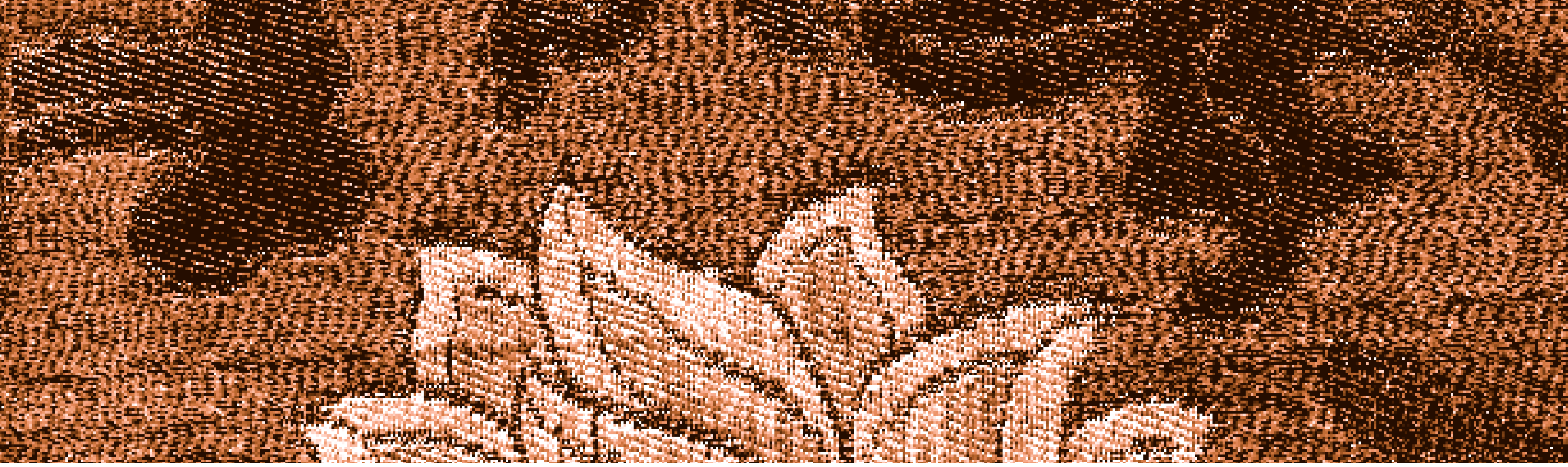


AVENUES

The Newsletter of the Pine Street Foundation

14

SUMMER 2006

Welcome to the summer issue of *Avenues*! In this issue are two very important articles:

BECOMING YOUR OWN ADVOCATE

This issue of *Avenues* contains the next article in our *Becoming Your Own Advocate* series. Starting on the opposite page, we discuss the impact cancer treatment can have on sexual functioning. By addressing this important topic, it is our hope that this article will facilitate a constructive discussion between patients and their partners and health care providers.

PUBLISHED RESEARCH

In January, the *Journal of Clinical Oncology* published our meta-analysis research on *Astragalus*-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer. See page 8 for more.

Finally, a special thank you to everyone who has so generously supported our work. We would be unable to conduct our clinical trials, publish our research, or offer our educational programs without your help.

Best wishes,

Michael Broffman, LAc

Michael McCulloch, LAc, MPH

RESEARCH UPDATE: CANINE SCENT DETECTION OF CANCER

The Pine Street Foundation's research on early cancer diagnosis using canine scent detection is now taking a strong step toward the future we envisioned early on in our work: the chemical analysis of exhaled breath, so that we can learn precisely what the dogs were cueing on when they distinguished cancer patients from controls. This is being realized through a collaboration with Dr. Touradj Solouki, professor of chemistry at the University of Maine.

With the financial support from the Defense Advanced Research Projects Agency (DARPA) and the National Science Foundation (NSF), Dr. Solouki and his team have developed the first state-of-the-art device (Gas Chromatography/Fourier Transform Ion Cyclotron Resonance Mass Spectrometry equipped with a Preconcentrator and a Cryofocuser) to acquire breath "fingerprints" to help identify biomarkers for the early detection of diseases.

In the next phase of our research, for which we are currently seeking funding from individuals and institutions, it is envisioned that direct comparisons between canine olfaction and high-tech breath fingerprinting in a carefully designed clinical trial will lead to tangible advances in the early detection of cancer.

We recently presented the details of our plan at a conference at New York University Medical Center in May, sponsored by the Lynne Cohen Foundation.

More information about this lecture, including our proposed methods, is available on our website.

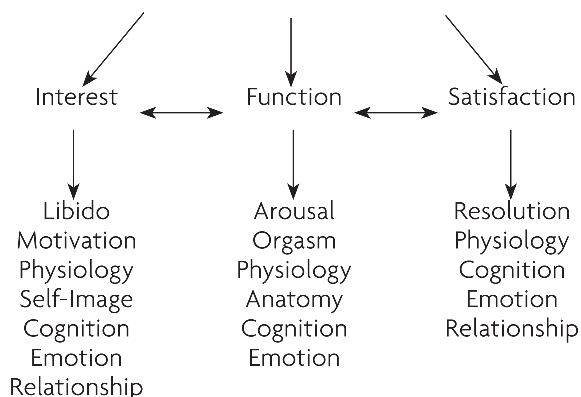
Please help support this work by making a donation. Visit www.pinestreetfoundation.org/donate or turn to page 11 for other ways to give.

