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# **CHARACTERISTICS OF TASTE AND SMELL ALTERATIONS IN PATIENTS TREATED FOR LUNG CANCER: TRANSLATION OF AND RESULTS USING A SYMPTOM-SPECIFIC QUESTIONNAIRE**

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This thesis is dedicated to my husband *Robert* and our sons *David* and *Chris*.

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## ABSTRACT

**Background:** Taste and smell alterations (TSAs) have been found to be common and distressing symptoms for patients with cancer. TSAs may also relate to other symptoms affecting food consumption and contribute to poor nutritional intake. Evidence-based knowledge to guide healthcare staff in identification and management of TSAs is lacking. Patients with lung cancer have been reported to perceive TSAs but these alterations are poorly understood.

**Aim:** This thesis explores the characteristics of TSAs in a lung cancer population from data obtained using a questionnaire translated and culturally adapted for the purpose.

**Methods:** Two studies are included in this thesis. The first study uses a 5-step method for translation and cultural adaptation of the Taste and Smell Survey (TSS) for use in a Swedish population. The second study uses the translated TSS to explore the characteristics of TSAs reported by patients after starting treatment for lung cancer and to elucidate how patients describe their TSAs. This study also explores how TSAs relate to demographics, nutritional intake, six-month weight change and other symptoms.

**Results:** The process for translation and cultural adaptation of the TSS produced a robust instrument in Swedish. Each of the 5-steps contributed information enhancing the quality of the translation, emphasising the value of using a multi-step process. Using the translated TSS, 61 out of a sample of 89 patients with primary lung cancer were found to report TSAs at some stage during the study period. Patients reporting TSAs were younger and more often smokers. Gender differences were seen in characteristics of TSAs reported with more women reporting stronger sensations of sour, bitter and smell and more men reporting weaker sensations of all tastes and smell. Patients reporting TSAs commonly reported other symptoms, notably loss of appetite, nausea and early satiety. A mean six-month weight loss of 6% was seen in patients reporting both TSAs and loss of appetite. Reduced enjoyment of eating was a key feature of patients' descriptions of TSAs. Energy intakes were seen to decline with increasing number of reported TSAs.

**Conclusions:** The translation and cultural adaptation of the TSS allows comparisons between English and Swedish speaking populations. Gender differences are seen in characteristics of reported TSAs and how TSAs are described. This highlights a need for further investigation of this phenomenon and may indicate that different approaches for identification and management of TSAs in men and women should be considered. Patients described TSAs in terms of both sensory changes encompassing taste and/or flavour, and hedonic changes indicating that TSAs are multi-dimensional. A consistent vocabulary might therefore facilitate more clear communication about TSAs among patients, healthcare staff and researchers.

**Key words:** cultural adaptation, gender, instrument, lung cancer, nutrition, symptoms, taste and smell, translation.

## LIST OF PUBLICATIONS

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## LIST OF ABBREVIATIONS

BMI	Body Mass Index
CVI	Content Validity Index
I-CVI	Item Content Validity Index
IDNT	International Dietetics and Nutrition Terminology
NSCLC	Non-Small Cell Lung Cancer
SCLC	Small Cell Lung Cancer
S-CVI/ave	Scale Content Validity Index/average
PG-SGA	Patient-Generated Subjective Global Assessment
SOL	Smak och lukt /Taste and Smell
T1 – T4	Interview time points 1-4
TNM	Tumor, Node, Metastasis
TSA <sub>s</sub>	Taste and Smell Alterations
TSS	Taste and Smell Survey





# 1 PROLOGUE

The focus of this thesis is on translating and using an instrument known as the Taste and Smell Survey (TSS) in the exploration of the characteristics of taste and smell alterations (TSAs) among patients with lung cancer, who have received or are receiving surgical or oncological treatment.

I have worked as a clinical dietitian in both the United Kingdom and Sweden primarily with patients with cancer. However, my first real awakening to the profound problems that TSAs can cause came in my contact with an otherwise healthy patient who had lost the senses of taste and smell after a head trauma. This patient grieved the loss of being able to enjoy the flavours of a meal previously such a normal part of everyday life. Eating had now become something that was necessary for survival rather than a pleasure. It was clear that this loss severely affected both family and social life and I felt painfully limited in the advice that I could give as a dietitian. I was aware that TSAs were among the symptoms experienced by patients with cancer. However, since so little information was available about TSAs and their management, I realised that this was a neglected area.

The Taste and Smell Project, in Swedish “Smak- och luktprojektet” and therefore called the SOL-project in this thesis, is a longitudinal project investigating TSAs, symptoms, quality of life and nutritional status and intake in patients with lung or gastrointestinal cancers. My initial role in the SOL-project was as translator of the Taste and Smell Survey, the instrument used to assess TSAs, and this work resulted in study I. My interest in translation has grown during my time living in Sweden where I have become increasingly conscious of the importance of the accurate translation of concepts into fluent and natural language. I then continued in the SOL-project as a research assistant, and subsequently a research student, where I was one of four researchers interviewing patients. During interviews with patients with lung cancer, I have become more aware of the variation in TSAs and the effect they can have on daily food consumption and mealtimes for patients and their family members. Study II uses data from the SOL-project to highlight TSAs, and in particular their characteristics, in order to contribute to improved awareness of these symptoms in patients with lung cancer. This may lead to the development of evidence-based advice and interventions available to dietitians and other healthcare staff.

It has been a fascinating and humbling experience interviewing the patients in this study who have so generously shared their experiences of TSAs and other symptoms. My ambition is that this thesis will do justice to their participation and contribute to the development of knowledge in this area.

## 2 BACKGROUND

### 2.1 THE SENSES OF TASTE AND SMELL

The senses of taste and smell play a critical role in motivating and guiding our choice of food [102]. The sense of smell also serves as an early warning system against, for example, smoke and gas and both taste and smell can help us detect potentially spoiled food products. However, taste and smell may in some ways be neglected senses – we might fear a loss of sight or hearing but perhaps assume that the loss of taste and smell would be more of a minor inconvenience in normal life.

The perception of the flavour of food is said to involve an interaction between the senses of taste, smell and somatosensations (texture, temperature and irritant sensation) [58]. The taste buds are lined with taste receptor cells and are located not only on the tongue but also the oropharynx, larynx and the upper third of the oesophagus [101]. The taste buds on the tongue are found on taste papillae, of which there are three different types: fungiform, foliate and circumvallate with each located on different parts of the tongue [24]. Taste buds have a life span of approximately 10 days and taste receptor cells are continually replaced [24].

Taste sensations arise when food or drink is taken into the mouth, whereby it comes into contact with the taste receptors and information about taste sensation is then transmitted to the brain via three cranial nerves (7<sup>th</sup>, 9<sup>th</sup> and 10<sup>th</sup>) that innervate the taste buds [24]. Free trigeminal nerve endings (5<sup>th</sup> cranial nerve) on the tongue detect sensations of touch, pain and temperature in the mouth [101]. At this point in time it is recognised that the sensation of taste is underpinned by five basic taste qualities: salt, sweet, sour, bitter and umami [24], although there may be others, and every taste receptor is reported to be capable of recognising all of these basic tastes [74]. The taste quality umami was first identified in the early 1900s by Ikeda in Japan and umami receptors were discovered in the year 2000 [66], however the taste of umami may not be well-recognised in western food cultures.

It has been estimated that 80-90% of what is perceived as taste of food is in fact smell [23]. Our nose has the capacity to recognise and distinguish countless volatile compounds and the recognition of tastes such as mint, strawberry, onion, cinnamon is largely due to sense of smell. Odour sensations are mediated by the olfactory nerve whereas information such as sharpness,

burn from chilli peppers or coolness from menthol is mediated by the trigeminal nerve [26].

The olfactory receptors of the olfactory nerve (1<sup>st</sup> cranial nerve) are located in the nasal epithelium. There are two distinct pathways for stimulating the olfactory receptors which may produce different sensations of food odours [18]:

- Sniffing or the orthonasal pathway is used to identify odours in the environment [18]. Odour compounds travel through the nostrils and dissolve within the mucous layer of the olfactory epithelium. The olfactory receptors are stimulated and signals are sent via the olfactory bulb to the brain [26]. The turnover time for renewal of the olfactory receptors is approximately 30 days [101].
- Retronasal stimulation occurs during eating when odours from food enter the nose through the pharynx. This occurs during the act of chewing which releases volatile molecules that travel from the back of the mouth to the nasal passages and olfactory epithelium. This process is necessary for food flavour identification [18].

## **2.2 THE SENSES OF TASTE AND SMELL AND EATING**

The sensual experience of food flavour is made up of tastes, smells, textures and temperature. The sight and even sound of food, in that auditory cues influence perception of food [119], can also affect the experience of food consumption. These sensory cues trigger processes of salivary, gastric and pancreatic secretions that prepare the body for the process of digestion even before food is ingested [72]. However, the function of food and eating in society goes beyond that of supplying nourishment. Food and mealtimes are strongly connected to religious, cultural, family and social activities and provide a central context throughout our lives for social interaction and companionship. Normal functioning sensory systems, including taste and smell, are therefore an important part of ordinary daily life.

## 2.3 FACTORS AFFECTING THE SENSES OF TASTE AND SMELL

Disorders of taste and smell function can be related to a number causes or conditions such as Alzheimers, cancer, head trauma, renal disease, medication, nutritional deficiencies, normal aging [26, 101]. Losses of taste and smell functions can be classified into three major types [101]:

- transport losses where stimuli cannot reach the taste or smell receptors due to e.g. blockage of taste buds or nasal airways, excessive dryness of the mouth.
- sensory losses caused by damage to sensory organs by e.g. radiation therapy, chemicals, medication, neoplasms.
- neural losses as a result of damage to neural pathways or central nervous system by e.g. head trauma, neoplasms, surgery, neurological diseases.

Prevalence of self-reported taste and smell dysfunction in the general population has been assessed in an epidemiological study in the United States in a nationally representative population of over 81,000 adult subjects [50]. Results, which were stratified into eight age groups across the age range 18 to 85+, indicated a prevalence of smell-only problems across all age groups from 0.94% - 4.71% of the study population, taste-only problems from 0.07% - 1.70 % and combined taste and smell problems from 0.19% - 2.06%. In all problem groups the lowest prevalence was seen in the 18-24 age group and highest in the 85+ age group.

The decline of taste and smell functions with age are reported to affect both detection and recognition thresholds [50, 100] and odour perception is thought to become more impaired than taste perception [100, 116]. Olfactory impairment begins around the age of 60 years and progresses with each decade with older people also losing the ability to discriminate between odours [100]. A number of anatomical and physiological changes in the olfactory system are thought to occur with advancing age. In addition, cognitive decline for example in memory for odour recognition or decreased lexical ability to name odours may also be factors contributing to inability to discriminate odours [116].

The causes of taste losses with normal aging are unknown although they may be due to reduction in number of taste buds [100] or to changes in taste cell membranes altering the function of taste receptors [20]. Detection thresholds for all tastes have been found to be raised in older people although the degree of loss is not uniform across all taste qualities [78, 100]. Taste and smell functions are

known to be affected by certain medical conditions such as cancer, Alzheimers, head injuries or their medication, which might also contribute to sensory losses reported among the elderly [33, 101].

