Introduction

Lung cancer, the leading cause of cancer deaths worldwide (1), demonstrates a high level of symptom burden (2-5). Poorly controlled symptoms and impaired quality of life can negatively affect treatment adherence (6,7) and are associated with worse therapeutic outcomes and prognosis (8-10). Symptom improvement has been an important efficacy endpoint for FDA drug approvals since the early
1980s (11). However, people with lung cancer still have unmet needs regarding symptom management and quality of life (12,13).

People with cancer commonly use or express interest in using integrative therapies such as herbs, acupuncture, mind-body practices, and lifestyle modifications with the intent of relieving symptoms, improving quality of life, and enhancing wellness (14-16). Patients’ positive outcome expectations, lower perceived barriers, and family support have been associated with use of integrative therapies (17,18). A systematic review of 45 National Cancer Institute (NCI)-designated comprehensive cancer center websites found that herbs (66.7%) is one of the most common integrative therapies mentioned (19). However, due to low quality evidence from mostly observational or case studies, herbs are often not recommended and the potential for harm is to be avoided (20-22), particularly for people with cancer who are undergoing active treatment (23,24).

Increased interest in herbal products and limited research evidence call for the conduct of more rigorous herbal clinical trials in the oncology setting.

Previous clinical trials of herbal products in oncology suffer from numerous limitations including poor study design, lack of randomization and blinding, poor outcome definition, insufficient sample size and analyses, and missing data (25-30). One of the biggest challenges to high quality clinical trials is recruitment and retention of study participants (31). An analysis of more than 700 NCI Cancer Therapy Evaluation Program (CTEP) trials revealed that 81.5% (n=623) of trials failed to achieve projected accrual goals, and 37.2% (n=284) failed to achieve the minimum patient enrollment at study closure (32). Poor trial accrual increases the cost of doing research and leads to underpowered studies that may undermine the potential efficacy of interventions.

In order to design high quality herbal clinical trials for managing specific symptoms in oncology, we need to examine the distribution of common symptoms so that enough patients can meet criteria for enrollment. In addition, the complexity of herbal ingredients and concerns over product consistency due to lack of regulation and standardization of herbal products may prevent patients from participating in clinical trials (33). Evaluating willingness to participate in herbal research among cancer patients will help researchers create recruitment strategies to ensure that trials are successfully completed on time. We conducted this study to quantify symptom burden and the factors associated with willingness to participate in herbal clinical trials among lung cancer patients. Our study results can inform the design of future herbal clinical trials for cancer symptom management and provide quality evidence for herbal use among cancer patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-865).

**Methods**

**Study design and patients**

We conducted a cross-sectional analysis among a consecutive convenience sample of patients seen in the outpatient thoracic medical oncology clinic at the Hospital of the University of Pennsylvania between June 2010 and October 2011. Eligible participants were 18 years of age or older, and had a primary diagnosis of lung cancer and a Karnofsky performance score of 60 or greater. Additional inclusion criteria included the approval of the patient’s oncologist and the patient’s ability to understand and provide informed consent in English. We did not exclude patients based on lung cancer stage or subtype [small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC)], cancer stage, cancer recurrence status, treatment types, or status. All patients provided informed consent before participating in the study. The Institutional Review Board of the University of Pennsylvania approved the study (IRB#810056). The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). We previously published additional details about study design and procedures (17,34).

**Study variables**

**Primary dependent variable: willingness to participate**

Our primary dependent variable was self-reported willingness to participate in herbal research. To measure patients’ attitudes towards participation in herbal clinical studies, we asked them: “If you were to have bothersome symptoms during or after the cancer treatment, how likely is it that you would participate in a study that involves herbs (natural products)?” We provided them with five response options including “very unlikely”, “unlikely”, “not sure”, “likely”, and “very likely”. We dichotomized the primary outcome into two categories based on their survey responses; we categorized responses of “very unlikely”, “unlikely”, and “not sure” as unlikely to participate in herbal studies, and responses of “likely” and “very likely” as likely to participate in herbal trials.
Secondary dependent variable: symptom burden
Our secondary dependent variable was symptom burden, which we measured using the core MD Anderson Symptom Inventory (MDASI) (35,36). The MDASI is a multi-symptom patient-reported outcome (PRO) measure that assesses the severity of symptoms at their worst in the last 24 hours on a 0–10 numeric scale, with 0 indicating “not present” and 10 indicating “as bad as you can imagine.” Enrolled patients used the MDASI to rate 13 symptoms including pain, fatigue, nausea, disturbed sleep, distress/feeling upset, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness/tingling. A lower score indicated fewer bothersome symptoms. In order to help inform future symptom trials, we chose a score of 4 or greater to indicate clinically moderate or severe symptoms (37,38).