Sexual Health & Cancer Treatment

UNDERSTANDING THE PROBLEM & FINDING SOLUTIONS

Problems with sexual functioning can be one of the most distressing consequences of cancer treatment.[1] Understanding and communicating these problems is an important part of the path towards finding solutions. Fortunately, thoughtfully designed and clearly reported research is becoming increasingly available on this subject. In this article, part of our continuing *Becoming Your Own Advocate* series, we focus on the results of recent clinical studies on the physical and emotional aspects of sexual health related to cancer treatment, discuss the common problems people experience, and offer solutions that have been developed to resolve or cope with these issues.

It is important to understand that sexual feelings, interest, and functioning can return after treatment. The goal of this article is to provide patients facing or going through cancer treatment with resources, evidence, and questions to ask.



Schematic Drawing of Concepts Involved in Sexuality and Sexual Functioning[3]

© 2004 Oncology Nursing Society

Sexuality and Sexual Health

The World Health Organization offers a holistic definition of sexuality, describing it as "a central aspect of being human throughout life" which "encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy, and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviors, practices, roles, and relationships." Similarly, the WHO describes sexual health as "a state of physical, emotional, mental, and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction, or infirmity."[2] The previous diagram shows several ways to illustrate the multifaceted landscape of sexual health and the dynamic relationship between a person's sexuality and their cognitive, physical, and relationship health.[3]

What Are the Effects of Cancer Therapy on Sexual Function? How Common Are They?

There are various sexual problems experienced by people living with cancer and, generally, 1) these problems can appear suddenly, usually during or immediately after treatment, although sometimes they may not appear for several months after treatment is finished,[4] 2) these problems also tend to be pervasive, impairing more than one phase of the normal cycle of sexual desire, response, and arousal. 3) Other symptoms related to cancer or its treatment, such as pain, nausea, fatigue, anxiety, disturbed sleep, or bowel and urinary symptoms that can be difficult to control, can make maintaining sexual activity all the more challenging.[4] 4) These effects can be long-lasting, persisting in some cases for many years.[4]

Sexual Problems Experienced by Women Who Have Cancer

As early as 1985, it was reported that up to 90% of female cancer survivors reported some type of problem related to sexual function.[1]

Breast Cancer Treatment

Menopause caused by breast cancer treatment can lead to a wide range of side effects, including vaginal dryness, pain during intercourse, alterations in mood, cognition and libido, and weight gain.[5, 6] These problems, however, may not be caused solely by the early onset of menopause. Compared to treatment with hormonal therapy, women treated for breast cancer with chemotherapy are six times more likely to report vaginal dryness and pain during intercourse, three times more likely to report decreased libido, and

For other articles in our *Becoming Your Own Advocate* series, visit www.pinestreetfoundation.org/byoa

seven times more likely to report difficulty achieving orgasm.[7] In a survey of 50 women treated for breast cancer with surgery and chemotherapy and/or radiation, while 90% of the subjects continued sexual activity after treatment, 48% reported low sexual desire, 38% reported pain during intercourse, and 42% had lubrication problems. About one-half of the women experienced changes in the relationship with their partner.[8] Other research suggests that these problems may occur more often in younger women.[9]

Breast Cancer Surgery and Self-Image

Compared to women who underwent mastectomy, those treated with breast conserving surgery had a more favorable body image and better psychological, relationship, and social adjustment.[10, 11]

Cervical Cancer

Among survivors of cervical cancer, those women treated with radiation had worse sexual functioning than did those treated with radical hysterectomy and lymph node dissection.[13] This information may be an important area of discussion in consultation visits for pre-treatment planning. An additional area of concern for women diagnosed with cervical cancer is whether there is a history of sexual abuse; including this information in the consultation discussion can also help guide treatment.[14]

Prostate Cancer

Among men treated for prostate cancer, the prevalence of sexual dysfunction is as high as 70%, although this is lower in men who were eligible for and decided to choose "watchful waiting," in which the disease is closely monitored, but no aggressive treatment is initiated yet.[4] Each of the various treatments for prostate cancer can cause sexual problems: Prostatectomy can cause erectile dysfunction in 30% to 98% of men, depending on whether both, one, or neither nerve bundles was spared. Radiation treatment for prostate cancer can cause erectile dysfunction in over 70% of men, although this occurs less often with brachytherapy, a type of radiation therapy. Over 80% of men treated with hormonal blockade report erectile dysfunction and a lack of libido one year after beginning treatment.[12]

Problems Related to Pain and its Treatment

A case report from the MD Anderson Cancer Center reported substantial improvement in sexual function in a male patient who was able to reduce his need for opiate pain medication.[15] (See "Integrative Cancer Pain Management" in the autumn 2005 issue of *Avenues*.)

How Do You Describe and Communicate Sexual Function?

