THE USE OF DIETARY SUPPLEMENTS AMONG INDIVIDUALS ENROLLED IN CLINICAL TRIALS FOR THE TREATMENT OF CANCER

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The use of dietary supplements by individuals with cancer is increasing. Many individuals with the diagnosis of cancer consume these supplements while undergoing treatment for cancer, including those enrolled in clinical trials. Clinical trials may involve the use of drugs or investigative agents, which are being studied to determine their safety and efficacy in the treatment of cancer.

The focus of this study was to determine if individuals enrolled in clinical trials for the treatment of cancer use dietary supplements (vitamins, minerals and herbs) and the reasons why they are using them. The study's aims were (1) to document the use of dietary supplements among patients with breast, prostate, and colorectal cancer who are enrolled in a clinical trial, (2) to evaluate the perceptions of oncologists regarding their patients' use of dietary supplements, and (3) to evaluate the design of clinical trials to determine the proportion that specifically address the use of dietary supplements. The study employed an exploratory, descriptive design whereby 99 patients with cancer who were enrolled in a clinical trial for the treatment of cancer were interviewed. A total of 53 oncologists were surveyed and the design of 70 multi-institutional breast, prostate and colorectal cancer clinical trials were reviewed.

The study findings indicate that patients with breast, prostate and colorectal cancer are consuming dietary supplements while enrolled in clinical treatment trials. In general, the reasons they are using the dietary supplements are to enhance their health and to do something to help themselves. The patients' perception is that they communicate this information to their oncologists, however, detailed information about the dietary supplements such as brand, type, dosage and frequency, is not routinely assessed and documented. In general, the design of the clinical trials did not specifically address the use of dietary supplements, and there were often discrepancies between the description in the study body and the accompanying case report forms.

The importance of these findings from a public health perspective is that patients are consuming unregulated substances while enrolled in a clinical trial for the treatment of cancer and potentially may be at risk for drug interactions.

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1 INTRODUCTION

The use of alternative therapies for the prevention and treatment of a variety of health problems is a widespread and growing phenomenon. Alternative therapies are defined as unproven treatments or interventions that are substituted for conventional (standard) therapy and do not conform to the standards of medical practice. Complementary/alternative medicine (CAM) is difficult to define, because it encompasses a broad spectrum of practices and beliefs (Eisenberg, 1993). Each particular therapy may be complementary if used in addition to medical treatment or, as an alternative, if the patient uses it instead of conventional therapy (Spencer, 1999). Commonly-used CAM interventions that are not taught in United States' (U.S.) medical schools and are not generally available in U.S. hospitals include: relaxation techniques, chiropractic therapy, massage, spiritual healing, commercial weight-loss programs, dietary interventions, herbal medicine, megavitamin therapy, self-help groups, energy healing, biofeedback, hypnosis, homeopathy, acupuncture, folk remedies, exercise and prayer (Eisenberg, 1993).

In 1990, Eisenberg conducted a landmark study to determine the prevalence, costs and patterns of use of alternative therapies among the general public. The study revealed that one in three respondents (34%) used some form of CAM therapy mostly for chronic, as opposed to life-threatening conditions (Eisenberg, 1993). In 1990, Americans made an estimated 425 million visits to providers of CAM, which exceeded the 388 million visits to U. S. primary care physicians during the same year (Eisenberg, 1993). In a follow up study, the number of individuals reporting use of at least one form of CAM had increased to 42% by 1997, the annual number of visits to CAM practitioners had increased to 629 million visits, and there was no change in the percent of respondents who had not informed their provider of their use of CAM therapies, 72% between 1990 and 1997 (Eisenberg, 1998).

The use of CAM for self- care has increased during the past decade (Wootton, 2001). CAM is used by patients with a variety of conditions such as: chronic back pain, fatigue, gastrointestinal problems, arthritis, acquired immunodeficiency syndrome, chronic renal failure and cancer (Eisenberg, 1993). Many practitioners believe that certain patient groups use CAM to a greater extent than the general population (Chavez, 1997). It has been estimated that 1 in 4 Americans who see their physicians for a serious medical condition such as cancer may be using CAM in addition to conventional medicine (Eisenberg, 1993).

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. It is estimated that 1, 368,030 new cancer cases were diagnosed in 2004 in the United States and 563,700 deaths (ACS, 2004). Cancer is the second leading cause of death in the United States, exceeded only by heart disease (ACS, 2004). The leading sites of cancer are prostate, breast, lung, and colorectal (ACS, 2004). The current five-year relative survival rate for all cancers combined is 62%. After adjusting for normal life expectancy, this survival rate represents persons who are living five years after diagnosis, whether disease-free, in remission, or under treatment with evidence of cancer (ACS, 2003).

Conventional treatment for cancer includes standard and investigative therapies. Cancer is typically treated with surgery, radiation, chemotherapy, hormones and/or immunotherapy. Patients may receive a single treatment modality or a combination of modalities either concurrently or separately. These methods of treatment are known as conventional therapy since they represent accepted practice that conforms to medical standards for cancer care. In contrast, investigative therapy involves a cancer clinical trial as a controlled experiment to assess the safety and efficacy of potential new treatments for cancer (NCI, 2001). Clinical trials are only undertaken when there is reason to believe that the treatment being studied may be of value to

the patient. There are some risks involved with clinical trials since it is not known in advance whether the treatment will be effective or exactly what side effects will occur.

It has been estimated that between 50 and 83% of individuals with the diagnosis of cancer use CAM (Sparber, 2000). Simultaneous use of CAM by cancer patients undergoing conventional medical treatment is extremely common (National Cancer Institute, 2002). In one study, 53 oncology patients were interviewed and only 11% reported that they had used complementary or alternative therapies. However, when asked about 17 specific CAM therapies, 85% of the patients had used relaxation, meditation, or prayer, 51% vitamins, 41% herbal therapies, 11% hydrazine sulfate, 8% shark cartilage, and 8% acupuncture (Chavez, 1997). In 1997, the most frequently-used forms of alternative medicine among cancer patients were relaxation therapy, chiropractic, acupuncture, massage therapy, herbal, vitamin, and mineral supplements (dietary supplements) (Dalen, 1998). Between 1990 and 1997, there was a 380% increase in the use of dietary supplements in the general population (Eisenberg, 1998).

The use of dietary supplements by cancer patients is increasing and patients may not be disclosing this information to their oncologists. Dietary supplements are products taken orally that contain one or more of the following substances in various combinations: a vitamin, mineral, herb or other botanical, or an amino acid. The lack of disclosure regarding the use of dietary supplements by cancer patients undergoing treatment is of concern because of the possibility of toxic side effects, as well as the potential for adverse interactions with the conventional or investigational medical treatments for cancer. For instance, the mechanisms of action of chemotherapeutic agents and antioxidant dietary supplements suggest that combining the two may increase the risk for cancer recurrence because some chemotherapeutic agents utilize reactive oxygen species as a mechanism for cytotoxicity (Tasaki, 2002). Similarly, some dietary

supplements may mimic or interfere with the hormonal therapy used in the treatment of hormone sensitive cancers such as breast and prostate (Tasaki, 2002). There are relatively little health education materials with respect to the possible benefits or the adverse effects of dietary supplements and the interactions between dietary supplements and conventional treatment for cancer (Smith, 1999). Dietary supplements do not require US Food and Drug Administration (FDA) approval or safety evaluation prior to marketing. However, dietary supplements have the potential for adverse reactions and interactions. It is therefore incumbent upon physicians to be aware of dietary supplement or CAM usage by their cancer patients.

Although studies have shown that patients with cancer often use dietary supplements in addition to conventional medical treatment, this information is frequently not reported to their physicians (Cassilleth, 1984). In one study, Adler (1999) found that 54% of patients who used dietary supplements reported not disclosing this information to their physicians. Likewise, Eisenberg (1993) found that 70% of patients taking dietary supplements did not report this information to their physicians. In addition, a Canadian study conducted with breast cancer patients found that 65-70% of the women who reported using unconventional therapies did not inform their oncologist (Smith, 1999). This raises the question of why a substantial proportion of cancer patients are not reporting their use of dietary supplements to their oncologists (Gray, 1998). Possible explanations include the failure of physicians to routinely inquire about the use of dietary supplements, or the perception that they do not need to ask the question since they believe that patients would volunteer this information (Gore, 2002). There is some evidence that the increased usage of dietary supplements does not correlate with an increased reporting of use to health care professionals (Gore, 2002). The lack of reporting may indicate a deficiency in

patient-provider communication and could potentially lead to negative health outcomes (Verhoef, 1999).

1.1 STATEMENT OF THE PROBLEM

There has been little research exploring the extent to which individuals who are being treated for cancer with investigative therapies use dietary supplements. To date, there have been two studies conducted in individuals on Phase 1 clinical trials for cancer and the use of CAM therapy. (Sparber, 2000, Dy, 2004). The study conducted by Sparber evaluated the use of a variety of CAM therapies among individuals hospitalized for Phase 1 treatment but did not specifically evaluate the use of dietary supplements. The more recent study conducted by Dy evaluated the use of dietary supplements by individuals enrolled on Phase I clinical trials for the treatment of cancer.

In the conduct of clinical trials with investigative therapy for cancer patients there is a strong emphasis placed on the randomized clinical trial (RCT). RCTs conducted for the treatment of cancer are designed to assess the efficacy and safety of an investigational agent as compared to those of standard treatment for the particular type of disease. Dietary supplements may contribute to an incorrect attribution of toxicity to an experimental drug, false positive responses, and unsafe combination of substances (Sparber, 2000). For these reasons it is important that information regarding the use of dietary supplements by individuals on a clinical trial be obtained. In addition, it is also important that clinical trial protocols be designed so that the participants are asked about their use of dietary supplements and this information is recorded. Failure to collect this information could potentially interfere with the outcomes of clinical trials and, in addition, potentially place patients at risk. Concurrent use of investigational agents and

dietary supplements may cause harmful drug interactions. It is therefore critical that the physician, patient and the public awareness be raised regarding the importance of communicating the use of dietary supplements.

1.2 SPECIFIC AIMS

The aims of this study are (1) to document the use of dietary supplements among patients with breast, prostate and colorectal cancer who are enrolled in treatment clinical trials with investigative therapies (2) to evaluate the perceptions of oncologists regarding their patients' use of dietary supplements and, (3) to evaluate the design of cancer clinical trials to determine the proportion that specifically address the use of dietary supplements.

1.3 RESEARCH QUESTIONS

The first component of this study involved surveying individuals with the diagnosis of breast, prostate, and colorectal cancer who were enrolled on therapeutic clinical trials. The survey was conducted to determine the following: 1.) the proportion of individuals who are actively using vitamins, minerals or herbal supplements (dietary supplements), 2.) the reasons patients on clinical trials give for using dietary supplements and, 3.) the proportion of patients who have disclosed this information to the treating oncologist.

Research Questions:

1. What proportion of patients enrolled on therapeutic clinical trials for breast, prostate, and colorectal cancer use vitamin, mineral or herbal supplements (dietary supplements) on a regular basis?

2. Among patients enrolled on therapeutic clinical trials for breast, prostate, and colorectal cancer, what dietary supplements are they using? What is the frequency of use of the particular dietary supplements?
3. Among patients enrolled on therapeutic clinical trials for breast, colorectal and prostate cancer that use dietary supplements, what reasons do they provide for doing so?
4. What proportion of patients who use vitamins, minerals, or herbal supplements while on a breast, colorectal or prostate cancer clinical trial, inform their oncologist of such use? and why? or why not?

The second component of the study involved surveying oncologists within the academic cancer center and community network settings who enroll patients with breast, colorectal and prostate cancer on therapeutic clinical trials. The purpose of this component of the study was to evaluate the oncologist's knowledge and perception of patient usage of dietary supplements while enrolled on therapeutic clinical trials.

Research Questions:

1. What proportion of oncologists routinely ask and document the use of dietary supplements of their patients?
2. What proportion of clinical oncologists think that their patients are telling them about their use of dietary supplements?

The third component of the study involved a review of clinical trials to determine the following research questions:

1. What proportion of therapeutic clinical trials for breast, colorectal and prostate cancer are designed to address the possible use of dietary supplements by the participants?
2. What proportion of the clinical trials clearly state that individuals enrolled on the clinical trial should not use dietary supplements?
3. What proportion of the clinical trials clearly define what is considered a dietary supplement?

2 LITERATURE REVIEW

2.1 COMPLEMENTARY AND ALTERNATIVE MEDICINE

There is no clear uniform definition of complementary and alternative medicine (CAM). Although the term *complementary therapies* is usually considered to be therapies used together with conventional medicine and the term *alternative therapies* is usually considered to refer to those used in place of conventional medicine (Verhoef, 1999). Frequently these terms are used interchangeably. Many of these therapies have not been sufficiently tested, if at all, to determine their safety and efficacy. CAM encompasses an array of techniques, modalities, and medical systems. It has been stated that "complementary therapies seem to have little in common other than their exclusion from mainstream medicine"(Ernst, 2002), and that "CAM encompasses primary care systems of medicine including traditional Chinese medicine and Ayurvedic medicine, which have unique diagnostic criteria and diverse therapeutic options, discrete therapies (e.g. shark cartilage, bee pollen, ozone therapy, etc) and almost everything in between" (Ernst, 2002). They encompass over 150 treatment modalities and a variety of diagnostic methods. CAM has been 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 currently a part of conventional medicine.

In 1992, the United States Congress recognized that CAM was a growing phenomenon that needed to be examined to determine whether its claims were valid. Subsequently the National Institute of Health (NIH) developed an Office of Unconventional Medicine Practices (Eskinazi, 1998). This office was later renamed the Office of Alternative Medicine (OAM). In 1998,

Congress established NCCAM. NCCAM is one of the 27 institutes and centers that make up the National Institute of Health (NIH). Its mission is to support research on complementary and alternative medicine, to train researchers in CAM, and to disseminate information to the public and professionals on CAM.

2.1.1 CAM USE BY THE GENERAL POPULATION

The creation of the NCCAM and the appropriation of funds by Congress for CAM research were the result of the growing use of CAM by the American public. Eisenberg (1990) conducted the first study documenting the extent to which CAM is used nationally. He conducted a national random telephone survey of 1539 individuals in the general population, to determine the prevalence, costs and patterns of use of 16 previously identified CAM therapies for health problems. The response rate was 67% and the results revealed that one in three respondents had used at least one form of CAM in the past year (Eisenberg, 1993). The frequency of use varied among socioeconomic groups, with the highest use reported by non-black persons from 25-49 years of age who had a relatively high level of education and income (Eisenberg, 1993). Expenditures associated with the use of CAM amounted to approximately $13.7 billion, three quarters of which was paid out of pocket (Eisenberg, 1993). The majority of users also sought medical treatment for the conditions for which they were using CAM. However, 72% of these individuals had not informed their physician of their use of CAM (Eisenberg, 1993). In 1997, Eisenberg reported the results of a follow-up survey and found that CAM use had increased by 25%, total visits to alternative practitioners had increased by 47% and total expenses paid for alternative practitioner services increased by 45%. The majority of people (58.3%) in Eisenberg's 1997 study were paying for CAM out of their pockets. CAM was used by patients with cancer, arthritis, chronic back pain, acquired immunodeficiency syndrome, gastrointestinal

problems, chronic renal failure, or eating disorders (Eisenberg, 1993). It was also noted that CAM therapies were generally used as adjuncts to conventional therapy. National surveys between the 1980s and 1990s reported that metabolic, dietary, and megavitamin approaches were among the most popular CAM approaches (Cassileth, 1994). In the 1990s, the most commonly used CAM therapies across all studies included mind-body approaches (meditation, relaxation, hypnotherapy, visualization, and other imagery techniques), reflexology, dietary approaches and food supplements, Chinese medications, botanical preparations, homeopathy, and spiritual healing (Ernst, 1998). Eisenberg found a 380% increase in the use of herbal medicines and a 130% increase in high-dose vitamin usage between 1990 and 1997. This placed approximately 15 million adults at potential risk for adverse interactions with their current prescribed medications (Eisenberg, 1998).

If patients might be at risk for adverse reactions, it would be important for their physicians to be aware of their use of herbal medicines and vitamins (dietary supplements). There was a growing concern as to whether this information was voluntarily communicated to the physician by the patient. Hensrud attempted to investigate this by conducting a study that compared the use of dietary supplements and nonprescription medications as reported on written questionnaires with use reported during structured interviews (Hensrud, 1999). The study involved 200 randomly selected subjects who were undergoing a periodic health examination in Internal Medicine at the Mayo Clinic. The prevalence of use of dietary supplements was 30.5% by written self-report, in comparison with 61% during a structured interview (Hensrud, 1999).

Evidence for the increasing use of CAM by the general public is also indicated by the annual increase in the number of visits to CAM practitioners. The annual out of pocket expense for the consumer also continues to increase since CAM it is not routinely covered by health insurance.

For whatever reasons, there also seems to be a lack of voluntary communication regarding the use of CAM by patients to their physicians. This lack of communication may place the patient at risk for adverse reactions.

2.1.2 CAM USE BY CANCER PATIENTS

Studies on the use of CAM by cancer patients have been conducted worldwide since the late 1970s (Cassileth, 1999). Prevalence studies have been conducted in at least 16 countries in Asia, Europe, North and South America as well as in Australia and New Zealand, (Cassileth, 1999). A total of 26 surveys in 13 countries, including 4 studies of pediatric patients, have been conducted (Ernst, 1998). The results of these studies indicate that the use of CAM therapies may vary widely, in adults from 7-64%, with the overall average or median use of CAM being 31.4% (Ernst, 1998). The large degree of variability has been suggested to be the result of different interpretations of "complementary/alternative medicine" on the part of the investigators and patients (Ernst, 1998).

In 1984, Cassileth reported that 13% of patients with cancer in the United States receiving conventional cancer treatment also engaged in the use of CAM (Downer, 1994). The most commonly used therapies were metabolic, dietary, megavitamins, mental imagery, immune therapy and spiritual healing (Downer, 1994). In a Canadian study, CAM usage varied based on the specific cancer diagnosis (Verhoef, 1999). The study findings revealed that CAM was used by 13% of those surveyed with the diagnosis of prostate cancer, 24% of those diagnosed with brain tumor and in 37% of those diagnosed with breast cancer (Verhoef, 1999). The results of these surveys seem to indicate CAM use may differ depending on the specific cancer diagnosis and perhaps also depending on gender.

The results of large surveys published in the Journal of Clinical Oncology have demonstrated that two thirds of individuals with cancer are engaged in the use of CAM (Burnstein, 2000). Richardson, et al. at the M. D. Anderson Cancer Center conducted cross-sectional prevalence surveys on the use of CAM among patients being treated in their clinic. The findings revealed that eighty-three percent of patients with a variety of malignancies and disease stages acknowledged the use of some form of CAM (Burnstein, 2000). On average, patients used four to five different forms of complementary medicine, including spirituality and psychotherapy.

