

Complementary and Alternative Medicine During Cancer Treatment: Beyond Innocence

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Key Words. CAM • Herbs • Interactions • Cancer • Regulation • Internet

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain why cancer patients use complementary and alternative medicine.
2. Describe possible dangers of complementary and alternative medicine during cancer treatment.
3. Advise patients on how to deal with complementary and alternative medicine before, during, and after conventional cancer treatment.

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ABSTRACT

Nowadays, complementary and alternative medicine (CAM) is popular all over the world. Billions of dollars are spent in this booming business. For several reasons, young, female, educated, and higher socioeconomic class cancer patients, in particular, have shown interest in these agents. Unfortunately, besides direct (and sometimes serious) side effects, several CAM ingredients are capable of interfering with the metabolism of concurrently used drugs, which may render the therapeutic outcome of the subscribed drug unpredictable. In the case of anticancer drugs, with their usually narrow therapeutic window, this may have dramatic consequences

and can lead to unacceptable toxicities in some cases or decreased therapeutic activity in others. Therefore, cancer patients should be warned for these possible interactions and be advised to discuss CAM use openly with their treating physician. The general concept that natural products are harmless should thus be changed into a more realistic and responsible attitude. A tightened legislation and regulation (including Internet advertising and sales) could play a crucial role in this awareness process. This should finally enable safe exploration of the potential advantageous aspects of CAM, while living with cancer. *The Oncologist* 2006;11:732–741

INTRODUCTION

The umbrella term “complementary and alternative medicine” (CAM) is defined by the National Center for Complementary and Alternative Medicine (NCCAM) as “a group

of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine; that is, medicine as practiced by holders of ‘medical doctor’ or ‘doctor of osteopathy’ degrees

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and their allied health professionals, such as physical therapists, psychologists, and registered nurses” [1]. Boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed [2]. Despite vigorous attempts, a large number of alternative definitions are available as there is no consensus over a single definition (Table 1) [1–3]. However, all descriptions are pointing in the same direction, but with a focus on different aspects. CAM includes practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Our review article mainly focuses on herbal remedies, botanical medicine (phytomedicine), vitamins, minerals, antioxidants, and metabolites (concurrently) used by cancer patients. As published information on this topic is impressive, it is not our goal to supply a complete overview, but just to outline clinically relevant topics for the practicing clinician dealing with patients suffering from a malignancy.

WORLDWIDE USE OF CAM

CAM is widely used among cancer patients throughout the world (Table 2). Because surveys vary in terms of definitions of CAM and of specific types of therapy included in questionnaires, the assessment of overall prevalence is somewhat complicated. Noninvasive therapies like acupuncture, chiropractic, massage, spiritual healing, meditation, and imagery are most common, but use of dietary supplements is rapidly gaining terrain [4–8]. As a result, the economic impact of CAM is enormous. In the U.S., it is estimated that expenditures for alternative medicine services increased 45% between 1990 and 1997 and were conservatively estimated at \$27 billion in 1997, which was comparable with the estimated out-of-pocket costs for all U.S. physician expenditures [9]. This increase in expenditure was primarily attributable to an increase in the proportion of the population seeking alternative therapies, rather than an increased number of visits per patient. An Australian

questionnaire of more than 3,000 people reported similar population-adjusted costs [10]. In 2000, increases of 120% and 62% were found in the costs of alternative medicines and therapists, respectively, and expenditure on alternative therapies was nearly four times the public contribution to all pharmaceuticals, since 1993. Recent retail numbers indicate about \$5 billion a year of “herbal” sales in Europe alone, where expenses in Germany account for 40% of this number, followed by France and Italy [11]. Other large European countries, like the United Kingdom and Spain, distribute only a small proportion in contrast to Germany.

Reflecting the growing interest of the public, politicians, and professionals in CAM, the budget of the NCCAM, which is part of the National Institutes of Health (NIH), increased from \$50 million in 1999 to more than \$120 million in 2006 [12]. Although only a small percentage of overall costs are claimed, insurance coverage of CAM is also further expanding [6].

Based on retail sales, the best selling over-the-counter herbal supplements in the U.S. in 2002 were garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), and echinacea (*Echinacea purpurea*) [13]. The other herbs in the top ten were soy (*Glycine max*), saw palmetto (*Serenoa repens*), ginseng (*Panax ginseng*), St. John’s wort (*Hypericum perforatum*), black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*), cranberry (*Vaccinium macrocarpon*), and valerian (*Valeriana officinalis*) [13, 14]. Other reports show that melatonin, coenzyme Q10, green tea extract, cell forte (inositol and inositol hexaphosphate), glucosamine, peppermint, EPA (fish oil), and ginger are also popular dietary supplements/natural products (Fig. 1) [15, 16].

The majority of research on the use of CAM is conducted in the U.S., with multiple recent surveys suggesting that between 25% and 84% of U.S. cancer patients have used CAM therapies at some point after their diagnosis, with variations in utilization rates depending on geographic area and type of cancer (Table 2) [17–25].

Table 1. Commonly used definitions of complementary and alternative medicine (CAM)

Source	Definition
National Center for Complementary and Alternative Medicine ^a	“Complementary and alternative medicine is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine; that is, medicine as practiced by holders of MD (medical doctor) or DO (doctor of osteopathy) degrees and their allied health professionals, such as physical therapists, psychologists, and registered nurses.”
Cochrane Collaboration ^b	“A broad domain of healing resources that encompasses all health systems, modalities and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems of a particular society or culture in a given historical period.”
British Medical Association ^c	“Those forms of treatment which are not widely used by the conventional healthcare professions, and the skills of which are not taught as part of the undergraduate curriculum of conventional medical and paramedical healthcare courses.”

^aFrom [1].

^bFrom [2].

