

Chemoprevention Trial Feasibility Using Botanicals in Exceptionally High Risk Populations for Lung Cancer

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Abstract

While chemoprevention with botanicals shows promise in reducing cancer risk, recruitment and retention of participants for trials continues to be costly and presents unique challenges. Knowledge of interest, willingness of target populations and evaluation of design challenges are critical to improve accrual in these chemoprevention trials.

Objective: The study assessed interest and willingness of former smokers to participate in a chemoprevention trial using a botanical agent.

Methods: An introductory letter and survey instrument were mailed to 609 consecutive, former heavy smokers, with no cancer, from a database of 826 subjects at the Moffitt Cancer Center.

Results: 202 (40.4%) subjects returned completed surveys. 92-96% reported interest in receiving free lung exams and knowing their lung cancer risk. 88% were interested in participating in a trial evaluating a botanical agent for lung cancer prevention. Over 92% of subjects reported willingness to comply with study requirements; multiple blood draws and trips to the Center, spiral CTs and chest x-rays. Subjects were relatively less enthusiastic (73-79%) about bronchoscopy, taking multiple study agents and assignment to placebo arm.

Conclusions: Our study strongly suggests feasibility, highlights potential challenges and the significant interest and willingness of this exceptionally high risk population to participate in chemoprevention trials.

Keywords: Former smokers; Chemoprevention; Lung Cancer

Introduction

Lung cancer is the leading cause of cancer-related deaths in both men and women in the United States as well the leading cause of cancer death worldwide [1]. The WHO/International Association now recognizes distinct histological lesions, which can be reproducibly graded as precursors of lung cancer. Lung carcinogenesis begins from normal bronchial epithelium and progresses to hyperplasia, metaplasia, dysplasia, carcinoma insitu to invasive cancer [2-6]. Nearly 90% of lung cancer patients have a history of smoking and over 50% of new lung cancers develop among individuals who have previously quit smoking [1]. In addition to strategies to sustain smoking cessation, former smokers may be a motivated target population for chemoprevention [2,7]. Distinct features of lung cancer such as significant mortality and morbidity; long latency; availability of histological lesions as an intermediate stage of lung cancer progression; and the high prevalence of US former smokers, provide a rationale and opportunity for evaluating agents for chemoprevention in this target population. Chemoprevention thus represents an integral part of the future of lung cancer control.

Several agents have been evaluated for the chemoprevention of lung cancer. Cox-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and enzastaurin (LY317615) have been evaluated for the chemoprevention of lung cancer in former or current smokers. However, poor effectiveness or cardiovascular and other toxicities have limited their clinical adoption [8,9]. Other chemopreventive agents evaluated include beta-carotene, alpha-tocopherol, retinol, retinyl palmitate, N-acetylcysteine, or isotretinoin [10-13]. Lung cancers were not prevented by these agents and increased lung cancer risk and toxicities were reported in specific subgroups, establishing the need to identify alternative chemoprevention agents with a more favorable

safety profile. Experience from these previous efforts with lung cancer chemoprevention including the CARET [14] and ATBC [15] trials have clearly demonstrated the need for more thorough preclinical and early phase work to better understand agent safety, dose and mechanism of action.

Botanicals have been shown to influence multiple biochemical and molecular cascades that inhibit mutagenesis, proliferation, induce apoptosis, suppress the formation and growth of human cancers, thus modulating several hallmarks of carcinogenesis, with a significantly superior safety profile than most agents evaluated to date in addition to a long history of use in the human population 38-41. However, unlike other trials with experimental drugs or vitamins and minerals, chemoprevention trials using botanicals present unique challenges to recruitment [12]. We and others have observed several barriers to recruitment in chemoprevention trials using botanicals including research environment, protocol and subject related factors [16]. Although institutional databases, mass media and community outreach efforts to recruit participation in clinical trials have demonstrated