The use of CAM by patients with cancer may vary depending on their diagnosis. However, there is increasing evidence that patients are using CAM while undergoing conventional treatment for cancer. Dietary supplements may be of particular concern since they may interact with cancer treatment and/or outcomes. It has also been reported that patients with cancer use these therapies in an attempt to cure the cancer, to reduce the symptoms of cancer, to minimize or control the side effects of conventional cancer treatments, and to gain control in decision making, enhance the immune system, or to provide emotional and psychological reassurance (Verhoef, 1999). Studies performed in outpatient oncology clinics in the United States and Switzerland found the main reason for CAM use was to do everything possible and maintain hope (Fernandez, 1998; Morant, 1991).

It has been stated that patients are accessing a growing body of information that often is one-sided and optimistic, and this has contributed to increased usage (Verhoef, 1999). The author believes that this increased usage has major implications for research and practice.

2.1.3 USE OF CAM BY PATIENTS WITH BREAST CANCER

The most prevalent forms of cancer with the exception of skin cancer are lung, breast, colorectal and prostate cancer. Although skin cancer accounts for 50% of the cancer diagnoses, the majority of skin cancer is not melanoma. Individuals with breast and prostate cancer who take certain dietary supplements are of particular concern since conventional treatment for these cancers may involve hormonal therapy and some dietary supplements may either mimic hormonal activity or block hormonal receptors. Thus, this activity could impact the outcome of the treatment.

Breast cancer originates from epithelial cells of the breast. The disease occurs mostly in women, but infrequently men can get breast cancer as well. Breast cancer is the most common cancer among women, other than skin cancer. It is the second leading cause of cancer death in women, after lung cancer. About 215,990 women in the United States were diagnosed with invasive breast cancer in 2004 and 40,110 women died from the disease (The American Cancer Society, Inc. 2004).

Dietary supplements appear to be more prevalent among women with breast and gynecologic cancer than among men and women with other types of cancer. Many women living with breast cancer have been vocal in their support of complementary medicine (The National Forum on Breast Cancer, 1994). For example, Balneaves (1999) stated that “past research has revealed complementary therapies to be an integral part of women’s experiences with this life-threatening and chronic disease.” To date there has been very limited documented evidence as to what specific therapies are used and if they are used in combination with conventional cancer treatment for breast cancer. Therefore it is impossible to determine if these therapies are impacting directly or indirectly conventional treatment and clinical outcomes

(Balneaves, 1999). Previous research on the use of complementary therapies by women living with breast cancer has revealed a preference for biological or physical therapies, including vitamin therapy, homeopathy and herbalism (Montbriand, 1995). There is ample evidence that a substantial proportion of breast cancer patients use CAM, but the use of specific products has not been studied (Boon, 2000). Boon (2000) has stated, "Understanding the prevalence of use of specific products and therapies is essential for future research, the design of information sources, and the overall management of patient care".

Dietary supplements with estrogenic effects may be of concern if a woman has breast cancer. Soy products are the major dietary source of isoflavonoid phytoestrogens. The estrogenic effects of isoflavonoids are of particular interest in relation to breast and prostate cancer (Weiger, 2002). Isoflavonoids compete with estradol for binding sites (similar to the antiestrogen tamoxifen). However, in vitro data suggest that it is possible for isoflavonoids to enhance rather than inhibit the proliferative effects of estradol on estrogen-dependent breast cancer cells, depending on the concentration. At present, it seems prudent to discourage the use of isoflavonoids in women with breast cancer (especially those with estrogen-receptor positive tumors) or endometrial cancer (Weiger, 2002). Data obtained from animal studies indicate that genistein can negate the inhibitory effect of tamoxifen on breast cancer growth; women taking tamoxifen should avoid soy supplements (Weiger, 2002).

In a study conducted by Boon (2000), 66.7% of breast cancer survivors who responded to the CAM survey reported using CAM, which is higher than the findings of other studies. Breast cancer patients with later stage cancer at diagnosis, as well as those receiving chemotherapy were statistically more likely to use CAM. Of 493 outpatient cancer patients, 63% used dietary supplements. Almost half of these individuals believed that these supplements were non-toxic

(Adler, 1999).) The majority of these users initiated their use of CAM less than three months after diagnosis (Adler, 1999).) The findings also revealed that the incidence of patients informing their physicians of CAM usage had increased from the 30%, which was reported in earlier studies to 46.4%. In contrast, Eisenberg, et al found no change in the percentage of Americans informing their physicians of CAM usage between 1990 and 1997(Boon, 2000). Despite women's satisfaction with conventional care (Balneaves, 1999), 43% of the women who revealed using complementary therapies did not discuss them with their physicians. These findings are similar to those in the general cancer population.

Women with breast cancer are using CAM including dietary supplements. It has been noted that these women may take dietary supplements while undergoing conventional treatment for breast cancer without their physician's knowledge. Some of the dietary supplements may be of concern since they mimic estrogenic activity, which may interfere with the conventional treatment outcomes.

2.1.4 USE OF CAM BY PATIENTS WITH PROSTATE CANCER

Prostate cancer is the most common cancer in American men, other than skin cancer. There were 230,110 new cases of prostate cancer diagnosed in the United States in 2004 and 29,900 deaths (The American Cancer Society, Inc. 2004). Prostate cancer is the second leading cause of cancer death in men, exceeded only by lung cancer. Although men of any age can get prostate cancer, it occurs most often in men over 50. In fact, more than 70% of all prostate cancers are diagnosed in men over the age of 65.

A recent study conducted among patients with prostate cancer in a radiology setting revealed that overall 37% of patients were using some form of dietary supplement. The use of dietary supplements among patients with prostate cancer is of concern because some of the supplements

may have a potential biologic impact on tumor behavior, therapeutic endpoints, and the measure of prostate-specific antigens values (Jones, 2002). The potential confounding effects of CAM use have been considered to be particularly relevant in prostate cancer, because of the use of a biochemical marker prostate-specific antigen (PSA) to assess disease status (Jones, 2002). A number of supplements such as lycopene and PC-SPES can lower the results of serum PSA thus confounding the results of standard or investigational therapy, and potentially impacting treatment recommendations (Jones, 2002).

The herbal supplement PC-SPES became popular among men with prostate cancer as an alternative to standard gonadotropin-releasing hormones (GnRH) agonist treatment and as a second-line treatment after failure of primary hormonal therapy (Smith, 2001). This preparation contains 8 herbs. Herbal therapies can have biological activity. Although PC-SPES has been promoted as a nonestrogenic food supplement, some of its constituents have potent estrogenic activity in yeast, mice and humans (DiPaola, 1998). It potentially has been promoted as bolstering the immune system in patients with prostate cancer that is refractory to estrogenic activity (Angell, 1998). In patients with prostate cancer, it causes clinically-significant reductions in serum testosterone concentrations, decreases in PSA concentrations, and has side effects similar to estrogen (DiPaola, 1998). This activity when used concurrently with standard or experimental therapy may therefore confound the results (DiPaola, 1998). Estrogens may also have toxic side effects and the safety of nutritional supplements also remains unknown. These data demonstrate that commercially-available, unregulated, dietary supplements may have biologic activity that can affect diseases, standard medical therapy and general health (DiPaola, 1998).

A recent pilot study of 16 men with androgen-independent metastatic prostate cancer taking PC-SPES has demonstrated activity by decreasing the PSA. However, there is nothing known about the long-term effects of this herbal preparation. Another dietary supplement, saw palmetto has been found to inhibit (alpha)-reductase, an enzyme involved in testosterone metabolism. The absence of long-term efficacy studies, high cost and documented estrogenic side effects makes it an unattractive alternative to GnRH.

Thus, many men with prostate cancer are also using dietary supplements while undergoing treatment for cancer. Some of these dietary supplements seem to alter the testosterone activity. It is still too early to determine the outcome of long-term use of dietary supplements with prostate cancer. There is also little documentation about the use of dietary supplements with conventional treatment for prostate cancer. However, a recent study conducted by Boon et al reported that men with prostate cancer who use CAM are becoming more diverse. CAM use is no longer related to geographic location, education or income (Boon, et al, 2003). Individual characteristics such as support group attendance, disease characteristics, and personal beliefs about CAM correlated more with CAM use than sociodemographic characteristics noted in earlier studies (Boon, et al, 2003). These findings demonstrate that physicians need to ask all their patients about their use of CAM and to monitor patients who use CAM for potential interactions (positive and negative) with conventional treatment (Boon, et al, 2003).

2.1.5 USE OF CAM BY PATIENTS WITH COLORECTAL CANCER

Other than skin cancer, colorectal cancer is the third most common cancer found in men and women in this country. According to the American Cancer Society Surveillance Research there were 106,370 new cases of colon cancer and 40, 570 new cases of rectal cancer diagnosed in

2004 in the United States. Combined, they resulted in 56,730 deaths or 10% of the cancer-related deaths.

In a recent Canadian study, Tough found that a range from 42-46% of patients with colorectal cancer used dietary supplements (Tough, 2002). The results of this study differed significantly from other studies in cancer patients, since 68% of the patients with colorectal cancer had revealed the use of dietary supplements to their physicians. However, the basis for this is unclear since there were no other studies regarding the use of dietary supplements and colorectal cancer.

Since colorectal cancer is one of the leading cancers, it is important that the use of dietary supplements be evaluated to determine if there is need for concern. The treatment of colorectal cancer often involves the use of investigative agents in clinical trials, so it is important that the use of dietary supplements by patients undergoing treatment be further explored.

2.1.6 REASONS FOR CAM USE AMONG CANCER PATIENTS

The growth in use of complementary or alternative therapies may have exploded over the past decade fueled by the public's desire to participate in their own health care and a perception that the medical profession has failed to find a cure for cancer (Bailar, 1997). The reasons for this increase in use includes public interest in natural or holistic therapies, the creation of a marketplace for CAM products and practitioners, limited regulation of dietary supplements, the Internet, an expanding health consciousness in society and, disillusionment with the health care system (Burnstein, 2000).

The reasons that individuals with cancer give for using dietary supplements are to improve the quality of their lives, to regain a sense of control, to alleviate actual or perceived symptoms not controlled by traditional therapy, and to enhance their immune system (Pension, 2001).

Dietary supplements may also appeal to patients whose needs are unmet by conventional medicine. Dietary supplement users tend to perceive their conventional physicians as repositories of scientific information. They perceive their CAM practitioners as incorporating emotional and overall support to their therapeutic armamentarium (Penson, 2001). This disconnect between patient expectations of their physician and CAM practitioners may explain why as many as 72% of patients fail to disclose dietary supplements usage to their conventional physician (Penson, 2001). Physicians not asking about dietary supplement usage perpetuate this situation. A recent study compared self-reported CAM use with chart documentation of CAM use and found only 35% of dietary supplement use among older adults documented in their medical records (Burstein, 200). Sixty-four percent of these older adults reported the use of CAM (Burstein, 2000).

In 1998, Astin conducted a national survey in the general population to explore the predictors of alternative health care use. She proposed three theories to explain the increasing use of alternative medicine. First, dissatisfaction with conventional medicine, with the perception that some chronic diseases or conditions such as arthritis, anxiety, and insomnia are not treated successfully by conventional medicine. According to this theory, individuals often turn to alternative therapies to find relief. A second theory postulates that patients seek to gain control since patients with the diagnosis of a chronic or life-threatening disease such as cancer often feel a loss of control. According to this theory, alternative therapies help them to regain control. Finally, Astin conjectured that alternative medicine might be more consistent with a person's values or beliefs. The study involved a randomized sample of 1500 individuals in the general population, of which 1035 completed the questionnaire (Astin, 1998). Contrary to the hypotheses, attitudes toward or experiences with conventional medicine were not predictive of

alternative health care use (Astin, 1998). The results revealed that users of alternative medicine tend to be better educated and hold a philosophical holistic (body, mind and spirit) orientation toward health (Astin, 1998). Users were generally in poorer health then nonusers and symptom relief was the main reported benefit.

Other studies have discovered a variety of rationales for dietary supplement use among cancer patients. These reasons include: the desire for physical and decisional control, to enhance the chance of survival, a reaction to a bad experience with conventional therapy, a desire to take action to improve their health, to boost the immune system and to increase their quality of life. (Montbriand, 1995).

2.1.7 PHYSICIAN KNOWLEDGE OF PATIENT CAM USE

Studies have shown that there is a lack of knowledge among general practitioners and oncologists about CAM as well as its use among their patients (Bourgeault, 1996). A study conducted in a major oncology center in the United States revealed that physicians who were treating patients for prostate cancer estimated that only 4% of them used CAM (Devine, 2000). In actuality, 37% of the patients used CAM.

A large discrepancy between physicians' estimates of patient use of CAM and reported use of CAM by patients themselves has been reported (Penson, 2001). Oncologists may be surprised to discover the frequency of CAM usage among their patients because they generally do not ask direct questions about its use. These findings were demonstrated in a study conducted with patients receiving radiation therapy (Burnstein, 2000). Routine history and physical and questions regarding the use of medications indicated that 5% of the patients were involved with CAM. However, when a subsequent series of questions specifically regarding CAM usage were asked, the number of individuals reporting CAM usage increased to 40%(Burnstein, 2000). This

phenomenon has been found not only with cancer patients but also among individuals with arthritis, AIDS and other chronic diseases. The findings published by Richardson, Boon and Burnstein (2000), further document that a communication gap exists between patient practices and physician awareness of these behaviors.

Although oncologists are increasingly aware of CAM use among their patients, usage continues to be inadequately evaluated or discussed. A study conducted by Richardson (2000) at the M.D. Anderson Cancer Center involving 453 patients revealed that patient disclosure of use to physicians was low. This study was conducted in the 1990s and was the first to assess the prevalence of CAM usage at a comprehensive cancer center in the United States (Richardson, 2000). This trend continues as in many reported studies, the majority of the patients do not tell their physician about the use of dietary supplements (Adler, 1999). On written self-reports, only 30% of patients reported the use of dietary supplements compared to 60% during a structured interview. (Hensrud, 1999) This clearly demonstrates the need for structured questions.

In a survey of 831 patients, who saw a physician within the previous 12 months 63-73% did not fully disclose the use of CAM. The main reasons were, “It was not important for the physician to know”, or “The doctor never asked”, or “It was none of the doctor’s business.” (Eisenberg, 2001).

Physician barriers to effective communication are varied: lack of education, poor multidisciplinary communication, lack of support, stress/depression/anxiety, lack of satisfaction, emotional burnout and insufficient time (Fallowfield & Jenkins, 1999).

The doctor-patient communication may be the most significant component of the medical encounter, with ramifications for patient satisfaction, compliance, conflict resolution, and clinical outcomes (Toos, 1995). The medical system is moving towards improved physician-patient

communication. In a 1999 report by the Association of American Medical Colleges, communication has become a clinical skill in medical education (Puchalski, et al, 1999). In a large primary care study, patients seem to prefer a patient-centered approach (Little, et al, 2001).

2.1.8 WHY IT IS IMPORTANT TO KNOW IF PATIENTS ON CLINICAL TRIALS FOR THE TREATMENT OF CANCER ARE USING CAM

Dietary supplements are often perceived as harmless; however, dietary supplements are not held to the same research standards as drugs. Therefore, individuals using dietary supplements while enrolled in a clinical treatment trial for cancer may be at potential increased risk of adverse interactions with the novel agents. After extensive lobbying by the food industry, Congress passed legislation in 1994, the Dietary Supplement Health and Education Act (DSHEA) that permitted herbal medicine and food supplements to be sold over the counter without FDA review. Prior to the DSHEA, the Food and Drug Administration (FDA) regulated dietary supplements under the 1958 Food Additive Amendments to the Federal Food, Drug and Cosmetic Act. This lack of mandated testing for the safety and efficacy of substances prior to marketing contributed to the economic boom of this industry. This legislation had profound effect on public behavior, with sales more than doubling after the passage. Herbal medications are currently held to lower standards than prescription medications, since animal investigations, randomized clinical trials, and post-marketing surveillance are not required (Penson, 2001). DSHEA noted that claims regarding diagnosis, cure, prevention or treatment of a disease could not be made.

Since dietary supplements are considered food products, when a toxic reaction occurs, the burden of proof for lack of safety rest with the FDA and not the manufacturer. Manufacturers are free to make claims and do not have to establish doses or perform any scientific testing. The

FDA must be provided with convincing evidence of adverse effects before it will remove an herbal supplement from the market (Penson, 2001).

Although in most cases the risk seems to be small, reports indicated that within a 5-year period (1993-1998) approximately 2,600 adverse events and 100 deaths associated with dietary supplements were reported to the FDA (Penson, 2001). Another concern is about the long-term effects of dietary supplements. Since there is no central process for the reporting of adverse events with dietary supplements, the FDA has difficulty building a case against a dietary supplement. Dietary supplements often contain pharmacologically active substances with anti-inflammatory, vasodilatory, antimicrobial, anticonvulsant, sedative, and antipyretic properties (Penson, 2001). Therefore, there is a theoretical potential for adverse effects and drug-drug interactions (Penson, 2001). Herbalists use unpurified plant extracts and the lack of quality control makes these substances vulnerable to contamination, adulteration and misidentification. Besides spiritual approaches, vitamins, minerals, and herbs (dietary supplements) were found to be the most frequently used CAM therapies (Richardson, 2000). Ninety-six percent of the participants in this study who engaged in the use of vitamins and herbs reported no ill effects, however the potential for harmful drug-herb-vitamin interaction is considered to still exist and thus it is felt that there is a greater need for the physician to elicit this information from the patient (Richardson, 2000). Richardson (2000) also contended that herbs and vitamins can distort the effects of conventional treatment and the use of antioxidants may enhance standard chemotherapy or reduce the side effects, depending on the agent and the antioxidant combination. To date, since there is a lack of scientific evidence, the issue remains controversial.

However, the use of vitamins and herbs may be affecting the evaluation of not only standard anti-cancer therapies but also the clinical trials being conducted to evaluate investigative cancer treatments. Studies reveal that individuals are using vitamins and herbs while receiving chemotherapy, radiation and surgery for cancer. Yet, there has been little done to evaluate the use of vitamins and herbs in the cancer population, particularly those individuals involved in therapeutic clinical trials.

A concern with the usage of dietary supplements in conjunction with standard treatment is that of associated risks. There are theoretical reasons for thinking that dietary supplements might biochemically interfere with chemotherapy or radiation treatments, interfere with treatment compliance or cause side effects that may contribute to organ dysfunction (Burnstein, 2000). To date, there are few data on the safety of vitamin and herbal supplements, although there are randomized clinical trials (RCT) studies currently being conducted for some of the more widely used supplements, such as high dose vitamin E, ginkgo biloba, natural anti-oxidants and inosine.

According to Greenwald (1998), the frantic expansion of this market comes with some risks to consumers. These products are not regulated in the US in sharp contrast to countries like Germany, where the government holds companies to strict standards for ingredients and manufacturing (Greenwald, 1998). So there is no way of knowing what is inside a bottle of nutritional supplements. There may be contamination with heavy metals or unlabeled pharmaceutical agents (Greenwald, 1998).