^cFrom [3].

Table 2. Impression of prevalence of complementary and alternative medicine (CAM) use by cancer patients worldwide

Study	Sample size	Study location	Population	Cancer type	Most common CAM treatment	Overall prevalence of CAM
Adams et al. [27]	11,202	Australia	Women aged 50–55	Mixed	Defined as consulting a naturopath/herbalist	15.7%
Sibbritt et al. [28]	9,375	Australia	Women aged 73–78	Mixed	Defined as consulting an alternative practitioner	14.5%
Girgis et al. [29]	888	Australia	Adults	Mixed	Herbal treatments and naturopathy (both 30%)	17.1%
Chrystal et al. [30]	200	New Zealand	Adults	Mixed	Vitamins, antioxidants, alternative diets, and herbal therapies	49%
Maskarinec et al. [17]	1,168	U.S. (Hawaii)	Adults in state tumor registry	Mixed	Spiritual healings, vitamins, herbs, dietary alterations	25%
Tough et al. [31]	871	Canada	Adults	Colorectal	Psychological and spiritual therapies (65%), vitamins and minerals (46%), herbs (42%)	49%
Morris et al. [18]	617	U.S. (Portland)	Adults in community hospital cancer registry	Mixed	Nutrition (63%), massage (53%), herbs (44%)	Breast: 84% Other: 66%
Lee et al. [19]	543	U.S. (San Francisco)	Men in state tumor registry	Prostate	Herbs (16%), counseling/support groups (10%), lifestyle diets (9%), megavitamins (4%)	30%
Burstein et al. [20]	480	U.S. (Massachusetts)	Adult women	Breast	Megavitamins (21%), self-help groups (28%), relaxation techniques (32%), herbs (20%), spiritual healing (18%), massage (15%), lifestyle diets (11%)	66.9%
Richardson et al. [21]	453	U.S. (Texas)	Adults	Mixed	Spiritual practices (80.5%), vitamins and herbs (62.6%), movement and physical therapies (59.2%)	83.3%
Patterson et al. [22]	356	U.S. (western Washington)	Adults	Breast, colorectal, prostate	Vitamins/minerals (64%), herbs (38%), meditation/prayer/group support (19%)	70%
Molassiotis et al. [33]	956	14 countries, mostly European, including Turkey and Israel	Adults	Mixed	Alternative medical systems: homeopathy, acupuncture (6.5%); biologically based therapies: medicinal teas, vitamins, minerals (24.9%); mind-body interventions: relaxation therapy, spiritual healing (13.3%), energy therapies (1.5%), massage (2.3%)	35.9%
Tas et al. [32]	615	Turkey	Adults	Mixed	Herbal agents (95%)	47.3%
Hyodo et al. [34]	3,100	Japan	Adults	Mixed	Chinese herbs, mushrooms, shark cartilage, vitamins (96%), Qigong (3.8%), moxibustion (3.7%)	44.6%
Cui et al. [35]	1,065	China (Shanghai)	Adult women	Breast cancer	Chinese medicine (87%), supplements (85%), physical exercises (66%), support group attendance (17%)	98%

Abbreviation: CAM, complementary and alternative medicine.

In 1998, a systematic review by Ernst and Cassileth [26], including 26 worldwide surveys, showed an average percentage of 31% of CAM use among adult cancer patients, with a range of 7%–64%. This is largely in line with other studies (Table 2) [27–32]. A recent descriptive survey conducted in 14 European countries showed that 36% of cancer patients used some form of CAM, again with a wide range among countries of 15%–73% [33]. In an Australian

population survey, there was an overall use of 52% of at least one nonphysician-prescribed alternative drug [10]. CAM is not only popular in Western societies, as is shown in a nationwide cross-sectional survey in Japan: in that study 45% (1,382 of 3,100) of cancer patients used some form of CAM [34]. In a population-based sample of 1,065 Chinese women with breast cancer, nearly all women (98%) reported use of CAM after diagnosis [35].

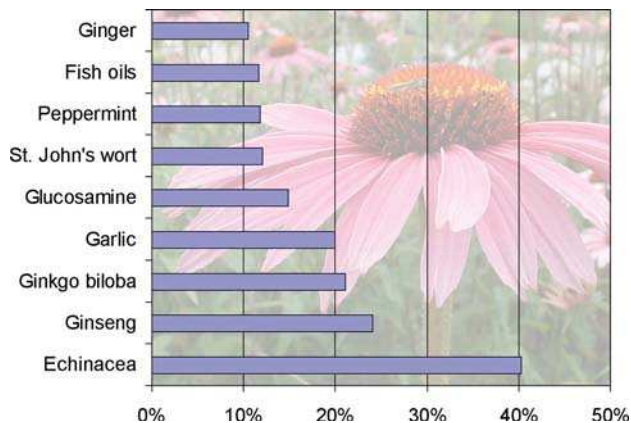


Figure 1. Use of popular natural products among adults in the U.S. Data are derived from the 2002 edition of the National Health Interview Survey conducted by the National Center for Health Statistics (NCHS) and 2004 data released by the NCHS and the National Center for Complementary and Alternative Medicine. Available at http://nccam.nih.gov/news/camsurvey_fs1.htm. The flowering echinacea (*Echinacea purpurea*) is printed as background.

REASONS FOR CAM USE

There are specific cancer-related reasons for using CAM. A Canadian survey of more than 900 cancer patients demonstrated that 94% experienced disease-related symptoms such as fatigue and anxiety that were not addressed by their conventional treatment [36]. Most cancer patients, in general, were satisfied with the conventional treatment they received for their cancer. Nonetheless, they were more likely dissatisfied with the attention paid to their symptoms and side effects. A second reason for CAM use is the presumed action as an anticancer agent (e.g., PC-SPEs, used by prostate cancer patients) [37, 38]. Several CAM products are under investigation in clinical trials for this reason; however, they have not been under appropriate trial development so far [39].