Covariates
We measured demographic factors such as age, gender, race, and education level through patient self-report. Clinical factors such as type of cancer, stage, and diagnostic history were obtained through chart abstraction. We dichotomized cancer stage into localized or metastatic disease in the analysis.

Statistical analysis
This dataset is a subset of a larger previously published study (31,32). We performed statistical analysis using STATA software (Mac version 15.0, StataCorp, College Station, TX). Descriptive statistics were used to examine the distribution of the outcomes and covariates. Next, we used \( \chi^2 \) tests to identify which covariates were associated with willingness to participate in herbal studies. Multivariate logistic regression analysis were conducted to identify independent predictors of willingness to participate in herbal studies, using only variables that had a P value of <0.10 in the \( \chi^2 \) analyses. All analyses were two-sided at a significance level of 0.05. The sample size was set by the parent study.

Results
Of the 382 consecutive patients approached, 340 (89%) agreed to participate. The main reasons patients declined participation were lack of interest 35 (9%) and lack of time (2%). Additionally, 12 subjects withdrew consent, 11 subjects did not return the survey, and 29 subjects were excluded from the analysis due to incomplete data, resulting in the final sample of 288 (see Figure 1). This population reflects a response rate of 75% among eligible subjects. Among 288 participants, 55% were female, 42% were >65 years, 54% had stage IV cancer, and 86% had NSCLC (see Table 1).

Willingness to participate in herbal clinical trials in lung cancer
Nearly half (n=133, 46%) of lung cancer patients indicated willingness to participate in an herbal clinical trial. In our univariate analysis, younger patients (P=0.059) with higher education (P<0.01) were more willing to participate in herbal clinical trials (see Table 1). We did not find any association between willingness to participate and race (P=0.59), gender (P=0.15), cancer stage (P=0.30), time since diagnosis (P=0.69), or histology (P=0.89). After adjusting for age, higher education remained significantly associated with willingness to participate [adjusted odds ratio (AOR) 1.87, 95% confidence interval (CI) 1.12–3.10, P=0.016, see Table 2]. The degree of symptom burden was also not associated with willingness to participate in an herbal clinical trial.
### Characteristics of survey participants and willingness to participate in herbal clinical trials in lung cancer (N=288)

| Clinical characteristics | Participants, N [%] | Willingness to participate N [%] | P value |
|--------------------------|---------------------|--------------------------------|---------|
| Gender                   |                     |                                |         |
| Male                     | 130 [45]            | 54 [42]                        | 0.15    |
| Female                   | 158 [55]            | 79 [50]                        |         |
| Age (years)              |                     |                                |         |
| Mean [SD]                | 62.9 [10.9]         |                                |         |
| ≤65                      | 167 [58]            | 85 [51]                        |         |
| >65                      | 121 [42]            | 48 [40]                        |         |
| Race                     |                     |                                |         |
| White                    | 241 [84]            | 113 [47]                       |         |
| Non-white                | 47 [16]             | 20 [43]                        |         |
| Education                |                     |                                |         |
| High school or less      | 102 [35]            | 36 [35]                        | <0.01   |
| College and above        | 186 [65]            | 97 [52]                        |         |
| Stage                    |                     |                                |         |
| Localized                | 133 [46]            | 57 [43]                        |         |
| Metastatic               | 153 [54]            | 75 [49]                        |         |
| Time since diagnosis (months) |                 |                                |         |
| ≤12                      | 149 [52]            | 65 [44]                        |         |
| >12 and ≤36              | 75 [26]             | 37 [49]                        |         |
| >36                      | 61 [21]             | 29 [48]                        |         |
| Histology                |                     |                                |         |
| NSCLC                    | 245 [86]            | 114 [47]                       | 0.89    |
| SCLC                     | 33 [11]             | 14 [42]                        |         |
| Other                    | 7 [2]               | 3 [43]                         |         |