Most of the questionnaires that have been developed for monitoring sexual side effects of cancer treatment focus on a specific treatment or body system and are therefore most useful in a research context. One example of this is the C-PET questionnaire, a simple checklist for monitoring side effects in women receiving hormonal therapy for breast cancer.[9] However, our goal in

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{ Founded 1989 }

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ON THE COVER
Detail of silk brocade on thangka painted and blessed by
His Eminence Kalu Rinpoche (1905-1989). India, circa 1971.

ABOUT *AVENUES*
Avenues are choices. When managing disease, there are many different possibilities to consider. Through this newsletter, the Pine Street Foundation seeks to illuminate some of these choices through evidence-based research in the hopes that by having more options, patients and health care providers will be able to make better, more informed treatment decisions.

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www.PineStreetFoundation.org

this article is to provide information that could help initiate a conversation about sexual problems; one very good example is the ALARM Model for the Assessment Of Sexual Functioning, developed by the American Cancer Society. (See "ALARM Model for the Assessment of Sexual Functioning" sidebar on the following page.)

Communicating With Your Health Care Provider

Medical providers should tell people who are about to begin cancer treatment what to expect, how to minimize the risk of problems, and what to do if they should occur. Practitioners should incorporate questions concerning sexual difficulties and intimacy into the initial evaluation of patients with cancer.[4]

What Can Help?

A substantial number of helpful treatments are available. Some are evidence-based, as described below, and others are based on common sense and personal insight.

Additionally, there are various clinical trials now underway across the country to help identify new solutions (see our website for more details and contact information).

» **Acupuncture:** In a pilot study, 15 women experienced improved anxiety and depression with reduced hot flashes, although they reported no change in libido.[16]

» **Communication:** A study conducted at the Indiana University Cancer Center found that a guided program of discussion and interactive computer questionnaires helped patients with prostate cancer to first identify and then address quality of life concerns. Participants met monthly over a six month period with an oncology nurse who helped them identify their needs using an interactive computer program. Patients in the program reported significantly better gains in sexual functioning than the controls receiving "usual care."[17]

» **Patient-Practitioner Communication:** A study of women with ovarian cancer found that they "wanted medical staff to discuss sexual issues" but that "health professionals rarely discuss sexual issues because of lack of time, embarrassment, or inexperience, and that professionals need training to help them communicate more comfortably with their patients about sexual issues." (See "Belief & Reality" sidebar on page 7.)[18] Patients can help by initiating a discussion where they feel it's appropriate and might be helpful.

» **DHEA:** In a group of women with adrenal insufficiency, one study reported that DHEA (50 mg daily) improved overall well-being, an increase in sexual interest, increased frequency of sexual thoughts, and improved satisfaction with both mental and physical aspects of sexuality.[19] That same dosage level has also been reported to help men with erectile dysfunction.[20-22] DHEA is not recommended, however, for people with breast, endometrial, or prostate cancers.[23,24]

» **Exercise:** A recent study found that physical activity was correlated with better sexual functioning in men who received external beam radiotherapy.[25] It is possible, and reasonable, that

WOMEN: "SEX ISN'T WORKING FOR ME. WHAT CAN I DO?"

To improve your desire, change your usual routine. You may want to rent an erotic video or read a "sexy" book with your partner.

Arousal disorders can be helped if you use a vaginal cream for dryness. Mineral oil also works. If you have gone through menopause, talk to your doctor about taking estrogen.

If you have a problem having an orgasm, masturbation can help you. Extra stimulation (before you have sex with your partner) with a vibrator may be helpful. You might need rubbing or stimulation for up to an hour before having sex. Many women don't have an orgasm during intercourse. If you want an orgasm with intercourse, you or your partner may want to gently stroke your clitoris.

If you're having pain during sex, try different positions. When you are on top, you have more control over penetration and movement. Empty your bladder before you have sex. Try using extra creams or try taking a warm bath before sex. If your sex pain doesn't go away, talk to your doctor.

If you have a tight vagina, you can try using something like a tampon to help you get used to relaxing your vagina. Your doctor can tell you more about this.

What Else Can I Do?

Learn more about your body and how it works. Ask your doctor about how medicines, illnesses, surgery, age, pregnancy, or menopause can affect sex.

Practice "sensate focus" exercises where one partner gives a massage, while the other partner says what feels good and requests changes (for example: "lighter" or "faster"). Fantasizing may increase your desire. Squeezing the muscles of your vagina tightly and then relaxing them may increase your arousal. Try sexual activity other than intercourse, such as massage, oral sex, or masturbation.

What About My Partner?

Talk with your partner about what each of you like and dislike, or what you might want to try. Ask for your partner's help. Remember that your partner may not want to do some things you want to try. Or, you may not want to try what your partner wants. You should respect each other's comforts and discomforts, which helps you and your partner have a good sexual relationship. If you find it difficult to talk to your partner, your doctor or a counselor may be able to help you.

Adapted from American Family Physician*, Vol 62, No 1 (July 1, 2000)*

ALARM MODEL FOR THE ASSESSMENT OF SEXUAL FUNCTIONING

ALARM refers to assessment of the following: sexual Activities, Libido-desire, Arousal and orgasm, Resolution, and any Medical history relevant to sexual functioning.