Studies using clinical testing methods conducted in the general population have indicated that women outperform men in odour and taste detection and identification and prevalence of olfactory impairment has been shown to be higher in adult men [17, 22, 64, 79]. Whilst women have been found to have lower thresholds for detection and identification of certain tastes results vary regarding which tastes qualities are better detected by women [76, 118].

Smoking is not clearly established as a cause of taste or smell impairment. Venneman et al. [112] reported that smokers have a higher risk for taste and smell impairment. This study was a cross-sectional population survey of over 1300 participants randomly drawn from the general population where clinical taste and smell tests were performed and participants interviewed about their smoking habits. Increasing number of smoked cigarettes related to increased smell impairment and heavy smoking to taste impairment. In contrast, a clinical and morphologic study of taste function was conducted by Konstantinidis et al. [62] in a randomly drawn sample of outpatients from an Otorhinolaryngology Department including both smokers and non-smokers. Changes in fungiform and filiform papillae of the tongues of smokers were reported but with no significant difference in clinical taste test results between the two groups. Brämerson et al. [22], in the Swedish Skövde population-based study in a random sample of 1900 adults, performed clinical tests of olfactory function and interviewed participants about smoking habits. No statistically significant correlation was found between smoking and olfactory function. However, in a recent study of tobacco withdrawal symptoms, patients who had stopped smoking were found to report improved senses of taste and smell during the week following smoking cessation [37].

## **2.4 TASTE AND SMELL ALTERATIONS IN PATIENTS WITH CANCER**

Taste and smell alterations (TSAs) have been reported at all stages of the cancer trajectory including prior to treatment [60], although this has not been extensively researched. TSAs are common side-effects of chemotherapy, as reported by Gamper et al. [42] in a review article, and radiotherapy for head/neck cancers [77, 91, 95]. In studies of patients in advanced stages of heterogeneous cancer diagnoses over 80% of patients reported TSAs [25, 56]. Causes of TSAs

in patients with cancer may be related to tumour metabolism and site or treatment [35]. Cancer treatments such as chemotherapy and radiation therapy act by destroying rapidly proliferating cells and may cause TSAs by destroying taste and olfactory receptor cells, disrupting saliva production or causing mucositis [35, 51]. In a Swedish study of a heterogeneous sample of patients with cancer, Bernhardson et al. [14] found that TSAs were the most commonly reported symptoms in patients receiving chemotherapy, with 75% of patients reporting alterations.

Whilst TSAs have been reported to be common and distressing symptoms which affect patients' daily lives [15, 61, 114] they are not well addressed by healthcare staff [19, 81]. Newell et al. [81] found significant differences between the perceptions of oncologists and their patients' reports of taste alterations. Routine methods for assessing taste alterations by clinicians working with oncology patients (oncology nurses, medical oncologists and oncology dietitians) were reported by Boltong et al. [19] to be lacking. Oncology dietitians were found to document taste problems but with little detail regarding characteristics or management strategies. The lack of evidence-based practice guidelines was cited by some clinicians as a reason for finding it difficult to discuss and manage patients' taste alterations. Using a checklist completed by patients with mixed advanced cancer diagnoses to explore the frequency of symptoms impacting on nutrition, Omlin et al. [84] also found that TSAs were frequently reported by patients but not routinely assessed by oncologists. Even here the lack of treatment options available was thought to explain why oncologists did not enquire about TSAs unless these symptoms were spontaneously reported by the patient. This is in line with Tishelman et al. [108] hypothesis that problems may be most readily recognised and legitimised by patients and staff when there are bio-medical strategies available to deal with them.

Bernhardson et al. [13] 2007 study reported patients describing that when suggestions were given by staff for dealing with TSAs they were often inadequate. Strategies that have been suggested to manage TSAs, for example changing food choice, adjusting flavourings, methods of food preparation and even type of cutlery used, lack systematic evaluation regarding how well they work [97, 103]. Studies in the use of dietary zinc supplementation to treat taste problems in patients with head and neck cancer receiving radiation therapy have produced differing results [47, 80]. Although TSAs are said to be commonly reported there has also been limited research regarding the quality and characteristics of TSAs that are experienced and reported by patients [25]. An

understanding of the different characteristics of TSAs is required for precision in evaluating which strategies are most effective for managing which types of TSAs.

Loss of taste sensation was suggested to be one of the main reasons that patients with cancer lost interest in food and missed meals on a regular basis [65]. Self-treating taste alterations by avoidance of certain foods could therefore limit nutritional intake. Canadian studies in patients in advanced stages of heterogeneous cancer diagnoses, found that patients reporting severe alterations in taste and smell sensation had lower energy intakes and experienced greater weight loss than patients not reporting changes [25, 56]. It has also been reported that patients with cancer experience TSAs concurrently with other symptoms that may impact negatively on food intake, such as loss of appetite, nausea and early satiety [14, 56, 87].

Lung cancer is often diagnosed in advanced stages and patients are regarded to have a large symptom burden at the time of diagnosis [54] which may include nausea, loss of appetite and altered taste sensation [44]. The prevalence of TSAs has been well-reported during radiation therapy for head/neck cancer and chemotherapy treatment for various types of cancer, and the characteristics of TSAs have been investigated in advanced stages of multiple cancer diagnoses. However the quality and characteristics of TSAs and the relationship of TSAs to other symptoms impacting on nutrition in a lung cancer population have not been previously investigated.

## **2.5 LUNG CANCER**

Lung cancer is globally the most common form of cancer and the fourth most common among men and women in Sweden. It is the leading cause of cancer deaths in Sweden and worldwide [73, 107]. Smoking accounts for 75-90% of lung cancers and the rate of incidence of lung cancer is thought to be directly related to the prevalence of smoking with a 15- 20 year lag time [52, 73]. The incidence and mortality from lung cancer in Sweden is different amongst men and women. Diagnosis and mortality from lung cancer is higher in women before the age of 60, whilst higher in men in the older age groups. There has been a steady increase in the number of lung cancer cases among women which is thought to reflect change in smoking habits from 20 years ago [107].

The majority of lung cancers can be classified as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) [52]. The TNM clinical



classification system forms the basis for the staging of lung cancer based on tumour size (T), whether cancer cells have spread to the regional lymph nodes (N) and whether the tumour has metastasised (M) [93]. NSCLC has 4 stages I – IV and SCLC two stages: limited disease (stages I-III) and extensive disease (stage IV).

The studies reported in this thesis are not treatment studies; however, an overview of the types of treatments for lung cancer used in the target population is presented.

### **2.5.1 Treatment of NSCLC**

NSCLC accounts for approximately 80% of reported cases of lung cancer [107] and includes the sub-types: adenocarcinoma, squamous cell carcinoma, large cell carcinoma and adenosquamous carcinoma. The choice of treatment is determined by the stage of the disease [52, 85].

Stages I-II: The tumour is restricted to the lung and localised lymph nodes. The patient is assessed for surgery with curative intent which may be followed by adjuvant chemotherapy. Stereo-tactical radiotherapy (SRT) may be considered if surgery is not an option.

Stages III: The disease is locally advanced and has spread to adjacent tissue and lymph nodes. Surgery may be considered although treatment is generally a combination of radiotherapy and chemotherapy.

Stage IV: The patient has separate tumour nodule(s) in a contralateral lobe, pleural nodules, or malignant pleural or pericardial effusion; or distant metastases. Palliation of symptoms is the goal of treatment. Chemotherapy and radiotherapy may be used to reduce tumour burden, treat symptoms and improve quality of life.

### **2.5.2 Treatment of SCLC**

SCLC is almost always caused by smoking and proliferates rapidly with many patients having widespread metastatic disease at diagnosis.

Patients with SCLC having limited disease are generally treated with a combination of chemotherapy and radiotherapy and patients with extensive disease with chemotherapy. SCLC is typically initially responsive to treatment but the response is short-lived. Surgery generally plays no role except in rare cases where the tumour has not spread [85].

## 2.6 SYMPTOMS IN PATIENTS WITH LUNG CANCER

Early stage lung cancer is generally described as asymptomatic and therefore often only identified incidentally from a chest X-ray performed for unrelated investigations [52]. Signs and symptoms in lung cancer can result from effects of local or regional progression of the primary tumour or distant metastases [52]. Clinical manifestations associated with lung cancer can include cough and with regional spread chest pain and dyspnoea. When the tumour spreads beyond the lungs the signs and symptoms can vary depending on their location [52]. Patients may also report clusters of symptoms which can include fatigue, weakness, nausea, vomiting, appetite loss, weight loss and altered taste sensation and which may continue during the course of the disease [44, 52].

Several theoretical frameworks have been developed to help in our understanding of symptoms. As a dietitian I had not previously had contact with symptom theory but through working in the SOL-project and discussions in the multi-professional research group I have gained an awareness of a number of different frameworks. One theory which I find has particular relevance to the studies in this thesis is the work of Armstrong [6] who refers to the experience of multiple symptoms and describes *symptoms experience* as the “perception of the frequency, intensity, distress and meaning occurring as symptoms are expressed and produced”. According to Armstrong, factors which affect the experience of symptoms include demographic characteristics (e.g. age, gender, culture, marital status); disease characteristics (e.g. type, treatment, medical factors) and individual characteristics (e.g. values, past experience and health knowledge). Armstrong maintains that it is the meaning or importance of symptoms to a patient that influences the patients’ perception of the symptoms. The meaning a patient assigns to symptoms experience may influence the symptom occurrence or the distress that the patient perceives. As different symptoms can occur in clusters, Armstrong also considers that it is likely that the experience of one symptom is affected by the presence of other symptoms, where symptoms may act as catalysts for other symptoms [6]. Each individual symptom as well as the interaction of a number of symptoms may therefore affect the meaning patients attribute to the experience of symptoms. In Armstrong’s concept of symptoms experience, meaning may include situational meaning (refers to effect on daily life, e.g. inability to drive or cook) or existential meaning (refers to symptoms as a reminder of sense of vulnerability, mortality). The research presented in this thesis focuses on TSAs and their interaction with other symptoms impacting on food intake. When reflecting upon the results I have done so with Armstrong’s

theory in mind, considering therefore not only the reported presence of symptoms by patients but also the meaning or importance these symptoms may have had for those patients.

## **2.7 WEIGHT LOSS IN PATIENTS WITH LUNG CANCER**

In 1980 Dewys et al. [31] reported that unintentional weight loss was shown to predict reduced survival in patients with different cancer diagnoses.

Involuntary weight loss in patients with cancer is also associated with reduced quality of life, impaired treatment outcomes and treatment toxicity [39, 83].

Khalid et al. [60] reported that 28% of patients with lung cancer had lost weight already at presentation and those with a weight loss  $\geq 5\%$  reported significantly more symptoms than those with no weight loss. A study in outpatients with cancer presenting for diagnosis, therapy or follow up, reported that median weight loss over the previous three months among patients with lung cancer was 6.5% [21].

A study by Ross et al. [98] showed that weight loss at presentation was associated with shorter survival time in patients with NSCLC, SCLC and mesothelioma treated with chemotherapy. Weight loss was associated with fewer chemotherapy cycles, more treatment delays and increased incidence of anaemia and weight stabilisation during treatment associated with better overall survival in patients with NSCLC and mesothelioma. Similar results were however not seen in patients with SCLC [98].