SD, standard deviation; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

### Characteristics related to symptom prevalence

Table 3 presents the moderate to severe symptoms that lung cancer patients experience as measured by the MDASI (≥4 on MDASI scale). The top five most prevalent symptoms among our study population were fatigue (57%), drowsiness (44%), disturbed sleep (43%), distress (42%), and shortness of breath (36%).

We also examined the symptoms by cancer stage. In our study, 153 (54%) patients had metastatic lung cancer. Although we found that a slightly higher percentage of patients with metastatic disease experienced symptom burden than those with localized disease, it did not reach statistically significance. This trend was reversed in shortness of breath. A greater proportion (44%) of people with localized disease experienced moderate to severe shortness of breath compared to those with metastatic disease (30%, P=0.012).

### Clustering of symptoms

We found that 30–40% of patients experienced co-
occurring symptoms. Among these, 41% of patients experienced both fatigue and drowsiness, 37% experienced fatigue and distress, and 36% experienced fatigue and disturbed sleep (Table 4).

**Discussion**

Lung cancer is a devastating disease with substantial symptom burden. In this survey study of nearly 300 cancer patients, we found that almost one in two patients were willing to participate in an herbal clinical trial. In addition, we identified the common symptoms of fatigue, drowsiness, distress, sleep disturbance, and shortness of breath that these studies can target. These findings set the foundation for designing adequately powered studies to evaluate the safety and efficacy of herbal trials for symptom control in lung cancer patients.

Advances in cancer therapies necessitate patient engagement in research activities. Less than <10% of adult cancer patients participate in clinical trials (39,40). Research examining accrual to herbal clinical trials is extremely limited, with only several studies investigating

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**Table 2** Multivariate logistic regression predicting willingness to participate

| Demographic and clinical variables | Multivariate analysis |  
|--------------------------|--------------|---|
|                          | AOR          | 95% CI   | P value |
| Age (years)              |              |          |         |
| ≤65                      | –            |          |         |
| >65                      | 0.71         | 0.44–1.16|         |
| Education                |              |          | 0.016   |
| High school or less      | –            |          |         |
| College and above        | 1.87         | 1.12–3.10|         |

Non-White: 77% Black/African American, 15% Asian, and 8% other. AOR, adjusted odds ratio; CI, confidence interval.

**Table 3** Advanced disease status and symptom prevalence (≥4 on the MDASI scale)

| Symptom                | N [%] | Stage                  |  
|------------------------|-------|------------------------|
|                        |       | Localized, N [%]       | Metastatic, N [%] | P value |
| Fatigue                | 165 [57] | 70 [53] | 95 [62] | 0.11 |
| Drowsiness             | 127 [44] | 55 [41] | 72 [47] | 0.31 |
| Disturbed sleep        | 123 [43] | 57 [43] | 66 [43] | 0.97 |
| Distress               | 121 [42] | 55 [41] | 66 [43] | 0.76 |
| Shortness of breath    | 103 [36] | 58 [44] | 45 [30] | 0.012 |
| Feeling sad            | 102 [35] | 43 [32] | 59 [39] | 0.27 |
| Dry mouth              | 92 [32] | 36 [27] | 56 [37] | 0.10 |
| Pain                   | 91 [32] | 35 [27] | 56 [37] | 0.069 |
| Difficulty remembering | 90 [31] | 41 [31] | 49 [32] | 0.83 |
| Lack of appetite       | 79 [28] | 36 [27] | 43 [28] | 0.75 |
| Nausea                 | 62 [22] | 27 [20] | 35 [23] | 0.62 |
| Numbness/tingling      | 52 [18] | 22 [17] | 30 [20] | 0.52 |
| Vomiting               | 21 [7]  | 12 [9]  | 9 [6]   | 0.31 |

MDASI, MD Anderson Symptom Inventory.
willingness to participate in complementary and alternative medicine (CAM). A prior study of 453 outpatients at the University of Texas MD Anderson Cancer Center revealed that approximately 74% of patients stated interest in CAM information and research, 39% among them expressed willingness to participate in CAM research (41). Another study found that 49.8% (N=148) of 300 breast cancer participants reported willingness to participate in an acupuncture clinical trial (42). Our study is the first to reveal that almost half of lung cancer patients (46.2%) are willing to participate in herbal clinical trials. This level of willingness can support the feasibility of conducting future rigorous herbal trials in patients affected by lung cancer.