Indirect toxicity is exemplified by drug-drug interactions. Perhaps the most common example involves the patient who is receiving chemotherapy or radiation and is taking herbs, high-dose vitamins or supplements before or during treatment (Eisenberg, 1997). These

substances may, hypothetically, inhibit or potentate the activity of conventional therapy (Eisenberg, 1997).

The reporting of adverse events associated with dietary supplements is voluntary; therefore, the actual number of adverse events is probably underestimated (Suchard, Suchard, Steinfeldt, 2004). It is predicted that incidences of side effects will increase as their consumption of dietary supplements continues to grow.

There is a need to better understand the use of dietary supplements by patients with cancer. In particular, 1.) there is little known about the specific therapies patients with cancer use, 2.) whether patients with cancer use dietary supplements in isolation or in combination with conventional therapies, and 3.) the side effects experienced by individuals using these therapies (Hilsden, 1999). This information would be the basis for developing clinical trials to evaluate the impact of dietary supplements used by patients with cancer.

2.1.9 PROFESSIONAL RESPONSIBILITY TO KNOW ABOUT CAM

According to Boon (2000), health care professionals are charged with providing patients with objective information regarding dietary supplements so that patients can make informed choices about their use. Patients often learn of dietary supplements from companies who make a profit by selling these products.

Richardson (2000) contended that the documentation of the use of dietary supplements should be a part of routine patient assessment for all cancer patients. He also noted that this information is necessary to educate patients regarding the potential vitamin-herb and treatment interaction. Therefore, open communication between the physician and patient may enhance the disclosure of this information.

Undisclosed use of alternative treatments can become problematic when physicians undertake expensive and extensive evaluations of a patient's condition only to discover that the condition is the result of vitamin or herbal use that the patient did not admit to taking (Dyer, 1996). "Toxic reactions have been reported from mega doses of vitamins and from herbal remedies"(Dyer, 1996). Safety issues are extremely complex and under-researched and undoubtedly risks do exist with dietary supplements. More importantly, absolute risks are almost irrelevant in view of whether a given dietary supplement does more good than harm; it is necessary to demonstrate risks against demonstrated benefits (Ernst, 2001). Since there is a lack of reliable data this is not achievable at this point in time.

The medical literature has reported the incidence of severe liver and kidney damage as the result of ingestion of some herbal remedies (Cassileth, 1996). Herbal remedies can cause toxic and allergic reactions; they have the potential to be mutagenic, carcinogenic, and teratogenic; they also can interact with medicines taken concomitantly (Ernst, 1999). Since these remedies are not subject to strict controls they may be contaminated with heavy metals, conventional drugs herbicides and pesticides (Ernst, 1999).

In the past 3 years, according to Eisenberg (1997), the lay press has reported a national trend of third party payers who provide alternative therapies as an expanded benefit. This trend poses a risk for the physician regarding how to responsibly advise patents that seek alternative treatments. The other extreme involves the risk of not asking the patient about alternative therapies known to be dangerous. When a patient with cancer uses dietary supplements, the physician has an obligation to provide evidence-based advice in a manner that shows respect for the patient's beliefs and choices. If a patient decides to take dietary supplements, close follow-up by the physician is essential, despite the physician's advice about the therapy.

In summary, patients with cancer are using dietary supplements and there is evidence that some may also take dietary supplements while being treated for their cancer. It is not known the extent to which individuals who are enrolled in clinical treatment trials for cancer are also using dietary supplements since patients may not routinely communicate the use of dietary supplements to their physicians. Some dietary supplements have the potential to interact with prescribed cancer treatments, so it seems important that the physician be aware of what the patient is taking.

In general, individuals take dietary supplements to feel better, stay healthy, prevent disease, treat disease, and increase energy. If they have cancer they may use dietary supplements to prevent metastasis, provide hope, prolong their life, prevent recurrence, and gain control. Other individuals with cancer may use dietary supplements because they are dissatisfied with conventional treatment, because they see the treatment as ineffective, producing side effects, or the medical care as impersonal, and too technical.

As cancer treatments have improved, cancer is becoming a chronic illness, particularly with certain types of cancer (e.g.: prostate, breast). Adjustment to cancer is not a single event but rather a series of ongoing coping responses to multiple crises of living with cancer. Alternative health care practices are a way in which cancer patients can be in control of their illness (Montbriand, 1995). The ingestion of a dietary supplement is associated with physical (taking) control, and decision-control (Montbriand, 1995).

2.1.10 THEORETICAL FRAMEWORK

The health belief model (HBM) was developed in the 1950s by a group of social psychologists in the U.S. Public Health Service, in an effort to explain the failure of people to participate in programs to prevent and detect disease (Hochbaum, 1958). Later, the model was extended to

apply to people's responses to symptoms (Kirscht, 1974) and to their behavior in response to diagnosed illness, particularly compliance with medical regimes (Becker, 1974). During the 1950s, academic psychology attempted to develop an approach of understanding behavior that grew out of two major learning theories, stimulus response and cognitive theory (Stretcher, 1997). Stimulus response theorists believe that behavior is the result of learning from events that reduce the physiological drives that activate the behavior. Cognitive theorists see behavior as a function of the subjective value of an outcome or an expectation; a certain action will achieve that outcome. The health belief model (HBM) is a value-expectancy theory that specifies the values and beliefs about health and their influence on choices. According to this theory an individual's beliefs are based on a "health belief model". The model assumes that individuals perceive that they are at risk because of their perceived susceptibility and severity (Jacobs, 2002). It also assumes that individuals perceive that a specific behavior may be beneficial because it results in a valued outcome. The HBM also assumes that individuals perceive that they are competent to overcome perceived barriers to take action. According to the assumptions of this model, persons engage in health promoting activities because they value health, define disease as a threat with serious avoidable consequences, and expect positive outcomes from activities (Stretcher, 1997).

The key concepts of the HBM are (Glanz, 1997):

1. Perceived susceptibility: one's feelings regarding their vulnerability to a disease or the risks of contracting it.
2. Perceived severity: one's feelings about the seriousness of the consequences or possible outcomes of the disease.

3. Perceived benefit: one's belief that a particular action will impact the threat of the disease in a positive manner.
4. Perceived barriers: factors that prevent taking action.
5. Cues to action: one's reminders to take action.
6. Self-efficacy: one's belief in his/her ability to take action.

Over the years, many investigations have helped to expand and clarify the HBM and to extend it beyond screening behaviors to include preventative actions to illness behaviors and to sick role behavior (Becker, 1974). In general, it is now felt that individuals will take action to ward off, to screen for, or to control illness if they regard themselves as susceptible to the illness. They may also take action if they believe that the illness may be serious, or if they believe that a course of action may be of value to decrease the severity of the illness. Action may also be taken if the anticipated barriers are not outweighed by the benefits (Stretcher, 1997).

As a model of decision-making under uncertainty, the health belief approach is a member of the value-expectancy family, in which the behavioral decisions are made to avoid the negatively valued outcomes (e.g., reduction of the threat) (Kirscht, 1994). In applying the HBM to illness behavior, there are four elements to consider in relation to decisions to act. The key elements include: 1.) health motivations aroused by the symptom experience; 2.) the threat posed by the symptoms, including physical harm and interference with functioning; 3.) the benefits, efficacy or value of an action to reduce the threat; 4.) the barriers or costs of the action (Kirscht, 1994). The HBM was developed to account for specific behaviors rather that health and illness behavior in general. There is no reason why it cannot, in principle, apply to choices or sequences of choices among an array of potential behaviors (Kirscht, 1994). In fact, according to Kirscht, 90% of decisions made to act on a complaint are "self-decisions" and are made based on beliefs

about symptoms (or the possibility of future conditions) and the perceived efficacy of action. Since the HBM deals with the likelihood of taking action, it should be able to account for the use of non-medically approved services as well (Kirscht, 1994).

The two key concepts of the HBM that seem to pertain to the use of dietary supplements are perceived benefits and lack of barriers (Adeniyi, 2000). Kaegi (1998) argues that there is a public misconception regarding the potential risks of dietary supplements. Thus, users of dietary supplements perceive both great benefits in terms of wellness, and few barriers, since they fail to acknowledge the side effects.

In contrast to conventional medicine, with its measured objectivity, CAM offers a constellation of expectations (Kaptchuk, 2002). The use of dietary supplements emphasizes personal responsibility, which often facilitates adherence. The act of switching to another medical system and exhibiting preference by action demonstrates an openness to actively participate and adhere. Paying out of pocket is another sign of commitment. In a survey conducted by Astin in 1998 to investigate possible predictors of alternative health care use, the perceived benefit of alternative therapies was the most frequent reason individuals used these therapies.

The diagnosis of cancer can be threatening because it is associated with fears of pain and death due to the disease and fears of painful, debilitating, or disfiguring treatment (Heidrich, 1994). Therefore, the diagnosis of cancer may be a potent motivation for engaging in adjustments related to self (Heidrich, 1994).

Cancer has a highly variable set of outcomes, depending on the time of detection, type of cancer, stage of cancer, and type of treatment (Beckham, 1997). Cancer has become more of a chronic illness due to the effectiveness of medical treatment. Self-efficacy is a cognitive variable

that has been shown to be relevant for adjustment in other patients with chronic conditions. It has been defined as an individual's "judgment of their capabilities to execute given levels of performance and to exercise control over events" (Beckham, 1997).

The diagnosis of cancer is a stressor of considerable magnitude. One particular source of stress is worry that the disease will not be cured, go into remission or that it recurs. Anecdotal evidence, clinical observation, and research studies indicate that some newly diagnosed women initiate behavioral or lifestyle changes in the period after diagnosis and initial treatments. Changes reported include information seeking, initiation of or increased use of stress management techniques, physical activity, and dietary changes.

3 METHODOLOGY

3.1 OVERVIEW

The literature indicates (Sparber, 2000, Eisenberg, 1998, Cassileth, 1999, Ernst, 1998, Boon, 2003, Dy, 2004) that an increasing number of individuals with cancer are taking dietary supplements. In addition, some of these individuals are enrolled in clinical trials for the treatment of their cancer. Given the potential for interactions to occur between the investigational agent(s) in a given trial and various dietary supplement(s) being taken, it is important that physicians be made aware of any dietary supplements that their patients may be using and that clinical trial protocols be designed in such a way so as to collect this information. To date, there has been little research done with cancer patients who are being treated on a clinical trial and their use of dietary supplements.

In response to this gap in knowledge, this study was designed as an exploratory, descriptive work to: 1.) document the use of dietary supplements by patients enrolled in breast, prostate or colorectal cancer clinical trials with investigative therapies; 2.) document the level of awareness of oncologists regarding their patients' use of dietary supplements while undergoing treatment on clinical trials; and, 3.) evaluate the extent to which clinical trials are designed to collect data regarding the patients' use of dietary supplements while enrolled in a clinical trial.

Data collection included: 1) interviews with a sample of patients enrolled in breast, prostate and colorectal cancer treatment clinical trials, 2) interviews with oncologists at the Hillman Cancer Center (HCC), an NCI designated comprehensive cancer center and 40 network

outpatient sites and, 3) a review of a sample of multi-institutional clinical trials for the treatment of cancer.

3.2 RECRUITMENT AND DATA COLLECTION PROCEDURES

3.2.1 PATIENTS

The process for selecting and recruiting the patient sample for this study involved contacting all the oncologists involved with the treatment of breast, prostate and colorectal cancer at the Hillman Cancer Center and the network sites. The researcher spoke with each of the oncologists regarding the study and asked permission to approach any eligible patients. The researcher explained to the oncologists that she was conducting a study to evaluate the use of dietary supplements in patients with the diagnosis of breast, prostate and colorectal cancer. All of the physicians were cooperative. After permission was obtained from the oncologists to recruit their patients to the study, the names of individuals with the diagnosis of breast, prostate or colorectal cancer were obtained from the HIPAA-approved cancer registry database. This database contains the names of individuals who have provided prospective signed consent to have their medical records reviewed and be approached for research studies. The medical records of 150 individuals with the diagnosis of breast, prostate and colorectal cancer were reviewed to determine if they were enrolled in a cancer treatment clinical trial. One hundred and thirty of the 150 individuals identified in the cancer registry database, were enrolled in a clinical trial for the treatment of breast, prostate or colorectal cancer. The oncologists and the clinical research coordinators who typically recruit patients to clinical trials, identified the individuals, among those eligible, who were unable to participate in the study, for example because they were too ill. Twenty-two of the 130 were ineligible. Eligible individuals were approached during their next

scheduled clinic appointment, the proposed study was explained and written informed consent was obtained. One hundred and eight individuals agreed to participate in the study. Patients who had agreed to participate in the survey were contacted by telephone by the researcher or the research assistant.

The research assistant was trained and provided a script developed by the researcher so that all participants were asked the questions in a consistent manner and that detailed information was obtained. The researcher monitored the research assistant's activities throughout the course of the study to ensure that the interviews were being administered properly. Participants were asked to have their dietary supplement bottles near them at the time of the telephone interview. This decreased the chance of confusion since the participant could read the name of the supplement and spell it if necessary during the interview. The average length of the telephone interview was thirty minutes. Participants were paid $25.00 for their time and effort.

3.2.2 PHYSICIANS

The physicians (oncologists) were recruited for this study at several monthly division meetings of the oncologists from the Hillman Cancer Center and its network sites. The researcher attended four departmental/division meetings to describe the proposed study and to solicit the participation of the oncologists. All the oncologists who participate in clinical trials (n=60) were asked to complete a short, self-administered survey consisting of six open- and closed-ended questions. They were asked about their perception of the use of dietary supplements by their patients who are currently enrolled in any kind of cancer treating trial, the vast majority of which are typically breast, prostate or colorectal cancer clinical trials, for the treatment of their cancer. They were asked to return the survey to a designated individual (not involved with the research) to maintain anonymity. Only surveys that were completed were included in the analysis.

Oncologists who did not attend the division meetings were contacted at subsequent meetings to solicit participation. Fifty-three (88.3%) of the oncologists with patients on active trials completed the survey.

The physicians recruited for this study were medical, radiation and surgical oncologists treating patients in urban and rural locations throughout Western Pennsylvania. The only selection criterion for the physicians was that they treated patients with the diagnosis of cancer. The oncologists were informed about the research, confidentiality and the fact that there were no foreseeable risks. The physicians were not paid for their participation in the study.

3.2.3 CLINICAL TREATMENT TRIALS

The initial goal was to evaluate the design of a sample of breast, prostate and colorectal cancer treatment trials conducted at cancer centers throughout the United States to determine if the trials specifically solicit information from participants on the use of dietary supplements. It is known that most clinical trials solicit information on concomitant medications but participants often do not include the use of dietary supplements. Case report forms (forms that are used to record patient-specific study related data) for the trials were also reviewed to determine if information on the use of dietary supplements was requested.

The 75 cancer centers that were to be surveyed were all members of the Association of American Cancer Institutes (AACI). The AACI membership list was obtained which included the names of key contacts at each center, as well as contact information. An electronic letter explaining the purpose of the research was sent to the contact person at each of the cancer centers requesting their participation. Each center that agreed to participate was asked to send copies of a total of 6 physician-initiated, clinical trials and their case report forms i.e. (2 breast, 2 prostate, 2 colorectal) to the researcher. This information was to be sent either as a hardcopy by

prepaid mail or electronically by disk or email. However, with the recent implementation of the HIPAA (Health Information Protection and Portability Act) guidelines, the majority of the centers expressed an interest to participate, but their institutions would not permit them to do so. The original intent of the HIPAA regulations was the protection of patient specific information. However, with the implementation of HIPAA there has been a heightened awareness regarding the release of any information. The institutions had concern over the sharing of information that was considered proprietary. After consultation with the dissertation committee chair, it was decided that the clinical trial protocol data would be collected from multi-institutional clinical trials that were on-going at the Hillman Cancer Center at the time of data collection since these trials generally have a number of institutions participating throughout the United States, many of whom are members of the AACI. In addition, these trials are generally sponsored by pharmaceutical companies, and the findings may have a larger impact from a public health perspective than if investigator-initiated studies were reviewed.

The researcher reviewed clinical trials that were open for accrual during a two-year period between the years of 2002 and 2004. A list of clinical trials that qualified was obtained from the Clinical Trials Management Application (CTMA) at the University of Pittsburgh Medical Center/University of Pittsburgh Cancer Institute. Initially, one hundred and five clinical trials were provided to the researcher for review. Seventy of the 105 trials qualified as a clinical trial for the treatment of breast, colorectal and prostate cancer; forty-three breast, fifteen colorectal and twelve prostate. The researcher reviewed each clinical trial and the accompanying case report forms (data collection forms) using a checklist that she had developed (see Instrumentation section).

3.3 PROTECTION OF HUMAN SUBJECTS

A copy of the research protocol for this study was submitted to the University of Pittsburgh Institutional Review Board (IRB) for Human Subject Research. This IRB serves as the IRB of record for the Hillman Cancer Center and the 40 network sites. The Principal Investigator outlined the purpose of the study and assurances of confidentiality to the participants. There were no known risks to the study. Data was coded to ensure confidentiality. The study was also prepared in accordance with the HIPAA regulations. The study was also reviewed and approved by the Hillman Cancer Center's HIPAA privacy officer and was in compliance with the current HIPAA regulations. See Appendix A.

3.4 INSTRUMENTATION

3.4.1 PATIENT SURVEY

The patient survey was designed to evaluate the participant's use of dietary supplements, the particular dietary supplements being consumed, the reasons individuals were using the dietary supplements and, if the use of the dietary supplement(s) had been communicated to the treating oncologist. The survey instrument consisted of 28 open and closed-ended questions. The general design of the survey instrument was informed by the Health Belief Model (HBM). Survey questions were developed to solicit information regarding the HBM constructs of perceived benefits, perceived barriers and self-efficacy. Research has shown that individuals with the diagnosis of cancer often feel the loss of control and due to the potential threat to their life, will often engage in alterations of their lifestyle that they perceive to be beneficial. The perceived benefits of using dietary supplements include avoidance of pharmacological toxicities,

a sense of personal control and self-efficacy regarding decision-making. The perceived barriers include potential toxicities and doubts about the safety and efficacy of dietary supplements.

The telephone survey instrument was developed for this study and was pilot-tested with twenty-five patients with the diagnosis of cancer who were being treated in a clinical trial for breast, colorectal or prostate cancer to determine if the questions were clearly understood. No changes were made to the instrument as a result of the pilot-testing. The reliability and validity of this instrument had not been previously established. The concerns regarding instrument bias are addressed in Chapter 5. See Appendix C for a copy of the instrument.

3.4.2 PHYSICIAN SURVEY

The physician survey, developed for this study, consisted of items that solicited information regarding the physician's (oncologist) perception of their patients' use of dietary supplements and the patients' communication of this information to them. In addition, demographic information regarding age and location of practice-- academic versus network was also collected. The reliability and validity of this instrument had not been previously established. The concerns regarding instrument bias are addressed in Chapter 5. See Appendix D.

