**Selected by
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Latest Publications You Should Not Miss

Brown PO, Palmer C: The preclinical natural history of serous ovarian cancer: defining the target for early detection. PLoS Med 2011. www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000114#abstract1.

Background: Ovarian cancer kills approximately 15,000 women in the United States every year, and more than 140,000 women worldwide. Most deaths from ovarian cancer are caused by tumors of the serous histological type, which are rarely diagnosed before the cancer has spread. Rational design of a potentially life-saving early detection and intervention strategy requires understanding the lesions we must detect in order to prevent lethal progression. Little is known about the natural history of lethal serous ovarian cancers before they become clinically apparent. We can learn about this occult period by studying the unsuspected serous cancers that are discovered in a small fraction of apparently healthy women who undergo prophylactic bilateral salpingo-oophorectomy (PBSO).

Methods and Findings: We developed models for the growth, progression, and detection of occult serous cancers on the basis of a comprehensive analysis of published data on serous cancers discovered by PBSO in *BRCA1* mutation carriers. Our analysis yielded several critical insights into the early natural history of serous ovarian cancer. First, these cancers spend on average more than 4 y as in situ, stage I, or stage II cancers and approximately 1 y as stage III or IV cancers before they become clinically apparent. Second, for most of the occult period, serous cancers are less than 1 cm in diameter, and not visible on gross examination of the ovaries and Fallopian tubes. Third, the median diameter of a serous ovarian cancer when it progresses to an advanced stage (stage III or IV) is about 3 cm. Fourth, to achieve 50% sensitivity in detecting tumors before they advance to stage III, an annual screen would need to detect tumors of 1.3 cm in diameter; 80% detection sensitivity would require detecting tumors less than 0.4 cm in diameter. Fifth, to achieve a 50% reduction in serous ovarian cancer mortality with an annual screen, a test would need to detect tumors of 0.5 cm in diameter.

Conclusions: Our analysis has formalized essential conditions for successful early detection of serous ovarian cancer. Although the window of opportunity for early detection of these cancers lasts for several years, developing a test sufficiently sensitive and specific to take advantage of

that opportunity will be a challenge. We estimated that the tumors we would need to detect to achieve even 50% sensitivity are more than 200 times smaller than the clinically apparent serous cancers typically used to evaluate performance of candidate biomarkers; none of the biomarker assays reported to date comes close to the required level of performance. Overcoming the signal-to-noise problem inherent in detection of tiny tumors will likely require discovery of truly cancer-specific biomarkers or development of novel approaches beyond traditional blood protein biomarkers. While this study was limited to ovarian cancers of serous histological type and to those arising in *BRCA1* mutation carriers specifically, we believe that the results are relevant to other hereditary serous cancers and to sporadic ovarian cancers. A similar approach could be applied to other cancers to aid in defining their early natural history and to guide rational design of an early detection strategy.

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R: A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2011. www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040325.

Background: Red meat and processed meat have been associated with carcinogenesis at several anatomic sites, but no prospective study has examined meat intake in relation to a range of malignancies. We investigated whether red or processed meat intake increases cancer risk at a variety of sites.

Methods and Findings: The National Institutes of Health (NIH)-AARP (formerly the American Association for Retired Persons) Diet and Health Study is a cohort of approximately 500,000 people aged 50–71 y at baseline (1995–1996). Meat intake was estimated from a food frequency questionnaire administered at baseline. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals within quintiles of red and processed meat intake. During up to 8.2 y of follow-up, 53,396 incident cancers were ascertained. Statistically significant elevated risks (ranging from 20% to 60%) were evident for esophageal, colorectal, liver, and lung cancer, comparing individuals in the highest with those in the lowest quintile of red meat intake. Further-

more, individuals in the highest quintile of processed meat intake had a 20% elevated risk for colorectal and a 16% elevated risk for lung cancer.

Conclusions: Both red and processed meat intakes were positively associated with cancers of the colorectum and lung; furthermore, red meat intake was associated with an elevated risk for cancers of the esophagus and liver.