We found that the patients with higher education were almost twice as likely to participate in herbal studies than those with lower education (AOR 1.87, 95% CI, 1.12–3.10, P=0.016). Prior studies have indicated that higher education is related to both greater CAM use among lung cancer patients (AOR 2.17, 95% CI, 1.29–3.64) (34) and more willingness to participate in acupuncture trials among breast cancer patients (AOR 4.24, 95% CI, 1.77–10.17) (42). This association has also been established previously in population-based studies (41,43) on CAM use and willingness to participate in conventional cancer clinical trials (44). Appropriately educating and engaging those with a lower education status will ensure that they are adequately represented in future studies.

An appropriately designed herbal clinical trial for cancer symptom management should enroll participants who are experiencing sufficiently severe symptoms to avoid the potential floor effect and null findings (45). Consistent with a prior study, our study population experienced fatigue, drowsiness, disturbed sleep, distress, shortness of breath, sadness, dry mouth, pain, and difficulty remembering (4). By targeting these common symptoms, future herbal clinical trials will have greater potential to reach their accrual goals.

Herbal clinical practice often targets multiple symptoms known as symptom clusters (45,46); however, limited clinical trials have investigated the efficacy of interventions for these symptom clusters. Our study indicated that several common co-occurring symptoms such as fatigue and disturbed sleep, fatigue and distress, and fatigue and shortness of breath can be targeted for future symptom intervention research. By properly integrating outcome measures and biomarkers, researchers can advance understanding of these co-occurring symptoms’ underlying mechanisms (45,47).

This study has several limitations that should be considered when interpreting its results. First, we only examined willingness to participate in an herbal clinical trial, which may differ than actual participation. However, past research suggests intention is a very strong predictor of actual behavior (48). Second, we used data from a cross-sectional survey conducted in an outpatient medical oncology clinic; the majority of the participants were white (84%) with a diagnosis of NSCLC (86%), which may limit the generalizability of our results. Third, although our study included important socio-demographic variables, it may have missed other co-variates. Lastly, our quantitative analyses only estimated rates of willingness to participate in an herbal trial. Future qualitative and mixed-methods research should investigate specific facilitators and barriers for lung cancer patients to participate in herbal trials.

### Conclusions

Lung cancer is a leading cause of mortality and morbidity worldwide. We found that approximately one in two lung cancer patients are willing to participate in an herbal trial. The association between education level and willingness to participate warrants future targeted efforts to adequately inform patients from lower education levels about research opportunities. Further, our study indicates that people with

| Symptoms               | Fatigue, N [%] | Drowsiness, N [%] | Disturbed sleep, N [%] | Distress, N [%] | Shortness of breath, N [%] |
|------------------------|---------------|-------------------|------------------------|-----------------|---------------------------|
| Fatigue                | 165 [57]      | 117 [41]          | 103 [36]               | 107 [37]        | 86 [30]                   |
| Drowsiness             | 127 [44]      |                   | 92 [32]                | 94 [33]         | 70 [24]                   |
| Disturbed sleep        | 123 [43]      |                   | 91 [32]                |                 | 65 [22]                   |
| Distress               | 121 [42]      |                   |                       | 69 [24]         |                           |
| Shortness of breath    |               |                   |                        |                 | 103 [36]                  |

Table 4 Patients experiencing the top 5 co-occurring symptoms
lungs cancer carry a substantial symptom burden, although the degree of symptom burden was unrelated to willingness to participate in herbal clinical trials. By conducting rigorous clinical trials of herbal or other interventions that target one or multiple symptoms, we have the potential to improve the lives of millions of individuals impacted by lung cancer.

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Footnote

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