The following sample questions can help facilitate a conversation between health professionals and cancer patients.

Activity (frequency of such current sexual activities as intercourse, kissing, and masturbation)

1. Prior to the appearance of any signs or symptoms of illness, how frequently were you engaging in intercourse (specific weekly or monthly estimate)?
2. On occasions other than when having intercourse (or an equivalent intimate activity), do you share other forms of physical affection with your partner, such as kissing or hugging (or both) on a daily basis?
3. In the recent past (in the last six months) have you masturbated? If so, estimate how often this has occurred (specific weekly or monthly estimate).

Libido-desire (desire for sexual activity and interest in initiating or responding to partner's initiations of sexual activity)

1. Prior to the appearance of your illness, would you have described yourself as generally interested in having sex?
2. Considering your current regular sexual relationship, who usually initiates sexual activity?
3. You indicated that your current frequency for intercourse is _____ times per week or month. Would you prefer to have intercourse more often, less often, or at the current frequency?

Arousal & Orgasm (occurrence of erection-lubrication and ejaculation-vaginal contractions, accompanied by feelings of excitement)

For Men

1. When you are interested in having sexual activity with your partner or alone, do you have any difficulty in achieving an erection? Do you feel emotionally aroused?
2. If you experience erectile difficulty, when did this problem start? How often does it occur? Do certain particular circumstances trigger its occurrence (with partner only, for example)? What do you understand to be the cause of the difficulty?
3. During sexual activity either alone or with a partner, do you have any difficulty with ejaculation (coming "too soon" or only after an extended period of time)?
4. If you experience premature or delayed ejaculation, how long would you estimate that it takes, on average, to ejaculate after intensive stimulation begins?

For Women

1. When you are interested in engaging in sexual activity, do you notice that your genitals become moist?
2. If you are postmenopausal, have you noticed any change in vaginal lubrication during sexual activity since the menopause, and are you currently taking hormone replacement therapy?
3. If you experienced arousal deficit, do you experience any pain with intercourse? How long have you had problems with becoming aroused during sexual activity? Do some circumstances cause you to feel more arousal than at other times?
4. During sexual activity either alone or with a partner, can you experience a climax or orgasm?
5. If orgasm does not occur, are you bothered at all by its absence?

Resolution (feelings of tension release after sexual activity and satisfaction with current sexual life)

1. After intercourse or masturbation, do you feel that sexual tension has been released?
2. On a scale from 1 (it could not be worse) to 10 (it could not be better), how would you rate your current sexual life?
3. Do you have any feelings of discomfort or pain immediately after sexual activity?
4. If you experience difficulty in resolution, what problems do you have after sexual activity? How long have they been occurring? What is your understanding of their cause(s)?

Medical History Relevant to Sexuality

1. Current age and medical history: Have you had diabetes or hypertension?
2. Psychiatric history: In the past, have you had emotional difficulties for which you have sought treatment?
3. Substance abuse history: Do you consume alcohol or nonprescription drugs that may cause disruption of sexual activity or responses?

Source: Andersen BL. How cancer affects sexual functioning. Oncology *(Williston Park). Jun 1990;***4***(6):81-88; discussion 92-84.*

similar benefits would be gained by patients receiving treatment for other types of cancers. (See "Exercise & Health" in the winter 2004 issue of *Avenues*.)

A specific type of therapeutic exercise, Kegel exercise, can be helpful for both men and women in increasing awareness of sexual response, increasing orgasmic intensity, and enhancing pelvic circulation and sphincter control.[26]

» **Medication Therapy:** A small case series of eight patients reported improvement with erectile dysfunction after a six-month treatment of testosterone and sildenafil.[27] As with DHEA, use of testosterone is not recommended in men with prostate cancer.[28] Bupropion may be helpful in people experiencing sexual side effects due to antidepressant medication or narcotic treatment for pain.[29] Selective serotonin re-uptake inhibitors may also help reduce hot flashes and improve sleep and libido.[30]

» **Massage:** While we located no studies specifically measuring improvement in sexual function in patients receiving massage therapy, there is evidence for its ability to lower cortisol levels (one of the stress hormones) and raise serotonin and dopamine levels (associated with feelings of well-being).[31] It is also a technique with a high degree of safety.

» **Reading:** There are a number of excellent books that candidly discuss the kinds of sexual problems both men and women are likely to face after treatment (see our website for specific titles). Solutions are also suggested, including information on body image, low sex drive, performance anxieties, medications, sex aids, and reconstructive surgery.[32]

» **Therapeutic Devices:** Women who have had pelvic surgery, radiation therapy, or graft-versus-host disease that resulted in reduced vaginal size or elasticity may be helped by a combined program of relaxation exercises along with vaginal dilators of gradually increasing size.[32] In a study of 15 women who had been treated for cervical cancer with radiation, a therapeutic device that enhances blood flow to the clitoris by creating gentle suction demonstrated significant improvements in sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and reduced pain after three months' use (Eros Therapy: www.urometrics.com or (877) 774-1442).[33] The author of a well-written paper on helping women with sexual dysfunction very candidly wrote that "treatment of orgasmic disorders relies on maximizing stimulation and minimizing inhibition."[26]

» **Cancer Treatment Strategies:** In some cases, the choice of treatment for cancer can help minimize sexual problems. For example, for men with prostate cancer, the use of intermittent hormonal blockade may have a better outcome than continuous blockade.[34]

CONCLUSIONS

Although much work remains to be done to develop better ways to prevent and treat sexual dysfunction related to cancer treatment, it is encouraging that researchers are focusing more and more on this important problem. It is our hope that this summary of information will be useful to patients, their partners, and health care providers.