Amri H, Haramati A: Using basic science to develop an innovative program in complementary and alternative medicine. J Int Assoc Med Sci Educ 2010;20:48–55.

The growing interest in Complementary and Alternative Medicine (CAM) and the increasing incorporation of its modalities in the United States' healthcare system have exposed a number of problems in the field. These include a shortage of qualified CAM providers, scarcity of evidence-based research, lack of trained scientists in the field, and the ubiquitous marketing of frequently uncontrolled CAM products. Thus, the development of a comprehensive and scientifically sound educational infrastructure has become a crucial initial step in redirecting these adverse trends.

With support from the NIH-sponsored curricular CAM initiative, faculty from the department of physiology and biophysics at Georgetown University developed a M.S. program in CAM in 2003. This unique, first of its kind, science-based graduate program offers a master's degree (MS) in physiology with an emphasis on CAM. The CAM-MS degree in physiology is designed to enable students to critically assess various CAM modalities, apply scientific rigor, and carry out evidence-based CAM research. The curriculum includes core science courses and CAM-related classes. Additionally, in order to emphasize the application of academic knowledge and further strengthen problem-solving skills, the students complete an eight-week summer practicum in a professional CAM-related environment.

Here, we report on our innovative and interdisciplinary CAM graduate program where creative teaching is implemented by basic scientists and enhanced by the application of their disciplines in tandem with the clinical expertise of CAM practitioners in the community. Thus, the faculty in the Department of Physiology and Biophysics is developing emerging cross disciplinary areas of study and interest in order to prepare new generations of future physicians, health professionals, educators, and researchers capable of objectively assessing the safety and efficacy of various CAM modalities, and introducing scientific rigor to much needed research into the various aspects of CAM therapies.

Salomonsen LJ, Skovgaard L, la Cour S, Nyborg L, Launsø L, Fønnebø V: Use of complementary and alternative medicine at Norwegian and Danish hospitals. BMC Complement Altern Med 2011;11:4.

Background: Several studies have found that a high proportion of the population in western countries use complementary and alternative medicine (CAM). However, little is known about whether CAM is offered in hospitals. The aim of this study was to describe to what extent CAM is offered in Norwegian and Danish hospitals and investigate possible changes in Norway since 2001.

Methods: A one-page questionnaire was sent to all included hospitals in both countries. The questionnaire was sent to the person responsible for the clinical activity, typically the medical director. 99 hospitals in the authority (85%) in Norway and 126 in Denmark (97%) responded. Given contact persons were interviewed.

Results: CAM is presently offered in about 50% of Norwegian hospitals and one-third of Danish hospitals. In Norway CAM was offered in 50 hospitals, 40 of which involved acupuncture. 19 hospitals gave other alternative therapies like biofeedback, hypnosis, cupping, ear-acupuncture, herbal medicine, art therapy, homeopathy, reflexology, thought field therapy, gestalt therapy, aromatherapy, tai chi, acupressure, yoga, pilates and other. 9 hospitals offered more than one therapy form. In Denmark 38 hospitals offered acupuncture and one Eye Movement Desensitization and Reprocessing Light Therapy. The most commonly reported reason for offering CAM was scientific evidence in Denmark. In Norway it was the interest of a hospital employee, except for acupuncture where the introduction is more often initiated by the leadership and is more based on scientific evidence of effect. All persons (except one) responsible for the alternative treatment had a medical or allied health professional background and their education/training in CAM treatment varied substantially.

Conclusions: The extent of CAM being offered has increased substantially in Norway during the first decade of the 21st century. This might indicate a shift in attitude regarding CAM within the conventional health care system.

Ilyioha I: Law's Dilemma: Validating Complementary and Alternative Medicine and the Clash of Evidential Paradigms. Evid Based Complement Alternat Med 2011;2011:389518.