CAM is used for its cancer preventive properties as well. An ideal preventive agent has little or no toxicity, high efficacy in multiple sites, capability of oral consumption, a known mechanism of action, low cost, and above all, general acceptance [40]. For example, more or less conscious use of green tea by men has gained its place in society. Indeed, in a recent case-control study a protective effect of green tea against prostate cancer was suggested [41], which is supported by in vitro research [40, 42]. The risk was thought to decline with increasing frequency, duration, and quantity of green tea consumption. However, it should be noted that conflicting results are reported by epidemiological studies on the use of green tea as a protective substance in relation to prostate cancer [41].

In addition to these reasons, cancer patients, in general, have the same reasons as other people for using CAM [43–45]. Disease-related symptoms not easily addressed by conventional treatment and concerns about the adverse effects of chemical/pharmaceutical medicines are some of them [4]. Also, an increased need for more personalized health and a greater public access to health information (i.e., the Internet) and popular media attention to CAM fuel its increasing use in many industrialized countries [9, 26, 34]. In addition, quality of life may also be a reason for CAM use [46]. However, results are conflicting regarding the self-reported quality of life among CAM users versus nonusers. In a recent report, a study performed at a community hospital comprehensive cancer center was described, which found a better quality of life among dietary supplement users compared with nonusers [46]. In contrast, earlier data showed opposite results [20, 47, 48]. It should be mentioned that these findings are not completely comparable because the latter studies used a broader definition for CAM.

In particular, CAM use appears to be more common among those with higher income, higher educational level, younger age, female gender, or history of CAM use [4, 9, 34, 48]. Also, cancer patients resort to CAM more frequently than patients with acute or chronic diseases, which are not malignant, probably explained by the reasons mentioned before [49]. In addition, use of chemotherapy and advanced disease are correlated with more frequent CAM use [4, 9, 34, 48]. A recent study describing the prevalence of CAM use in patients enrolled in early-phase chemotherapy trials at the Mayo Clinic Comprehensive Cancer Center showed a high use of such products [50]. More than 80% of patients simultaneously used pharmacologic CAM (like vitamins, herbs, and minerals) in addition to their experimental chemotherapeutic agents [50], which is (currently) often an exclusion criterion and/or formally not allowed during this type of treatment. Additionally, a recent study in nearly 500 cancer patients revealed that 65% of the 131 patients being treated with chemotherapy alone said they used CAM in conjunction with their chemotherapy, whereas “only” 35% of the 142 patients receiving radiotherapy reported CAM use [25].

Colorectal and breast cancer patients, in particular, seem to be likely to use dietary supplements, compared with lung cancer patients [51, 52]. An increased perception of the risk of cancer recurrence and cancer-related death are associated with CAM use by breast cancer patients, as concluded in a study by Rakovitch et al. [52]. In contrast, in another recent study, it was concluded that CAM users are less likely to believe they will die from breast cancer [53]. In both studies, no relationship between CAM use and anxiety and/or depression could be found. This is noteworthy

because both anxiety and depression are frequently mentioned as an important explanation for the more frequent use of CAM, in particular CAM influencing mood (like St. John's wort or medicinal cannabis) [54–57].

Most cancer patients combine, rather than replace, conventional therapy with CAM [4, 6, 20, 44, 58]. This is clearly demonstrated in a survey by Cassileth et al. [44], in which 304 in-patients of a cancer center and 356 patients under the care of unorthodox practitioners were interviewed. Of all patients studied, 8% never received any conventional therapy, and 54% of patients on conventional treatment also used unorthodox treatments.

DANGERS OF CAM USE

As concluded from a recent report that was based on in-person interviews with prostate cancer patients, CAM users consider CAM as safe and holistic [59]. Meanwhile, this is coupled with a perception of conventional medicine as being an aggressive and isolated treatment for their cancer. Users report a belief in the potential efficacy of CAM, even if they are aware of the lack of any (scientific) evidence. Although nonusers expressed similar concerns about side effects of conventional treatment and considered CAM harmless as well, they assigned different priorities to these issues in their decision making [59]. Seidl and Stewart [60] interviewed 13 menopausal women who were experiencing symptoms attributed to menopause and were using alternative therapies. Because of their “natural” origin, the women perceived the alternative treatments to be safe.

In spite of such common perceptions in the community (both patients and physicians), there is accumulating evidence indicating that not all CAM is free from harm. There are concerns regarding direct adverse events, for example, allergic reactions (urticaria, angioedema, skin reactions), and gastrointestinal complaints [61]. Among others, hepatotoxicity and neurotoxicity have also been reported for popular herbs [61]. For instance, greater celandine (*Chelidonium majus*) preparations, frequently used for gastrointestinal discomfort, may induce mild to severe forms of acute (cholestatic) hepatitis [62]. The Chinese herbs *Stephania tetrandra* and *Magnolia officinalis*, used in weight-loss pills, are associated with nephropathy-like interstitial renal fibrosis [63–65]. As a result of the replacement of *S. tetrandra* by a botanical known to contain aristolochic acid, *Aristolochia fangchi*, possibly as a consequence of a manufacturing error, products containing this herb have even been associated with induction of urothelial carcinoma, because *A. fangchi* is nephrotoxic and carcinogenic [66]. In addition, the effect of most CAM on the unborn child is unknown in most cases, although its use by pregnant women is frequent [61].