BELIEF & REALITY: COMMUNICATION ABOUT SEXUAL ISSUES & CONCERNS IN PATIENTS

It can be helpful for patients and health care providers to know what each other is thinking. Both patients and providers may envision an ideal conversation (beliefs) that may be impeded by circumstance or other concerns (reality).

Patients' Beliefs
(the ideal outcome they might like to have)
» Yes, medical staff should have talked to me about sexual issues.
» It would help you understand that it is normal to feel like I did after the chemo and the operation.
» I could have understood why I was having sexual problems if they'd have said you might have problems sexually because we've removed this or that.
» It would have provided reassurance—a light at the end of the tunnel.
» You should know what's going to happen instead of it hitting you like a ton of bricks.

Providers' Beliefs
(the ideal information or questions they might like to offer)
» Yes, we should discuss sexual issues with patients.
» The following sexual problems may occur and why.
» Reassurance that sexual activity will not cause a recurrence.
» Reassurance that sexual problems are normal.
» Advice or help is available.

Patients' Reality
(the undesirable outcome they may have experienced)
» No, medical staff didn't talk to me about sexual issues.
» I didn't know much about how sex would be affected...I just had to go through and find out for myself.
» You have no idea about how the cancer will affect you sexually.
» Nobody talks about sex, and you wonder whether it is right that you feel different.
» The doctor said that if I was having problems with sex, the hospital had creams to help me, but nothing else was said.

Providers' Beliefs
(the discomfort or uncertainties they may have realized)
» No, we don't often discuss sexual issues with patients.
» It's not my responsibility.
» Talking about sexual issues is embarrassing.
» I am not sure what types of sexual problems patients experience.
» I don't feel confident talking to patients about sexual issues.
» I wait until a patient asks about sex.
» There's no time to discuss sexual issues.

Source: Stead, M. L., J. M. Brown, et al. (2002). "Communication about sexual problems and sexual concerns in ovarian cancer: a qualitative study." West J Med ***176****(1): 18-9.*

RESEARCH

Astragalus-Based Chinese Herbs & Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer: A Meta-Analysis of Randomized Trials

MICHAEL MCCULLOCH, CAYLIE SEE, XIAO-JUAN SHU, MICHAEL BROFFMAN, ALAN KRAMER, WEI-YU FAN, JIN GAO, WHITNEY LIEB, KANE SHIEH, & JOHN M COLFORD JR

ABSTRACT

Purpose. Systemic treatments for advanced non-small-cell lung cancer have low efficacy and high toxicity. Some Chinese herbal medicines have been reported to increase chemotherapy efficacy and reduce toxicity. In particular, *Astragalus* has been shown to have immunologic benefits by stimulating macrophage and natural killer cell activity and inhibiting T-helper cell type 2 cytokines. Many published studies have assessed the use of *Astragalus* and other Chinese herbal medicines in combination with chemotherapy. We sought to evaluate evidence from randomized trials that *Astragalus*-based Chinese herbal medicine combined with platinum-based chemotherapy (versus platinum-based chemotherapy alone) improves survival, increases tumor response, improves performance status, or reduces chemotherapy toxicity. ***Methods.*** We searched CBM, MEDLINE, TCMLARS, EMBASE, Cochrane Library, and CCRCT databases for studies in any language. We grouped studies using the same herbal combinations for random effects meta-analysis. ***Results.*** Of 1,305 potentially relevant publications, 34 randomized studies representing 2,815 patients met inclusion criteria. Twelve studies reported reduced risk of death at 12 months. Thirty studies reported improved tumor response data. In subgroup analyses, *Jin Fu Kang* (a type of *Astragalus*-based herbal formula) in two studies reduced risk of death at 24 months and in three studies increased tumor response. *Ai Di* injection (another type of *Astragalus*-based herbal formula) stabilized or improved Karnofsky performance. ***Conclusion.*** *Astragalus*-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy for non-small-cell lung cancer. These results require confirmation with rigorously controlled trials.

INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States, accounting for 27% and 31% of all cancer deaths in women and men, respectively.[1] Although lung cancer deaths in men have declined substantially (from 92 in 100,000 in 1995 to 84 in 100,000 in 2001), death rates in women only recently began to stabilize in 1995 (at approximately 42 in 100,000 between 1995 and 2001) after increasing for two decades between 4% and 6% per year.[2] Lung cancer is now the leading cause of cancer death in women.[1] Seventy-five percent of all lung cancer occurrences are non-small-cell lung cancer.