This paper examines the (in)compatibility between the diagnostic and therapeutic theories of complementary and alternative medicine (CAM) and a science-based regulatory framework. Specifically, the paper investigates the nexus between statutory legitimacy and scientific validation of health systems, with an examination of its impact on the development of complementary and alternative therapies. The paper evaluates competing theories for validating CAM ranging from the RCT methodology to anthropological perspectives and contends that while the RCT method might be beneficial in the regulation of many CAM therapies, yet dogmatic adherence to this paradigm as the exclusive method for legitimizing CAM will be adverse to the independent development of many CAM therapies whose philosophies and mechanisms of action are not scientifically interpretable. Drawing on history and research evidence to support this argument, the paper sues for a regulatory model that is accommodative of different evidential paradigms in support of a pluralistic healthcare system that balances the imperative of quality assurance with the need to ensure access.

Lorenc A, Ilan-Clarke Y, Robinson N, Blair M: How parents choose to use CAM: a systematic review of theoretical models. BMC Complement Altern Med 2009;9:9.

Background: Complementary and Alternative Medicine (CAM) is widely used throughout the UK and the Western world. CAM is commonly used for children and the decision-making process to use CAM is affected by numerous factors. Most research on CAM use lacks a theoretical framework and is largely based on bivariate statistics. The aim of this review was to identify a conceptual model which could be used to explain the decision-making process in parental choice of CAM.

Methods: A systematic search of the literature was carried out. A two-stage selection process with predetermined inclusion/exclusion criteria identified studies using a theoretical framework depicting the interaction of psychological factors involved in the CAM decision process. Papers were critically appraised and findings summarised.

Results: Twenty two studies using a theoretical model to predict CAM use were included in the final review; only one examined child use. Seven different models were identified. The most commonly used and successful model was Andersen's Sociobehavioural Model (SBM). Two papers proposed modifications to the SBM for CAM use. Six qualitative studies developed their own model.

Conclusion: The SBM modified for CAM use, which incorporates both psychological and pragmatic determinants, was identified as the best conceptual model of CAM use. This model provides a valuable framework for future research, and could be used to explain child CAM use. An understanding of the decision making process is crucial in promoting shared decision making between healthcare practitioners and parents and could inform service delivery, guidance and policy.

Metcalf A, Williams J, McChesney J, Patten SB, Jetté N: Use of complementary and alternative medicine by those with a chronic disease and the general population – results of a national population based survey. BMC Complement Altern Med 2010; 10:58.

Background: The use of complementary and alternative medicine (CAM) is becoming more common, but population-based descriptions of its patterns of use are lacking. This study aimed to determine the prevalence of CAM use in the general population and for those with asthma, diabetes, epilepsy and migraine.

Methods: Data from cycles 1.1, 2.1 and 3.1 of the Canadian Community Health Survey (CCHS) were used for the study. The CCHS is a national cross-sectional survey administered to 400,055 Canadians aged ≥12 between 2001–2005. Self-reported information about professionally diagnosed health conditions was elicited. CCHS surveys use a multistage stratified cluster design to randomly select a representative sample of Canadian household residents. Descriptive data on the utilization of CAM services was calculated and logistic regression was used to determine what sociodemographic factors predict CAM use.

Results: Weighted estimates show that 12.4% (95% Confidence Interval (CI): 12.2–12.5) of Canadians visited a CAM practitioner in the year they were surveyed; this rate was significantly higher for those with asthma 15.1% (95% CI: 14.5–15.7) and migraine 19.0% (95% CI: 18.4–19.6), and significantly lower for those with diabetes 8.0% (95% CI: 7.4–8.6) while the rate in those with epilepsy (10.3%, 95% CI: 8.4–12.2) was not significantly different from the general population.

Conclusion: A large proportion of Canadians use CAM services. Physicians should be aware that their patients may be accessing other services and should be prepared to ask and answer questions about the risks and benefits of CAM services in conjunction with standard medical care.

Rubinstein SM, van Middelkoop M, Kuijpers T, Ostelo R, Verhagen AP, de Boer MR, Koes BW, van Tulder MW: A systematic review on the effectiveness of complementary and alternative medicine for chronic non-specific low-back pain. Eur Spine J 2010;19:1213–1228.