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success in epidemiological studies and treatment trials, we have not experienced the same success in recruitment to early phase trials with FDA approved botanicals [14,15]. Similarly, marketing of the protocol to community physicians and staff using study specific, tested (literacy level and cultural sensitivity) [17], recruitment resources and personal visits by principal investigators to discuss study specific recruitment and retention strategies with community physicians yielded no subjects for chemoprevention trials. Community doctors were assured that subjects will be returned to their practice post trial completion. Our study 12 revealed that committed academic physicians with a specific knowledge and interest in the promise of botanicals for cancer chemoprevention were critical to study recruitment and retention in these chemoprevention trials. These findings are unique and should inform future researchers to carefully consider the use of techniques that will be the most effective, considering the significant cost associated with these various strategies [12].

In addition to ensuring agent effectiveness, safety and committed academic physicians, the ability of research teams and institutions to recognize subject-related factors is critical to recruiting eligible subjects in chemoprevention trials, who are willing to adhere to study agents and protocols, particularly in randomized clinical trials with botanicals that are easily accessible over-the-counter [14-16]. It is therefore important for research teams to evaluate the feasibility and willingness of specific target populations to participate in these trials, prior to initiating these clinical trials. Results of such studies are crucial to inform the design of future chemoprevention trials, specifically in identifying feasibility of the research team to: recruit the required sample size; identify the necessary number of sites and staffing needs, identify barriers and facilitators for participation and educational needs of potential participants regarding relevant risks and benefits [15]. Further, identifying and addressing patient perception of burden with specific procedures required of the trial is a key factor in improving accrual in chemoprevention trials. The aim of the current study was to gain insights of former heavy smokers to assess their interest and willingness to participate in a phase II chemoprevention clinical trial using a botanical agent to prevent lung cancer.

Methods

The Moffitt Cancer Center's Thoracic Oncology program has an established infrastructure to conduct chemoprevention trials and maintains a database of over 1000 former smokers who are recruited specifically from a population undergoing lung cancer screening at the Lifetime Screening Program at the Moffitt Cancer Center. Forty (40) subjects from this database have previously been recruited to other chemoprevention trials successfully [8]. We included subjects from this database who met the following inclusion criteria: age 50 years or over, a 30 pack-year history of smoking but had quit smoking, metaplasia or dysplasia on at least 1 bronchoscopy specimen. Key exclusion criteria included a prior history of malignancy in the past 5 years (except nonmelanoma skin cancer, localized prostate cancer with definitive therapy but no history of hormone therapy, cervical carcinoma in situ, stage I NSCLC 12 months post-surgery without evidence of recurrence), current evidence of lung cancer, any prior chemotherapy or hormone therapy for the purpose of cancer treatment, previous radiation to the chest in the past 5 years, significant cardiopulmonary comorbidity, and a history of asthma that required oxygen, inhaled steroids, or bronchodilators. Subjects in this database had previously consented to be contacted for future research projects but had not been contacted for chemoprevention trials in the past. This exceptionally high risk population had not been surveyed with regard

to their interest and willingness to participate in chemoprevention trials using botanicals.

After obtaining approval from the Institutional Review Board at the University of South Florida, an introductory letter and survey were randomly mailed to the first 609 subjects in this database until 200 surveys were returned. The introductory letter and survey were developed to: (a) provide an introduction to the purpose of the survey; (b) obtain age, gender, education and current smoking status; (c) obtain data regarding acceptance of specific study related procedures that may potentially be barriers, burden or facilitators to participation in this clinical trial; (d) obtain self-perception of lung cancer risk (0-10 scale to represent 0-100% chance of developing lung cancer); (e) identify interest in participating in chemoprevention trials, specifically evaluating a botanical for lung cancer chemoprevention using a botanical agent; and (f) obtain permission and preferred mode of future contact.

Statistical Considerations

We required a minimum of 200 respondents to estimate the proportion favorable responses to the survey (acceptable, would participate) within 7% using a 95% confidence interval. Simple descriptive statistics on demographics (gender, education, smoking histories) and evaluations of specific procedures required in a chemoprevention study were obtained to inform the design of a chemoprevention trial and specifically to estimate a realistic sample size.