Weight loss in patients with cancer may be a result of abnormal metabolism combined with a reduced food intake which may be related to symptoms such as nausea, loss of appetite or TSAs [39, 21].

## **2.8 ASSESSMENT OF TASTE AND SMELL ALTERATIONS IN RESEARCH**

A number of methods have been described for the investigation of taste and smell function and TSAs. Clinical tests have been used to determine recognition and detection thresholds for the five basic tastes qualities as well as smell. Methods where patients self-report presence of TSAs have also been used. Clinical testing can be time-consuming and difficult to perform precisely although some commercial tests are available which attempt to simplify and

standardise this task. Methods for conducting such tests include for example the University of Pennsylvania Smell Identification Test (UPSIT), Sniffin' Sticks and the olfactometer. Approaches used to measure taste function include localised tests on different parts of the tongue, whole mouth tests and electrogustometry [11, 50].

Measurements of clinical sensory thresholds of identification and detection do not however measure the perception of distorted sensations (e.g. metallic tastes, false unpleasant smells) nor do they assess the complexities of the integrated perception of taste and smell when eating food [25] which is my interest in this thesis. For the assessment of TSAs in relation to food consumption, methods which allow patients to self-report presence of perceived TSAs are therefore used.

Information obtained using self-reporting of symptoms is dependant on the type of instrument used for assessment. Questions about taste and smell have been included as part of general symptom questionnaires [44, 61] but response choices are usually limited to indication of presence or absence of TSAs rather than the description of characteristics of TSAs. One example of this is the scored PG-SGA (Patient-Generated Subjective Global Assessment) [8], used by clinical dietitians to assess nutritional status in patients with cancer, where both taste and smell changes are included as symptoms that may have impacted on a patient's food intake over the previous two weeks. An instrument of particular specificity is therefore required to be able to investigate the characteristics of TSAs. One such instrument in English is the Taste and Smell Survey (TSS) [49]; however, at the time this research commenced no equivalent instrument existed in Swedish. In this thesis the TSS has therefore been translated into Swedish for the purpose of investigating characteristics of TSAs reported by patients with lung cancer.

## **2.9 TRANSLATION OF INSTRUMENTS**

If a suitable instrument for measuring a particular construct in the language of the study population does not exist then researchers are presented with two options: either a new instrument can be developed or an existing instrument which has been previously used in research projects in another language can be translated and adapted to the new culture [45]. Translating and culturally adapting an existing instrument has the advantage of allowing discussion with researchers who have previously used the instrument. It also gives the potential for comparing data from studies in different countries and facilitates future meta-

analysis of data obtained using the same instruments and methods. Given these benefits together with the enormous time and effort required to develop a new instrument the process of translating an instrument, although arduous, may therefore be favoured.

If data from studies in two countries using the same instrument are to be compared, it is paramount that any differences observed should be due to the phenomena being studied and not due to errors in translation of meaning of words and concepts [71]. When instruments are to be used for research it is not sufficient to just translate a questionnaire literally as the literal translation of words may not always reflect their connotative meaning in different cultures [10]. The challenge is therefore to produce an instrument that is relevant and understandable in the new language and culture whilst still retaining the meaning and intent of the items [104].

A stepwise method for assessing equivalence of instruments that are developed in one culture and to be used in another has been presented by Flaherty et al. [41] which includes five major dimensions of cross-cultural equivalence: content, semantic, technical, criterion and conceptual (Table 1).

**Table 1- Five Dimensions of Cross-Cultural Equivalence**

<b>Dimension of equivalence</b>	<b>Definition</b>
<i>Content</i>	The content of each item of the instrument is relevant in each culture being studied
<i>Semantic</i>	The meaning of each item is the same in each culture after translation
<i>Technical</i>	Data collection method is comparable in each culture regarding data yielded
<i>Criterion</i>	The interpretation of the measurement result is the same when the concept is compared to the norm for each culture
<i>Conceptual</i>	The instrument measures the same theoretical construct in each culture

Adapted from Flaherty et al. [41], page 258.

The aim in translation is therefore to develop an instrument that is equivalent in all five dimensions, although Eremenco et al. [36] point out that it is hard to achieve 100% equivalence. Despite a number of different guidelines suggesting methods of translation and cross-cultural adaptation [9, 36, 45, 115] there is no

accepted gold standard regarding which particular techniques are to be used in the process or how they should be combined [71]. Empirical evidence regarding whether one method is superior to another is lacking, as are studies comparing alternative methods [46].

An approach which has often been recommended for translation of instruments is that of forward-back translation [9, 36, 45, 115]. This method involves translation into the target language by one or more translator(s) followed by translation back to the source language by another translator(s). Differences in the forward and back translated versions are then compared and discrepancies addressed. Although back-translation is still widely used weaknesses in this method have been raised [46, 104, 105]:

- Hagell et al. [46] compared versions of a questionnaire translated using back-translation and a dual panel approach. No psychometric differences were observed; however, lay people and the target population preferred the wording of the dual panel version. The back translation version also resulted in more missing item responses.
- A good forward translation is likely to result in a version different in lexical form from the original so that the back translation also differs from the original. Similarity of meaning is preferable to similarity of lexical form so comparing the source and translated versions, therefore, gives no information about the quality of the forward translation [105].
- Although back translation is regarded as a type of quality indicator of the forward translation this relies on an assumption that back translators are more competent than forward translators. It may however be the back translation that is poor [105].
- Back-translation may mislead regarding linguistic equivalence as good back translators can make sense of a poor translation and errors are therefore not highlighted [104, 105].
- Linguistic equivalence may be suggested by back translation although literally correct words and phrases may not convey the same meaning in the different languages and cultures [55].

Since there is no empirical evidence in favour of one technique or combination of techniques for translation and cultural adaptation, the use of rigorous multi-step procedures using multiple techniques is recommended to achieve cross-cultural equivalence [3, 71].

## **2.10 CULTURE AND FOOD**

Culture can be defined as the way of life, especially the general customs and beliefs, of a particular group of people at a particular time [27]. Food and the role food plays in society are strongly associated with national and cultural identity [69]. Anthropologists Farb and Armelagos and culinary historian Elisabeth Rozin suggest that all groups have a defining style of culinary activity or 'cuisine' [38, 99]. This is a system of communication learnt from childhood which can be thought of as a type of cultural language. The structure of a group's cuisine is identified by the following four elements: which foods are selected, how foods are prepared, the characteristic flavours and seasonings used and the rules or norms for how food is eaten. In particular, the flavourings used by a group are said to convey a sense of culinary identification and familiarity both within and outside of the group [99]. An awareness of this cultural element, intrinsic to the concept of food flavourings, is therefore relevant when translating instruments to be used for research on TSAs.

### 3 PROBLEM STATEMENT AND AIMS

TSAs have been commonly reported as distressing symptoms during treatment for cancer and in its advanced stages. Taste alterations have been reported in patients with lung cancer but little is known about the characteristics of TSAs in patients who have started treatment for lung cancer, how TSAs impact on their nutritional intake or how TSAs relate to other symptoms which may affect their food consumption. It is also not clear how patients with lung cancer describe their TSAs or the impact they have on eating and food enjoyment. Evidence-based guidelines for detection and management of TSAs are lacking. An understanding of the characteristics of TSAs in patients with lung cancer may facilitate development of such guidelines, which dietitians and other healthcare staff could then use to help patients manage TSAs. In order to investigate characteristics of TSAs among patients in Sweden, a symptom-specific questionnaire in Swedish is required.

The overall aim of this thesis is therefore to investigate the features and characteristics of TSAs reported by patients after starting treatment for lung cancer using a questionnaire translated and culturally adapted to the Swedish language and culture.

The specific aims of this thesis are to:

- translate into Swedish and culturally adapt the Taste and Smell Survey (TSS) (study I).
- describe and discuss experiences of the process used for translation and cultural adaptation of the TSS (study I).
- explore:
  - the features of patients reporting and not reporting TSAs (study II).
  - if TSAs relate to protein and energy intakes and six-month weight change (study II).
  - the characteristics of reported TSAs and relate these to age, gender and smoking habits (study II).
  - how other symptoms relate to TSAs (study II).
- elucidate the ways in which patients describe their TSAs (study II).



## 4 ETHICAL CONSIDERATIONS

Dietitians, as well as other health care professionals, who carry out research are obliged to follow the laws regarding research ethics and the ethical rules and guidelines that apply to medical and social research in Sweden. The foundations for these rules and guidelines are the ethical principles for medical research involving human subjects in The World Medical Association's Declaration of Helsinki (2008) [117]. All efforts have been made to fully respect these principles in the studies in this thesis.

All research that is carried out should be of a high standard and focus on questions that are relevant to society. In study I, the ethical importance of producing a valid, robust instrument for research purposes that will function in an equivalent way in English and Swedish has been considered. Copyright has been respected and permission obtained from the original constructors to translate and use the TSS in Swedish. Patients who participated in think-aloud interviews to pre-test the translated TSS were recruited by nurses on the ward after being informed about the purpose of the study. All data was treated confidentially and the participants could not be identified.

Before and during study II consideration was given to the burden or anxiety that questions about senses of taste and smell, weight history and recording food intake over three days may impose on patients with lung cancer. In serious illnesses such as lung cancer poor food intake and weight loss may be regarded by the patient and their family care-givers as reminders of disease or signs of deterioration [86]. The patients interviewed were all given full autonomy regarding their participation, interviewers were sensitive to signs that a patient was doubtful about continuing and emphasised that participation was voluntary and could be retracted at any time. The experience of the interviewers throughout the data collection was that many patients expressed positive feelings about participation, about being able to contribute something of scientific interest and the fact that their experiences and opinions were taken seriously. This willingness to participate in research is in line with other researchers experiences. For example, in Terry et als. [106] study, patients in palliative care expressed wanting to participate in research for reasons such as altruism, an increased sense of personal value, being able to maintain a sense of autonomy and the value of helping to improve care by research. In some situations the interview raised questions from patients about their clinical condition and in such cases the patient was advised to contact the hospital staff. Throughout the data

collection, data analysis and writing processes the interpretation of patient reports and descriptions has been actively discussed within the research group.

Data for study II is derived from the SOL-project which received research ethics approval from the Regional Research Ethical Review Board in Stockholm, Sweden (*Dnr 2009/1463-31/3, 2010/1849-32, 2011/1324-32*) prior to start. All participants were informed verbally and in writing about the aims of the study. Written informed consent was obtained on recruitment and it was emphasised that participation was voluntary and could be terminated at any time with no disadvantage to further care and treatment. Data collected in this study was treated confidentially and the participants could not be identified. The data was only accessible by the researchers and was used solely for the purposes described in the approved ethical application. Patients were able to choose the location for the interviews and could refrain from answering any questions they found intrusive.

## **5 PRESENTATION OF STUDIES**

This thesis is composed of two studies which are very different in character. Study I served as a foundation for study II as it aimed at translating and culturally adapting the Taste and Smell Survey (TSS), a questionnaire which assesses patients' self-reported TSAs (see appendix 1 and 2). Study II uses data derived from a longitudinal taste and smell project called the SOL- Project (Smak- och luktprojektet in Swedish) which investigates taste and smell perception using the translated TSS, other symptoms, quality of life and nutritional status and intake in patients with lung or gastrointestinal cancers. In the SOL-project patients are interviewed close to diagnosis and before start of treatment (T1) and then at two-monthly intervals (T2, T3, T4). The SOL-project is carried out in collaboration with a research group at the University of Alberta, Edmonton, Canada. In study II, data from one of the longitudinal interviews is used to explore the characteristics of perceived TSAs and how patients describe TSAs. The relation of TSAs to demographics, nutritional intake, weight change and other symptoms is also explored. Both quantitative methods and content analysis of open-ended questions are employed.