Product quality of CAM is highly variable, with varying concentrations of its major and characteristic ingredients [61]. This appears to be the case both in countries where no strict regulation for these products exists (e.g., the U.S.) and in countries where stricter regulation has been formulated (e.g., Germany) [61]. In addition, pollution with pathogenic micro-organisms, pesticides, heavy metals, etc., is no exception, which makes health risks even higher [61]. For example, for cannabis, which can be used for palliative purposes by cancer patients [56], it was recently demonstrated that cannabis bought in Dutch “coffee shops” can be contaminated by bacteria and fungi that may harm seriously ill patients [67]. Micro-organisms found included *Escherichia coli* and several *Penicillium*, *Cladosporium*, and *Aspergillus* species. To avoid risks associated with pollution, users of CAM should be extra careful, because herbs that seem safe under normal conditions for healthy people may not be so safe for certain patient groups (such as cancer patients) [54].

Beside these direct side effects, CAM has the potential to interact with (anticancer) drug metabolism. Interactions between CAM and commonly prescribed drugs have been studied extensively and reported in detail [54, 68, 69]. Interactions between CAM and anticancer agents are currently less well documented. For St. John's wort, an herbal product thought to have a mild antidepressant action, interactions with irinotecan (Camptostar®; Pfizer Pharmaceuticals, New York), imatinib (Gleevec®; Novartis Pharmaceuticals Corporation, East Hanover, NJ), and docetaxel (Taxotere®; sanofi-aventis, Bridgewater, NJ) have been studied [70–72]. Recently, the effect of milk thistle (*Silybum marianum*; used for its tonic, demulcent, and antidepressant effects) on irinotecan pharmacokinetics was also described [73]. Currently, research is ongoing, for instance to study the effects of medicinal cannabis on irinotecan and docetaxel metabolism [74]. Clinically significant interactions were seen in some of these cases, as shown in more detail in the accompanying article by Meijerman et al. [75] in this issue of *The Oncologist*. Although not studied in detail yet, potential interactions with anticancer agents may also be expected for compounds other than the ones just mentioned, like echinacea, garlic, ginkgo, ginseng, and kava (*Piper methysticum*) [13]. Basically, interactions are mostly thought to be the result of interactions at the enzymes level (like those of the cytochrome P450 metabolic pathways) and drug-transporting proteins (ATP-binding cassette transporters), which can be influenced in activity and expression by CAM ingredients [75]. If given together, some CAM may indirectly induce the metabolism of cytotoxic agents, potentially leading to nontherapeutic systemic drug levels. In addition, other CAM may inhibit

the metabolism of cytotoxic agents, leading to potentially lethal toxicities if the metabolic step inhibited inactivates the given drug. Taking into account that a relatively high percentage of patients participating in phase I trials seems to use CAM [50], without notifying their physician on this fact, this could have serious (negative) consequences for both participating patients and for the development of new anticancer agents.

Additionally, because most CAM contains (several) constituents with unknown pharmacological capacities, the effect of the combination with conventional or experimental treatment may be totally unpredictable. For instance, in the case of St. John's wort, ingredients with inhibitory and inducing capacities are known, and depending on the amount of the individual components, the interactive effect may totally differ. Apart from this, the duration of intake of this herbal product is also thought to influence the type of effect (first inhibition, later on induction) on drug-metabolizing and transporting proteins [76], further decreasing the possibility of predicting the occurrence of undesired clinical effects.

QUALITY CONTROL

European and U.S. Legislation

In 1999, a European Community (EC) directive came into effect that made it easier to get marketing authorization for herbal medicines for which "well-established" data on efficacy and safety are available [11]. Five years later, another directive was implemented, which made it possible to also register traditional herbs that had been used for more than 30 years (and also for at least 15 years in the EC) not meeting the criteria for the group of preparations mentioned above [11]. All other compounds are regulated as "food" products. For registration, a special committee evaluates the herbals and, after acceptance, it lists its manufacturers, indications, doses, routes of administration, etc. [11]. Health authorities are capable of labeling these products with advice for proper use. These procedures will increase the transparency of CAM, and the "quality check" will stimulate companies to meet registration criteria and consumers to use registered products. As mentioned earlier, this does not mean that there are no caveats left, as, for instance, concentrations of characteristic constituents may still vary substantially among products available on the market [77]. Unfortunately, it also leads to confusing situations in which herbs are sold both as medicines and food products, with their own regulations, which is, for instance, currently the case for herbal teas.

The introduction of medicinal cannabis to the Dutch drug market nicely illustrates the above-mentioned regulation. In more and more countries, including some parts of the

U.S., production (at home) and use of cannabis for medicinal purposes is tolerated or even legally permitted [56, 78]. As in other countries, The Netherlands has established a national agency on medicinal cannabis (the Office of Medicinal Cannabis), under whose responsibility a standardized cannabis product for medical treatment purposes is produced and distributed [79]. The variants produced are not contaminated by micro-organisms [67], and their legal availability meeting pharmaceutical quality opens doors to initiate well-designed clinical trials investigating safety and efficacy. Because there are a lot of gaps in our knowledge on fundamental questions related to the administration of medicinal cannabis, such issues need to be resolved urgently [56, 80].

In the U.S., the Food and Drug Administration (FDA) regulates foods, drugs, and cosmetics in interstate commerce [11]. As a result of the 1994 Dietary Supplements Health Education Act, manufacturers are allowed to distribute their dietary supplements without proven safety and efficacy, as long as they do not claim a link between their product and a specific disease [81]. Meanwhile, they may, for instance, make structure/function claims, still without proof of safety and efficacy. This act has led to an enormous growth in the market for dietary supplements [81]. The FDA has no authority to approve or analyze these products before they are brought to the market [82]. In the U.S., it has also been proposed to change the regulations, including requirements that all health claims be supported by data approved by the FDA, and that an accurate list of ingredients is provided on the product label [82].