The surveys were returned by mail and scanned by the Moffitt Survey Methods Core Facility (SMC). The database was password-protected and only the data entry person and project manager had access to it. All data from the database was transmitted electronically to the study biostatistician. As part of our effort to ensure subject confidentiality, all names and PHI data that might uniquely identify a subject were expunged from this database prior to transmission. This process was supervised jointly by the PI and study biostatistician.

Results

Table 1 provides the demographic characteristics of the responders by gender. A total of two hundred and two (202) men (50.2%) and women (49.8%) provided data for analyses, a response rate of 33%. A total of 609 individuals on the list were mailed the survey of which 405 (67%) were not returned (391: Undeliverable or no response, 16: temporarily away). Two additional surveys were returned, but with responses to only a few items and were not included in analyses. 97% of the respondents were over age 60 and 56% had an undergraduate education or higher. The average years smoked was 40.7 (SD 11.9). Although the target population had initially indicated that they had quit smoking, 29.7% reported that they had relapsed and were current smokers. However, 76% of the responders believed that they had a 50% chance or greater of developing lung cancer.

Table 2 presents the reported interest and motivational factors to participating in chemoprevention trials to prevent lung cancer. In response to interest and motivation to participate, 92-96% reported interest in receiving free lung exams, health status monitoring and knowing their lung cancer risk. 88% were interested in being a part of a trial to evaluate a botanical agent for lung cancer prevention.

Table 3 presents data on reported acceptability of specific procedures required of chemoprevention trials to prevent lung cancer. Over 92% of subjects reported a willingness to comply with study

Demographic Variables	Men	Women	All
Gender	101 (50.2)	100 (49.8)	202
Age: 51-60	2 (2.0)	1 (1.0)	3 (1.5)
Age: 61-70	49 (50.0)	64 (65.3)	114 (57.9)
Age: 71-80	47 (48.0)	33 (33.7)	80 (40.6)
Education: Less than diploma/GED	0 (0.0)	0 (0.0)	0 (0.0)
Education: Diploma or GED	29 (29.0)	30 (30.9)	60 (29.7)
Education: Trade School	11 (11.0)	12 (12.4)	23 (11.4)
Education: Undergraduate	29 (29.0)	30 (30.9)	59 (29.2)
Education: Graduate/Professional	31 (31.0)	25 (25.8)	56 (27.7)
Smoking-related Variables	Men	Women	All
Years smoked: M (SD)	41.5 (12.0)	39.8 (11.8)	40.7 (11.9)
Currently using tobacco	35 (35.0)	25 (25.5)	60 (29.7)
Lung cancer chances>50%	71 (72.4)	79 (79.8)	151 (76.3)

Notes: Except where noted, values are number of respondents with percentage in parentheses. Percentages presented are based on number of responders to the item. For years smoked, the values are sample mean (M) and standard deviation (SD).

Table 1: Descriptive Statistics for all Responders by Gender.

Interested/Participate	Men	Women	All
Free lung exams	94.9 (92.7, 97.1)	92.9 (90.4, 95.5)	93.9 (92.2, 95.6)
Testing natural compound	90.6 (87.7, 93.6)	85.7 (82.2, 89.3)	88.2 (85.9, 90.5)
Improve lung cancer treatment	99.0 (98.0, 100.0)	92.9 (91.5, 96.3)	96.5 (95.2, 97.8)
Regular health evaluations	92.9 (90.3, 95.5)	92.2 (90.3, 95.5)	92.9 (91.1, 94.7)
Knowing my lung cancer risk	95.9 (93.9, 97.9)	89.0 (85.9, 92.1)	92.5 (90.6, 94.3)

Notes: Values are percentage of respondents expressing interest or willingness to participate with 95% confidence interval values in parentheses.

Table 2: Interest and motivational factors to participating in Chemoprevention Trials to prevent Lung Cancer.