### **5.1 STUDY I - METHOD**

In study I the process used for translation and cultural adaptation of the TSS is described and discussed.

#### **5.1.1 Translation of the TSS**

The method for translation and cultural adaptation of the TSS is illustrated in Figure 1 and the steps are then described in detail.

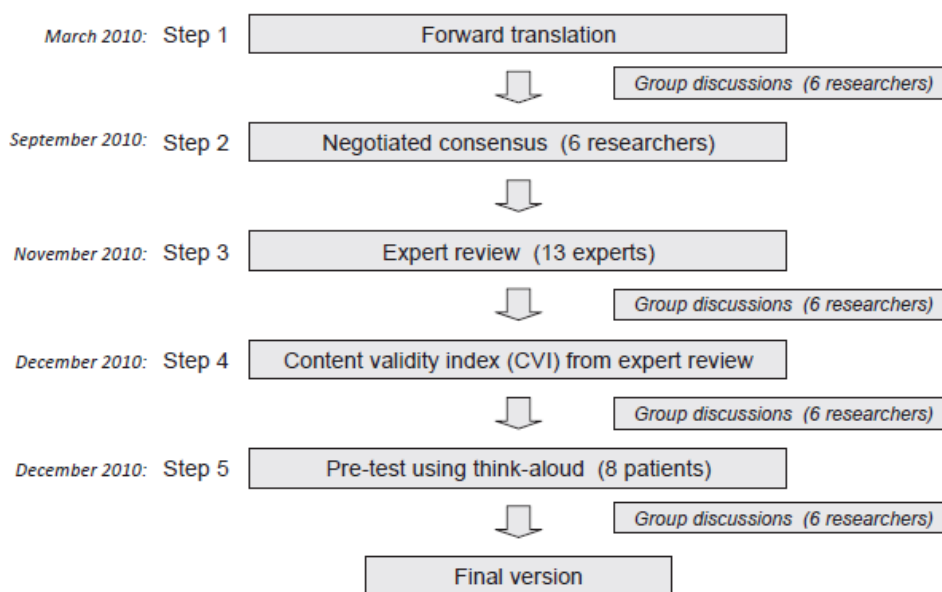


Figure 1 – The 5 steps used in the translation and cultural adaptation process

#### Step 1 - Forward translation

I carried out the initial translation from English to Swedish. With experience as a clinical dietitian, predominantly in oncology, in both the UK and Sweden, I had the advantage of being familiar with the patient group and the objectives underlying the questionnaire.

#### Step 2 - Negotiated consensus

The multidisciplinary research group conducting the study comprises two registered nurses, three registered dietitians and an oncologist representing both healthcare researchers and clinicians. All have an in-depth understanding of the concepts addressed by the TSS. Two of the group have English as native language (United Kingdom and United States) but have lived in Sweden for over 20 years whilst the others are native Swedish speakers; all are proficient in both languages. The group members examined and assessed the preliminary translation, both individually and in group discussions. A consensus version of the translation was then produced in a final meeting. Group discussions in the research group were also held after each of the following steps.

#### Step 3 - Expert review

The consensus version was sent out to a multidisciplinary panel of 13 experts who had been purposefully chosen with regard to their varied and relevant clinical expertise and their proficiency in English and Swedish. This panel

included six nurses, five dietitians, one physician and a physiotherapist. Three were of non-Swedish background and one had English as mother tongue. The group comprised three men and 10 women, all of whom worked actively within various areas of healthcare and some also within research. The experts were sent both the original questionnaire and the consensus translation and asked to rate each item of the questionnaire independently using a web-based survey without access to other reviewers' ratings. Experts were asked to rate the translation for:

- a. linguistic correlation with the original
- b. applicability and comprehensibility in a Swedish context.

Each item was rated on a four-point scale (see Table 2).

**Table 2 - Scale for rating of items**

	<b>Linguistic correlation with the original</b>	<b>Applicability and comprehensibility in a Swedish context</b>
<b>1</b>	no correlation	not understandable
<b>2</b>	slight correlation	slightly understandable
<b>3</b>	quite good correlation	quite understandable
<b>4</b>	very good correlation	highly understandable

Experts were also encouraged to contribute suggestions for improving items. The questionnaire was revised after discussion in the research group based on experts' ratings and suggestions before being sent for a second review to a smaller panel of experts selected from the first panel.

#### Step 4 - Content Validity Index (CVI).

Content validity is the degree to which the items in an instrument represent and are relevant to the construct being measured in the population being studied [89]. The CVI method was used to measure inter-rater agreement using expert ratings of the translated items on the four-point scale in Table 3. These four points were then collapsed into a dichotomy and the CVI for each item (I-CVI) is the proportion of experts who gave the item a positive rating i.e. rated it as 3 or 4. The CVI for the whole instrument (S-CVI/ave) is the average I-CVI for all items on the scale [89]. The minimum recommended I-CVI is 0.78 and an S-CVI/ave of 0.90 is the goal for a questionnaire to be considered as having excellent content validity [90].

## Step 5 – Pretesting

Feedback on the translated instrument from the target population was obtained using a pre-test. Cognitive interviewing techniques can be used for pre-testing an instrument. One such method is think-aloud interviewing which assesses how respondents perceive questions and whether their understanding of the questions corresponds to that of the researchers. I carried out the think-aloud pre-testing with eight patients undergoing chemotherapy treatment of which four were diagnosed with lung cancer and four with gastrointestinal cancer, reflecting the target group of the SOL-project. This group of patients comprised five women and three men. Patients were asked to verbalise their thoughts after reading each question, their reasoning when formulating their answer and to indicate if any words, phrases or sentence formulations were difficult to understand. During the interview I made detailed notes of the dialogue including any hesitations or comments and, if relevant, patients' facial expressions and body language. The data derived from these interviews were analysed using inductive content analysis with inspiration from Thorne's interpretive description.

In order to provide an estimate of internal reliability, Cronbach's alpha was calculated based on initial data using the translated TSS that had been collected in the SOL-project.

## **5.2 STUDY I - RESULTS**

In this section, I describe and discuss the experiences of the process used for translation and cultural adaptation of the TSS focusing on what I consider to be the strengths and weaknesses of the process. (See appendix 1 and 2 for the English and Swedish versions of the TSS).

### **5.2.1 Strengths**

As I was familiar with the concepts of the subject area this was a strength when carrying out the initial translation. The strength of the negotiated consensus step was that the international, multidisciplinary research group includes members who are native speakers of both the source and the target languages. All members also had an in-depth understanding of the objectives underlying the questionnaire which together with the mix of skills and experience in the research group facilitated discussions from linguistic, professional and cultural perspectives when comparing the translated and original versions. Discussions included for example, that the term "a food" was thought to include both food and beverages in English but needed more specification in the Swedish

translation. The phrase “Have you ever” (har du någonsin) was removed in the translated version as it was felt to convey different time frames in Swedish and English. Also, the English TSS solely addresses patients already diagnosed with cancer asking them to compare their current senses of taste and smell to before diagnosis. As interviews in the SOL-project were to be held with patients during diagnostic work up for lung cancer as well as later during the disease trajectory, the instructions were modified so as not to cause distress to patients who may think we have information about their diagnosis. Swedish patients were therefore asked to compare their senses of taste and smell at interview to how they were before the onset of diagnostic investigations.

The strength of the expert review was the large and varied panel of experts used as it has been indicated that the risk of chance agreement diminishes as the number of experts increases [90]. All experts reviewed the translation independently which allowed individual rather than group suggestions thus avoiding the risk of collusion. Useful comments were provided regarding choice of translation of particular words, for example “worse” (sämre or värre) and “interfere” (påverka or störa), to ensure consistency of use and that the correct nuance was reflected in the translation. The cultural relevance of using tonic water as an example of bitter taste was questioned, although since a better example could not be found this was retained as a potentially useful example to some respondents.

A further strength in the process was that the ratings from the expert review were used to assess content validity. Since content validity of instruments can vary across populations [48] it was considered paramount to establish content validity of the TSS in the Swedish language and culture. CVI was calculated after first and second expert reviews and the final CVI had scores of 1.0 for S-CVI/ave for both linguistic correlation with the original and applicability and comprehensibility in a Swedish context. These scores are considered excellent [90].

In contrast to traditional pilot-testing, think-aloud provides not only information about any problems with the translation of the instrument but can also highlight causes of any misunderstandings and the extent to which the items are understood in the way that the researcher intended [34]. The sample who pre-tested the translated TSS was representative of the target respondent population. Feedback from and content analysis of the think-aloud interviews provided some useful insights regarding a number of items. For example, an

instruction was added that the item “how would you rate your TSAs” referred to degree of impact on daily life caused by changes in senses of taste/smell rather than the degree of abnormality of sense of taste and/or smell. One patient also suggested including a question about which foods were easier to eat when experiencing TSAs and this was added to the instrument battery used in the SOL-project.

Finally, results from Cronbach’s alpha indicate that the process has produced a reliable instrument for use in the second study of this thesis.

### **5.2.2 Weaknesses**

Since it has been recommended that translators should translate into their native language [115] the choice of translator of the TSS could be considered a weakness. However, the initial translation was subjected to scrutiny and discussion by members of the research group comprising native speakers of both source and target languages.

Inherent in the negotiated consensus step is that with the achievement of consensus comes the possible risk for collusion [109]. A further weakness in this step is that the group are all highly-educated health professionals who may not be culturally representative of the target population. This highlights the importance of pre-testing by patients representing the target group.

Risk of chance agreement is a weakness that has been raised regarding CVI particularly as the four ratings are collapsed into two groups. Polit et al. [90] suggest that this risk is minimised by increasing the number in the expert review panel which was why a large group of experts was selected.

Drawbacks to pre-testing using think-aloud have been raised [29, 34]. It represents an artificial situation for the responders who may read the questions more thoroughly than otherwise and affect their answers. Less articulate patients may also be more reluctant to participate or might have difficulty articulating their thought processes.

## **5.3 STUDY II - METHOD**

Study II analyses selected interviews from the SOL-project with patients diagnosed with primary lung cancer who have started treatment. Patients under investigation for lung cancer were consecutively recruited to the SOL-project



from the Department of Lung and Allergy Medicine at Karolinska University Hospital, Stockholm, Sweden from January 2011 until June 2012. Patients aged 18 years or over who lived in Stockholm were eligible for inclusion if they could complete interviews in Swedish. Patients were not eligible if they had previously received a diagnosis of head/neck cancer or radiation treatment to the head/neck area within the past three months as these diagnoses and treatment are known to have a major effect on senses of taste and smell and food consumption. Patients diagnosed with or treated for another form of cancer within the previous six months were also excluded.