Even more important than federal rules, state laws control much of CAM practice. As a result, regulations may vary from state to state and mainly involve health care license, scope of practice, and malpractice. In 2004, fewer than one third of all states had health freedom laws or regulations protecting patient access to CAM [83]. In most states with health freedom laws, these laws/regulations protect the patient's right to access CAM offered by licensed physicians, but not by all other CAM practitioners [83].

Internet

In addition to articles and advertisements in papers and magazines and on television and the radio, in recent years, the role of the Internet as an easily accessible source for knowledge has rapidly emerged. The Pew Internet Project for Health reported that more than 60% of people who used the Internet were looking for health information, half of whom were looking for information on CAM [84]. Analysis of several U.S. nationwide representative datasets revealed that people who seek online health information were more frequently female, were frequently not full-time employed, were frequently engaged in other Internet activities, had

more specific health reasons (diagnosed with new health problem, ongoing medical condition, prescribed new medication or treatment), and/or were helping another person deal with health issues [85]. About half of the Pew survey respondents found credibility in what they read, saying that they thought that almost all or most information they had found on the Internet was reliable [84]. However, information on the Internet is not always as reliable as patients may think, which imposes a serious risk to patients vulnerable to misleading information. Moreover, medical products, and in particular CAM, can easily be purchased on the Internet without a prescription.

As demonstrated in various studies, the quality of Web sites on CAM varies enormously. Content quality is often poor and a shocking and surprising amount of misinformation regarding CAM for cancer can be found on the Internet [86, 87]. Recently, Schmidt and Ernst [88] investigated 32 Web sites to evaluate the quality of information on CAM, among others, for cancer. They concluded that the majority of evaluated Web sites provided valuable and reliable information, especially for the prevention of cancer. However, several web sites issued information on CAM that is, in the least, misleading. Five of the 32 investigated Web sites gave information biased in favor of its own products or services, and only 10 gave references to scientific literature. Some Web sites even promoted and discussed CAM treatments (like shark cartilage, the Gerson's diet, and mistletoe [*Viscum album* L]), for which no compelling safety and efficacy data could be found in regular medical databases. A few sites were outright dangerous, as they advised patients against using conventional therapies [88].

Using another approach, Morris and Avorn [89] investigated the Internet for eight widely used herbal supplements. Eighty-one percent of the 338 investigated retail Web sites made at least one health claim. More than half of them claimed to treat, prevent, diagnose, or cure specific diseases. Despite regulations prohibiting such claims without the FDA's disclaimer, of all sites with a health claim, more than half omitted the standard federal disclaimer. Additionally, on average, only 28% (both retail and nonretail sites) provided referenced information [89].

As concluded by many researchers [88, 90], there is an urgent need to raise public awareness about the quality of Web sites on CAM and about the usefulness of Internet information. Major cancer organizations and other impartial interest groups should investigate Web sites and create and administer a seal of approval, for safety and reliability [88]. Morris and Avorn [89], as do others [81], take a step further; they conclude that in this era of evidence-based medicine, more effective regulation and vigilance are required to put CAM on the same basis as other medicinal products.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

As stated before, CAM use among cancer patients is substantial, and potential interactions with (conventional or experimental) chemotherapy should make the clinician aware of the dangers. As a result, it is of utmost importance to clarify its use before exposing patients to drugs with a narrow therapeutic window, like most anticancer agents [91]. Because patients may, for instance, be ashamed to openly admit CAM use to their treating physicians, true use may be underestimated [92, 93]. On the other hand, others say that reports of prevalence are often exaggerated, as surveyors may use a different definition of CAM [94]. In clinical practice, in every patient contact, the clinician should keep in mind that most (cancer) patients will not spontaneously report CAM use. A previously mentioned study revealed that, of the 48% of cancer patients using concomitant CAM (median two CAMs per patient), a vast majority did so without their doctor knowing [25].

Herbal products are commonly perceived as "natural" and therefore as "innocent," a perception that is hard to change [95]. As a consequence, denial on purpose is most often not the case because patients may not realize the seriousness of CAM use and will thus answer "no" if asked for concurrent drug use [45]. This is illustrated by the example of St. John's wort tea. Some herbal teas, like the St. John's wort variants, are produced by companies regarded as highly reliable and trustworthy in the community and sold in the supermarket as tea. Patients may drink this tea at home, not explicitly being aware of the associated risks they would avoid if they had to buy such a product in their local pharmacy or drugstore. The physician should therefore actively ask for herbal and supplement use, while explaining their potential hazards [4, 54]. An objective and nonjudgmental attitude of the medical doctor is clearly essential to encourage patient disclosure [4, 54]. Patients should not get the feeling of being accused of use CAM, but should explicitly be advised to avoid CAM prior to and during (chemo)therapy. If such avoidance is not possible, the consequences for therapy should be evaluated in detail. Clearly, governments, cancer organizations, and patient organizations also have their responsibilities to achieve this common goal. Likewise, the risks associated with the use of the Internet as an information source for and retailer of CAM, whether as preventive, curative, or palliative treatment, should be more explicitly brought to the attention of cancer patients.

Meanwhile, we should not disqualify CAM use per se. CAM therapies such as acupuncture, meditation, and music therapy can be beneficial for cancer patients [96–98]. There is evidence to support some of the CAM approaches, in particular in the symptom management and supportive

care of cancer patients [99]. They may control symptoms and enhance quality of life [5, 56]. More and more medical centers now develop programs that integrate conventional medicine with complementary approaches that have some high-quality scientific evidence of safety and effectiveness [94]. The term “integrative oncology” has been created for this combination [94]. Hopefully, more research in this field of science will help more patients and treating physicians to further explore effective and safe approaches and become aware of the existence of the possible dangers, as

both conventional treatment and CAM have found a prominent place in modern society.