The purpose of this systematic review was to assess the effects of spinal manipulative therapy (SMT), acupuncture and herbal medicine for chronic non-specific LBP. A comprehensive search was conducted by an experienced librarian from the Cochrane Back Review Group (CBRG) in multiple databases up to December 22, 2008. Randomised controlled

trials (RCTs) of adults with chronic non-specific LBP, which evaluated at least one clinically relevant, patient-centred outcome measure were included. Two authors working independently from one another assessed the risk of bias using the criteria recommended by the CBRG and extracted the data. The data were pooled when clinically homogeneous and statistically possible or were otherwise qualitatively described. GRADE was used to determine the quality of the evidence. In total, 35 RCTs (8 SMT, 20 acupuncture, 7 herbal medicine), which examined 8,298 patients, fulfilled the inclusion criteria. Approximately half of these (2 SMT, 8 acupuncture, 7 herbal medicine) were thought to have a low risk of bias. In general, the pooled effects for the studied interventions demonstrated short-term relief or improvement only. The lack of studies with a low-risk of bias, especially in regard to SMT precludes any strong conclusions; however, the principal findings, which are based upon low- to very-low-quality evidence, suggest that SMT does not provide a more clinically beneficial effect compared with sham, passive modalities or any other intervention for treatment of chronic low-back pain. There is evidence, however, that acupuncture provides a short-term clinically relevant effect when compared with a waiting list control or when acupuncture is added to another intervention. Although there are some good results for individual herbal medicines in short-term individual trials, the lack of homogeneity across studies did not allow for a pooled estimate of the effect. In general, these results are in agreement with other recent systematic reviews on SMT, but in contrast with others. These results are also in agreement with recent reviews on acupuncture and herbal medicine. Randomized trials with a low risk of bias and adequate sample sizes are direly needed.

Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M: Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One 2010;5:e11414.

Background: Anecdotal information and case reports suggest that intravenously administered vitamin C is used by Complementary and Alternative Medicine (CAM) practitioners. The scale of such use in the U.S. and associated side effects are unknown.

Methods and Findings: We surveyed attendees at annual CAM Conferences in 2006 and 2008, and determined sales of intravenous vitamin C by major U.S. manufacturers/distributors. We also queried practitioners for side effects, compiled published cases, and analyzed FDA's Adverse Events Database. Of 199 survey respondents (out of 550), 172 practitioners administered IV vitamin C to 11,233 patients in 2006 and 8876 patients in 2008. Average dose was 28 grams every 4 days, with 22 total treatments per patient. Estimated yearly doses used (as 25g/50ml vials) were 318,539 in 2006 and 354,647 in 2008. Manufacturers' yearly sales were 750,000 and 855,000 vials, respectively. Common reasons for treatment included infection, cancer, and fatigue. Of 9,328 patients for whom data is available, 101 had side effects, mostly minor, including lethargy/fatigue in 59 patients, change in mental status in 21 patients and vein irritation/phlebitis in 6 patients. Publications documented serious adverse events, including 2 deaths in patients known to be at risk for IV vitamin C. Due to confounding causes, the FDA Adverse Events Database was uninformative. Total numbers of patients treated in the US with high dose vitamin C cannot be accurately estimated from this study.

Conclusions: High dose IV vitamin C is in unexpectedly wide use by CAM practitioners. Other than the known complications of IV vitamin C in those with renal impairment or glucose 6 phosphate dehydrogenase deficiency, high dose intravenous vitamin C appears to be remarkably safe. Physicians should inquire about IV vitamin C use in patients with cancer, chronic, untreatable, or intractable conditions and be observant of unexpected harm, drug interactions, or benefit.

Venkatesha SH, Rajaiah R, Berman BM, Moudgil KD: Immunomodulation of autoimmune arthritis by herbal CAM. Evid Based Complement Alternat Med 2011; 2011:986797.