3.4.3 CLINICAL TRIAL DESIGN CHECKLIST

The researcher developed a short checklist so that each clinical trial was reviewed in a consistent manner. The checklist included specific information about the trial including the phase of the trial, the type of cancer being treated and the sponsor of the trial, as well as items that addressed the design of the case report forms. The researcher reviewed each clinical trial and the accompanying case report forms to determine if the words "dietary supplement" was mentioned and if this information was to be collected. . See Appendix E.

3.5 STATISTICAL ANALYSIS

Given that this study was a descriptive, exploratory analysis of whether information regarding patient use of dietary supplements is systematically being reported to oncologists and recorded on clinical trial case report forms used for data collection, the statistical analyses consisted primarily of descriptive statistics, including frequencies, ranges, and averages to describe patient and physician characteristics, patient use of dietary supplements, communication of use, physician perception of use as well as to describe the findings of the review of the clinical trials and case report forms. When proportions were used as summary measures, 95% confidence intervals for estimates were obtained using the Clopper-Pearson approach.

The data from the open-ended questions addressing the reasons patients use dietary supplements, their perception of the effectiveness of the supplements, communication patterns with their physicians, and the role they play in maintaining their health were read and analyzed by organizing responses into categories in order to facilitate interpretation of patterns emerging from the raw data. Three researchers read the raw data independently and emergent themes and differences were discussed until a consensus was reached.

Pearson chi-square tests with Yate's continuity correction were used to explore potential differences in the use of dietary supplements between males and females patients. A one-sided binomial test was used to determine if patients inform their oncologists of their use of dietary supplements, to determine if oncologists ask specific questions regarding patient use of dietary supplements and, to determine if oncologists felt that patients openly communicated their use of dietary supplements to them. Patient data was coded and entered into SAS format. The code sheets are located in Appendix G. The analyses were done using S-Plus 6.1, StatXact 4.0.1 and NCSS 97.

4 RESULTS

4.1 PATIENT RESPONSE RATE

A total of 108 patients were recruited into the study. Eight of the patients did not want to participate when contacted by telephone for the interview. They were too ill and asked not to be called back. One individual did not complete the telephone interview and five subsequent attempts to contact her were unsuccessful, including messages being left at the home. The total accrual to the study was 99 patients.

4.1.1 PATIENT DEMOGRAPHIC CHARACTERISTICS

The characteristics of the patients who participated in the study are described in Table 1. The majority of the patients were Caucasian (91%), female (79%), older-- between 51-60 years of age (32%) and better educated-- with 61% having some education beyond high school. Forty-eight percent (48%) of the patients had incomes greater than $41,000 and 26% earned more than $61,000 annually. Sixteen patients chose not to respond to this question. Ninety-six percent of patient participants had some health insurance.

4.1.2 DIAGNOSIS, STAGE OF CANCER AND PHASE OF CLINICAL TRIAL

Table 2 describes the diagnosis of the patients, stage of disease and phase of clinical trial to which they were recruited. Seventy-seven percent (77%) of the patients had a diagnosis of breast cancer, 16% prostate cancer and 7% colorectal cancer. Patients were staged as follows: 14% Stage I, 36% Stage II, 17% Stage III and 27% had advanced disease, Stage IV. Five percent (5%) of the patients had cancers that had not been staged—such as hormone refractory

prostate cancers and metastatic disease. The majority of the participants were enrolled in a Phase II or III clinical treatment trials 51% and 44% respectively.

Table 1: Patient Demographics (n = 99)

Trait	Percent
Age in Years	
21-30	1%
31-40	7%
41-50	21%
51-60	32%
61-70	25%
71-80	12%
No Response	1%
Sex	
Female	79%
Male	21%
Race	
Caucasian	91%
African American	5%
Hispanic	1%
No Response	3%
Educational Level	
8-11 years	2%
High school graduate or GED	26%
Some college or vocational/technical training	24%
College graduate	17%
Graduate/ Professional education	19%
No response	11%

Table 1 (cont'd)

Average Yearly Income	
Less than $20,000	18%
$21,000 - $40,000	18%
$41,000 - $60,000	22%
Over $61,000	26%
No response	16%
Health Insurance	
Yes	96%
No response	4%

Table 2: Patient Diagnosis, Stage of Cancer and Phase of Clinical Trial

Trait	Percent
Diagnosis	
Breast	77%
Prostate	16%
Colorectal	7%
Stage of Cancer	
Stage 1	14%
Stage 2	36%
Stage 3	17%
Stage 4	27%
Unstaged	5%
Phase of Clinical	
Pilot	1%
Phase I	1%
Phase II	51%
Phase II/III	2%
Phase III	44%
Phase IV	1%

4.1.3 USE OF DIETARY SUPPLEMENTS

The participants were asked about their use of dietary supplements. Dietary supplements included vitamins, minerals and/or herbs, as well as any other natural remedies such as teas, potions or tinctures. A potion is a mixture of liquid vitamins; minerals or herbs prepared for a specific condition or symptom. Eighty-four of the patients surveyed had taken a dietary supplement at some time in their life and 71 participants were currently doing so. Of those currently taking a dietary supplement. Fifty-seven patients were taking the dietary supplements prior to the diagnosis of cancer, while the remainder started using dietary supplements following the diagnosis of cancer. The overall estimated proportion of patients using supplements was 72% with a 95% CI of (62%, 80%). The estimates and their confidence intervals of using supplements for patients with each type of disease are shown in Table 3.

Eight of the 15 patients who had never taken dietary supplements stated that they would consider taking dietary supplements in the future.

Table 3: Estimates and 95% CIs of Patients using Dietary Supplements by Cancer Diagnosis

Diagnosis	# of Patients	#of Patients using Supplements	Percentage (95% CI)
Breast	76	55	72% (0.61,0.82)
Prostate	16	12	75% (0.48,0.93)
Colorectal	7	4	57% (0.18,0.90)
Total	99	71	72% (0.62,0.80)

In addition, the use of dietary supplements by male and female participants was explored. Table 4 shows the distribution of dietary supplement use by gender. Fifteen of 21 men (71%) and 56 of 78 women (72%) use supplements. There was no difference associated with the use of dietary supplements by gender ($p=0.81$).

Table 4: Estimates and 95% CIs of Male and Female Users of Dietary Supplements

Sex	N	# of Patients using Supplements	Percentage (95% CI)
Female	78	56	72% (0.60,0.81)
Male	21	15	71% (0.48,0.89)
Total	99	71	72% (0.62,0.80)

4.1.4 TYPE OF DIETARY SUPPLEMENTS USED

Patients were asked what dietary supplements they were taking and the frequency with which they took them. They were also asked to have the bottles nearby at the time of the telephone interview so that they could spell the names if there was any confusion. This would also help with recall.

Table 5 lists the dietary supplements that patients were taking at the time of data collection. Some of the patients were taking multiple supplements. Forty-four percent (n=25) of the fifty-seven patients who took dietary supplements prior to the diagnosis of cancer, added new supplements to their regimen following their diagnosis. Patients were taking a variety of brands of multivitamins so it was often difficult to determine if the particular brand was high dose.

Table 5: Dietary Supplements Taken by Participants

Dietary Supplement	# Participants
Vitamins	
*Multi-vitamin	54
*Vitamin E	13
Vitamin C	9
High dose multi-vitamin	5
Vitamin B	
B Complex	3
*Vitamin B-6	1
Vitamin B-12	1
Folic acid	2

Table 5 (continued)

Lycopene	24
Coenzyme 10	7
Minerals	
*Calcium	53
*Selenium	48
Herbs	
Bilberry	1
*Echinacea	6
Elevthero	1
Evening primrose	2
Feverfew	1
Garlic	4
Ginger	1
*Gingko Baloba	4
Ginseng	3
*Glucosamine	1
*Goldenseal	4
*Kavakava	1
Red Clover	1
Saw Palmetto	1
St. John's Wort	1
Miscellaneous	
*Aloe vera	2
*Fish Oil	1
Flax Seed Oil	1
*Noni juice	2
Soy Isoflavones	1

* Indicates supplements added following the diagnosis of cancer

Table 6 describes the length of time that participants who were taking dietary supplements prior to the diagnosis of cancer had been doing so. The majority of these patients were taking supplements for less than twenty years.

Table 6: Length of Time Dietary Supplements were Used

Time	Percent
Less than 1 year	10%
1-5 years	26%
6-10 years	21%
11-15 years	5%
16-20 years	3%
Over 20 years	32%
Missing Data	3%
Total	100%

4.1.5 RE ASONS FOR TAKING DIETARY SUPPLEMENTS

The patients were asked to explain why they were taking dietary supplements. Table 7 summarizes the reasons that patients gave. Some of the patients responded with more than one answer.

Sixty-two percent of the patients took dietary supplements for general health reasons. Some of these same patients mentioned that by taking dietary supplements, they felt this provided them with a sense of having some "control" over what was happening to them. Nineteen percent of the patients took dietary supplements for specific health related problems on symptoms. Only nine percent of the patients specifically mentioned taking the dietary supplements because they had cancer.

In addition, the patients were asked if they were aware of any positive or negative effects from dietary supplements. Thirty-five percent thought that there could be negative things about taking dietary supplements, 63% did not feel that there was anything negative and the one participant was unsure. When patients were asked if they had heard about individuals who had experienced negative or positive effects from dietary supplements, 38% responded they were

aware of individuals who had effects from dietary supplements. But only two of these individuals had heard of negative effects. The patients' perception of positive effects from dietary supplements were all related to positive health outcomes.

Table 7: Reasons for Taking Dietary Supplements

Response	Percent
General	
Health	27%
Supplement diet	13%
For energy	5%
Normal routine	5%
To feel better	2%
For good nutrition	1%
Build immune system	10%
Specific health problems	
To prevent bone loss	7%
For hot flashes	5%
To help with arthritis	2%
Relief of symptoms	1%
For neuropathy	1%
To preserve eye health	1%
For hair loss	1%
For finger nails	1%
Cancer related	
To help with cancer	6%
For breast cancer	3%
Someone else told them	
Doctor's recommendation	7%
Because of friend	1%
Unsure	1%
Total	100%

Fourteen percent (14%) of the patients personally experienced side effects while taking dietary supplements. The side effects experienced were gastrointestinal, breast engorgement and hair growth from taking saw palmetto, red rash and itching, burning sensation and flushing from taking niacin. Eighty-two percent (82%) of the patients reported not experiencing any side effects. Three did not respond.

4.1.6 INFORMATION –SEEKING REGARDING DIETARY SUPPLEMENTS

Patients were asked if they did any research on the dietary supplements they were taking prior to using them. If they responded positively, they were also asked what type of research or the source of their information. Twenty-seven of the seventy-one patients taking dietary supplements (38%) obtained information on the specific dietary supplement prior to their use. Table 8 summarizes the sources of information utilized by participants.

4.1.7 FACTORS INFLUENCING CHOICE OF DIETARY SUPPLEMENTS

Patients were asked what influenced their decision to purchase a particular brand or type of dietary supplement. Several of the patients provided multiple answers to this question. Most of the patients stated that they do not take the same brand of a supplement consistently. Price, advertisements and the potential benefits of the supplements influence the majority of the patients' decisions regarding the specific supplements they purchased. Table 9 describes the factors that had influenced the patients' choices.

In addition, the patients were asked how much they spent on dietary supplements. Sixty-eight percent (n=47) of the patients spent less than $20.00 a month, 28% (n=19) spent between $20.00 and $50.00 a month, 3 spent over $50.00 a month and 3 patients were unsure of how much they spent monthly. Approximately 6% of participants had an insurance plan which covered the cost of their dietary supplements.

Table 8: Source of Information Regarding Dietary Supplements

Trait	Percent
Magazines	
Health magazines/newsletter	7%
Prevention magazine	11%
Reader's Digest	4%
GNC magazine	7%
Women's magazines	3%
Books	
Holistic Health counselor	4%
Dietary books	4%
"Let's Eat Right & Well"	4%
Dr Andrew Weil, MD	4%
Books on cancer and nutrition	4%
Internet	26%
Friends	15%
Television	7%
Total	100%

Table 9: Factors Influencing Choice of Supplements

Response	Percent
Price	19%
Advertisement	18%
Supplement benefits	16%
Friends/family	13%
Physician’s advice	11%
Product loyalty	7%
Ingredients	5%
Own research	5%
Convenience	3%
Nothing in particular	2%
Product quality	1%
Product sales person	1%
Total	100%

4.1.8 PATIENTS' PERCEPTIONS REGARDING EFFECTIVENESS OF DIETARY SUPPLEMENTS

Participants were asked if they thought the dietary supplements were effective or doing what they had hoped that they would do. The fifty-seven patients who were taking the dietary supplements prior to the diagnosis of cancer responded as follows to this question: 54% felt that they were effective, 35% were not sure if the supplements were effective, 7% were indifferent and 4% felt that the dietary supplements had been ineffective. Nevertheless, all fifty-seven continued to take the dietary supplements and had no desire to stop. The 14 individuals who had started to take the dietary supplements following the diagnosis of cancer did not feel that they had been taking the dietary supplements long enough to evaluate their effectiveness.

4.1.9 COMMUNICATIONS WITH ONCOLOGISTS REGARDING USE OF DIETARY SUPPLEMENTS

Patients were asked if they communicated their use of dietary supplements to their oncologist. Of the 71 patients currently taking supplements, 87% (87% with 95% CI, 62%, 86%) said they had informed their oncologists of such use. A one-sided binomial test was used to see if this proportion exceeds 50%. We found that the proportion of the patients informing their oncologists of the use of dietary supplements was significantly greater than 50% ($p<0.0001$).

In addition, the patients were asked how they communicated the use of dietary supplements to their oncologists. Twenty-two percent of those who had informed their oncologist responded that they communicated this information via information collected on a form that they were asked to fill out and therefore they assumed that their oncologist was aware of their use of dietary supplements. However, there was no verbal communication between the patient and the oncologist. According to patients, only 5 of their oncologists specifically asked them if they took dietary supplements. The majority of the patients, 66%, (n=41) responded that they

volunteered the information regarding their use of dietary supplements to their oncologist, hoping to receive a response but most were told by their oncologists to continue to take the dietary supplements, 3 oncologists suggested additional supplements and 2 patients were told to discontinue the dietary supplements. Seventeen percent (n=7) of the patients received no response from their oncologist when they brought up the use of dietary supplements.

4.1.10 DISCONTINUING THE USE OF DIETARY SUPPLEMENTS

Patients were asked if they would discontinue the use of a dietary supplement if their oncologist recommended that they do so. 83% (n=59) of the patients taking a supplement initially stated that they would discontinue the use if their oncologist recommended it. However, during the course of the conversation with the interviewer, 31% (n=22) stated that they would only stop using the dietary supplements after an intense discussion with their oncologist and that he/she would have to provide convincing facts/reasons for discontinuing the dietary supplements. Twenty percent (n=14) of the patients felt that their oncologists were knowledgeable regarding the dietary supplements that they were taking and they would follow their oncologist's recommendations. Twenty-three percent (n=16) of the patients said they have "faith and trust in their oncologist" and "would do whatever he/she asked them to do". Sixteen percent (n=11) of the patients would not discontinue the use of dietary supplements despite recommendation from their oncologist.

4.1.11 THE PATIENTS' ROLE IN THEIR HEALTH CARE

Patients were asked three open-ended questions regarding their health; the first question asked who the patient thought was responsible for his/her health. The responses are summarized in Table 10. Three-fourths of participants (n=75) responded that they were responsible for their own health. Eight percent felt that their physician shared the responsibility for their health.

Table 10: Participants Response Regarding Who is Responsible for Their Health

Response	Percent
Patient	76%
Physician and patient	8%
Patient and God	3%
Beyond anyone control	3%
Physician	2%
No response	2%
Environment	1%
Physician, God and myself	1%
Patient and spouse	1%
Patient and environment	1%
Patient, environment and physician	1%
Patient and genetics	1%
Total	100%

The second question asked the patients to describe the role they played in their health care. Table 11 describes the various roles that patients felt they played in their health care. Patients often provided multiple answers to this question. The majority of the patients felt that they played an active role in their health and did so by exercising, eating a balanced diet and participating in regular health screenings. Actively participating in treatment decisions was viewed by a number of the patients as another significant role.

Finally, patients were asked what role, if any, they felt they played in getting well. Some of the patients provided multiple answers. Almost all (n=97) of the patients felt that they played a role in their recovery. Approximately half (n=53) of the participants felt this happened by maintaining a positive attitude. Forty-five percent expressed that they had made changes in their lifestyle, in particular, dietary changes such as eating a healthier diet, getting regular exercise, and getting adequate rest. Twenty-seven percent felt that compliance with their treatment regimen and their physician's recommendations was something within their control and they

hoped it would have a positive influence on their health. Prayer, seeking additional information related to their cancer and treatment, and accepting family support were other mechanisms that participants identified, albeit less frequently, as factors that played a role in their recovery.

Table 11: Patients' Role in Their Health

Response	Percent
Maintains a healthy life style	42%
Actively participates in treatment decisions	23%
Assumes responsibility for health	21%
Complies with medical regimen	14%
Maintains a positive attitude	12%
Maintains strong faith	12%
Does not follow a positive lifestyle	1%
Neglectful in the past	1%
Total	126%

*Numbers are greater than 100% because individuals were able to choose more than one answer.

4.1.12 THE PATIENT-ONCOLOGIST RELATIONSHIP

Patients were asked two open-ended questions about their relationship with their oncologist. First, patients were asked to describe the relationship they had with their oncologist. The vast majority of patients (96%) expressed having a good relationship with their oncologist. Two patients responded that the relationship was not good and two others did not know. Second, patients were asked to describe the things that they felt contributed to the positive or negative relationship. The patients' responses are listed in Table 12.

The two participants who did not feel that they had a good relationship with their oncologist said that it was due to a lack of communication. The physicians never returned their calls personally. The majority of the participants described the communication with their oncologist (medical, surgical, radiation) as being good because the oncologist took time to answer their

questions, made sure they provided explanations that the individual understood and often used analogies or examples to simplify explanations. Most of the participants relayed stories that provided examples of the communication pattern between themselves and their physician. It was important to the participants that their oncologist listen to them and this was validated by the oncologist's responses to their questions, remembering things that were of importance to the participant and observing and explaining non-verbal cues. Also spending time with the participant also contributed to a positive relationship. However, time was measured not in minutes but by the quality of the time spent. Repeatedly, the participants commented on the oncologist's honesty, compassion and openness as being important.

Table 12: Factors Influencing the Patient-Oncologist Relationship

Response	Percent
Ability to communicate	42%
Caring attitude	26%
Honesty	16%
Positive outlook	8%
Medical knowledge	4%
Patient calls not returned	2%
Unsure	2%
Total	100%

4.1.13 PATIENTS' PERCEPTIONS OF THE CAUSE OF THEIR CANCER

Patients were asked what they felt contributed to the development of their cancer. This question was of interest since the perception of what contributes to the development of cancer may influence how one responds or copes with the diagnosis. Some participants responded to this question with multiple answers. Table 13 summarizes the responses.