AUTHORS' NOTE

Metin Tascilar and Floris A. de Jong contributed equally to this work.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

REFERENCES

- National Center for Complementary and Alternative Medicine (NCCAM). The Use of Complementary and Alternative Medicine in the United States. Available at http://nccam.nih.gov/news/camsurvey_fs1.htm. Accessed March 3, 2006.
- Zollman C, Vickers A. What is complementary medicine? *BMJ* 1999;319:693–696.
- British Medical Association (BMA). Complementary Medicine—New Approaches to Good Practice. Available at <http://www.bma.org.uk/ap.nsf/content/publicpetitioncam>. Accessed March 3, 2006.
- Cauffield JS. The psychosocial aspects of complementary and alternative medicine. *Pharmacotherapy* 2000;20:1289–1294.
- Cassileth BR, Deng G. Complementary and alternative therapies for cancer. *The Oncologist* 2004;9:80–89.
- Lafferty WE, Bellas A, Corage Baden A et al. The use of complementary and alternative medical providers by insured cancer patients in Washington State. *Cancer* 2004;100:1522–1530.
- Cohen L, Warneke C, Fouladi RT et al. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer* 2004;100:2253–2260.
- Yoo HJ, Ahn SH, Kim SB et al. Efficacy of progressive muscle relaxation training and guided imagery in reducing chemotherapy side effects in patients with breast cancer and in improving their quality of life. *Support Care Cancer* 2005;13:826–833.
- Eisenberg DM, Davis RB, Ettner SL et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998;280:1569–1575.
- MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. *Prev Med* 2002;35:166–173.
- De Smet PA. Herbal medicine in Europe--relaxing regulatory standards. *N Engl J Med* 2005;352:1176–1178.
- National Center for Complementary and Alternative Medicine (NCCAM). Funding Strategy: Fiscal Year 2006. Available at <http://nccam.nih.gov/research/strategy/2006.htm>. Accessed March 3, 2006.
- Sparreboom A, Cox MC, Acharya MR et al. Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004;22:2489–2503.
- Blumenthal RS, Becker DM, Yanek LR et al. Detecting occult coronary disease in a high-risk asymptomatic population. *Circulation* 2003;107:702–707.
- Werneke U, Earl J, Seydel C et al. Potential health risks of complementary alternative medicines in cancer patients. *Br J Cancer* 2004;90:408–413.
- McCune JS, Hatfield AJ, Blackburn AA et al. Potential of chemotherapy-herb interactions in adult cancer patients. *Support Care Cancer* 2004;12:454–462.
- Maskarinec G, Shumay DM, Kakai H et al. Ethnic differences in complementary and alternative medicine use among cancer patients. *J Altern Complement Med* 2000;6:531–538.
- Morris KT, Johnson N, Homer L et al. A comparison of complementary therapy use between breast cancer patients and patients with other primary tumor sites. *Am J Surg* 2000;179:407–411.
- Lee MM, Chang JS, Jacobs B et al. Complementary and alternative medicine use among men with prostate cancer in 4 ethnic populations. *Am J Public Health* 2002;92:1606–1609.
- Burstein HJ, Gelber S, Guadagnoli E et al. Use of alternative medicine by women with early-stage breast cancer. *N Engl J Med* 1999;340:1733–1739.
- Richardson MA, Sanders T, Palmer JL et al. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol* 2000;18:2505–2514.
- Patterson RE, Neuhaus ML, Hedderson MM et al. Types of alternative medicine used by patients with breast, colon, or prostate cancer: predictors, motives, and costs. *J Altern Complement Med* 2002;8:477–485.
- VandeCreek L, Rogers E, Lester J. Use of alternative therapies among breast cancer outpatients compared with the general population. *Altern Ther Health Med* 1999;5:71–76.
- Adler SR, Fosket JR. Disclosing complementary and alternative medicine use in the medical encounter: a qualitative study in women with breast cancer. *J Fam Pract* 1999;48:453–458.
- Vapiwala N, Mick R, DeNittis A et al. Initiation of complementary and alternative medical therapies (CAM) by cancer patients (pts) during radiation therapy (RT). *Proc Am Soc Ther Radiat Oncol* 2005;63 (suppl 1):S451.
- Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. *Cancer* 1998;83:777–782.
- Adams J, Sibbritt D, Young AF. Naturopathy/herbalism consultations by mid-aged Australian women who have cancer. *Eur J Cancer Care (Engl)* 2005;14:443–447.
- Sibbritt DW, Adams J, Young AF. A longitudinal analysis of mid-age women's use of complementary and alternative medicine (CAM) in Australia, 1996–1998. *Women Health* 2004;40:41–56.
- Girgis A, Adams J, Sibbritt D. The use of complementary and alternative therapies by patients with cancer. *Oncol Res* 2005;15:281–289.
- Chrystal K, Allan S, Forgeson G et al. The use of complementary/alternative medicine by cancer patients in a New Zealand regional cancer treatment centre. *N Z Med J* 2003;116:U296.

