins of any commonly consumed juice and contains the unique ellagitannin, punicalagin. Punicalagin is the largest molecular weight polyphenol known. Ellagitannins are not absorbed intact into the blood stream but are hydrolyzed to ellagic acid. They are also metabolized by gut flora into urolithins which are conjugated in the liver and excreted in the urine. These urolithins are also bioactive and inhibit prostate cancer cell growth. Inhibition of Nuclear Factor Kappa-B activation has been shown in prostate cancer cells and in human prostate cancer xenografts in mice. In clinical studies, pomegranate juice administration led to a decrease in the rate of rise of Prostate Specific Antigen after primary treatment with surgery or radiation. Continued translational research on the chemopreventive potential of pomegranate ellagitannins is ongoing. [References: 39]

Powolny, AA and S. V. Singh. **Multitargeted Prevention and Therapy of Cancer by Diallyl Trisulfide and Related Allium Vegetable-Derived Organosulfur Compounds** *Cancer Lett.* 2008 Oct 8; 2692: 305-314. Allium vegetables, such as garlic, have been used for medicinal

purposes throughout the recorded history. The known health benefits of Allium vegetables constituents include cardiovascular effects, improvement of the immune function, lowering of blood glucose level, radioprotection, protection against microbial infections, and anti-cancer effects. Initial evidence for the anti-cancer effect of Allium vegetables was provided by population-based case-control studies. Subsequent laboratory studies showed that the Allium vegetable constituents, such as diallyl disulfide, S-allylcysteine, and ajoene can not only offer protection against chemically induced cancer in animal models by altering carcinogen metabolism, but also suppress growth of cancer cells in culture and in vivo by causing cell cycle arrest and apoptosis induction. Suppression of angiogenesis and experimental metastasis by Allium constituents has also been reported. Defining the mechanism by which sulfur compounds derived from Allium vegetables inhibit cancer cell growth has been the topic of intense research in the last two decades. Some Allium vegetable constituents have also entered clinical trials to assess their safety and anti-cancer efficacy. This article summarizes preclinical and limited clinical data to warrant further clinical evaluation of Allium vegetable constituents for prevention and therapy of human cancers. [References: 66]

Psychosocial

Espie, CA, L. Fleming, J. Cassidy, et al. **Randomized Controlled Clinical Effectiveness Trial of Cognitive Behavior Therapy Compared with Treatment as Usual for Persistent Insomnia in Patients with Cancer**. *Journal of Clinical Oncology.* 2008 Oct 1; 2628: 4651-4658.
PURPOSE: Persistent insomnia is a common complaint in cancer survivors, but is seldom satisfactorily addressed. The adaptation to cancer care of a validated, cost-effective intervention may offer a practicable solution. The aim of this study was to investigate the clinical effectiveness of protocol-driven cognitive behavior therapy (CBT) for insomnia, delivered by oncology nurses. PATIENTS AND METHODS: Randomized, controlled, pragmatic, two-center trial of CBT versus treatment as usual (TAU) in 150 patients (103 females; mean age, 61 years.) who had completed active therapy for breast, prostate, colorectal, or gynecological cancer. The study conformed to CONSORT guidelines. Primary outcomes were sleep diary measures at baseline, post-treatment, and 6-month follow-up. Actigraphic sleep, health-related quality of life (QOL), psychopathology, and fatigue were secondary measures. CBT comprised five, small group sessions across consecutive weeks, after a manualized protocol. TAU represented normal clinical practice; the appropriate control for a clinical effectiveness study. RESULTS: CBT was associated with mean reductions in wakefulness of 55 minutes per night compared with no change in TAU. These outcomes were sustained 6 months after treatment. Standardized relative effect sizes were large for complaints of difficulty initiating sleep, waking from sleep during the night, and for sleep efficiency (percentage of time in bed spent asleep). CBT was associated with moderate to large effect sizes for five of seven QOL outcomes, including significant reduction in daytime fatigue. There was no significant interaction effect between any of these outcomes and baseline demographic, clinical, or sleep characteristics. CONCLUSION: CBT for insomnia may be both clinically effective and feasible to deliver in real world practice.

Lutgendorf, SK, D. M. Lamkin, K. DeGeest, et al. **Depressed and Anxious Mood and T-Cell Cytokine Expressing Populations in Ovarian Cancer Patients.** *Brain, Behavior, & Immunity.* 2008 Aug; 226: 890-900.
The adaptive immune response of ovarian cancer patients has been linked to survival, and is known to be impaired in the tumor microenvironment. Little is known about relationships between biobehavioral factors such as depressed mood and anxiety and the adaptive immune response in ovarian cancer. Thirty-seven patients with epithelial ovarian cancer and 14 patients with benign ovarian neoplasms completed psychosocial questionnaires pre-surgery. Lymphocytes from peripheral blood, tumor, and ascites (fluid around the tumor), were obtained on the day of surgery. Expression of the Type-1 cytokine interferon-gamma (IFN gamma), and the Type-2 cytokine interleukin-4 (IL-4) by T-helper (CD4(+)) and T-cytotoxic (CD8(+)) cells was measured under autologous tumor-stimulated, polyclonally-stimulated, or unstimulated conditions. Links with mood were examined. Among cancer patients, marked elevations in unstimulated and tumor-stimulated Type-2 responses were seen, particularly in ascites and tumor-infiltrating lymphocytes (P values<0.01). With polyclonal stimulation, lymphocytes from all compartments expressed elevated Type-1 cytokines (P values<0.014). Depressed and anxious mood were both associated with significantly lower ratios of polyclonally-stimulated CD4(+) cells producing IFN gamma (TH(1) cells) vs. IL-4 (TH(2) cells) in all compartments (depressed mood: P=0.012; anxiety: P=0.038) and depressed mood was also related to lower ratios of polyclonally-stimulated CD8(+) cells producing IFN gamma (TC(1)) vs. IL-4 (TC(2)) (P=0.035). Although effects of polyclonal stimulation should be generalized with caution to the in vivo immune response, findings suggest that depressed and anxious mood are associated with greater impairment of adaptive immunity in peripheral blood and in the tumor microenvironment among ovarian cancer patients.

CAM of the Month

Ramasamy, K and R. Agarwal. **Multitargeted Therapy of Cancer by Silymarin** *Cancer Lett.* 2008 Oct 8; 2692: 352-362.
Silymarin, a flavonolignan from milk thistle (Silybum marianum) plant, is used for the protection against various liver conditions in both clinical settings and experimental models. In this review, we summarize the recent investigations and mechanistic studies regarding possible molecular targets of silymarin for cancer prevention. Number of studies has established the cancer chemopreventive role of silymarin in both in vivo and in vitro models. Silymarin modulates imbalance between cell survival and apoptosis through interference with the expressions of cell cycle regulators and proteins involved in apoptosis. In addition, silymarin also showed anti-inflammatory as well as anti-metastatic activity. Further, the protective effects of silymarin and its major active constituent, silibinin, studied in various tissues, suggest a clinical application in cancer patients as an adjunct to established therapies, to prevent or reduce chemotherapy as well as radiotherapy-induced toxicity. This review focuses on the chemistry and analogues of silymarin, multiple possible molecular mechanisms, in vitro as well as in vivo anti-cancer activities, and studies on human clinical trials. [References: 68]