Table 13: Patients' Perceptions Regarding the Development of their Cancer

Response	Percent
Family History of Cancer	37%
Unknown	29%
Hormone Replacement	17%
Stress	14%
Environment	11%
Lifestyle	11%
Neglected Health	3%
Trauma	1%
Physical Abuse	1%
Total	124%

*Numbers are greater than 100% because individuals were able to choose more than one answer.

Thirty-seven percent (37%) of the patients identified family history as a reason they developed cancer. The second most frequent response was that the patient didn't know what caused their cancer (29%). Hormone replacement therapy (17%) and stress (14%) were the next most frequent responses. Some of the participants also discussed the environment as contributing to the development of their cancer. They referred to the intake of meat from animals that were fed antibiotics, neighborhoods close to power plants, steel mills, workplaces where they were exposed to chemicals and food additives. The reference made to lifestyle included smoking, lack of exercise, being overweight and poor dietary habits. There were a few less frequently identified factors.

4.2 PHYSICIAN SURVEY

4.2.1 PHYSICIAN RESPONSE RATE

A total of 60 oncologists were recruited to this study. Fifty-three questionnaires were returned, 52 were completed and 1 was missing the demographic data. Seven of the oncologists did not respond. The data from the 1 questionnaire with the missing demographic data was also included in the analysis.

4.2.2 DEMOGRAPHIC PROFILE OF PHYSICIANS

Table 14 describes the characteristics of the oncologists who participated in the study. Over 73% (n=39) of the physicians were between the ages of 41-60 years. Four participants refused to respond to this question.

Table 14: Characteristics of Physicians

Trait	Percent
Age in Years	
31-40	10%
41-50	36%
51-60	38%
Over 60	8%
Missing	8%
Practice Site	
Hillman Cancer Center	34%
Office	15%
UPMC Cancer Center (free standing site)	34%
UPMC Hospital	9%
Other	2%
Combination	4%
Missing	2%

Fifty-two physicians responded to the question regarding the type of setting within which they practiced. See table above.

4.2.3 PHYSICIAN PERCEPTION, DISCLOSURE AND SUPPLEMENT RECOMMENDATIONS

The physician participants were asked a series of six questions regarding the use of dietary supplements by their patients who were being treated on a clinical trial for cancer. The first two questions were closed-ended questions. The first question asked the physician what percentage of their patients who were being treated on a clinical trial for cancer took dietary supplements. Dietary supplements included vitamins, minerals and herbs. Table 15 describes the physician responses. The responses indicated that the majority of physicians felt that their patients were using dietary supplements while enrolled on a clinical trial for the treatment of their cancer. However, 64% of the physicians felt that this practice involved 50% or less of their patients who were enrolled in a clinical trial for treatment.

Second, physicians were asked if they made a point of asking their patients if they used dietary supplements. Forty (75% with 95% CI, 62%, 86%) of the 53 physicians responded that they ask their patients about the use of dietary supplements.

Table 15: Physician's Perceptions of Patient Use of Dietary Supplements while on a Clinical Trial

Response	Frequency	Percent
Less than 25%	16	30%
25-50%	18	34%
51-75%	14	26%
Over 75%	5	10%
Total	53	100

Table 16 describes the types of physicians' responses to patients who communicate regarding the use of dietary supplements. Twenty-eight percent (n=15) of the physicians stated that they personally review the supplements that their patients are taking to be certain that they are safe and will not interfere treatment. This review was accomplished by the physician asking the patients to bring in the supplements so that they can review the ingredients or by reviewing the list provided by the patients. Seventeen percent of the physicians stated that they tell their patients to continue to use the supplements, while another fifteen percent discourage the use of high doses, mega-doses, or excessive use. Eight percent of the physicians inform their patients that there is little available on the interactions of dietary supplements with treatment, but there is no mention of their discouraging the use of the dietary supplements. Although 11% of physicians do recommend that their patients discontinue the use of dietary supplements, most discouraged the use only while the patient was enrolled in a clinical trial or receiving radiation or chemotherapy. The patients were told that they could resume the use of dietary supplements once treatment had been discontinued. The other responses included 6% of physicians who do not respond at all to their patients' use of dietary supplements, 6% who tell them it is not worth the money, 4% who responded as non-applicable, 4% who tell them to continue use unless they develop side effects and 2% who discusses the usage with his/her patients.

Table 16: Physician's Responses

Response	Frequency	Percent
Personally review the supplements to determine safety.	15	28%
Continue to use.	9	17%
Avoid high doses.	8	15%
Discourage Use.	6	11%

Table 16 (continued)

Do not know if the supplements may interact with treatment.	4	7%
Say nothing to patient.	3	6%
Not worth the money.	3	6%
No Response to survey.	2	4%
Continue to use unless side effects occur	2	4%
Open discussion with patient.	1	2%
Total	53	100%

Table 17: Where Patients are Referred by their Oncologists

Type of Referral	Frequency
Center for Complementary Medicine	1
Dietician/ Nutritionist	1
Dr. Judy Balk (herbal phytoestrogens)	1
Maria Yarmus	1
UPMC	1
Dr. Dan Wagner	1
Total	6

The third item in the physician questionnaire was a combination of open and closed questions regarding whether the physicians refer patients who use dietary supplements and, if so, to whom. Eighty-nine percent (n=47) of the physicians do not refer their patients who are taking dietary supplements to anyone. Eleven percent (n=6) of the physicians refer their patients to the other resources listed in Table 17 above.

4.2.4 PHYSICIAN'S PERCEPTION REGARDING THE COMMUNICATION OF DIETARY SUPPLEMENTUSE

The final questions asked the oncologists if they felt that their patients were communicating the usage of dietary supplements to them. Thirty-two of the 53 oncologists (60% with 95% CI, 46%,

74%) believe that their patients openly communicate their usage of dietary supplements to them. There was significant evidence to show that more then 50% of oncologists believe that their patients openly communicate their usage of supplements to them.

4.3 CLINICAL TRIALS

4.3.1 CLINICAL TRIAL REVIEW RATE

One hundred and five trials were available for review by the researcher, of which seventy qualified as a clinical trial for the treatment of breast, colorectal and prostate cancer-- forty-three breast, fifteen colorectal and twelve prostate. The researcher reviewed each clinical trial and the accompanying case report forms (data collection forms) using a checklist that she had developed.

4.3.2 PROFILE OF THE CLINICAL TRIALS

A clinical trial is one of the final stages of a long and careful cancer research process. Studies are done with cancer patients to find out whether promising approaches to cancer treatment are effective. The clinical trials are detailed descriptions of study conduct. The clinical trials are divided into sections. Each clinical trial also has accompanying case report forms (CRFs) which are used to record the patient specific data. Table 18 summarizes the detail of the clinical trails that were reviewed, including the type of trial, the phase and the sponsor.

Nine percent (n=6) of the studies reviewed were pilot and phase I. Phase I studies are the first step in testing a new approach in humans. These studies evaluate how a new drug should be administered and the frequency with which it should be given. These studies generally divide patients into smaller groups (cohorts) so that each cohort is treated at an increased dose of the new drug/therapy. The highest dose with an acceptable level of side effects is determined so that further testing can be done.

Table 18: Description of Clinical Trials

Trait	Frequency	Percent
Disease Site		
Breast	43	62%
Colorectal	15	21%
Prostate	12	17%
Phase		
Pilot	3	4%
I	3	4%
I/II	5	7%
II	32	47%
III	26	37%
IV	1	1%
Sponsor		
Pharmaceutical	33	47%
Cooperative Group	32	46%
Physician-Initiated Pharmaceutical	5	7%

Seven percent (n=5) were Phase I/II studies. These studies are generally a combination of Phase I and II and may actually have two components-- an initial Phase I study and then if that appears to be favorable, it moves into a Phase II study.

The majority of the studies, 47% (n=32) reviewed were Phase II studies. Phase II studies study the safety and effectiveness of a new agent and how it affects the body. These studies usually focus on a particular type of cancer.

Thirty seven percent (n=26) were Phase III studies. Phase III studies test a new drug, or a combination of drugs in comparison to the current standard treatment. Individuals are generally randomized to either the standard or the new drug group to avoid bias. Bias consists of human

choices, beliefs or any other factors besides those being studied that can affect a clinical trial's results.

There was one study classified as a Phase IV study. Phase IV studies are conducted to further evaluate the long-term safety and effectiveness of a treatment. Most often these studies occur after the agent has been approved for standard use.

The clinical trials that were reviewed were sponsored by pharmaceutical companies, were physician-initiated or cooperative group-sponsored. All of these trials were open for accrual at other cancer centers throughout the United States.

Table 19 summarizes the findings of the review of the clinical trials. Each study was reviewed in detail to determine if the use of dietary supplements was addressed in any of the multiple sections of the study text. In general, the use of dietary supplements was rarely addressed in any section of the clinical trial.

4.3.3 PRE-ELIGIBILITY

The pre-eligibility section of 2 studies out of 70 identified a list of prescribed drugs that were included as an appendix to the study. In the appendices of both studies there was a list which included a number of dietary supplements, which would make the individual ineligible for study entry if they were currently being taken.

4.3.4 ELIGIBILITY

The eligibility section of one breast study did not permit the use of hormonal agents. However, there was no listing of what was considered a hormonal agent. There are some dietary supplements that mimic hormonal agents in activity.

4.3.5 INELIGIBILITY

The ineligibility section of five studies addressed certain prescribed drugs, which would make the individual ineligible for study entry. Two of the five studies addressed specific dietary supplements, Vitamin E (breast study), and PC-SPES (prostate study). The other three studies addressed only the use of prescribed drugs.

4.3.6 STUDY TEXT

One study addressed the use of dietary supplements within the text of the protocol. However, the use of dietary supplements was not mentioned throughout any of the other sections of the study. Therefore, in this particular study there is the potential that a patient could actually be enrolled on the trial before this information was noted unless careful attention was paid to the content (text) of the study.

4.3.7 CONCOMITANT MEDICATIONS

In 27% (n=19) of studies the concomitant medication section addressed the use of other medications. However, in 14% (n=10) of the studies prescribed medications were to be recorded but there was no mention regarding the use of dietary supplements. The other 13% (n=9) of the studies stated that all prescribed medications as well as any over-the-counter medications were to be recorded. Six percent (n=4) of the nine studies specifically addressed the use of specific dietary supplements, PC-SPES and St. Johns wort. The remaining five studies provided no specific examples of over the counter medications.

4.3.8 REMOVAL FROM STUDY SECTION

Patients were required to be removed from the study in only one of the seventy studies if at any time while enrolled on the clinical trial the individual consumed medications which had been listed previously in the study as making the individual ineligible for study entry.

Table 19: Outcome of the Review of the Clinical Trials Regarding the Use of Dietary Supplements

Section	Frequency	
	Yes	No
Pre-Study	2	68
Eligibility	0	70
Ineligibility	3	67
Protocol Text	1	69
Concomitant Meds	4	66
Removal from Study	1	69

4.3.9 CASE REPORT FORMS (CRFs)

Case report forms (CRFs) are data collection tools which are used to record patient data throughout the course of the clinical trial. The CRFs are generally study specific. The purpose of this review was to determine if the 70 sets of CRFs required the collection of any data that may not have been detailed within the text of the clinical trial. On occasion, the CRFs are more detailed than the study. Table 20 summarizes the findings of the review of the CRFs.

4.3.10 PRE-STUDY CRFs

The pre-study (entrance criteria) CRFs did not address the use of dietary supplements in any of the 70 studies. These findings were inconsistent with the review of the actual studies in which two of the studies addressed the use of dietary supplements in the pre-study section of the study text.

4.3.11 ELIGIBILITY CRFs

The findings of the review of the eligibility-related CRFs was consistent with the review of the study text. In both cases, dietary supplement use was not addressed.

4.3.12 INELIGIBILITY CRFs

There was a discrepancy between the ineligibility section of the clinical trial and the CRFs addressing ineligibility. Three studies addressed the use of dietary supplements within the ineligibility section; however, the ineligibility CRFs did not address the use of dietary supplements. The study section of the clinical trials stated that individuals who were using dietary supplements were not eligible for study participation. The CRFs of the same 3 studies did not address the use of dietary supplements. The concern would be that these ineligibility criteria, although noted within the study text could be inadvertently missed when the individual was screened for study entry since there was an inconsistency between the study text and the CRFs.

4.3.13 CONCOMITANT MEDICATION CRFs

The concomitant medication CRFs addressed the use of dietary supplements in fifteen of the seventy studies. This finding was inconsistent with the findings of the review of the clinical trial concomitant medication section in which n=4 addressed the use of dietary supplements within the concomitant medication section of the study. In reviewing the fifteen study-specific concomitant medication CRFs, it was noted that 5 of the CRFs addressed the use of one or two specific dietary supplements, PC-SPES and St. John's wort but no other dietary supplement. Eight of the studies had concomitant medication CRFs that required all over-the-counter medications to be listed in addition to prescribed medications. In 6 of the 8 studies, there were examples of over-the-counter medications to be recorded; the lists also provided examples of dietary supplements such as saw palmetto, lycopene, and DHEA. The lists were not all inclusive so that the individual screening the participant for study entry would have to be familiar with dietary supplements. The two other sets of CRFs referred to detailed reference manuals, which

were a part of the studies in which long lists of prescribed medications, and over-the-counter medications were listed. The lists included a variety of dietary supplements in both studies.

Table 20: Summary of Case Report Forms Regarding Use of Dietary Supplements

Section	Frequency	
	Yes	No
Pre-Eligibility	0	70
Eligibility	0	70
Ineligibility	0	70
Concomitant Meds	15	70

4.4 THE POTENTIAL FOR DRUGS/INVESTIGATIONAL AGENT AND DIETARY SUPPLEMENT INTERACTIONS

The 70 clinical trials that were reviewed involved the use of all the drugs or investigational agents listed in Table 21 for the treatment of breast, prostate or colorectal cancer. In addition, Table 21 also lists the various dietary supplements that were being taken by the patients on the 70 clinical trials. The dietary supplements with an asterisk are those with the *potential* for interaction with the drug(s)/investigational agents being used on the 70 clinical trials. This information was collected to determine if there was any potential for interaction between the various dietary supplements that patients were taking and the drug(s)/investigational agents being used in the clinical trails. **However, it is important to note that no one-to-one analysis was done.**

Table 21: Potential Drug and Dietary Supplement Interactions

Drug/Investigational Agent		Dietary Supplement	
ABX-EGF	IL2	Aloe vera	Soy Isoflavones*
Acotel	Iressa	B Complex	St. John's wort*
Adriamycin*	Irinotecan*	Bilberry	Vitamin B-12
Alimta	Letrozole	Calcium	Vitamin B-6
AMG162	Leucovorin	Coenzyme 10	Vitamin C
Anastrozole	MAC-321	Echinacea*	Vitamin E
Arimidex	Oxaliplatin	Elevthero	
Bevacizumab	Perifosine	Evening primrose	
Bupropion	Taxol*	Feverfew	
Capecitabine	Taxotere*	Fish Oil	
Casodex*	Thalidomide*	Flax Seed Oil	
Celebrex	Venlafaxine*	Folic acid	
Celecoxib	Vinorelbine*	Garlic*	
Clodronate		Ginger	
CPG7909		Gingko Baloba*	
Cyclophosphamide*		Ginseng*	
Cytoxan		Glucosamine*	
DN-101		Goldenseal*	
Docetaxel*		High dose multi-vitamin	
Epirubicin		Kava Kava*	
Epothilone		Lycopene	
Exemestane*		Multi-vitamin	
Floxatin		Noni juice	
Gemcitabine		Red Clover	
GW572016		Saw Palmetto*	
Herceptin		Selenium	

* Drugs and dietary supplements that may have the potential for interaction

5 DISCUSSION

5.1 OVERALL IMPORTANCE OF THE STUDY

This study revealed that patients with breast, prostate and colorectal cancer are using dietary supplements while enrolled on clinical trials for the treatment of their cancer. Currently, many of the effects of dietary supplements are unknown but there is the potential for harmful drug interactions when supplements are used with particular drugs/investigational agents for the treatment of cancer. To date, there have been only two studies done investigating the use of CAM by individuals in trials for the treatment of cancer, and both of these focused on patients in Phase I trials who use dietary supplements (Dy, 2004; Sparber, 2000). Phase I studies are pharmacology studies, not treatment studies, that seek to determine drug dosing schedules and safety profiles of the drugs being investigated. The use of dietary supplements in this population is critical information for researchers to have. This study contributes to the literature by examining if individuals who are enrolled in Phase II and III trials are using dietary supplements since they could also be at risk for potential drug interactions. To the best of my knowledge, it is the first to evaluate the use of dietary supplements in individuals with breast, prostate and colorectal cancer who are enrolled in all phases of clinical trials for the treatment of cancer.

5.1.1 USE OF DIETARY SUPPLEMENTS

The study findings documented that 72% of the patients surveyed were using dietary supplements while enrolled in a clinical trial for treatment of their cancer. The participants in this study were older, between the ages of 51-60 years, than those in previous studies evaluating the general use of CAM therapies in cancer patients. Their educational and income levels were

also consistent with the demographic profile of participants in previous studies of CAM usage. The findings of this study revealed that the patients were primarily enrolled in Phase II (51%) and Phase III (44%) clinical trials.

Eighty-seven percent of the patients using dietary supplements in the study felt that they had communicated this information to their oncologists. However, 22% of these individuals assumed that this information had been communicated because they wrote the information on a form. There was not any verbal communication or physician acknowledgement of receipt of this information. In addition, only 7% of the participants could recall their oncologist specifically asking them about the use of dietary supplements. However, 75% of the oncologists caring for the patients in the study stated that they specifically ask their patients about the use of dietary supplements. There is a difference between the patients' and the physicians' perceptions regarding the communication of this information. The concern is that this information may not be routinely collected; therefore patients may be taking dietary supplements that place them at potential risk for drug interactions.

The findings of this study revealed that the patients were taking a variety of brands of dietary supplements and that they did not consistently purchase the same brand. In addition, the frequency with which they took certain dietary supplements varied. This is important information since the amount of a particular dietary supplement may be cause for concern. For example, in reviewing the various brands of multivitamins that patients were taking, high dosage formulas or the frequency with which they took the supplements placed them at potential risk. Therefore, it cannot be assumed that patients who are taking only multivitamins are not at risk for drug interactions while being treated in a clinical trial.