### **5.3.1 Recruitment**

Patients meeting the inclusion criteria were informed about the SOL-project by clinic nurses at their first clinic appointment. A researcher contacted by telephone the patients who had expressed interest in receiving further information. Details about the purpose of the project, the voluntary nature of participation and the patients' right to withdraw at any point were explained. A first interview (T1) was booked with patients interested in participating and held at a mutually convenient location which was usually in the patients' home or at the recruiting clinic. Follow up interviews were held at two-monthly intervals (T2, T3, T4). The interviews lasted approximately one hour.

### **5.3.2 Data collection**

Data from the following two instruments and the 3-day food record diary utilised in the SOL-project were analysed in study II.

#### *The Taste and Smell Survey (TSS)*

This instrument was developed by Heald et al. [49] in the 1980's to investigate TSA's reported by HIV patients (see appendix 1 and 2). The researchers first developed the instrument based on their clinical experience and pilot-tested it in a group of 10-15 patients, after which vague questions were revised before use in an HIV study population. The TSS has subsequently been used in a series of studies by our collaborators at the University of Alberta, Edmonton, Canada, investigating perceptions of TSAs reported by patients with advanced cancer [12, 25, 56].

The TSS is a 16-item questionnaire which allows patients to self-report and describe perceptions of TSAs. Nine questions address the following aspects of

taste: changes in sense of taste, changes in the way a food or beverage tastes, presence and character of a bad taste in the mouth, changes in intensity of sensation of salt, sweet, sour, bitter tastes, effect of medication on sense of taste and a rating of abnormal sense of taste. A total taste score from 0-10 can be generated, with one point given for each taste change plus two points if the patient rates their overall abnormal sense of taste as severe or incapacitating. Five questions address the following aspects of smell: changes in sense of smell, changes in the way a food or beverage smells, effect of medication on sense of smell, change in strength of odour sensation and a rating of abnormal sense of smell. A total smell score from 0-6 can be generated, with one point for each smell change plus two points if the patient rates their overall abnormal sense of smell as severe or incapacitating. The TSS includes two questions which do not generate a score and which address the taste and smell of medications, which was of particular relevance to HIV-medication. Follow-up open-ended questions allow patients to freely describe TSAs both in general and also in relation to food and beverages. Two single global questions relate to the effect of taste and smell alterations on quality of life. A total TSS score is generated by adding together the taste and smell scores. Higher TSS scores do not necessarily mean that patients are more disturbed by TSAs but instead highlight the number of different aspects of TSAs that the patient reports experiencing. In study II the total score was used to identify the interview when the patient reported experiencing the highest number of alterations in senses of taste and smell, and patients were stratified into groups according to scores to investigate the relationship between TSAs and weight change, energy intakes and protein intakes.

#### *Scored Patient-Generated Subjective Global Assessment, PG-SGA*

The scored PG-SGA is a validated instrument adapted from the PG-SGA for clinical and research assessment of nutritional status in patients with cancer using a 4-box format (see appendix 3). The four boxes relate to 1) current weight and self-reported height and weight history, 2) rating of food intake, 3) symptoms affecting food intake over the previous two weeks, and 4) activities and function. Data from Boxes 1 and 3 are used in study II. The symptoms which are assessed using the scored PG-SGA as affecting food intake are: loss of appetite, nausea, vomiting, constipation, diarrhea, mouth sores, dry mouth, things taste funny/no taste, feel full quickly, smells bother me, problems swallowing, pain, other. In study II responses assessing taste and smell on the PG-SGA were not analysed as this data was obtained using the TSS. The scored PG-SGA also includes an overall numerical score based on responses in all four boxes which can be used to rate nutritional status although this was not

used in study II [8]. The PG-SGA had been previously translated into Swedish by Persson et al. [88].

#### *Food record diary*

Patients were asked to complete a 3-day food-diary in conjunction with all interviews. Patients were given information about recording in detail the date and time of food and beverage consumption, amounts consumed, ingredients of mixed dishes and any brand names of food items. A set of standard household measures for estimating portion sizes was given to each patient.

#### *Other data*

Calibrated scales were used to measure patients' body weight which was used when calculating energy and protein intakes per kg body weight. Patients were also asked to self-report height as well as current weight and weight six months ago in order to assess six-month weight loss. Patients were asked about their smoking habits and whether or not they prepared their own meals.

At each interview, the researcher read the questions and documented patients' verbal responses using direct quotes where possible. Detailed field notes were made after each interview. The type of lung cancer, stage of disease as well as dates and type of treatment given were determined retrospectively from the patients' medical records.

### **5.3.3 Data selection from the longitudinal SOL-project**

In order to obtain a rich dataset, the interview with each patient in the SOL-project where they reported the highest number of changes after start of treatment was identified using the total score generated from the TSS. This interview was purposefully selected for analysis. Patients were dichotomised into TSAs and no-TSAs groups based on responses to six questions on the TSS specifically addressing presence and characteristics of TSAs shown in Table 3.

**Table 3 – Dichotomisation into TSAs and no-TSAs groups**

<b>Taste and Smell Survey questions</b>	<b>Response alternatives</b>	<b>Dichotomisation</b>
Have you noticed any changes in your sense of taste?	<b>YES</b> / no <i>If YES please describe:</i>	TSAs – one or more responses in capital letters
Have you noticed any changes in your sense of smell?	<b>YES</b> / no <i>If YES please describe:</i>	
Have you ever noticed that a food tastes different than it used to?	<b>YES</b> / no <i>If YES please describe:</i>	
Have you ever noticed that a food smells different than it used to?	<b>YES</b> / no <i>If YES please describe:</i>	
Comparing my sense of taste now to the way it was before initiation of the diagnostic process a) salt tastes... b) sweet tastes... c) sour tastes... d) bitter tastes ...	<b>STRONGER</b> as strong <b>WEAKER</b> <b>I CANNOT TASTE IT AT ALL</b>	No-TSAs – no responses in capital letters
Comparing my sense of smell now to the way it was before initiation of the diagnostic process odours are...	<b>STRONGER</b> as strong <b>WEAKER</b> <b>I CANNOT SMELL AT ALL</b>	

Characteristics of TSAs were investigated using responses to the above six questions about changes in intensity of sensation of four basic tastes and smell, and descriptions of TSAs in the four open-ended questions. Umami taste is not included in the TSS as it is not thought to be easily identified in western food cultures.

Not all patients felt able to complete food diaries in conjunction with all interviews. For patients in the TSAs group the interview after start of treatment with highest TSS scores when a food diary was completed was chosen, or alternatively the interview with highest TSS scores if food diaries were never completed.

For the no-TSAs group the first interview after start of treatment when a food-diary had been completed was selected; alternatively, if no food diaries had been completed, the first interview after start of treatment was selected.

Due to patients' different treatment trajectories the time point for first interview after start of treatment varied. There was a larger variation in the TSAs group than the no-TSAs group in the length of time between start of treatment and interview indicating that in some patients with TSAs it took longer for TSS scores to reach their highest during the study period.

### **5.3.4 Data analysis**

Before interview selection and analysis a random control of data entry from the interviews was carried out on a 10% sample where the proportion of inconsistent data entry needing correcting was 0.5%. Patients' smoking habits were categorised into smokers, former smokers (not smoked in >1 year) and never smokers (includes occasional smokers) in line with the Swedish National Registry for Lung Cancer [96].

#### *Statistical analysis*

To explore how the groups TSAs and no-TSAs differ a Chi<sup>2</sup>-test or Fisher Exact test (if estimated group number less than 5) was used to compare gender, smoking habits, type of lung cancer, stage of disease, treatment before interview and if treatment was ongoing at interview. Presence of symptoms reported on Box 3 of the scored PG-SGA was also compared between TSAs and no-TSAs groups using these tests. Mean age was compared in relation to groups TSAs and no-TSAs using a t-test. Either Chi<sup>2</sup>-test or Fisher Exact test was used to explore characteristics of reported TSAs in relation to gender, age and smoking habits. The statistical significance level was consistently set at  $p \leq 0.05$ .

#### *Analysis of nutritional intake*

The software program Dietist XP developed by "Kost och Näringsdata", which builds on the food database of the Swedish National Food Agency was used to calculate energy and protein intakes; each patient's food-diaries were analysed by one of two dietitians; both were familiar with this software program. Serving sizes and weight of food portions were estimated using a reference table [59] and a detailed audit trail was kept and consulted during calculations. A 10% randomly selected sample of data from all food diaries in the SOL-project was

re-entered to check consistency of coding; the proportion of inconsistent coding needing correcting was 0.4 %. Average energy intakes were calculated in absolute amounts and per kilogram measured body weight and average protein intakes per kilogram measured body weight.

Since, in the longitudinal data from the SOL-project, the highest TSS scores for patients ranged from 1 – 15 it was decided to stratify patients according to scores to explore the relationship between energy and protein intakes and TSS scores (Table 6). We had initially planned to use the same grouping our collaborators in Canada used in their studies of TSAs and energy intakes. They used the following four groups based on scores: insignificant TSAs (scores 0-1), mild TSAs (scores 2-4), Moderate TSAs (scores 5-9) and severe TSAs (scores 10-16) [25, 56]. However, since in study II the group with scores 0-1 contained 28 patients and the group with scores 2-4 only 6 patients we decided to collapse this data into one group, which also gave a more even distribution of scores. Three groups based on scores were therefore formed as follows: no-TSAs – mild (scores 0- 4), moderate TSAs (scores 5-9) and severe TSAs (scores 10-16).

#### *Content analysis of responses to open-ended questions*

Patients described their TSAs in response to the open-ended questions using single words, phrases or sentences. These responses were analysed inductively using content analysis [53]. All text from patient descriptions of TSAs was read through several times to identify meaning units based on phrases or words. These meaning units were then grouped under 14 headings representing key concepts. The headings were then collapsed into six defined categories. Random lists of meaning units were then sent to three independent coders for re-coding to ensure reliability and Cohen's kappa was calculated. The average Cohen's kappa was 0.85 although one category received a low kappa result at 0.67.

Discrepancies in coding were examined and after discussion with the research group the categories were re-defined into the following six categories:

- Reports a change in general taste **or** a change in general intensity of taste **or** a change in intensity of any of the four basic tastes (salt, sweet, sour, bitter) without describing an emotional response to the change.
- Reports reduced liking of specific foods **or** reduced enjoyment of eating.
- Specifies particular foods that work well.
- Describes other symptoms related to eating problems e.g. appetite, nausea, early satiety, swallowing, oral problems.

- Describes taste changes using comparisons with metal, paper, wood, medicine or using other likenesses.
- Describes changes in sense of smell.

After a second re-coding Cohen's kappa for inter-rater agreement was 0.89.

## **5.4 STUDY II - RESULTS**

### **5.4.1 Study sample**

Patients who had started treatment for primary lung cancer were selected from the larger SOL-project data set resulting in a sample of 89 patients. The interview with each patient where TSS scores were highest and the patient had completed a food diary was purposefully selected as previously described. TSAs were reported by 61 of these 89 patients at one or more interviews and of those 25 patients had reported perceiving TSAs already at T1 which was held prior to start of treatment.

All four interviews (T1 – T4) within the longitudinal SOL-project were completed by 67% of the 89 patients in study II, with 61% of the no-TSAs group and 70% of TSAs group completing all interviews. Some patients chose to use their right to withdraw and discontinued their participation early for a variety of reasons. Some patients also missed interviews due to not being in Stockholm, for health reasons or because the patient could not be reached by the interviewer in time.