Despite treatment advances, new systemic therapies for advanced non-small-cell lung cancer developed in the last few decades continue to have both low efficacy and high toxicity. Meta-analyses have shown that, compared to treatment with surgery alone, adjuvant treatment with chemotherapy reduces the risk of death at 2 years by only 13%;[3] adjuvant chemoradiotherapy reduces that risk by 14%;[4] adjuvant radiotherapy alone conversely increases that risk by 21%.[5,6] The addition of platinum-based drugs to standard

This Pine Street Foundation research paper was first published in the January 20th, 2006, issue of the *Journal of Clinical Oncology* (Volume 24, Number 3). More information can be found on our website: www.pinestreetfoundation.org

chemotherapy protocols increased 12-month survival by 5% and tumor response by 62%, but with significantly increased hematologic toxicity, nephrotoxicity, and nausea and vomiting.[7] The 12-month survival for platinum-based regimens has been found in meta-analysis to be 34% (95% confidence interval [CI], 33% to 36%).[7] More recently, the addition of the epidermal growth factor receptor tyrosine kinase–inhibitor drug, gefitinib, to carboplatin/paclitaxel chemotherapy in a phase III randomized, controlled trial demonstrated no additional benefit in survival or time to progression.[8] These poor outcomes in survival, tumor response, quality of life, and toxicity for patients with advanced non-small-cell lung cancer emphasize the need for additional improvements in approaches to treatment.

In China, herbal medicine is frequently combined with chemotherapy in the treatment of lung cancer. Of particular interest is the herb *Astragalus membranaceus* (Fisch.), which may potentiate host immune function by stimulating macrophage and natural killer cell activity,[9] and enhance immune recognition of lung cancer cells by inhibiting production of T-helper cell type 2 cytokines[10] (T-helper cell subsets implicated in the development of immunological tolerance to tumor progression).[11] In a recent clinical trial, single-agent *Astragalus* herbal treatment in combination with platinum-based chemotherapy, compared with platinum-based chemotherapy alone, has been shown to significantly reduce risk of death at 12 months (risk ratio [RR]=0.62; 95% CI, 0.43 to 0.89) and 24 months (RR=0.75; 95% CI, 0.58 to 0.97).[12] In clinical practice and in most published trials, however, *Astragalus* rarely is used as single-agent therapy; it usually is combined with other herbal medicines.

This meta-analysis was motivated by the large number of published trials of *Astragalus*-based Chinese herbal medicines combined with platinum-based chemotherapy and the continuing problems with low efficacy and high toxicity in standard chemotherapy treatment of advanced non-small-cell lung cancer. Our *a priori* hypotheses were that adding *Astragalus*-based Chinese herbal medicine to platinum-based chemotherapy, compared with treatment with platinum-based chemotherapy alone, could prolong survival, increase tumor response, stabilize or improve performance status, and reduce chemotherapy toxicity.

METHODS

Study Identification

We conducted a systematic search of the following databases: CBM China BioMedical Bibliographic Database (1978 to August 2004; www.imicams.ac.cn/cbm), TCMLARS (1984 to August 2004; www.cintcm.com), MEDLINE (1966 to August 2004; www.pubmed.gov), EMBASE (1974 to August 2004; www.embase.com), Cochrane Library (1988 to August 2004; www.cochrane.org), and Cochrane Central Register of Controlled Trials (1966 to August 2004; www.cochrane.org). We used an extensive list of search terms (the full search strategy is available on request from the authors). The search was designed to find initially all trials involving non-small-cell lung cancer, chemotherapy, Chinese herbal medicine, and randomized controlled trials (and multiple synonyms for each term). We also searched for references from within the bibliographies of all eligible studies. No restrictions were placed on the publication language. Two reviewers (MM and CS) independently identified studies and translated abstracts and relevant data portions of eligible studies.

Study Eligibility

We screened titles and abstracts and retained those that were described as randomized, recruited patients with advanced non-small-cell lung cancer, provided the treatment group with Chinese herbal medicines containing the herb *Astragalus* in combination with standard platinum-based chemotherapy, provided the control group with platinum-based chemotherapy alone, and reported data on at least one of our outcomes of interest (survival, tumor response, performance status, or toxicity) with sufficient detail to permit calculation of the risk ratios of each outcome and 95% CIs. We obtained full-text copies of all abstracts or titles that potentially met our inclusion criteria and conducted a thorough screening of those articles obtained to confirm they met our inclusion criteria.

All inclusion and exclusion criteria and the categorization of outcomes were made before any meta-analysis of the data. Our decision to group together for this meta-analysis those studies using platinum-based chemotherapy was based on the fact that this therapy is currently a standard treatment for advanced non-small-cell lung cancer. Following the example set by D'Addario et al[7] and the Cochrane Collaboration's Non-Small-Cell Lung Cancer Collaborative Group,[3] platinum-based chemotherapy was grouped together as a therapeutic class when assessing efficacy of treatment for non-small-cell lung cancer. Each stage of the planning, design, analysis, and reporting of this meta-analysis was conducted in accordance with the QUOROM Statement guidelines.[13]

Data Extraction

Two reviewers (MM and CS) independently extracted data on patient characteristics, treatment details, clinical outcomes, and study quality.[14,15] We searched for data on survival outcomes of any type (total survival, cause specific survival, and disease-free survival, with either crude data or adjusted measures), objective tumor response, reduction in chemotherapy toxicity, and improved or stabilized performance status. To evaluate Chinese herbal medicine in total as a therapeutic system, we first grouped together for meta-analysis the data from all studies meeting our

inclusion criteria. Then, to evaluate the efficacy of specific herbal formulas, when we found more than one study using the exact same herbal formula, we grouped together for meta-analysis the data from those specific studies.