Rheumatoid arthritis (RA) is a debilitating autoimmune disease of global prevalence. The disease is characterized by synovial inflammation leading to cartilage and bone damage. Most of the conventional drugs used for the treatment of RA have severe adverse reactions and are quite expensive. Over the years, increasing proportion of patients with RA and other immune disorders are resorting to complementary and alternative medicine (CAM) for their health needs. Natural plant products comprise one of the most popular CAM for inflammatory and immune disorders. These herbal CAM belong to diverse traditional systems of medicine, including traditional Chinese medicine, Kampo, and Ayurvedic medicine. In this paper, we have outlined the major immunological pathways involved in the induction and regulation of autoimmune arthritis and described various herbal CAM that can effectively modulate these immune pathways. Most of the information about the mechanisms of action of herbal products in the experimental models of RA is relevant to arthritis patients as well. The study of immunological pathways coupled with the emerging application of genomics and proteomics in CAM research is likely to provide novel insights into the mechanisms of action of different CAM modalities.

Busato A, Künzi B: Differences in the quality of interpersonal care in complementary and conventional medicine. BMC Complement Altern Med 2010;10:63.

Background: The study was part of a nationwide evaluation of complementary and alternative medicine (CAM) in Swiss primary care. The aim of the study was to compare patient-physician relationships and the respective patient-reported relief of symptoms between CAM and conventional primary care (COM).

Methods: A comparative observational study in Swiss primary care with written survey completed by patients who visited a GP one month earlier. 6133 patients older than 16 years of 170 certified CAM physicians, of 77 non-certified CAM physicians and of 71 conventional physicians were included. Patients completed a questionnaire aimed at symptom relief, patient satisfaction, fulfilment of expectations, and quality of patient-physician interaction (EUROPEP questionnaire).

Results: CAM physicians treated significantly more patients with chronic conditions than COM physicians. CAM Patients had significant higher healing expectations than COM patients. General patient satisfaction was significantly higher in CAM patients, although patient-reported symptom relief was significantly poorer. The quality of patient-physician communication was rated significantly better in CAM patients.

Conclusions: The study shows better patient-reported outcomes of CAM in comparison to COM in Swiss primary care, which is related to higher patient satisfaction due to better patient-physician communication of CAM physicians. More effective communication patterns of these physicians may play an important role in allowing patients to maintain more positive outcome expectations. The findings should promote formative efforts in conventional primary care to improve communication skills in order to reach the same levels of favourable patient outcomes.

Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ: Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 2010;5:e15591.

Background: Placebo treatment can significantly influence subjective symptoms. However, it is widely believed that response to placebo requires concealment or deception. We tested whether open-label placebo (non-deceptive and non-concealed administration) is superior to a no-treatment control with matched patient-provider interactions in the treatment of irritable bowel syndrome (IBS).

Methods: Two-group, randomized, controlled three week trial (August 2009–April 2010) conducted at a single academic center, involving 80 primarily female (70%) patients, mean age 47 ± 18 with IBS diagnosed by Rome III criteria and with a score ≥ 150 on the IBS Symptom Severity Scale (IBS-SSS). Patients were randomized to either open-label placebo pills presented as ‘placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes’ or no-treatment controls with the same quality of interaction with providers. The primary outcome was IBS Global Improvement Scale (IBS-GIS). Secondary measures were IBS Symptom Severity Scale (IBS-SSS), IBS Adequate Relief (IBS-AR) and IBS Quality of Life (IBS-QoL).

Findings: Open-label placebo produced significantly higher mean ($\pm$ SD) global improvement scores (IBS-GIS) at both 11-day midpoint (5.2 ± 1.0 vs. 4.0 ± 1.1 , $p < .001$) and at 21-day endpoint (5.0 ± 1.5 vs. 3.9 ± 1.3 , $p = .002$). Significant results were also observed at both time points for reduced symptom severity (IBS-SSS, $p = .008$ and $p = .03$) and adequate relief (IBS-AR, $p = .02$ and $p = .03$); and a trend favoring open-label placebo was observed for quality of life (IBS-QoL) at the 21-day endpoint ($p = .08$).

Conclusion: Placebos administered without deception may be an effective treatment for IBS. Further research is warranted in IBS, and perhaps other conditions, to elucidate whether physicians can benefit patients using placebos consistent with informed consent.