### **5.4.2 Features of patients reporting TSAs and no-TSAs**

Statistically significant differences with regard to age and smoking habits were found when the features of patients in the TSAs group and no-TSAs group were compared. Those reporting TSAs were on average younger ( $p=0.003$ ), with women on average slightly younger than men in both groups, although this difference was not statistically significant.

Patients reporting TSAs were statistically significantly more often smokers than former smokers, with a statistically significant difference between smokers and former smokers ( $p= 0.001$ ). No statistically significant differences were seen between the TSAs and the no-TSAs groups regarding gender, type of lung cancer, stage of disease or whether treatment was ongoing at time of interview. There was also no statistically significant difference seen regarding type of

treatment before interview between TSAs and no-TSAs groups, although some treatment groups were small (Table 4). More women than men reported being responsible for or playing some role in their meal preparation in both TSAs and no-TSAs groups, which was statistically significant in the whole study population ( $p < 0.001$ ) and in both TSAs ( $p < 0.001$ ) and no-TSAs groups ( $p = 0.016$ ).



**Table 4 - Characteristics of study population**

		<b>TSA</b> <b>n=61 (69 %)</b>	<b>No-TSA</b> <b>n=28 (31 %)</b>	<b>Study population</b> <b>n = 89</b>
<b>Gender</b>				
	Men n (%)	25 (63)	15 (37)	40
	Women n (%)	36 (73)	13 (27)	49
<b>Age at interview<sup>a</sup></b>				
	Mean (SD)	66 (9)	71 (6)	67 (9)
	Median (min-max)	66 (49 – 88)	72 (59 – 86)	67 (49 -88)
<b>Smoking habits<sup>b</sup></b>				
	Non-smoker n (%)	5 (63)	3 (38)	8
	Smoker n (%)	31 (89)	4 (11)	35
	Former smoker n (%)	25 (54)	21 (46)	46
<b>Type of lung cancer</b>				
	NSCLC	54 (71)	22 (29)	76
	SCLC	2	1	3
	Other (carcinoid, mesothelioma, multiple tumour types)	5	3	8
	Unverified	0	2	2
<b>Stage of disease</b>				
	Stage I- II	27 (71)	11 (29)	38
	Stage III	11 (65)	6 (35)	17
	Stage IV	23 (68)	11 (32)	34
<b>Treatment before interview: n (%)</b>				
	Surgery	13 (57)	10 (43)	23
	Chemo, surgery + chemo	29 (71)	12 (29)	41
	RT, SRT	5	2	7
	Target	2	1	3
	Concomitant RT/chemo	9	2	11
	Sequential RT/chemo	3	1	4
<b>Treatment ongoing at interview</b>				
		24 (63)	14 (37)	38
<b>Number of days since treatment start</b>				
	Mean (min – max)	74 (9 – 191)	45(7 – 148)	65 (7 – 191)

Abbreviations: TSAs = Taste and smell alterations, NSCLC=non-small cell lung cancer, SCLC= small cell lung cancer, RT = radiotherapy, SRT= stereotactic radiation therapy, chemo = chemotherapy, SD = standard deviation. Significant difference (p-value  $\leq 0.05$ ) between TSAs and no-TSAs groups regarding: <sup>a</sup> age, <sup>b</sup> number of smokers compared to former smokers, min=minimum, max=maximum.

### **5.4.3 TSAs, protein and energy intakes and weight change**

Energy and protein intakes were seen to decrease across the groups in relation to increased TSS scores (Table 5). Average intakes for the total group of patients who completed food-diaries were below ESPEN guidelines for estimated recommended energy requirements for ambulatory patients with cancer of 30-35 kcal/kg/day [5] and at minimum level regarding estimated recommended protein intakes per kg of 1g/kg/day [5]. Six-month self-reported weight change for the 88 patients in the analysis (one patient could not recall weights) indicated a mean weight loss of 4%, with weight loss increasing between the no-mild TSAs (3%) and moderate TSAs (5%). The mean weight loss in the severe TSAs group was 3% which is the same as in the no-mild TSAs group, however the severe TSAs group was small and there was a high standard deviation. The mean six month weight loss for the 18 patients in the analysis who reported both TSAs and loss of appetite was 6% (data not shown).

**Table 5 – Nutritional intakes by TSAs based on TSS scores**

		<b>No-Mild TSAs n= 34 (14 food diaries missing)</b>	<b>Moderate TSAs n=26 (7 food diaries missing)</b>	<b>Severe TSAs n=4 (4 food diaries missing)</b>	<b>Total n =64 (25 food diaries missing)</b>
<b>Energy intake (Kcal/kg BW)</b>	Mean $\pm$ SD	27 $\pm$ 9	26 $\pm$ 8	18 $\pm$ 8	26 $\pm$ 9
	Median (min-max)	26 (8 – 52)	26 (12 – 46)	16 (11 – 30)	26 (8 – 52)
<b>Protein intake (g/kg BW)</b>	Mean $\pm$ SD	1.1 $\pm$ 0.3	1.0 $\pm$ 0.3	0.7 $\pm$ 0.3	1.0 $\pm$ 0.3
	Median (min-max)	1.1 (0.3 – 1.8)	0.9 (0.6 – 2.0)	0.7 (0.5 – 1.1)	1.0 (0.3 – 2.0)
<b>Energy intake (Kcal)</b>	Mean $\pm$ SD	1888 + 485	1796 + 353	1440 + 945	1823 + 476
	Median (min-max)	1948 (846 – 3007)	1827 (1189 – 2560)	1092 (742 – 2836)	1866 (742 – 3007)
		<b>No-Mild TSAs n = 48</b>	<b>Moderate TSAs n= 32 (1 weight missing)</b>	<b>Severe TSAs n=8</b>	<b>Total n = 88 (1 weight missing)</b>
<b>Six-month weight change (%)</b>	Mean $\pm$ SD	-3 $\pm$ 6	-5 $\pm$ 6	-3 $\pm$ 9	-4 $\pm$ 6
	Median	-2	- 3	- 5	-3
	Max loss %	-14	- 23	- 12	- 23
	Max gain %	+9	+ 8	+ 12	+ 12

Abbreviations: TSAs = taste and smell alterations, min = minimum, max = maximum, Kcal = kilo-calories, Kg = kilogram, g = gram, BW = body weight

Misreporting of food intake has been related to weight status with the risk that responders will under-report increasing with increased BMI [43, 92]. This was examined in the data by stratifying the patients according to BMI based on the World Health Organisation's BMI classification [113] as  $<18.5 \text{ kg/m}^2$ ,  $18.5 - 24.99 \text{ kg/m}^2$ ,  $\geq 25 \text{ kg/m}^2$ ; data regarding BMI was available for 83 of the total 89 study patients as six patients were not weighed at interview. Although there was a slight decrease in energy intake with increasing BMI this was not statistically significant (Table 6).

**Table 6 – Energy intake by BMI**

	<b>BMI &lt;18.5</b> n= 3	<b>BMI 18.5 – 24.99</b> n=34 (10 food diaries missing)	<b>BMI <math>\geq 25</math></b> n= 25 (11 food diaries missing)	<b>Total</b> n= 62 (21 food diaries missing)
<b>Energy intake</b> (mean+SD)	1921 $\pm$ 210	1875 $\pm$ 486	1741 $\pm$ 498	1823 $\pm$ 476
<b>Median</b> (min – max)	2015 (1680 – 2068)	1932 (742 – 3007)	1728 (846 – 2837)	1866 (742 – 3007)

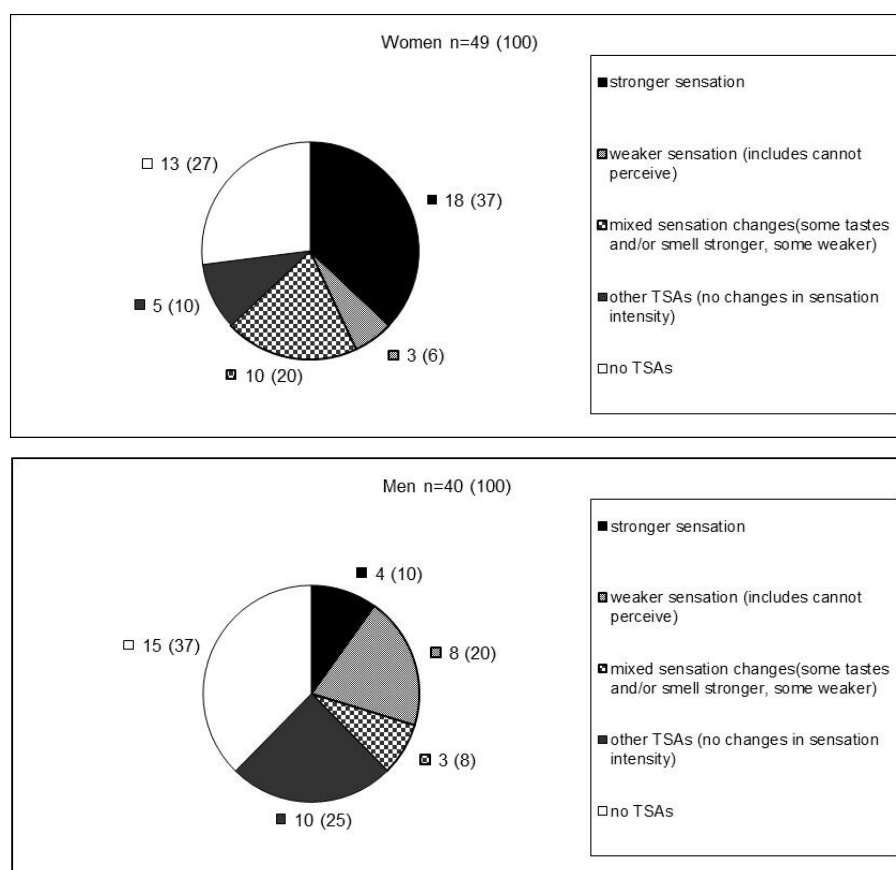
#### 5.4.4 Other symptoms and TSAs

Results from Box 3 of the scored PG-SGA indicated that 31 patients reported symptoms keeping them from eating enough over the previous two weeks. Of these 31 patients, 27 were in the TSAs group and 4 in the no-TSAs group which is a statistically significant difference ( $p=0.006$ ). Symptoms most commonly reported were loss of appetite, early satiety and nausea. Of the 21 patients reporting loss of appetite, 19 were in the TSAs group and 2 in the no-TSAs group which is also a statistically significant difference ( $p=0.013$ ).