Acceptable/Participate	Men	Women	All
Staying on and complying with agent/questionnaires/visits	93.7 (91.2, 96.2)	90.9 (88.0, 93.8)	92.3 (90.4, 94.2)
Taking capsules twice daily	75.0 (70.6, 79.4)	70.7 (66.1, 75.3)	73.0 (69.8, 76.2)
Bronchoscopy at start and end	83.5 (79.7, 87.3)	73.7 (69.3, 78.2)	78.7 (75.8, 81.6)
At least 3 trips to research site	95.8 (93.8, 97.9)	83.8 (80.1, 87.5)	89.8 (87.6, 92.0)
At least 3 blood draws	95.9 (93.9, 97.9)	94.9 (92.8, 97.2)	95.4 (93.9, 96.9)
Two spiral CTs and chest X-rays	97.9 (96.5, 99.4)	94.8 (92.6, 97.1)	96.4 (95.1, 97.7)
Chance of placebo assignment (Randomized)	72.6 (68.1, 77.2)	74.7 (70.4, 79.1)	73.8 (70.7, 77.0)

Notes: Values are percentage of respondents expressing interest or willingness to participate with 95% confidence interval values in parentheses.

Table 3: Acceptability of Specific Procedures Required of Chemoprevention Trials.

requirements; multiple blood draws and trips to the study site, spiral CTs and chest X-rays. Subjects were relatively less enthusiastic (73-79%) about undergoing bronchoscopy, taking multiple study agents daily (dose of study agent) and possible assignment to a placebo arm. Overall, there were no statistically significant differences between men and women in their responses to the survey.

Discussion

Barriers and challenges to subject recruitment and retention, commitment to participation and compliance are inherent to all clinical trial design and organization. These challenges are significantly associated with protocol and patient-related factors, including the behavioral dynamics of the research team, institutional infrastructure, community and participating subjects [14]. Although other research teams [8,16] have examined feasibility of strategies used to recruit former smokers in chemoprevention trials, these strategies remain costly, not targeted to specific populations nor contemporary. Once the target population, the source of subjects and agent to be evaluated have been identified, it is critical for research teams to carefully examine the potential challenges and facilitators unique to the target population, study agent and disease site as a first step of the design phase of a lung cancer chemoprevention trial. These initial steps can significantly

minimize logistic complexity of protocols, maximize participant eligibility, simplify data collection, and take into account the complex behavioral dynamics of the clinical trial process. To our knowledge, this is the first study to assess the interest, feasibility and willingness of former and current heavy smokers to participate in chemoprevention trials using a botanical agent to prevent lung cancer.

When considering exceptionally high risk target populations for chemoprevention of lung cancer, research over the past decade has demonstrated that the clinical and biologic response of potential chemoprevention agents differs between active and former smokers [2]. Studies have also demonstrated that the extent of DNA damage, histologic abnormalities and adverse outcomes were far greater in current smokers compared to former smokers [9,18]. Based on these studies, it is clear that the target population for specific agents and dose selected must be established. However, based on our observation, over 30% of subjects from our database of former smokers had resumed smoking. These observations clearly establishes the need to continuously screen and monitor smoking status of subjects using objective markers such as urinary cotinine levels to ensure that subjects are non-smokers at trial entry and continue to remain smoke free during the active phase of intervention in these trials. It may also be important to include concurrent smoking cessation and education

programs that inform subjects of potential risks of smoking while participation in the clinical trial and early stopping rules incorporated in the study design.

Lung cancer chemoprevention trials have historically utilized various recruitment strategies such as mass mailing study information and eligibility questionnaires to age selected health insurance subscribers to more contemporary approaches such as using social media sites [19]. However, these strategies have limitations in that they may be unsuccessful in recruiting of economically disadvantaged as well as low literacy individuals, who are underrepresented among individuals with health insurance or with ready access to social media sites. Our group was able to access a database that was successfully utilized to recruit subjects for a secondary chemoprevention trial from this population, similar to what would be proposed based on this study [8] at exceptional risk that had prior familiarity with the environment and research teams. However, we noted significant attrition of subjects who were no longer at their mailing address. Based on this observation, it was evident that this database needs more frequent and at least annual updates with multiple sources by which subjects may be contacted, including e-mails in addition to continuously adding new subjects from the screening program to the pool.