5.1.2 POTENTIAL FOR DRUG-DRUG INTERACTIONS

The findings revealed that patients were taking some dietary supplements, which may be potentially harmful while being treated for cancer. These were echinacea, garlic, gingko biloba, ginseng, glucosamine, goldenseal, kava kava, saw palmetto, soy isoflavones, and St John's wort. There is the potential that these herbs may increase or decrease the effectiveness of the drugs or investigational agents being studied in the clinical trials. This would present a challenge in dosing of the drugs and, in addition, it may place the patient at risk for toxicities. There is also the possibility that dietary supplements may alter the rate of absorption and elimination of the drugs being used to treat the cancer (Sparreboom, 2004), although, the interactions are most likely to occur due to altered pharmacokinetics of the drugs (Zhou, 2003). The use of herbs in particular, by patients who are undergoing treatment for cancer, may affect all aspects of pharmacokinetics. Most known drug interactions occur due to the changes in the metabolic routes related to altered expression or functionality of cytochrome P450 (CYP) isozymes (Sparreboom, 2004). This class of enzymes, particularly CYP3A4 isoform is responsible for the oxidation of the majority of the chemotherapeutic agents being used for the treatment of cancer. Studies in animal models have indicated that garlic at high concentrations may induce the activity of CYP3A4 (Raucy, 2003).

Echinacea is an herbal preparation used primarily for its immunostimulatory effect. The immunostimulatory effect is generally seen with short-term use; with chronic use (>6 or 8 weeks) echinacea may become immunosuppressive, causing a decrease in the white blood cells (Kemp, 2002). This decrease in white blood cells can place the patient who is undergoing treatment with chemotherapy in a life-threatening situation. In addition, echinacea is also a mild

inhibitor of CY3A4, which is a P450 enzyme (Budzinski, 2002). These enzymes metabolize a variety of drugs that are used to treat cancer patients.

Ginkgo biloba is a potent antagonist of platelet activating factor thereby increasing the fluidity of the blood (Kudolo, 2002). This can place some patients at risk for bleeding; this has the potential to increase when ginkgo biloba is used in combination with some drugs being used to treat cancer. There is also the potential that gingko biloba may interfere with some of the chemotherapy agents (alkylating agents, anthracyclines, epipodophyllotoxins, and platinum analogues) and radiation therapy by acting as free-radical scavengers (Weiger, 2002).

St John's wort is a complex mixture of over two-dozen compounds. Clinical trials are now reporting significant pharmacokinetic interactions with St John's wort and drugs from a variety of therapeutic classes (Izzo, 2001). The interactions between St John's wort and anticancer drugs is significant since there is likely to be clinical and toxicological implications, however more extensive testing is needed regarding possible interactions (Sparreboom, 2004).

This study also revealed that the clinical trials in which some of the patients were enrolled involved the use of chemotherapeutic drugs that are known to interact with a particular dietary supplement. The drugs, which were identified, include docetaxel, exemestane, irinotecan, adriamycin, casodex, cyclophosphamide, taxol, taxotere, thalidomide, venlafaxine and vinorelbine. In addition, some of the patients were also taking some preparations such as Noni juice the contents of which are unknown.

5.1.3 PHYSICIAN AWARENESS OF THE USE OF DIETARY SUPPLEMENTS

The oncologists surveyed were aware of their patients' use of dietary supplements. However, only 6 of the oncologists referred patients to someone who had an expertise in this area. In fact, a number of the patients reported that their oncologists did not discourage use of the dietary

supplements while on a clinical trial, however they were told not to take large doses, mega doses or antioxidants. This study did not evaluate whether the patients understood what these instructions actually meant. This is an avenue of research that needs to be explored. However, the study did reveal that some patients might have been on high dosages of dietary supplements particularly multivitamins and also antioxidants.

5.1.4 REASONS PATIENTS TOOK DIETARY SUPPLEMENTS

The general design of the patient survey instrument was informed by the Health Belief Model (HBM). Survey questions were developed to solicit information regarding the HBM constructs of perceived benefits, perceived barriers and self-efficacy. Research has shown that individuals with the diagnosis of cancer often feel the loss of control and due to the potential threat to their life, will often engage in alterations of their lifestyle that they perceive to be beneficial. The perceived benefits of using dietary supplements identified in this study include avoidance of pharmacological toxicities, a sense of personal control and self-efficacy regarding decision-making. The perceived barriers include potential toxicities and doubts about the safety and efficacy of dietary supplements.

Patients revealed that they were taking the dietary supplements because they wanted to enhance their general health, in fact, 44% of the patients admitted adding additional supplements once they were diagnosed with cancer and an additional 20% initiated the use of dietary supplements. The use of dietary supplements provided them with a feeling that they were doing something to help themselves. A few of the patients did admit that they were using the dietary supplements to help with particular treatment-related side effects. These findings suggest that the Health Belief Model is a plausible exploratory framework to understand patient behavior with regard to this issue.

The majority of the patients did not view the dietary supplements as harmful and most often received the information regarding the dietary supplements from magazines, the internet and well-meaning friends. This indicates that there is a need for patients to have access to resources that can help them to make an informed decision regarding the use of dietary supplements. The literature has revealed that patients with cancer who use complimentary and alternative medication (CAM) have a lower reported satisfaction with their physicians. This lowered satisfaction is related to the patients' perception that communication with their physician could be improved. Often, the patients reported that they were not acknowledged as a person and viewed just as a diagnosis. By contrast, the patients in this study were satisfied with their oncologists and the health care system in general.

5.1.5 CLINICAL TRIALS AND THE USE OF DIETARY SUPPLEMENTS

The clinical trials and the accompanying case report forms (CRFs), which were evaluated, were sponsored by pharmaceutical companies and national cooperative groups. The study findings revealed that 6% of the clinical trials specifically addressed the use of dietary supplements within the context of the study and 21% of the study-related case report forms (CRFs) also addressed this issue. This discrepancy may present a potential for this information to be missed since individuals placing patients on clinical trials do not always record patient related information initially on CRFs. Since this information is not within the body of the clinical trial there is concern that it could be initially overlooked. In addition, terms such as over-the-counter drugs and concomitant medications may be interpreted differently by individuals, including those entering the patients into the clinical trials.

Anecdotally, the researcher spoke with the individuals who were responsible for screening and entering patients into clinical trials. This was necessary for the recruitment of the patients.

Twenty of these individuals who were nurses stated that they do not ask the patients if they are taking dietary supplements, unless the study specifically states that a particular dietary supplement is of concern.

5.2 STUDY SIGNIFICANCE

There are several major strengths of this study. First, to the best of my knowledge it is the first study to evaluate the use of dietary supplements by individuals who are enrolled in all phases of clinical trials for the treatment of cancer. Second, it is the only study, which has evaluated a sample of clinical trials for the treatment of cancer to determine if they address the use of dietary supplements. There is no reason to believe that these clinical trials would not be representative of clinical trials being conducted for breast, prostate, and colorectal cancer throughout the United States, since the 70 clinical trials that were reviewed were multi-institutional and sponsored by national cooperative groups or pharmaceutical companies. Finally, the comprehensive cancer center in which the study was conducted may well be representative of other cancer centers throughout the country. There is no reason to believe that similar findings would not be found at other comprehensive cancer centers.

5.3 STUDY LIMITATIONS

There were several limitations to the study. First, the results may not be generalizable to individuals with other types of cancer, since participation was limited to individuals with the diagnosis of breast, prostate and colorectal cancer. However, this was the first study exploring the use of dietary supplements in all phases of clinical trials so the types of cancer were limited by the researcher. There was also interest on the part of the researcher in exploring breast and

prostate cancer since they were hormonally sensitive and some dietary supplements mimic hormones. Second, there is the possibility of self-selection bias with the patient and physician samples. In addition, during the time of recruitment there were a limited number of available clinical trials for the treatment of prostate and colorectal cancer; therefore, the majority of the study participants were females with the diagnosis of breast cancer. However, statistically there was no difference found in the use of dietary supplements by gender.

Second, this was an exploratory study and the intent was to evaluate if individuals with cancer were using dietary supplements. The survey instruments that were used to evaluate the patients and physicians had not been previously used. If one were to replicate this study using these instruments then it would be necessary to validate the instruments.

5.4 CONCLUSION

Many of the effects of dietary supplements are unknown, but there is the potential for interactions to occur between the supplements and the drugs/investigational agents being studied in the clinical trials. Patients are taking dietary supplements and feel that they are harmless because they can purchase them over-the-counter and internet.

It is important that patients who are being evaluated for enrollment in a clinical trial for the treatment of cancer undergo a detailed assessment of any dietary supplements. This assessment should be well-documented and be ongoing, since it may change over time and throughout the course of the disease.

There is also a need to educate the health care providers about dietary supplements and to make information and resources available to them so that they can be educated and are better able to educate their patients.

Investigators and sponsors of clinical trials for the treatment of cancer should also be educated regarding the importance of designing clinical trials and the accompanying case report forms so that information on dietary supplements is recorded upon enrollment.

There is no reason to believe that the use of dietary supplements will decrease in the near future. It is therefore, important that the general public and, in particular, patients with the diagnosis of cancer undergoing treatment be aware of the implications of taking dietary supplements. In addition, they also need to be aware that dietary supplements are unregulated substances, which may potentially be harmful, particularly when used in combination with drugs or other medications.

5.5 FUTURE RESEARCH

The findings also suggest a number of areas in which future research may be beneficial. First, future studies should evaluate individuals with any diagnosis of cancer who are enrolled in a clinical trial for the treatment of cancer. This would help to determine if individuals with a particular type(s) of cancer are more likely to use dietary supplements. Second, the survey instrument should evaluate the particular brand of the dietary supplement being used since all brands are not identical. Third, the use of dietary supplements may shift over the course of a patient's illness, so the use of a longitudinal study may provide a clearer picture of how other variables influence the use of dietary supplements. Fourth, a random survey of oncologists should be conducted to determine if there is a need to educate the oncologists and health care providers with regards to the use of dietary supplements in patients in clinical trials for treatment of cancer. In addition, patients with cancer are often receiving supportive therapies that may include, growth factors, anticoagulants, hormonal agents, and these substances may also have the

potential to interact with dietary supplements. It would be beneficial to perform a 1:1 analysis with the dietary supplements being used and a particular drug, investigational agent or supportive therapy agent. This could possibly provide information regarding drug – drug interactions.

It is also important that the patients' understanding of terms such as high dose, mega-dose, antioxidants, etc be evaluated since there are many terms used in relation to dietary supplements that the patient may misunderstand. Finally, there is a need for further evaluation of physician/patient relationship.

APPENDIX A: INSTITUTIONAL REVIEW BOARD APPROVAL LETTERS

University of Pittsburgh

Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 578-3424
(412) 578-8553 (fax)

MEMORANDUM:

TO: Linda Barry Robertson, RN, MSN

FROM: Christopher Ryan, Ph.D., Vice Chair

DATE: November 25, 2003

SUBJECT: IRB# 0311012: The Use of Dietary Supplements Among Individuals Enrolled in Clinical Trials for the Treatment of Breast, Prostate, and Colorectal Cancer (UPCI 03-097)

The above-referenced proposal has received expedited review and approval from the Institutional Review Board under 45 CFR 46.110 (5,7).

Please include the following information in the upper right-hand corner of all pages of the consent form:

Approval Date: 11/25/2003
Renewal Date: 11/24/2004
University of Pittsburgh
Institutional Review Board
IRB # 0311012

Adverse events which occur during the course of the research study must be reported to the IRB Office. Please call the IRB Adverse Event Coordinator at 578-8565 for the current policy and forms.

The protocol and consent forms, along with a brief progress report must be resubmitted at **least one month prior** to the expiration date noted above for annual renewal as required by Assurance No. M-1259, given to DHHS by the University of Pittsburgh.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

CR/sn

MEMORANDUM:

TO: Linda Barry Robertson, RN, MSN

FROM: Christopher Ryan, PhD, Vice Chair

DATE: November 19, 2004

SUBJECT: IRB #0311012: The Use of Dietary Supplements Among Individuals Enrolled in Clinical Trials for the Treatment of Breast, Prostate, and Colorectal Cancer (UPCI 03-097)

Your renewal of the above-referenced proposal has received expedited review and approval by the Institutional Review Board under 45 CFR 46.110 (5) (7).

Please include the following information in the upper right-hand corner of all pages of the consent form:

Approval Date: November 18, 2004
Renewal Date: November 17, 2005
University of Pittsburgh
Institutional Review Board
IRB #0311012

Adverse events, which occur during the course of the research study, must be reported to the IRB Office. Please call the IRB Adverse Event Coordinator at 412-383-1519 for the current policy and forms.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month prior** to the expiration date noted above for annual renewal as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

CR:dj

APPENDIX B: PATIENT INFORMED CONSENT

UPMC Cancer Centers
Hillman Cancer Center

University of Pittsburgh
Institutional Review Board
IRB# 0311012 UPCI #03-097
Approval Date: 11/25/03
Renewal Date: 11/24/04
Version Date: 8/20/03

University of Pittsburgh Cancer Institute
University of Pittsburgh Graduate School of Public Health

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

TITLE: The Use of Dietary Supplements Among Individuals Enrolled in Clinical Trials for the Treatment of Breast, Prostate, and Colorectal Cancer (UPCI 03-097)

PRINCIPAL INVESTIGATOR: Linda Barry Robertson RN, MSN

SOURCE OF SUPPORT: UCSUR Research Development Grant funds

Subject's Initials _____

INTRODUCTION:
You have been asked to volunteer in a research study. Taking part in this study is entirely voluntary and up to you to decide. In order to decide whether or not you wish to take part, you should understand enough about its purpose, procedure, risks, and benefits as outlined in the following pages to make an informed decision. This process is known as Informed Consent.

Feel free to ask about anything that is not clear, or request additional information. Take as much time as you want to decide whether or not you wish to take part.

Why is this research being done?
This study is being done in order to learn more about the use of dietary supplements by cancer patients. Dietary supplements include such things as: vitamins, minerals, and herbal remedies. The study will also look at how the doctors of cancer patients view the use of dietary supplements and whether or not research studies of cancer drugs account for the use of dietary supplements in their design.

Who is being asked to take part in this research study?
Men and women age 18 and older who have breast, prostate, or colorectal cancer are being asked to participate in this study. Approximately 140 subjects will participate in this study at the University of Pittsburgh Medical Center (UPMC) Cancer Centers. In addition, approximately 15 doctors from the University of Pittsburgh Cancer Institute will be asked to complete anonymous questionnaires as part of this study.

What procedures will be performed if you participate in this study?
If you decide to take part in this research study, you will be asked to schedule a 30-minute phone interview with the investigator. During the interview you will be asked about your use of dietary supplements (if any) and your thoughts and feelings about them. You will also be asked some more general questions about your health and your health care. If there are any questions that make you uncomfortable or that you do not wish to answer, you have the option not to answer them.

No personal identifiers (name, date of birth, social security number, etc.) will be recorded with your answers to the phone interview questions. The results of your phone interview will not be linked to you in any way.

What are the possible risks of this research study?
It is possible that some of the questions asked of you may make you feel uncomfortable. In addition, your name, phone number, and diagnosis (i.e., breast, prostate, or colorectal cancer) will be recorded on a study enrollment log by the investigator. This log will only be used to keep track of the number of subjects enrolled in this study and to contact them for the phone interview. As stated above, this log will not be linked in any way to the answers you provide during the phone interview. In addition, all efforts (as described below) will be made to maintain the confidentiality (privacy) of this list. However, it is possible that this enrollment log could be viewed by individuals not involved in this study, resulting in the unintentional disclosure of your personal health information.

Subject's Initials _____

What are possible benefits from taking part in this study?
There is no direct benefit to you for your participation in this study. It is hoped that the knowledge gained by completion of this study will result in a greater understanding of the use of dietary supplements by cancer patients.

What are the costs of participating in this study?
There are no costs involved with your participation in this study.

Will I be paid if I take part in this research study?
You will receive $25 for your participation in this study.

Who will know about my participation in this research study?
Any information about you obtained from this research will be kept as confidential (private) as possible. The enrollment log which will contain your name, phone number, and diagnosis will be stored in a locked filing cabinet. It will not be linked in any way to the answers you provide during the phone interview. You will not be identified by name in any publication of the research results.

Will this research study involve the use or disclosure of my identifiable medical record information?
This research study will involve the recording of current identifiable (pertaining to only you) medical information from your hospital and/or other health care provider (e.g. physician office) records. This information that will be recorded will be limited to your name, phone number, and diagnosis. The information will be used to determine your eligibility for this study and to allow the investigator to contact you for the phone interview.

This research study will not result in identifiable information that will be placed into your medical records held at UPMC and the UPMC Cancer Centers.

Who will have access to my identifiable medical record information related to my participation in this research study?
In addition to the investigator listed on the first page of this consent form and her research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical record information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release your identifiable research information (which may include your identifiable medical record information) in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform you, as required by Pennsylvania law, the appropriate agencies.

Subject's Initials _____

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?
The investigators may continue to use, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of 5 years and for as long (indefinite) as it may take to complete this research study.

Is my participation in this research study voluntary?
Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

May I withdraw, at a future date, my consent for participation in this research study?
You may withdraw, at any time, your consent for participation in this research study, to include the use of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If I agree to take part in this research study, can I be removed from the study without my consent?
It is possible that you may be removed from the research study by the investigator without your consent.

Subject's Initials _____

****

VOLUNTARY CONSENT:
All of the above has been explained to me and all of my current questions have been answered. I understand that, throughout my participation in this research study, I am encouraged to ask questions about the any aspect of this research study including the use and disclosure of my identifiable medical record information. Such future questions will be answered by the investigators listed on the first page of this form.

Any questions I have about my rights as a research participant or the research use of my medical information will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (412-578-8570).

By signing this form, I agree to participate in this research study and for the use and disclosure of my medical record information for the purposes described above. A copy of this consent form will be given to me.

_____ _____
Participant's Signature Date

CERTIFICATION OF INFORMED CONSENT:
I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

_____ _____
Signature of Person Obtaining Consent Date

_____ _____
Printed Name of Person Obtaining Consent Role In Research Study

11-13-2003

APPENDIX C: PATIENT SURVEY

Thank you for agreeing to speak with me today.

The purpose of this survey is to learn more about the thoughts and feelings of patients who have cancer and their use of dietary supplements. In addition, we would also like to ask you some general questions about your health and your opinions about your health care. This information will help us to treat our patients more effectively. This survey should take approximately 20 minutes to complete.

You will be asked a series of questions. The first part of the questionnaire focuses on patients' use of dietary supplements.

I will be happy to repeat the list at any time and please feel free to ask me to slow down if I am reading too quickly.

Please answer as honestly as you can since this information is very valuable.

Have you ever taken dietary supplements such as vitamins, minerals, and/or herbs or any other natural remedies such as teas, potions, or tinctures? A potion is a mixture liquid vitamins, mineral, herbs in most instances specially prepared for a specific condition or symptom.

1. Yes (If yes, proceed to Question 2)
2. No (If no, proceed to Question 1a)

1a.) Would you consider taking dietary supplements in the future?

1. Yes (Ask why?) **THEN PROCEED TO Question 9-11.**

2. No (Ask why not?) **THEN PROCEED TO Question 17.**

Do you currently take dietary supplements such as vitamins, minerals, and/or herbs or any other natural remedies such as teas, potions, or tinctures?