#### 5.4.5 Characteristics of reported TSAs

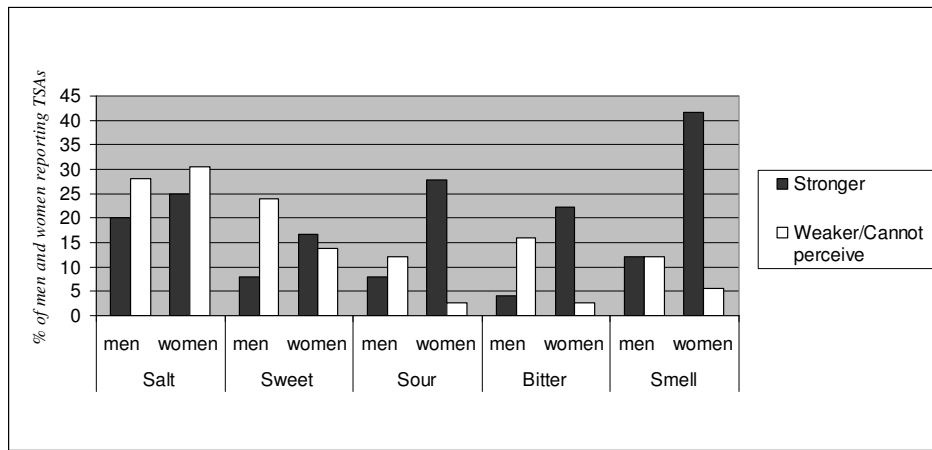
Results showed a variation in characteristics of reported TSAs and were therefore stratified into four groups, with three groups regarding changes in intensity of sensations of salt, sweet, sour and bitter tastes and sense of smell: 1) stronger sensation, 2) weaker sensation, 3) mixed sensation changes and a fourth group, 4) regarding other TSAs with no change in intensity of sensation. These groups were compared in relation to age, gender and smoking habits. No

statistically significant differences were seen between groups regarding age and smoking but an unanticipated phenomenon seen was statistically significant differences regarding gender. More women reported stronger sensation ( $p = 0.007$ ) and more men reported weaker sensation ( $p = 0.04$ ) and other TSAs with no change in the intensity of sensation ( $p = 0.02$ ) (Figure 2).



**Figure 2 – Number of patients reporting changes in sensation of taste and smell by gender**  
*Abbreviations: TSAs = taste and smell alterations*

Further analysis was carried out looking at the changes in perception of four basic tastes and smell in relation to gender. A higher percentage of women with TSAs reported those related to stronger compared to weaker sensation of sour and bitter tastes as well as sense of smell. A higher percentage of men with TSAs reported those related to weaker compared to stronger sensation of all tastes (Figure 3).



**Figure 3 - Reported changes in intensity of basic tastes and smell by gender**

*Frequencies of reported changes in intensity of basic tastes and smell are expressed as the percentage of men (n=25) and the percentage of women (n=36) reporting TSAs.*

*Abbreviations: TSAs = taste and smell alterations*

#### 5.4.6 How patients describe their TSAs

Descriptions of TSAs given in response to open-ended questions generated 216 meaning-units which were grouped into six categories. The group relating to reduced liking of food and reduced enjoyment of eating contained most meaning units with a total of 68, which at times was expressed with quite strong words (e.g. disgusting). Other descriptions of TSAs referred to changes in intensity of sensation of four basic tastes and also to other changes such as foods tasting metallic, all foods tasting the same or lacking taste, or foods tasting distorted or different from usual. Proportionally more of the 216 meaning-units were contributed by women. No pattern could be seen regarding the types of foods spontaneously indicated to work well. In reports of reduced liking of specific foods, coffee was the food most frequently mentioned. Although asked to describe TSAs, patients were found to discuss other symptoms such as loss of appetite, early satiety and nausea, which reflected the symptoms reported by patients with TSAs in the scored PG-SGA. Descriptions of changes in sense of smell related not only to food and cooking smells but also to chemical smells such as perfumes, smoke, disinfectant and exhaust fumes (Table 7).

Table 7 – Examples of citations of patient descriptions of TSAs

Descriptions of TSAs
<p><b>Reports a change in general taste <u>or</u> a change in general intensity of taste <u>or</u> a change in intensity of any of the four basic tastes (salt, sweet, sour, bitter) <u>without</u> describing an emotional response to the change.</b></p> <p><i>“Everything tastes different for example cordials and fizzy drinks”</i>  <i>“Cereal and yoghurt now have a distorted taste”</i>  <i>“Meatballs, for example, have no taste”</i>  <i>“Taste of spices just doesn’t come through”</i>  <i>“Sour is too sour”</i>  <i>“Sweet tastes sweeter”</i>  <i>“Need to add more salt and sugar to food”</i></p>
<p><b>Reports reduced liking of <u>specific</u> foods or reduced enjoyment of eating</b></p> <p><i>“Juice tastes sharp, have drunk it though it doesn’t taste nice”</i>  <i>“Red wine tastes disgusting”</i>  <i>“Milk is disgusting”</i>  <i>“Coffee is not nice anymore”</i>  <i>“Everything tasted disgusting and the same”</i>  <i>“Sweetcorn tastes disgusting although I usually like it”</i>  <i>“I can’t stand coffee or eggs now”</i>  <i>“I hate chicken now”</i>  <i>“What I sometimes think will taste nice isn’t nice”</i></p>
<p><b>Specifies particular foods that work well</b></p> <p><i>“Salty biscuits work better”</i>  <i>“I can only drink lemon tea”</i>  <i>“I have lived on fruit and vegetables, nothing else works”</i>  <i>“All food that is tart works well”</i>  <i>“Could only eat neutral tasting foods like wafer biscuits and cooked vegetables”</i></p>
<p><b>Describes other symptoms related to eating problems e.g. appetite, nausea, early satiety, swallowing, oral problems</b></p> <p><i>“Nothing tastes good – its related to appetite”</i>  <i>“Want to eat but I feel full quickly”</i>  <i>“Don’t have a good appetite, the longing and desire for food is not there”</i>  <i>“A persistent underlying feeling of nausea affects my sense of taste”</i></p>
<p><b>Describes taste changes using comparisons with metal, paper, wood, medicine or using other likenesses</b></p> <p><i>“Everything tastes metallic, even water”</i>  <i>“Everything tastes like paper”</i>  <i>“Tastes of medicine”</i>  <i>“Like everything is wrapped in cotton”</i>  <i>“After radiotherapy everything tasted like old tree stumps”</i></p>
<p><b>Describes changes in sense of smell (both increased and decreased sensitivity)</b></p> <p><i>“Feel nauseous from the smell of food frying nearby”</i>  <i>“For a period everything smelt of chemotherapy”</i>  <i>“I smell a musty odour at home that my husband doesn’t”</i>  <i>“Eat meat but it smells awful when its being cooked”</i>  <i>“Very sensitive for the smell of after-shave and perfume, feel nauseous”</i></p>

## 6 DISCUSSION

The two studies in this thesis, whilst striving towards the common aim of assessing characteristics of TSAs, have different purposes and therefore employ different designs and analyses.

### 6.1 METHOD DISCUSSION STUDY I

The use of the multi-step process in study I was guided by the suggestion of Maneesriwongul et al. [71] to utilise multiple techniques in the translation and cultural adaptation of instruments to add rigour to the process. Important choices were made regarding the individual steps used. After having utilised the TSS in study II, I now consider the translation process in relation to Flaherty et als. [41] five dimensions of equivalence, which although not a measure of equivalence provides a useful framework for reflection (Table 8).

**Table 8 – Dimensions of cross-cultural equivalence and where they were addressed in the translation process**

<b>Dimension of equivalence</b>	<b>Process</b>
<i>Content</i>	Negotiated consensus, Expert review, CVI
<i>Semantic</i>	Choice of translator, Negotiated consensus, Expert review, CVI, think-aloud
<i>Technical</i>	Negotiated consensus
<i>Criterion</i>	Negotiated consensus, Expert review
<i>Conceptual</i>	Choice of translator, Negotiated consensus, Expert review, think aloud

*Content equivalence* refers to whether the content of each item of the instrument is relevant to the phenomenon in each culture being studied. This was addressed by negotiated consensus, expert review and was then assessed by calculating CVI which was excellent after some modifications of the translation. A potential weakness of the negotiated consensus step was that the target population was not represented; this step could therefore be refined by including members of the target population in the negotiated consensus group so that they are involved at an earlier stage in the process. Questions on the TSS regarding TSAs and medication were important for studies in the HIV-infected population for which the TSS was originally developed. However, after using the TSS in study II these questions were found not to yield useful information from patients with cancer and therefore not relevant to the phenomenon being studied. There is a risk of



chance agreement when CVI is calculated, although this is minimised by using a large group of experts [90]. The advantage of CVI over other methods of assessing consistency of rating e.g. coefficient alpha and the kappa statistic is that it provides information regarding individual items [90].

*Semantic equivalence* is when the meaning of each item is the same in each culture after translation into the language and idiom of each culture. The process used for translating the TSS addressed semantic equivalence in all of the steps. Flaherty suggests that the key to establishing semantic equivalence is the use of back-translation [41]. Although back translation was deliberately not chosen in study I due to the limitations that have been previously highlighted, one possible future refinement to the initial translation step may be to have two initial translations prepared by different translators. This would provide extra material for discussion during negotiated consensus which could further increase the quality of the process of achieving semantic equivalence. No issues were raised regarding semantics during data collection.

*Technical equivalence* refers to whether the method of assessment (e.g. written, interview) is comparable in each culture with respect to the data that it yields. In study II the TSS was used during structured interviews whereas the constructors of the instrument allowed patients to complete the questionnaire by themselves. However the experience of the interviewers in the SOL-project was that the quality and volume of information obtained from the open-ended questions was enhanced by the interview situation. As the interviewer asked the questions and documented responses the burden on the patient was reduced and also gave the possibility to ask follow up questions. This aspect should therefore be carefully identified and considered during cross-cultural comparison of results.

*Criterion equivalence* refers to the instrument being able to assess the variable in the cultures studied and that the interpretation of the results is the same in both cultures. As previously noted, during negotiated consensus it was discussed that the term “food” in English was considered to include both food and beverages which was verified when data from our collaborators in Canada was examined. Since this was not thought to be the case in Swedish, this was specified. Also, as pointed out in the expert review, the original Swedish translation of the word “interfere” did not reflect the negative nuance of the word so this was revised. Criterion equivalence refers not to whether the phenomenon occurs but to whether the criteria actually measure the same phenomenon in both cultures. By fine-tuning the translation of these items as a result of the issues raised in

negotiated consensus and expert review we enhanced the criterion equivalence of the instrument.

Finally *conceptual equivalence* refers to whether the instrument measures the same basic concept in each culture. Conceptual equivalence was addressed during the translation process by using a translator familiar with the underlying concepts and in the steps of negotiated consensus, expert review and think-aloud. However, after data collection and analysis from study II, it became clear that although the open-ended questions asked about TSAs, patient responses often referred to other symptoms such as loss of appetite. During the think-aloud interviews some of the patients pre-testing the translated TSS also responded in terms of appetite. One additional complication of this in Swedish, which we became aware of early in the data collection process, is that some patients have described TSAs using the phrase “ingenting smakar” (nothing tastes). It was not always clear from this response whether the patient was referring to appetite or sense of taste. This highlights an additional benefit of using the TSS in an interview situation where ambiguities such as this could be addressed by follow up questions. However, it should be noted that these points relate to the complexity of the phenomenon of TSAs and limitations of the instrument rather than the translation.

## **6.2 METHOD DISCUSSION STUDY II**

Study patients were recruited from the Department of Respiratory Medicine and Allergy, which is the only department in Stockholm which investigates suspected lung cancer. However, when comparing patients in this study with the lung cancer population in Stockholm, the age of patients is comparable but the proportion of women in this study was slightly higher than in the population of patients with lung cancer in Stockholm. There was also a higher proportion of patients classified as stage I-II lung cancer and a lower proportion classified as stage IV in this study [96]. A possible explanation for this is that the patients who felt able to participate in the study were predominately those who were “healthier” among this group of severely ill patients. Those who were more seriously ill were possibly more likely to refrain from participation and therefore under-represented. This phenomenon has been reported in earlier research (see for example [68]) and is a factor known to be a challenge in healthcare studies.