Analysis of Outcomes

Survival. Given that all of the studies identified in our systematic search reported crude survival data as the number of patients in each treatment group who died by 6, 12, 24, or 36 months, we calculated the probability of failure (death) as the number of patients who had died by each time point divided by the total number of patients enrolled at the start of the trial for each treatment group. This approach is intentionally conservative: if some patients dropped out of the study, retaining them in the denominator as we have done would lower the estimate of effectiveness. This is analogous to an intention-to-treat analysis.[18] The risk ratios of treatment failure (death) at each time point was calculated as the proportion who died in the *Astragalus*-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR less than 1 favors the combination regimen. This is the same approach taken by D'Addario et al[7] in a meta-analysis of 12-month survival rates in the treatment of advanced non-small-cell lung cancer patients with platinum-based versus non-platinum-based chemotherapy.

Objective Tumor Response. The probability of tumor response was calculated as the number of patients experiencing any response (complete response plus partial response) divided by the total number in each treatment group. The RR of tumor response was calculated as the probability of tumor response in the combination group, divided by this proportion in the chemotherapy group; RR more than 1 favors the combination regimen.

Performance Status. RR more than 1 favors the combination regimen.

RESULTS

Studies Retrieved

Our systematic search identified 1,305 potentially relevant abstracts, of which 92 were identified as requiring full-text article retrieval. Close screening of these 92 studies excluded 58 because no patients received *Astragalus* (n=33), patients randomly assigned to herbal therapy in some cases received herbal medicine not actually containing the specific herb *Astragalus* (n=6), the article did not describe a controlled trial (n=3), no platinum drugs were included in chemotherapy (n=3), there were no usable end points (n=9), or the article was a duplicate of another study (n=4). This resulted in 34 studies accepted for meta-analysis.

Survival

We identified seven studies reporting a total of 529 patients that reported reduced risk of death at 6 months for *Astragalus* combinations versus chemotherapy alone (RR=0.58; 95% CI, 0.48 to 0.71): five using various *Astragalus*-based combinations (RR=0.61; 95% CI, 0.49 to 0.78)[26-30] and two using a specific herbal formula, *Jin Fu Kang* (RR=0.61; 95% CI, 0.28 to 1.34).[31,32] We identified 12 studies with a total of 940 patients that reported reduced risk of death at 12-months (RR=0.67; 95% CI, 0.52 to 0.87): one using single-agent *Astragalus* (RR=0.62; 95% CI, 0.43 to 0.88),[12] nine using various *Astragalus*-based combinations (RR=0.67; 95% CI, 0.49 to 0.90),[26-30,33-36] and two using formula *Jin Fu Kang* (RR=0.91; 95% CI, 0.20 to 4.01).[31,32] We identified nine studies with a total of 768 patients that reported reduced risk of death at 24 months (RR=0.73; 95% CI, 0.62 to 0.86): one using single-agent *Astragalus* (RR=0.75; 95% CI, 0.58 to 0.97),[12] six using various *Astragalus*-based combinations (RR=0.80; 95% CI, 0.66 to 0.96),[27,29,33-36] and two using formula *Jin Fu Kang* (RR=0.58; 95% CI, 0.49 to 0.68).[31,32] We identified six studies with a total of 556 patients that reported reduced risk of death at 36 months (RR=0.85; 95% CI, 0.77 to 0.94): one using single-agent *Astragalus* (RR=0.89; 95% CI, 0.74 to 1.08),[12] four using various *Astragalus*-based combinations (RR=0.86; 95% CI, 0.73 to .998),[27,33,35,36] and one using formula *Jin Fu Kang* (RR=0.79; 95% CI, 0.67 to 0.92).[32] Among studies reporting median survival, none included confidence intervals, *P* values, or variance. We were therefore unable to perform a meta-analysis of median survival.