1. Yes (If yes, proceed to Question 2a)

2. No (If no, proceed to Question 17)

2a.) What specifically do you take? Please try to remember everything that you are taking. (Make sure that you PROBE: As they name a substance be sure to ask if they take anything else. The goal is to obtain the name of everything that they are taking.)

2b.) Sometimes individuals may not realize that what they are taking is considered a dietary supplement. So, now I am going to read the names of some dietary supplements that people like you may use. As I read each name, please tell me if you are currently using that dietary supplement. I will then ask several other questions about each dietary supplement that you are taking. I will be happy to repeat the list at any time and please feel free to ask me to slow down if I am reading too quickly.

Q2a SUPPLEMENTS	Q2b Why do you take this dietary supplement? (Be specific)	Q2c Has this dietary supplement worked as you expected?			Q2d How often do you take this dietary supplement?				
		1. Yes	2. No	3. Not sure	1. 1x/ day	2. 2x/day	3. 3x/day	4. Weekly	5. Monthly
Aloe Vera									
Bilberry									
Black Cohosh									
Cayenne Pepper									
Chamomile									
Chasteberry									
CoEnzyme 10									
Devil's Claw									
Echinacea									
Elevthero									
Evening Primrose									
Feverfew									
Garlic									
Ginger									
Ginkgo									
Ginseng									
Goldenseal									
Hawthorn									
Hops									
Horse Chestnut									
Kava-Kava									
Licorice									
Lycopene									
Milk Thistle									
Nettle									
Passion Flower									
PC-SPES									
Peppermint									
Phytoestrogens									
Pygeum									
Red clover									
Soy isoflavones									
St. John's Wort									
Saw Palmetto									
Senna									
Valerian									
Witch Hazel									

Q2a **Vitamins**	**Q2b** **Why do you take this dietary supplement** **(Be specific)**	**Q2c** **Has this dietary supplement worked as you expected?**			**Q2d** **How often do you take this dietary supplement?**					
		1. Yes	2. No	3. Not sure	1. 1x/ day	2. 2x/day	3. 3x/day	4. Weekly	5. Monthly	6. Other
Beta Carotene										
Vitamin A										
Vitamin D										
Vitamin E										
Vitamin K										
Vitamin C										
Vitamin B1 (thiamin)										
Vitamin B2 (Riboflavin)										
Vitamin B3 (Niacin)										
Vitamin B5 (Pantothenic Acid)										
Vitamin B6 (Pyridoxine)										
Vitamin B12 (Cobolamin)										
Folate (Folic Acid)										
Biotin										
Minerals										
Calcium										
Magnesium										
Potassium										
Sodium										
Phophorus										
Zinc										
Iron										
Copper										
Iodine										
Chromium										
Selenium										
Others										

Did you use dietary supplements before you were diagnosed with cancer?

1. Yes (If yes, proceed to Question 3a)
2. No (If no, proceed to Question 4)

3a.) Approximately how long have you used dietary supplements?

1. Less than a year
2. 1-5 years
3. 6-10 years
4. 11-15 years
5. 16-20 years
6. over 20 years

3b.) Why did you take dietary supplements prior to the diagnosis of cancer?

3c.) What did you expect the dietary supplements to do for you?

3d.) Have the dietary supplements worked as you hoped they would? Please be specific.

3e.) Have you taken any new dietary supplements since you were diagnosed with cancer?

1. Yes (If yes, what specifically?)

2. No

4. How long have you been taking the dietary supplements since you were diagnosed with cancer? Please be as specific as you can.

Less than a month
1-3 months
4-6 months
7-9 months
10-12 months
over a year
several years

5. Individuals with cancer may take dietary supplements for many reasons. Can you tell me why you are currently taking dietary supplements?

6. Have you done any reading or looked on the Internet about the dietary supplements that you are taking?

1.Yes (If yes, proceed to Question 6a)

2. No (If no, proceed to Question 7)

6a.) Where did you find the information on the dietary supplements that you are currently taking?

7. Did someone recommend that you take dietary supplements?

1. Yes (If yes, proceed to Question 7a)

No (If no, proceed to Question 8)

7a.) Who recommended dietary supplements to you?

8. There are many dietary supplements on the market. What influenced your decision to take the dietary supplements that you are currently taking?

9. In your opinion what are the positive things about taking dietary supplements? (Please tell me what they are.)

10. In your opinion, are there any negative things about taking dietary supplements? (Please tell me what they are.)

11. Have you heard of anyone having any positive or negative effects from taking the dietary supplements you are taking?

1. Yes (If yes, proceed to Question 11a)

2. No (If no, proceed to Question 12)

11a.) What were the effects? (Make sure you PROBE: for positive and negative effects.)

12. Have you personally experienced any side effects while taking dietary supplements?

1.Yes (If yes, proceed to Question 12a)

2. No (If no, proceed to Question 13)

12a.) What were the side effects? (Please be as specific as you can)

12b.) For each side effect, please rate it on a scale of 1-3, with 1= mild; 2 = moderate and 3 = severe.

Q 12b **List Name of each Supplement**	**Q12b** **List each Side Effect**	**Q12b** **Rate Intensity of each Side Effect**		
		1=mild	2=moderate	3=severe

13. Have you told your oncologist that you are taking dietary supplements?

1. Yes (If yes, proceed to 13a)

2. No (If no, proceed to 13b)

13a.) What was your oncologist's reaction?

13b.) What do you think your oncologist would say if you told him/her you were taking dietary supplements?

14, Would you stop taking the dietary supplements if your oncologist told you to do so?

1.Yes (If Yes, Why?)

2. No (If No, why not?)

15. Approximately how much do you spend on dietary supplements per month?

1. Less than $20.00
2. $20-50.00
Over $50.00

16. Does your health care insurance pay or reimburse you for dietary supplements?

1.Yes
2.No

Now I am going to ask you some general questions about your health and your health care. There are no right or wrong answers so please just give me your opinion. These next few questions deal with your opinions about the role you play in your overall health.

17. In your opinion, who have you felt is responsible for your health?

17a.) Has your opinion changed since you were diagnosed with cancer?

1.Yes (If so, how?)

2. No

18. Do you feel that you play a role in your health?

1. Yes (If yes, Please describe that role.)

2. No (If no, why not?)

19. Do you feel that you take an active role in maintaining your health by doing things such exercising, eating a balanced diet, participating in regular health screenings, etc?

1.Yes

2. No

I am now going to ask you some general questions about your health and your health care. There is no right or wrong answer so please answer as honestly as you can.

20. Are you satisfied with the care you are receiving for your cancer?

1.Yes (If yes, why?)

2. No (If no, why not?)

21. Would say that you have a good relationship with your oncologist?

1.Yes (If yes, What are the good things about the relationship?)

No (if not, why not?) PROBE: What would you like to see changed?

22. Do you and your oncologist communicate well?

1.Yes (If yes, Can you give me an example of a typical good conversation that you have had with your oncologist?)

2. No (If no, Can you give me an example of a typical conversation that you have had with your oncologist that did not go very well?)

23. Do you feel that you can discuss anything with your oncologist?

1.Yes

2.No

24. Does your oncologist listen to you?

1.Yes

2. No

25. Do you feel that your oncologist meets your healthcare needs?

1.Yes

2. No (If no, proceed to Question 25a)

25a.) What healthcare needs do you have that have not been met by your oncologist?

Sometimes individuals with cancer have their own thoughts about how they developed the cancer. So, I would like to ask you a few questions about your thoughts. Again, there are no right or wrong answers.

26. What do you think caused you to develop cancer?

27. Do you want to be actively involved in your treatment decisions?

1. Yes (If yes, proceed to Question 27a)

2. No (If no, proceed to Question 27b)

27a.) Can you describe how you participate in your cancer treatment decisions? (PROBE to obtain examples.)

27b.)Why have you chosen not to participate in your cancer treatment decisions?

28. Do you feel that you play a role in your getting well?

1. Yes (If yes, proceed to Question 28a)

2. No (If no, proceed to Question 28 b)

28a.) How do you play a role in your getting well?

28b.) Why do you feel that you do not play a role in your getting well?

Demographics

This will be abstracted from the database. Do not ask these questions.

Diagnosis

1. Breast Cancer
2. Prostate Cancer
3. Colorectal Cancer

Stage of Cancer

Phase of clinical trial

1. Phase 1
2. Phase 2
3. Phase 3

Age

1. Under 20 years
2. 21-30 years
3. 31-40 years
4. 41-50 years
5. 51-60 years
6. 61-70 years
7. 71-80 years
8. over 80 years

Sex

1.Female

2. Male

Educational Level (Please circle the highest level of education completed)

1. less than 8 years
2. 8-11 years
3. high school graduate or GED
4. some college or vocational/technical training
5. college graduate
6. graduate/professional education

Race

1.Caucasian
2.African American
3.Native American Indian
4.Asian
5. Hispanic

Income Levels (Average yearly income)

Less than $10,000
$11,000-20,0000
$21,000-40,000
$41,000-60,000
$61,000-80,000
$81,000-100,000
over $100,000

Type of Health Insurance (Please list all health insurance, including supplemental insurance.)

Highmark Blue Cross
Medicare
Medicaide
Medicaide HMO
UPMC Health Plan
Other (please list)

Thank you for your time.

LBR 03/05/04

APPENDIX D: PHYSICIAN SURVEY

The purpose of this survey is to obtain information regarding your perception of your patients' use of dietary supplements while enrolled in a clinical trial for the treatment of cancer. To date, there has been little documented research done with individuals enrolled in clinical trials and their use of dietary supplements. However, it is well known that individuals with the diagnosis of cancer do use dietary supplements. This research is being done as partial fulfillment of the requirements for a doctorate in public health. It is the researcher's intent to use the results of this study as a basis for further studies on the use of dietary supplements.

1. Among your patients who are enrolled on clinical trials for the treatment of cancer, what percentage do you think use dietary supplements (vitamins, minerals, and herbs) on a regular basis? (Please circle your response)

    1. Less than 25%
    2. 25-50%
    3. 51-75%
    4. Over 75%

2. Do you ask your patients about the use of dietary supplements? (Please circle your response)

    1. Yes 2. No

3. If a patient tells you that he or she is using dietary supplements, what do you typically say or do? (Please be specific)

4. Do you refer your patients who are using dietary supplements to anyone? (Please circle your response)

    1. Yes (Please proceed to 4a) 2. No

    4a. To whom or where do you refer patients who use dietary supplements?

5. Do you recommend dietary supplements to your patients?

    1. Yes (if so, what specifically) 2. No
6. Do you feel that your patients are communicating their usage of dietary supplements to you?

1. Yes 2. No

Demographics

Practice Site (Please circle your response)

1.Hillman Cancer Center
2.Office
3.UPMC Cancer Center freestanding site
4.UPMC hospital

Age Range (Please circle your response)

1. 31-40 years
2. 41-50 years
3. 51-60years
4. Over 60 years

Thank you for your time.

The results of the study will be shared with you upon completion.

LBR 6/10/03

APPENDIX E: CLINICAL TRIALS CHECK LIST

1.) Name of Institution

2.) Phase of Trial: I II III IV

3.) Disease Site: Breast Prostate Colorectal

4.) Sponsor: Pharma Physician-Initiated Other (Be specific)

5.) List all study drugs

6.) Components of trial to be reviewed for information regarding the use of dietary supplements (vitamins, minerals, herbs): If the use of dietary supplements has been addressed in a section, circle ***YES*** and specifically indicate what was stated. If it is not addressed then indicate by circling ***NO***.

Pre-eligibility (screening) work-up	Yes	No
Eligibility criteria	Yes	No
Ineligibility criteria	Yes	No
Protocol	Yes	No
Concomitant medication section	Yes	No
Removal from study section	Yes	No

7.) Review of Case report forms (CRFs):

Pre-study work-up (entrance criteria)	Yes	No
Eligibility criteria	Yes	No
Ineligibility criteria	Yes	No
Concomitant medication sheet	Yes	No

8.) Are the use of dietary supplements specifically addressed in any of the CRFs? (Be specific)

APPENDIX F: CANCER CENTER LETTER

Date

Cancer Center Address

Dear Cancer Center Administrator:

My name is Lyn Barry Robertson and I am a Doctoral student at the University of Pittsburgh in the graduate school of public health. My dissertation focuses on the use of dietary supplements (vitamins, minerals and herbs) by individuals with the diagnosis of breast, prostate and colorectal cancer enrolled on a clinical treatment trial.

While there has been a great deal written about the use of dietary supplements by individuals with the diagnosis of cancer, there is little known about the use of dietary supplements by individuals enrolled on clinical treatment trials for cancer. This is of particular interest since clinical trials are designed to scientifically evaluate the safety and efficacy of investigational agents. However, it is not known if clinical trials for cancer address the use of dietary supplements in their design or data collection instruments. In an attempt to fill in this gap in information I would like to review a sample of clinical treatment trials for breast, prostate and colorectal cancer from cancer centers nationally.

I would ask that each center forward to me by either by email or disk: 2 breast, 2 prostate and 2 colorectal trials with case report forms. The trials can be any phase but should not be sponsored by a cooperative group. Since many cancer centers participate in the same cooperative groups I would like to avoid duplication of trials. It is my intent to review the design of the trials and the data collection instruments.

If you are interested in participating I have enclosed a blank disk and a prepaid mailing envelope in case you prefer to send me the documents. If you prefer to email the documents to me please forward them to *robertsonlk@msx.upmc.edu*. All information will be kept confidential and the disks and emails will be destroyed upon completion of the study.

My intention is to share my findings with participants upon completion of my dissertation. If you have any questions please feel free to either email me or call me at 412-647-8588.

Thank you in advance for considering this request.

Sincerely,

Lyn B. Robertson RN MSN

APPENDIX G: SPSS DATA FILE CODES

Sysfile Info: C:\Documents and Settings\...\Lyn\patientsurvdataset.sav

File Type: SPSS Data File

Creation Date: 19-APR-2004 07:40:58

Total # of Defined Variable Elements: 474
# of Named Variables: 302

Data Are Not Weighted

Data Are Compressed

File Contains Case Data

Variable Information:

Name		Position
IDNUM	* No label * Measurement level: Nominal Format: A8 Column Width: 8 Alignment: Left	1
ALOEVERA	* No label * Measurement level: Scale Format: F8.2 Column Width: 8 Alignment: Right Value Label 1.00 Yes 2.00 No	2
ALOEWHY	* No label * Measurement level: Nominal Format: A8 Column Width: 8 Alignment: Left	3
ALOEWORK	* No label * Measurement level: Scale Format: F8.2 Column Width: 8 Alignment: Right Value Label 1.00 Yes 2.00 No 3.00 Not Sure	4
ALOEFREQ	* No label * Measurement level: Scale Format: F8.2 Column Width: 8 Alignment: Right Value Label 1.00 1x/day 2.00 2x/day 3.00 3x/day 4.00 weekly 5.00 monthly	5
BILBERRY	* No label * Measurement level: Scale Format: F8.2 Column Width: 8 Alignment: Right Value Label 1.00 Yes 2.00 No	6

```
BILBWHY   * No label *                                                  7
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          Format: A8  Column Width: 8  Alignment: Left

BILBWORK  * No label *                                                  8
          Measurement level: Scale
          Format: F8.2  Column Width: 8  Alignment: Right

          Value    Label

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           2.00    No
           3.00    Not Sure

BILBFREQ  * No label *                                                  9
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          Format: F8.2  Column Width: 8  Alignment: Right

          Value    Label

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           2.00    2x/day
           3.00    3x/day
           4.00    weekly
           5.00    monthly

BLACKCOH  * No label *                                                 10
          Measurement level: Scale
          Format: F8.2  Column Width: 8  Alignment: Right

          Value    Label

           1.00    Yes
           2.00    No

BLCOWHY   * No label *                                                 11
          Measurement level: Nominal
          Format: A8  Column Width: 8  Alignment: Left

BLCOWORK  * No label *                                                 12
          Measurement level: Scale
          Format: F8.2  Column Width: 8  Alignment: Right

          Value    Label

           1.00    Yes
           2.00    No
           3.00    Not Sure

BLCOFREQ  * No label *                                                 13
          Measurement level: Scale
          Format: F8.2  Column Width: 8  Alignment: Right

          Value    Label

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           2.00    2x/day
           3.00    3x/day
           4.00    weekly
           5.00    monthly

CAYPEPP   * No label *                                                 14
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          Format: F8.2  Column Width: 8  Alignment: Right

          Value    Label

           1.00    Yes
```

```
           2.00    No


CAYWHY     * No label *                                                  15
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

CAYWORK    * No label *                                                  16
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

CAYFREQ    * No label *                                                  17
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

CHAMOMIL   * No label *                                                  18
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No

CHAMWHY    * No label *                                                  19
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

CHAMWORK   * No label *                                                  20
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

CHAMFREQ   * No label *                                                  21
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

CHASBERR   * No label *                                                  22
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
```

```
           2.00    No


CHASWHY    * No label *                                                  23
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

CHASWORK   * No label *                                                  24
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

CHASFREQ   * No label *                                                  25
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

COE10      * No label *                                                  26
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No

COEWHY     * No label *                                                  27
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

COEWORK    * No label *                                                  28
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

COEFREQ    * No label *                                                  29
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           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

DEVCLAW    * No label *                                                  30
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
```

```
           2.00    No


DEVWHY     * No label *                                                  31
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DEVWORK    * No label *                                                  32
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

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            2.00    No
            3.00    Not Sure

DEVFREQ    * No label *                                                  33
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

ECHINAC    * No label *                                                  34
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No

ECHWHY     * No label *                                                  35
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

ECHWORK    * No label *                                                  36
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

ECHFREQ    * No label *                                                  37
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

ELEVTHER   * No label *                                                  38
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
```

```
           2.00    No


ELEVWHY    * No label *                                                  39
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

ELEVWORK   * No label *                                                  40
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

ELEVFREQ   * No label *                                                  41
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

EVEPRIM    * No label *                                                  42
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No

EVEWHY     * No label *                                                  43
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           Format: A8  Column Width: 8  Alignment: Left

EVEWORK    * No label *                                                  44
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

EVEFREQ    * No label *                                                  45
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

FEVERFEW   * No label *                                                  46
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           Value    Label

            1.00    Yes
```

```
           2.00    No


FEVWHY     * No label *                                                    47
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           Format: A8  Column Width: 8  Alignment: Left

FEVWORK    * No label *                                                    48
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

FEVFREQ    * No label *                                                    49
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           Value    Label

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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

GARLIC     * No label *                                                    50
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No

GARLWHY    * No label *                                                    51
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GARLWORK   * No label *                                                    52
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

GARLFREQ   * No label *                                                    53
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

GINGER     * No label *                                                    54
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
```

```
           2.00    No


GINGWHY    * No label *                                                  55
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

GINGWORK   * No label *                                                  56
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

GINGFREQ   * No label *                                                  57
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

GINGKO     * No label *                                                  58
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No

GINKWHY    * No label *                                                  59
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

GINKWORK   * No label *                                                  60
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    Yes
            2.00    No
            3.00    Not Sure

GINKFREQ   * No label *                                                  61
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

GINSENG    * No label *                                                  62
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label
```

```
           1.00    Yes
           2.00    No

GINSWHY    * No label *                                                  63
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

GINSWORK   * No label *                                                  64
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

           1.00    Yes
           2.00    No
           3.00    Not Sure

GINSFREQ   * No label *                                                  65
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

           1.00    1x/day
           2.00    2x/day
           3.00    3x/day
           4.00    weekly
           5.00    monthly

GOLDSEAL   * No label *                                                  66
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           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

           1.00    Yes
           2.00    No

GOLDWHY    * No label *                                                  67
           Measurement level: Nominal
           Format: A8  Column Width: 8  Alignment: Left

GOLDWORK   * No label *                                                  68
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

           1.00    Yes
           2.00    No
           3.00    Not Sure

GOLDFREQ   * No label *                                                  69
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label

           1.00    1x/day
           2.00    2x/day
           3.00    3x/day
           4.00    weekly
           5.00    monthly

HAWTHORN   * No label *                                                  70
           Measurement level: Scale
           Format: F8.2  Column Width: 8  Alignment: Right

           Value    Label
```

```
           1.00    Yes
           2.00    No

HAWWHY     * No label *                                                    71
           Measurement level: Nominal
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HAWWORK    * No label *                                                    72
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           2.00    No
           3.00    Not Sure

HAWFREQ    * No label *                                                    73
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           3.00    3x/day
           4.00    weekly
           5.00    monthly

HOPS       * No label *                                                    74
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           2.00    No

HOPSWHY    * No label *                                                    75
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HOPSWORK   * No label *                                                    76
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           2.00    No
           3.00    Not Sure

HOPSFREQ   * No label *                                                    77
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           2.00    2x/day
           3.00    3x/day
           4.00    weekly
           5.00    monthly

HORCHEST   * No label *                                                    78
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           1.00    Yes
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           2.00    No


HORWHY     * No label *                                                    79
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HORWORK    * No label *                                                    80
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            2.00    No
            3.00    Not Sure

HORFREQ    * No label *                                                    81
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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

KAVAKAVA   * No label *                                                    82
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            2.00    No

KAVAWHY    * No label *                                                    83
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KAVAWORK   * No label *                                                    84
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            2.00    No
            3.00    Not Sure

KAVAFREQ   * No label *                                                    85
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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

LICORICE   * No label *                                                    86
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            1.00    Yes
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           2.00    No


LICOWHY    * No label *                                                  87
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LICOWORK   * No label *                                                  88
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            2.00    No
            3.00    Not Sure

LICOFREQ   * No label *                                                  89
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            4.00    weekly
            5.00    monthly

MILKTHIS   * No label *                                                  90
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            2.00    No

MILKWHY    * No label *                                                  91
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MILKWORK   * No label *                                                  92
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            3.00    Not Sure

MILKFREQ   * No label *                                                  93
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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

NETTLE     * No label *                                                  94
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           2.00    No


NETTWHY    * No label *                                                  95
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NETTWORK   * No label *                                                  96
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           Value    Label

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            2.00    No
            3.00    Not Sure

NETTFREQ   * No label *                                                  97
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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

PASSFLOW   * No label *                                                  98
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            2.00    No

PASSWHY    * No label *                                                  99
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PASSWORK   * No label *                                                 100
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            2.00    No
            3.00    Not Sure

PASSFREQ   * No label *                                                 101
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            3.00    3x/day
            4.00    weekly
            5.00    monthly

PCSPES     * No label *                                                 102
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           2.00    No


PCSWHY     * No label *                                                  103
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PCSWORK    * No label *                                                  104
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           Value    Label

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            2.00    No
            3.00    Not Sure

PCSFREQ    * No label *                                                  105
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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

PEPMINT    * No label *                                                  106
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           Value    Label

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            2.00    No

PEPWHY     * No label *                                                  107
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PEPWORK    * No label *                                                  108
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           Value    Label

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            2.00    No
            3.00    Not Sure

PEPFREQ    * No label *                                                  109
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           Value    Label

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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

PHYTOEST   * No label *                                                  110
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           Value    Label

            1.00    Yes
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           2.00    No


PHYTWHY    * No label *                                                  111
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PHYTWOR    * No label *                                                  112
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           Value    Label

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            2.00    No
            3.00    Not sure

PHYTFREQ   * No label *                                                  113
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           Value    Label

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            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

PYGEUM     * No label *                                                  114
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           Value    Label

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            2.00    No

PYGWHY     * No label *                                                  115
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PYGWORK    * No label *                                                  116
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           Value    Label

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            2.00    No
            3.00    Not Sure

PYGFREQ    * No label *                                                  117
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            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

REDCLOV    * No label *                                                  118
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           Value    Label

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           2.00    No


REDWHY     * No label *                                                    119
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REDWORK    * No label *                                                    120
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            2.00    No
            3.00    Not Sure

REDFREQ    * No label *                                                    121
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            1.00    1x/day
            2.00    2x/day
            3.00    3x/day
            4.00    weekly
            5.00    monthly

SOYISOFL   * No label *
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BIBLIOGRAPHY

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 48: 453-458, 1999.

American Cancer Society, Cancer Facts and Figures, 2003.

Angell M, Kassirer JP: Alternative medicine-The risks of untested and unregulated remedies. N Eng J Med 339(12): 839-841, 1998.

Astin JA: Why patients use alternative medicine: Results of a national survey. JAMA 279:1548-1553, 1998.

Astin JA: Why patients use alternative medicine: results of a national survey. JAMA 279(19): 1548-1553, 1998.

Bailar JC, Gornik HL: Cancer undefined. N Engl J Med 336:1569-1574, 1997.

Balneaves LG, Kristjanson LJ, Tataryn D: Beyond convention: describing complementary therapy use by women living with breast cancer. Patient Educ Counsel 38(2): 143-153, 1999.

Balluz L, Okoro C, Bowman B, Serdula M, Mokdad A: Vitamin or supplement use among adults, Behavioral Risk Factor Surveillance System, 13 states, 2001. Public Health Rep 120: 117-123, March-April 2005.

Boon H, Stewart M, Kennard MA, Gray R, Sawka C, et al: Use of complementary/alternative medicine by breast cancer survivors in Ontario: Prevalence and perceptions. J Clin Oncol 18(13): 2515-2521, 2000.

Boon H, Westlake K, Stewart M, Gray R, Fleshner N, Gawin A, Brown JB, Gool V: Use of complementary/alternative medicine by men diagnosed with prostate cancer: prevalence and characteristics. Urology 62(5): 849-853, 2003.

Bourgeault IL: Physicians' attitudes towards patients' use of alternative cancer therapies. Can Med Assoc J 155(12): 1679-1685, 1996.

Bullock ML, Pheley AM, Kiresuk TJ, Lenz SK, Cullion PD: Characteristics and complaints of patients seeking therapy at a hospital based alternative medicine clinic. J Altern and Comp Med 3(1): 31-37.

Burnstein H J: Discussing complimentary therapies with cancer patents: What should we be talking about? J Clin Oncol 18(13): 2501-2504, 2000.

Burnstein HJ, Gelber S, Guadagnoli E, Weeks JC: Use of alternative medicine by women with early-stage breast cancer. N Engl J Med 340(22): 1733-1739, 1999.

Cady R: Are there legal issues of concern for nurses when patients use complementary and alternative medicine? MCN Am J Matern Child Nurs 27(2): 119, 2002.

Calixto, JB: Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Braz J Med Biol Res 33(2): 179-189, 2000.

Cassileth B: Complementary therapies: Overview and state of the art. Cancer Nurs 22(1): 85-90, 1999.

Cassileth BR, Lusk EF, Strouse TB, et al: Complementary unorthodox treatments in cancer medicine: A study of patients, treatment, and practitioner. Ann Intern Med 101:105-112, 1984.

Cassileth BR: Unorthodox cancer medicine. Cancer Invest 4:591-598, 1986.

Chavez ML, Chapman RL: In search of literature on alternative therapies. AM J Syst Pharm 54(22): 2635-2638.

Dalen J E: "Conventional" and "Unconventional" medicine: can they be integrated? Arch Intern Med 158 (20): 2179-2181, 1998.

DiPaola RS, Zhang H, Lambert GH, Meeker R, Licitra E, Rafi MM, Zhu BT, Spaulding H, Goodin S, Toledano MB, Hait WN, Gallo MA: Clinical and biologic activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. N Eng J Med 339(12): 785-791, 1998.

Downer SM, Cody MM, McCluskey P, Wilson PD, Arnott SJ, Lister TA, Slevin ML: Pursuit and practice of complementary therapies by cancer patients receiving conventional treatment. BMJ 309(6947): 86-89, 1994.

Dy G, Bekele L, Hanson L, Furth A, Mandrekar S, Sloan J, Adjei A: Complementary and alternative medicine use by patients enrolled onto phase I clinical trials. J Clin Onc 22(23): 4810-4815, 2004.

Dyer K: Recognizing the potential of alternative medical practices. JAMA 275(8): 578, 1996.

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 280:1569-1575, 1998.

Eisenberg DM, Kessler RC, Foster C, et al: Unconventional medicine in the United States: Prevalence, costs, and patterns of use. N Engl J Med 328:246-252, 1993.

Eisenberg DM: Advising patents who seek alternative medical therapies. Ann Int Med 127(1): 61-69, 1997.

Eisenberg D, Kessler R, Van Rompay M, Kaptchuk T, Wilkey S, Appel S, Davis R: Perceptions about complementary therapies relative to conventional therapies among adults who use both: Results from a national survey. Ann Intern Med 135: 344-351, 2001.

Elder N, Gillcrist A, Minz R.: Use of alternative health care by family practice patients: Arch Fam Med 6: 181-184, 1997.

Ernst E, Cassileth BR: The prevalence of complementary /alternative medicine in cancer. Cancer 83(4): 777-782, 1998.

Ernst E, Cassileth BR: The prevalence of complementary/alternative medicine in cancer: A systematic review. Cancer 83:777-782, 1998.

Ernst E, Fugh-Berman A: Complimentary and alternative medicine: What is it all about? Occup and Environ Med 59(2): 140144, 2002.

Ernst E: Adverse reactions to herbal treatments. J R Soc Med: 92(7): 386, 1999.

Ernst E: Herbal medicines: where is the evidence? Growing evidence of effectiveness is counterbalanced by inadequate regulation. BMJ 321(7258): 395-396, 2000.

Ernst E: The Lord's report on complementary/alternative medicine: something for everyone (editorial). J R Soc Med 94(2): 55-56, 2001.

Ernst E: The role of complementary and alternative medicine. BMJ 321(7269): 1133-1135, 2000.

Ernst E: Harmless herbs? A review of the literature. Am J Med 104(2): 170-178, 1998.

Eskinazi D, Hoffman FA: Progress in complementary and alternative medicine: contribution of the national institutes of health and the food and drug administration. J Altern Complement Med 4: 459-467, 1998.

Fallowfield L, Jenkins V: Effective communication skills are the key to good cancer care. Eur J Cancer 35(11): 1592-1597, 1999.

Fernandez CV, Stutzer CA, MacWilliam L, Fryer C: Alternative and complementary therapy use in pediatric oncology patients in British Columbia: Prevalence and reasons for use and nonuse. J Clin Oncol 16(4): 1279-1286, 1998.

Foster DF, Phillips RS, Hamel MB, Eisenberg DM: Alternative medicine use in older Americans. J Am Geriatr Soc 48(12): 1560-1565, 2000.

Frank D: Weighing the alternatives: Lessons from the Paradoxes of Alternative Medicine. Ann Intern Med 129(12): 1068-1070, 1998.

Gevitz N: Three perspectives on unorthodox medicine. In: Gevitz N, ed. Other healers: unorthodox medicine in America. Baltimore: John Hopkins University Press, 1988: 1-28.

Goldman P: Herbal medicines today and the roots of modern pharmacology. Ann Intern Med 135(8 Part 1): 594-600, 2001.

Goldsmith M, Levitt C, Duarte-Franco E, Kaczorowski J: Complementary health care services: a survey of general practitioners' views. Can Med Assoc J 153 (1): 29-35, 1995.

Gore A, Mills O, Gonzalez L, Volokhonsky H: Herbal supplement use among patients in a rural health system. Hosp Pharm 37(3): 267-273, 2002.

Gray RE, Fitch M, Greenber M: A comparison of physician and patient perspectives on unconventional cancer therapies. Psychoncology 7: 445-452, 1998.

Greenlee H, White E, Patterson R, Kristal A: Supplement use among cancer survivors in the Vitamins and Lifestyle (VITAL) Study Cohort. J Altern Complement Med 10(4): 660-666, 2004.

Greenwald J: Herbal Healing. Time 152(21): 58-60, 1998.

Halperin JD, Zabora JR, Brintzenhofeszoc K: The emotional health of oncologists. Oncology Issues 12, 1997.

Hensrud DD, Engle DD, Scheitel SM: Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination. Mayo Clin Proc 74(5): 443-447, 1999.

Hilsden RJ, Verhoef MJ: Complementary therapies: evaluating their effectiveness in cancer. Patient Educ Couns 38(2): 101-108, 1999.

Jacobs L: Health beliefs of first-degree relatives of individuals with colorectal cancer and participation in health maintenance visits: a population based survey. Cancer Nurs 25(4): 251-265, 2002.

Jacobson JS, Workman SB, Kronenberg F: Research on complementary/alternative medicine for patients with breast cancer: A review of the literature. J Clin Oncol 18:668-683, 2000.

Jacobson JS, workman SB, Kronenberg F: Research on complementary/alternative medicine for patents with breast cancer: A review of the biomedical literature. J Clin Oncol 18(3): 668-683, 2000.

Jazieh A, Kapp M, Ioraida M, Ghouse M, Khalil M, Savidge M, Sethuraman G: The use of dietary supplements by veterans with cancer. J Altern Complement Med 10(3): 560-564, 2004.

Jones H, Metz J, Devine P, Hahn S, Whittington R: Rates of unconventional medical therapy use in patients with prostate cancer: standard history versus directed questions. Urology 59(2): 272-276, 2002.

Joos SK, Hickman DH, Gordon GH, Baker LH: Effects of physician communication skills in medicine. J Gen Intern Med 11: 147-155, 1995.

Kaptchuk TJ, Eisenberg DM: The persuasive appeal of alternative medicine. Ann Intern Med 129(12): 1061-1065, 1998.

Kaptchuk TJ: The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med 136(11): 817-825, 2002.

Kessler DA: Cancer and herbs. N Engl J Med 342(23): 1742-1743, 2000.

Lerner IJ, Kennedy BJ: The prevalence of questionable methods of cancer treatment in the United States. CA Cancer J Clin 42:181-191, 1992.

Maskarinec G, Gotay CC, Tatsumura Y, Shumay DM, Kakai H: Perceived cancer causes: use of complementary and alternative therapy. Cancer Practice (SPELLING) 9 (4): 183-190, 2001.

Miller LG: Herbal medicines: selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med 158(20): 2200-2211, 1998.

Montbriand M: Alternative therapies as control behaviors used by cancer patients. J Adv Nurs 22: 646-664, 1995.

National Cancer Institute (Web site). cancer.nci.nih.gov. 2002.

O'Hara M, Keifer D, Farrell K, Kemper K: A review of 12 commonly used medicinal herbs. Arch Fam Med 7: 523-536, 1998.

Patterson R, Neuhouser M, Hedderson M, Schwartz S, Standish L, Dawen D, Marshall L: Types of alternative medicine used by patients with breast, colon, or prostate cancer: predictors, motives, costs. J Altern Complement Med 8(4): 477-485, 2002.

Penson RT, Castro CM, Seiden MV, Chabner BA, Lynch TJ: Complementary, alternative, integrative, or unconventional medicine. The Oncologist 6:463-473, 2001.

Planta M, Gunderson B, Petit JC: Prevalence of the use of herbal products in a low-income population. Fam Med 32 (4): 252-257, 2000.

Puchalski CM, Epstein LC, Fox E, Johnston MA, Kallenberg GA, Kitchens LW, Larson DB, Lu FG, McLaughlin MA, O'Donnell JF, Sarraf K, Swyers JP, Woolliscroft J, Anderson MB: Report III Contemporary issues in medicine: Communication in medicine. Medical School Objectives Project, 1999.

Richardson MA, Sanders T, Palmer, JL, Greisinger A, Singletary SE: Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol 18(13): 2505-2514, 2000.

Salmenpera L, Suominen T, Sirkka L: Oncology nurses' attitudes towards alternative medicine. Psycho-Oncology 7: 453-459, 1998.

Shumay D, Maskarince G, Gotay C, Heibz E, Kakai H: Determinants of the degree of complementary and alternative medicine use among patients with cancer. J Altern Complement Med 8(5): 661-671, 2002.

Smith MR: Complementary and alternative therapies for advanced prostate cancer. Hem Onc Clin Nor Amer (CHECK THIS) 15 (3): 1-13, 2001.

Sparber A, Bauer L, Curt G, Eisenberg D, Levin T, Parks S, Steinberg S, Wootton J: Use of complementary medicine by adult patients participating in cancer clinical trials. ONF 27(4): 623-630, 2000.

Sparber A, Jonas W, White J, Derenzo E, Johnson E, Bergerson S: Cancer clinical trials and subject use of natural herbal products. Cancer Invest 18(5): 436-439, 2000.

Suchard JR, Suchard MA, Steinfeldt JL: Physician knowledge of herbal toxicities and adverse herb-drug interactions. J Emerg Med 11: 193-197, 2004.

Tasaki K, Maskarinec G, Shumay DM, Tatsumura Y, Kakai H: Communication between physicians and cancer patients about complementary and alternative medicine: exploring patients' perspectives. Psycho-Oncology 11: 212-220, 2002.

The National Forum on Breast Cancer. The report on the national forum on breast cancer. Health Canada, Ottawa, 1994.

Tough SC, Johnston DW, Verhoef MJ, Arthur B, Bryant H: Complementary and alternative medicine use among colorectal patients in Alberta, Canada. Altern Ther Health Med 2: 54-6,58-60, 62-64, 2002.

URL:http://www.thomsonhc.com/hcs/librarian

Verhoef MJ, Hilsden RJ, O'Beirne M: complementary therapies and cancer care: an overview. Patient Educ Couns 38(2): 93-100, 1999.

Vincent C, Furnham A: Complementary medicine: state of evidence. JR Soc Med 92(4) 170-177, 1999.

Vogelzang J L: What you need to know about dietary supplements. Home Health Nurse 19(1) 50-52, 2001.

Wolsko PM, Eisenberg DM, Davis RB, Ettner SI, Phillips RS: Insurance coverage, medical conditions, and visits to alternative medicine providers: results of a national survey. Arch Intern Med 162(3): 281-287, 2002.

Yoon SL, Horne CH: Herbal products and conventional medicines used by community-residing older women. J Adv Nurs 33(1) 51-59, 2001.