With respect to subject-related factors, chemoprevention trials are targeted to high risk, otherwise healthy individuals who have no symptoms of disease [11], making it important for tapping into the intrinsically motivating factors for recruitment. Our survey results demonstrate that former and current heavy smokers were fully aware of their exceptional risk of lung cancer and were highly enthusiastic and eager to participate in chemoprevention trials that may reduce this risk. Other factors that were important to participants personally included free lung exams, regular health evaluations, knowing their lung cancer risk and testing novel, plant-based compounds to further reduce their risk of cancer. Similar results of interest and willingness to participate in chemoprevention trials have been observed in high risk subjects for colon cancer. The most highly rated benefits of trial participation were the possibility of reducing one's chance of getting cancer and the possibility of preventing others from getting cancer in the future [20].

In spite of the lack of evidence, high risk populations, cancer patients and survivors are interested and have access to botanicals and other biologics over the counter, many of which are available in similar doses as those used in chemoprevention trials, and marketed aggressively [14,21]. This increased availability has encouraged subjects to opt out of participation in randomized clinical trials, where they have a chance at being assigned to a placebo arm [9,22,23]. Subjects have been unwilling to be randomized to placebo-control arms of trials, especially if the trial involves immense burden to them such as compliance to agent and diet, frequent visits, completion of monitoring tools and most importantly if these studies include invasive procedures for biomarker evaluation such as biopsy, fine needle aspirations or bronchoscopy [21]. Similarly, Hudmon et al, [24] reported that approximately 50% of the subjects objected to participation in future trials involving placebos. These barriers have significant implications in recruitment and retention of subjects and most importantly the risk of subjects taking other OTC agents of similar potency. To overcome these challenges, research teams may incorporate education of subjects on the topics of: (a) importance and need for randomized clinical trials; (b) standardization of agents and bioavailability issues with OTC supplements compared to agent provided by research team under approval by Food and Drug Administration (FDA) as an investigational

new drug (IND); and (c) most importantly regarding compliance to instructions to avoid taking other similar agents during the active phase of the trial. Additionally incorporating cross-over trial designs where all subjects will have the opportunity to receive study agent and placebo may be a more acceptable option. Emphasizing the importance of trial requirements thorough counseling at study presentation has been observed to improve recruitment of better research team and subject dynamics [14,25,26].

Subject burden is a critical issue that determines recruitment and retention in chemoprevention trials. Although subjects were willing to come frequently to the study site and obtain blood draws for safety monitoring, chest x-rays and spiral CTs, there seemed a relatively decreased enthusiasm for the invasive procedure of having a bronchoscopy at start and end of the study. Similar results were reported by Hudson et al [24] in a study of subjects at high risk for colon cancer where the most troublesome barrier reported by subjects was having colonoscopies. Several blood-based, sputum and other biomarkers appear promising. However, to date, data from prospective trials are limited with regard to the validity of the diagnostic potential of these markers [27]. Future chemoprevention trials must include correlative studies concurrently evaluating markers obtained from invasive procedures such as biopsy using bronchoscopy with non-invasive markers obtained from sputum or bronchial brushings. If valid, these biomarkers obtained using non-invasive procedures can significantly reduce the burden to subjects, improve safety and incorporated in the design of future chemoprevention trials to evaluate agents for lung cancer chemoprevention. Similarly, subjects were less enthusiastic about multiple dosing of study agents. Although several botanicals have demonstrated safety and bioavailability, the doses at which they produce changes in relevant intermediate endpoint biomarkers and because of their short half-lives, large and frequent dosing may be required. For example, although the bioavailability and safety of the botanical, curcumin at doses ranging from 4 g/day up to 15 g/day [28] has been documented, the major issues reported by subjects were pertaining to increased burden due to large oral doses of curcuminoid mixtures in addition to frequency of dosing due to its short half-life of 2-4 hours. With a better understanding of the characteristics of these dietary phenolics, recent research has focused on developing formulations of curcumin to dramatically improve bioavailability, increase half-life, provide sustained effects and reduce patient burden towards improved compliance. Two major strategies have been pursued to improve the bioavailability of curcumin [29,30]. The first is a combination with adjuvants capable of increasing the absorption of curcumin, like piperine, quercetin, or turmeric oil [31-33]. The second strategy has been the inclusion of curcumin in a lipophilic matrix (liposomes, Phytosomes, and lipid micro- and nanoparticles) or encapsulation with micellar surfactants or casein. Based on our study although subjects were willing to take the botanical agent, other studies have reported concerns voiced by subjects who were made aware of agent or procedural side effects described in the consent form or when symptoms developed during run-in phase of the CARET trial [18]. The choice of formulation, doses and frequency of administration of chemoprevention agents must utilize such formulations, taking into consideration patient burden, and clearly discussion of the incidence and severity of potential side effects and symptoms may be useful, ultimately ensuring compliance to study agent and protocol.