- 31 Tough SC, Johnston DW, Verhoef MJ et al. Complementary and alternative medicine use among colorectal cancer patients in Alberta, Canada. *Altern Ther Health Med* 2002;8:54–56, 58–60, 62–64.
- 32 Tas F, Ustuner Z, Can G et al. The prevalence and determinants of the use of complementary and alternative medicine in adult Turkish cancer patients. *Acta Oncol* 2005;44:161–167.
- 33 Molassiotis A, Fernandez-Ortega P, Pud D et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol* 2005;16:655–663.
- 34 Hyodo I, Amano N, Eguchi K et al. Nationwide survey on complementary and alternative medicine in cancer patients in Japan. *J Clin Oncol* 2005;23:2645–2654.
- 35 Cui Y, Shu XO, Gao Y et al. Use of complementary and alternative medicine by Chinese women with breast cancer. *Breast Cancer Res Treat* 2004;85:263–270.
- 36 Ashbury FD, Findlay H, Reynolds B et al. A Canadian survey of cancer patients' experiences: are their needs being met? *J Pain Symptom Manage* 1998;16:298–306.
- 37 Kosty MP. PC-SPES: hope or hype? *J Clin Oncol* 2004;22:3657–3659.
- 38 Straus SE. Herbal medicines--what's in the bottle? *N Engl J Med* 2002;347:1997–1998.
- 39 Vickers AJ, Kuo J, Cassileth BR. Unconventional anticancer agents: a systematic review of clinical trials. *J Clin Oncol* 2006;24:136–140.
- 40 Siddiqui IA, Adhami VM, Saleem M et al. Beneficial effects of tea and its polyphenols against prostate cancer. *Mol Nutr Food Res* 2006;50:130–143.
- 41 Jian L, Xie LP, Lee AH et al. Protective effect of green tea against prostate cancer: a case-control study in southeast China. *Int J Cancer* 2004;108:130–135.
- 42 Gupta S, Ahmad N, Mohan RR et al. Prostate cancer chemoprevention by green tea: in vitro and in vivo inhibition of testosterone-mediated induction of ornithine decarboxylase. *Cancer Res* 1999;59:2115–2120.
- 43 Cassileth BR. Complementary therapies: the American experience. *Support Care Cancer* 2000;8:16–23.
- 44 Cassileth BR, Lusk EJ, Strouse TB et al. Contemporary unorthodox treatments in cancer medicine. A study of patients, treatments, and practitioners. *Ann Intern Med* 1984;101:105–112.
- 45 Kronenberg F, Mindes J, Jacobson JS. The future of complementary and alternative medicine for cancer. *Cancer Invest* 2005;23:420–426.
- 46 Lis CG, Cambron JA, Grutsch JF et al. Self-reported quality of life in users and nonusers of dietary supplements in cancer. *Support Care Cancer* 2006;14:193–199.
- 47 Cassileth BR, Lusk EJ, Guerry D et al. Survival and quality of life among patients receiving unproven as compared with conventional cancer therapy. *N Engl J Med* 1991;324:1180–1185.
- 48 Paltiel O, Avitzour M, Peretz T et al. Determinants of the use of complementary therapies by patients with cancer. *J Clin Oncol* 2001;19:2439–2448.
- 49 Kappauf H, Leykauf-Ammon D, Brunsch U et al. Use of and attitudes held towards unconventional medicine by patients in a department of internal medicine/oncology and haematology. *Support Care Cancer* 2000;8:314–322.
- 50 Dy GK, Bekele L, Hanson LJ et al. Complementary and alternative medicine use by patients enrolled onto phase I clinical trials. *J Clin Oncol* 2004;22:4810–4815.
- 51 Gupta D, Lis CG, Birdsall TC et al. The use of dietary supplements in a community hospital comprehensive cancer center: implications for conventional cancer care. *Support Care Cancer* 2005;13:912–919.
- 52 Rakovitch E, Pignol JP, Chartier C et al. Complementary and alternative medicine use is associated with an increased perception of breast cancer risk and death. *Breast Cancer Res Treat* 2005;90:139–148.
- 53 Helyer LK, Chin S, Chui BK et al. The use of complementary and alternative medicines among patients with locally advanced breast cancer - a descriptive study. *BMC Cancer* 2006;6:39.
- 54 De Smet PA. Herbal remedies. *N Engl J Med* 2002;347:2046–2056.
- 55 Stevinson C, Ernst E. Hypericum for depression. An update of the clinical evidence. *Eur Neuropsychopharmacol* 1999;9:501–505.
- 56 de Jong FA, Engels FK, Mathijssen RH et al. Medicinal cannabis in oncology practice: still a bridge too far? *J Clin Oncol* 2005;23:2886–2891.
- 57 Radbruch L, Nauck F. [A review of side effects and complications with cannabinoid treatment]. *Schmerz* 2003;17:274–279. German.
- 58 Lerner IJ, Kennedy BJ. The prevalence of questionable methods of cancer treatment in the United States. *CA Cancer J Clin* 1992;42:181–191.
- 59 Singh H, Maskarinec G, Shumay DM. Understanding the motivation for conventional and complementary/alternative medicine use among men with prostate cancer. *Integr Cancer Ther* 2005;4:187–194.
- 60 Seidl MM, Stewart DE. Alternative treatments for menopausal symptoms. Qualitative study of women's experiences. *Can Fam Physician* 1998;44:1271–1276.
- 61 De Smet PA. Health risks of herbal remedies: an update. *Clin Pharmacol Ther* 2004;76:1–17.
- 62 Benninger J, Schneider HT, Schuppan D et al. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Gastroenterology* 1999;117:1234–1237.
- 63 Vanherweghem JL, Depierreux M, Tielemans C et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet* 1993;341:387–391.
- 64 Lord GM, Cook T, Arlt VM et al. Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 2001;358:1515–1516.
- 65 Lampert N, Xu Y. Chinese herbal nephropathy. *Lancet* 2002;359:796–797.
- 66 Nortier JL, Martinez MC, Schmeiser HH et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000;342:1686–1692.
- 67 Hazekamp A, Sijrier R, Verpoorte R et al. [Cannabis bought in the pharmacy is better]. *Pharmaceutisch Weekblad* 2005;140:402–405.
- 68 Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200–2211.
- 69 Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 2001;61:2163–2175.
- 70 Mathijssen RH, Verweij J, de Bruijn P et al. Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002;94:1247–1249.
- 71 Frye RF, Fitzgerald SM, Lagattuta TF et al. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* 2004;76:323–329.
- 72 Komoroski BJ, Parise RA, Egorin MJ et al. Effect of the St. John's wort constituent hyperforin on docetaxel metabolism by human hepatocyte cultures. *Clin Cancer Res* 2005;11:6972–6979.