Tumor Response

We identified 30 studies representing a total of 2,472 patients that reported tumor response data (RR=1.34; 95% CI, 1.24 to 1.46): seven using specific formula *Ai Di* injection (RR=1.19; 95% CI, 0.99 to 1.44),[37-43] two using single-agent *Astragalus* (RR=1.57; 95% CI, 0.85 to 2.93),[12,44] 18 using various *Astragalus*-based combinations (RR=1.34; 95% CI, 1.21 to 1.47),[27-30,34-36,45-55] and three using formula *Jin Fu Kang* (RR=1.76; 95% CI, 1.23 to 2.53).[31,32,56]

Performance Status

We identified 12 studies representing a total of 1,095 patients that reported performance status data (RR=1.36; 95% CI, 1.21 to 1.54): four using specific formula *Ai Di* injection (RR=1.28; 95%CI, 1.12 to 1.46),[37,38,43,57] one using single-agent *Astragalus* (RR=1.22; 95% CI, 0.98 to 1.52),[12] five using various *Astragalus*-based combinations (RR=1.32; 95% CI, 1.16 to 1.49),[36,48,50,51,53] and two using formula *Jin Fu Kang* (RR=1.68; 95% CI, 0.82 to 3.44).[32,56]

DISCUSSION

These findings are subject to several limitations. Our meta-analysis results suggest that combining platinum-based chemotherapy with *Astragalus*-based Chinese herbal medicine in the treatment of non-small-cell lung cancer may increase survival, tumor response, and performance status, when compared to treatment with platinum-based chemotherapy alone.

However, confirmation of these conclusions in rigorously controlled, randomized trials is required before more firm conclusions about this therapy can be drawn.

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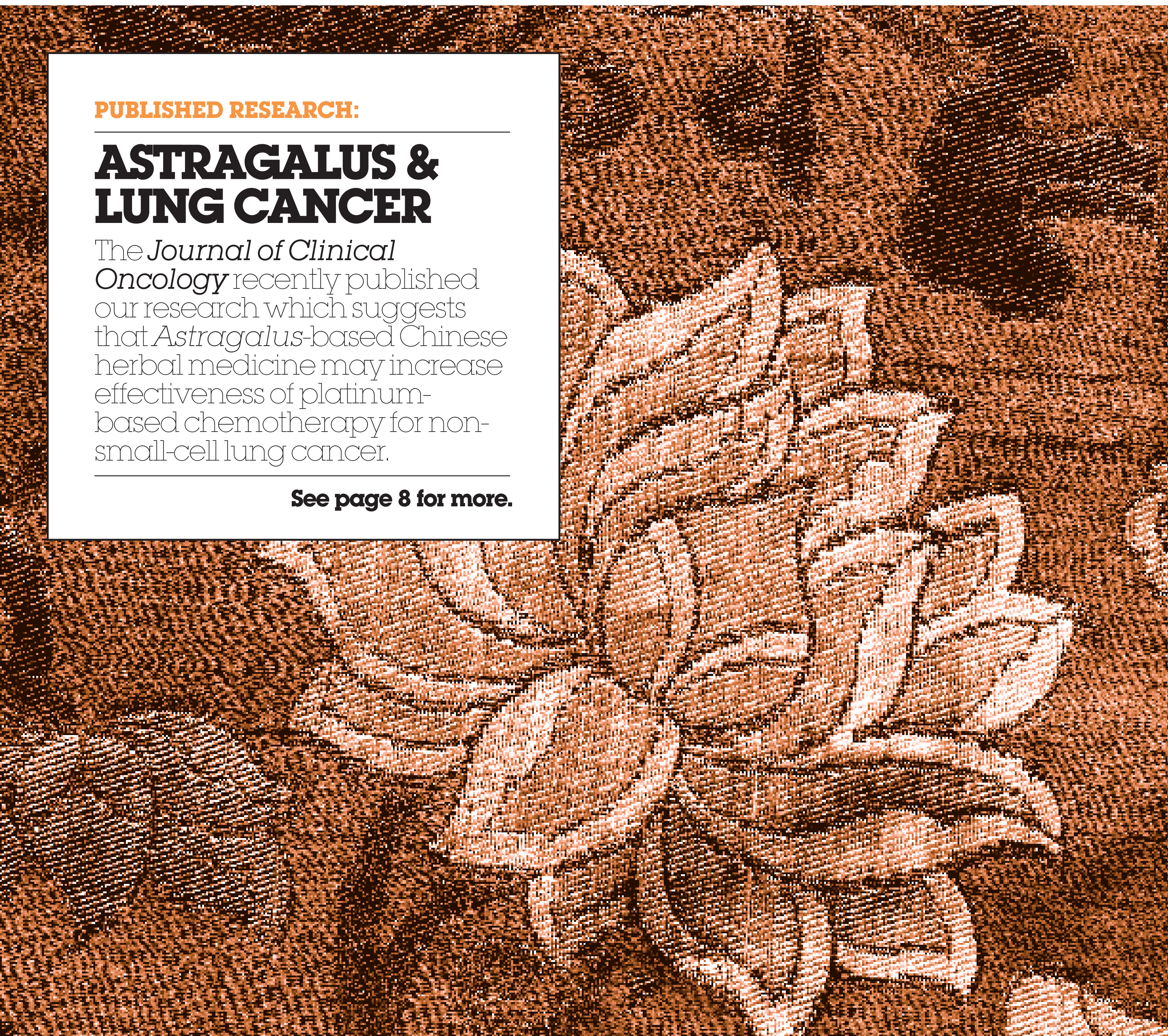

PUBLISHED RESEARCH:

ASTRAGALUS & LUNG CANCER

The *Journal of Clinical Oncology* recently published our research which suggests that *Astragalus*-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy for non-small-cell lung cancer.

See page 8 for more.