The current study has several limitations. The study was limited to evaluating a focused target population of former smokers at exceptional risk for lung cancer based on a long smoking history and as such not relevant to other high risk populations who are non-smokers. . The

study also focused on utilizing botanical agents for chemoprevention and does not inform research teams on other pharmaceutical agents, potentially with a greater toxicity profile than botanicals for lung cancer chemoprevention. Additionally, although we surveyed the first 609 subjects in our database, 407 (69%) of subjects contacted had moved or relocated and were unable to be contacted. This group of non-responders may represent relatively younger, less educated or lower socio economic demographics, whose data we were unable to capture in this survey. The non-responders may also include subjects who feel stigmatized or those who may have reverted to smoking. Our survey failed to include questions with regard to psychosocial barriers to participation in chemoprevention trials (such as feeling stigmatized because of their smoking status and worries about being coerced into stopping smoking) [34]. These factors may have implications both in recruitment and retention of subjects in chemoprevention trials targeting former smokers adding to subject-related challenges to recruitment. Future studies may target the general population using other methods of contact such as social media [20,21,35,36] to examine factors that may be unique to this target population. Finally, public health research about people's intention to perform a health behavior indicates it is not always in sync with actual behavior [37]. However, behavioral intentions are a good marker of attitude and, in turn, attitudes are the best predictors of actual behavior [38]. In the absence of data on actual participation rates in chemoprevention trials for former heavy smokers, these data represent the best available evidence of feasibility of recruitment [39].

Conclusions and Future Directions

Our study strongly identified the significant interest and willingness of former smokers to participate in a chemoprevention trial using a botanical agent aimed at prevention of lung cancer. The acceptability of participation from a subject's perspective is necessary for ultimate trial success. Additionally, it highlights potential challenges that can inform and refine the research design of future clinical trials that are more realistic as well as feasible. Research teams should continue to utilize a contemporary approach with pretrial development as well as frequent evaluation, flexibility to revise and remove barriers [14,40] and continuous implementation of novel solutions to facilitate recruitment and remove barriers in chemoprevention trials to assure responsiveness to emerging challenges and potential solutions in the evolving scientific literature. A frequently updated (addresses, phone numbers) database was utilized for the survey-based study and may be a good starting point to recruit high risk subjects in clinical trials, especially with subjects who had a recent visit. However, we observed a significant attrition of subjects from this database. Alternately, prospective recruitment of subjects in clinical trials in addition to integration of recruitment into low dose CT screening programs may offer an excellent venue for approaching high risk subjects, who are motivated by virtue of participation in a screening program. These strategies will ultimately be critical to move this field of chemoprevention forward to prevent lung and other major cancers [41,42].

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Conflicts of Interest

None

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