- 73 van Erp NP, Baker SD, Zhao M et al. Effect of milk thistle (*Silybum marianum*) on the pharmacokinetics of irinotecan. *Clin Cancer Res* 2005;11:7800–7806.
- 74 de Jong FA, Engels FK, Sparreboom A et al. Influence of medicinal cannabis (MC) on the pharmacokinetics (PK) of docetaxel (DOC) and irinotecan (CPT-11). *Proc Am Assoc Cancer Res* 2005;46.
- 75 Meijerman I, Beijnen JH, Schellens JHM. Herb-drug interactions in oncology: focus on mechanisms of induction. *The Oncologist* 2006;11:938–939.
- 76 Wang Z, Hamman MA, Huang SM et al. Effect of St John's wort on the pharmacokinetics of fexofenadine. *Clin Pharmacol Ther* 2002;71:414–420.
- 77 Kressmann S, Muller WE, Blume HH. Pharmaceutical quality of different Ginkgo biloba brands. *J Pharm Pharmacol* 2002;54:661–669.
- 78 de Jong FA, Engels FK, Mathijssen RH et al. Medicinal cannabis in oncology practice: still a bridge too far? - In reply. *J Clin Oncol* 2005;23:7756.
- 79 Office of Medicinal Cannabis, Dutch Ministry of Health. Medicinal Cannabis: Information for Health Care Professionals, version 15 March, 2004. Available at <http://www.cannabisbureau.nl/pdf/basic%20text%20cannabis%20EN%20vs%2015%20Mar%2004%20.pdf>. Accessed March 3, 2006.
- 80 Hart S, Fischer OM, Ullrich A. Cannabinoids induce cancer cell proliferation via tumor necrosis factor alpha-converting enzyme (TACE/ADAM17)-mediated transactivation of the epidermal growth factor receptor. *Cancer Res* 2004;64:1943–1950.
- 81 Cohen MH. Complementary and integrative medical therapies, the FDA, and the NIH: definitions and regulation. *Dermatol Ther* 2003;16:77–84.
- 82 Bent S, Ko R. Commonly used herbal medicines in the United States: a review. *Am J Med* 2004;116:478–485.
- 83 Parkman CA. Regulatory issues in CAM. *Case Manager* 2004;15:26–29.
- 84 Fox S, Rainie L. Vital Decisions: How Internet Users Decide What Information to Trust When They or Their Loved Ones Are Sick. Washington, DC: Pew Internet & American Life Project, 2002.
- 85 Rice RE. Influences, usage, and outcomes of Internet health information searching: multivariate results from the Pew surveys. *Int J Med Inform* 2006;75:8–28.
- 86 Martin-Facklam M, Kostrzewa M, Schubert F et al. Quality markers of drug information on the Internet: an evaluation of sites about St. John's wort. *Am J Med* 2002;113:740–745.
- 87 Matthews SC, Camacho A, Mills PJ et al. The internet for medical information about cancer: help or hindrance? *Psychosomatics* 2003;44:100–103.
- 88 Schmidt K, Ernst E. Assessing websites on complementary and alternative medicine for cancer. *Ann Oncol* 2004;15:733–742.
- 89 Morris CA, Avorn J. Internet marketing of herbal products. *JAMA* 2003;290:1505–1509.
- 90 Eysenbach G, Powell J, Kuss O et al. Empirical studies assessing the quality of health information for consumers on the world wide web: a systematic review. *JAMA* 2002;287:2691–2700.
- 91 Hyodo I, Eguchi K, Nishina T et al. Perceptions and attitudes of clinical oncologists on complementary and alternative medicine: a nationwide survey in Japan. *Cancer* 2003;97:2861–2868.
- 92 Bourgeault IL. Physicians' attitudes toward patients' use of alternative cancer therapies. *CMAJ* 1996;155:1679–1685.
- 93 Yates JS, Mustian KM, Morrow GR et al. Prevalence of complementary and alternative medicine use in cancer patients during treatment. *Support Care Cancer* 2005;13:806–811.
- 94 Cassileth BR, Vickers AJ. High prevalence of complementary and alternative medicine use among cancer patients: implications for research and clinical care. *J Clin Oncol* 2005;23:2590–2592.
- 95 Weitzman S. Alternative nutritional cancer therapies. *Int J Cancer Suppl* 1998;11:69–72.
- 96 Rosenthal DS, Dean-Clower E. Integrative medicine in hematology/oncology: benefits, ethical considerations, and controversies. *Hematology (Am Soc Hematol Educ Program)* 2005:491–497.
- 97 NIH Consensus Conference. Acupuncture. *JAMA* 1998;280:1518–1524.
- 98 Shen J, Wenger N, Glaspy J et al. Electroacupuncture for control of myeloablative chemotherapy-induced emesis: a randomized controlled trial. *JAMA* 2000;284:2755–2761.
- 99 Ernst E. The role of complementary and alternative medicine in cancer. *Lancet Oncol* 2000;1:176–180.

ADDITIONAL READING

- Deng D, Cassileth BR. Integrative oncology: Complementary therapies for pain, anxiety, and mood disturbance. *CA Cancer J Clin* 2005;55:109–116.
- De Smet PA. Herbal remedies. *N Engl J Med* 2002;347:2046–2056.
- Sparreboom A, Cox MC, Acharya MR et al. Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004;22:2489–2503.
- Weiger WA, Smith M, Boon H, et al. Advising patients who seek complementary and alternative medical therapies for cancer. *Ann Intern Med* 2002;137:889–903.

See also “Herb-Drug Interactions in Oncology: Focus on Mechanisms of Induction,” by Irma Meijerman, Jos H. Beijnen, and Jan H.M. Schellens, on p. 742.