For the most part interviews were held outside the clinical care environment and often in patients’ homes which may have provided a more comfortable environment for patients. Using face-to-face interviews with patients gives the

advantage of being able to clarify misunderstandings and make the respondent feel confident during the interview. A major advantage of the interview process is that the data obtained from the open-ended questions may not have been as easy for patients to report in a written postal survey. However response bias may occur in face-to-face interviews if the patient answers in a way they feel pleases or satisfies the interviewer [63]. Two dietitians and two nurses performed the structured interviews with patients. All the interviewers were female and whether this can result in interviewer or response bias remains unclear. Inherent in the use of multiple interviewers is the risk that initial and follow up questions are asked and answers documented in different ways. De-briefing with in-depth discussions was held among all the interviewers throughout the entire data collection period to minimise this risk.

There were patients who made it clear early on that they were not able to complete food diaries and others who later felt unable to do so due to deteriorating health or demanding treatment regimes; however, it was decided that interviews should be carried out to obtain information about TSAs and symptoms despite this.

The self-reported nature of measures of body weight and food intake is a possible limitation in study II. Six-month weight loss was calculated from patients' self-reports of current weight and weight six months previously. Patients' ability to recall and self-report body weight is a possible source of error. Whilst essential for nutritional research, assessment of dietary intake is not easy and limitations in all methods have been described [43]. Methods that are used to measure individuals actual and/or usual food consumption include 24-hour recall, estimated food records, weighed food records, dietary history and food frequency questionnaires [43]. The 24-hour recall and food frequency questionnaire methods are the quickest and least burdensome to the patient. The 24-hour recall relies on memory but as many patients with lung cancer are elderly this was not thought to be an appropriate method for study II. The food frequency questionnaire method was not suitable as it measures "usual" food intake whereas study II focused on patients' "actual" food intake around the time of the interview which may differ from their usual intake. Self-reported food record is a common method used in research studies despite its vulnerabilities and was considered to be the most appropriate method to assess actual food consumption in this study population. It was decided to use a 3-day estimated food record in study II to capture day-to-day variation in food intake of patients

with lung cancer whilst also avoiding the risk of patients becoming weary of recording.

Errors that can occur using food records to assess dietary intake include respondents changing their eating habits during recording [94] or misreporting intake [92]. Obesity has been linked to underreporting [67] and in study II although increasing BMI did associate with decreasing energy intakes this was not statistically significant. This trend could be due to over- and underreporting at low and high BMI's respectively or to patients with low BMI's increasing their energy intake to address or avoid weight loss. Mean energy intakes in relation to body weight in this study population were, however, found to be consistent with another study investigating energy intake and dietary energy density in patients with cancer in palliative care [110]. Thorough information was given to patients at all interviews regarding recording of food intake and standard household measures were supplied to aid estimation of portion sizes. Where possible, uncertainties in food records were clarified with the patient on receipt of the food diaries.

Methods for assessing misreporting include the use of bio-markers such as doubly-labelled water or urine nitrogen excretion to check energy and protein intakes respectively but these methods were not considered feasible in this study [43]. The Goldberg cut-off has also been used to identify under-reporters by identifying reported energy intakes that are too low to sustain long term survival. This method is only useful as a check for habitual intake in patients in energy balance and as many of our patients reported weight loss over six months was not an appropriate method [43]. Another method is to exclude patients who report extreme energy intakes outside  $\pm 3SD$ 's of the mean and are therefore identified as outliers regarding energy intake [110]; however, none of the patients in study II had intakes outside of these limits.

Risks for errors due to coding mistakes, incorrect estimation of portion sizes and difficulties in calculating mixed dishes were minimised in a number of ways. Calculation of intakes in study II was performed by just two registered dietitians with all food diaries from each individual patient being calculated by the same dietitian as far as possible. This gave the advantage that the dietitian became familiar with the patient's particular style of recording and thus facilitating consistency of calculation. The dietitians used a reference table to estimate serving sizes and weight of food portions and kept and consulted a detailed audit trail of calculations throughout.

Although it is known that some medications and co-morbid conditions are known to affect taste and smell perception [26, 101] this was not within the scope of this study which purposefully investigated a naturally occurring sample of patients with lung cancer.

### **6.2.1 Statistical analysis**

In study II many variables have been tested which incurs a risk of finding spurious significance. The sample groups are also at times small which can involve a risk for failing to find statistical significance that may exist between the groups in question, however several statistically significant results were found despite this. The p-value was consistently set at  $\leq 0.05$  as the tests were of an explorative nature and it is important not to miss clinically important differences.

## **6.3 REFLECTIONS ON THE RESULTS**

### **6.3.1 The translated TSS**

Results from study I indicate that the process used for translation and cultural adaptation of the TSS has produced a robust instrument in Swedish which can be used in comparisons with the English version. These results reinforce the value of using multiple steps since knowledge gained at each step highlighted issues which could be corrected thereby enhancing the quality of the translation. After analysing the results from study II it was clear that there are limitations with the TSS but these were not found to be due to the translation but rather to the instrument itself. Another factor to be considered regarding the cross-cultural usefulness of the TSS is that the instrument does not include the fifth basic taste umami, which is not thought to be well-recognised in western food cultures.

### **6.3.2 TSAs in relation to gender**

Gender differences in characteristics of TSAs could lead to men and women altering their diets in different ways to cope with these changes. This could have nutritional implications in that dietary advice to patients may need to be tailored to accommodate different characteristics of TSAs experienced by different gender groups.

One possible explanation for the gender differences noted in study II could be physiological differences in men and women's senses of taste and smell. As previously discussed, in the general population, studies show that women

perform better in taste detection and identification tests and olfactory impairment is more prevalent in adult men [17, 22, 32, 64, 79]. Results from study II show that there was no statistically significant difference between the number of men and women reporting TSAs, suggesting that ability to detect TSAs was not related to gender. However a statistically significant difference by gender was found in the reported characteristics of TSAs.

Exposure to and experience of different flavours and odours may affect preferences and ability to perceive and discriminate flavours in different groups [116]. For example, in a study comparing German and Japanese participants responses to odours, descriptive ability and how well-liked the participants rated the odours were higher for familiar odours and seemed to be influenced by culturally specific eating habits [7]. In the 2012 report of the dietary habits and nutrient intake among adults in Sweden by the National Food Agency, differences in food choices among men and women in the general population were found with women choosing more fruit, vegetables and fibre than men, less meat than men and limiting salt intake [4]. These differences may result in gender differences in exposure to different tastes and flavours which may then affect the experience of TSAs.

Women contributed proportionally more meaning-units in the open-ended questions than men. Gender is thought to be one of a number of factors influencing the way symptoms are perceived and expressed [6]. There may therefore be gender differences in willingness to report and talk about TSAs, although there have been some conflicting reports in the literature regarding reporting of symptoms by men and women [28, 70]. Nicholas [82], writing about male gender-role socialisation in cancer in the United States, discusses that men may feel that seeking help, expressing emotions, reporting treatment side-effects and symptoms, and asking for information from healthcare staff are not acceptable behaviours for men. A paper by Courtenay which examined gender and health in the United States discussed how men may also be reluctant to speak about their health as they want to avoid appearing weak or feeling subordinate to healthcare professionals [30]. Women are also more used to detecting, responding to and discussing bodily cues and symptoms as a result of their experiences of menstruation, pregnancy and menopause [111]. However, Lövgren et al. [68] when investigating symptoms reported by men and women with lung cancer in Sweden found that women reported more negative emotional reactions but otherwise found no major differences in prevalence and intensity of symptoms reported by gender.

In both the TSAs and no-TSAs groups more women than men described being responsible for or involved in the preparation of their meals. This closer contact with food and food preparation may also affect the range and extent of vocabulary that men and women have regarding food tastes and smells and therefore lead to differing abilities in verbalising TSAs. Armstrong's [6] concept of symptoms experience describes how the meaning that symptoms experience has for patients may influence occurrence or perceived distress from symptoms. Men and women may therefore view and respond to particular symptoms differently or assign different meaning to different symptoms. As more women are responsible for preparation of meals they may find TSAs more distressing thus assigning different meaning or importance to TSAs than men.

### **6.3.3 Other symptoms**

Patients reporting TSAs more often also reported other symptoms such as loss of appetite, nausea and early satiety. This finding is in line with studies in patients with varying cancer diagnoses receiving chemotherapy and with advanced cancer where TSAs were also related to symptoms of poor appetite, nausea and early satiety [14, 56]. Whilst it is important to focus on individual symptoms it is also relevant to consider symptom clusters and how different symptoms influence each other. It is hypothesised by Armstrong [6] that when two or more symptoms are experienced concurrently, it is likely that the experience of one enhances the other. In study II the average weight change for the study group showed a loss of 4% over six months prior to interview, however the group of patients reporting both TSAs and loss of appetite had a mean weight loss of 6%. This indicates that patients with lung cancer experiencing TSAs and loss of appetite may be more at risk for weight loss and this area warrants further research.

### **6.3.4 Energy intake**

The analysis of this study was exploratory in nature and as such was not adequately powered to draw firm conclusions regarding differences in intakes between TSS score groups. However, energy intake was found to be low for the whole group and also decreased with increasing TSS scores. It is therefore hypothesised that there is a link between higher TSS scores and reduced energy intake in patients with lung cancer as has also been shown in patients with advanced cancer [25, 56].

### 6.3.5 TSAs, flavour or hedonics?

In the open-ended questions patients were specifically asked to describe changes in taste and smell both generally and in relation to the consumption of food and drink. Patients seem however to experience a range of symptoms that they identify as taste and responses related not only to general changes and intensity changes in taste and smell sensation, but also the loss of enjoyment of food and reports of other symptoms which had affected eating. Patients' understanding of TSAs seems therefore to go beyond the altered perception of the basic tastes of salt, sweet, sour and bitter. Instead, patients responded in terms of the broader sensory concept of flavour as well as the hedonics of food. Researchers describe food hedonics as referring to the extent to which eating and drinking is pleasurable and distinguishes between two components involved in food consumption: "liking" and "wanting" [16, 40, 75]. "Liking" is defined as the immediate experience or anticipation of pleasure from the orosensory stimulation of eating a food [75]. "Wanting" (or hedonic appetite) is the motivation or desire to consume a specific food [40]. When asked to describe their taste changes patients responded in terms of both sensory changes (taste and flavour) and hedonic changes (wanting and liking). Examples of citations from responses relating to sensory changes are:

- *Sour is too sour*
- *Need to add more salt and sugar to food*
- *Meatballs, for example, have no taste*
- *Taste of spices just doesn't come through*
- *Everything tastes metallic, even water*
- *Cereal and yoghurt now have a distorted taste*

Examples of citations from responses relating to hedonic changes included the following:

- *Sweetcorn tastes disgusting although I usually like it*
- *Coffee is not nice anymore*
- *What I sometimes think will taste nice isn't nice*
- *Nothing tastes good – it's related to appetite*
- *Don't have a good appetite, the longing and desire for food is not there*
- *I eat meat but it smells awful when it's being cooked*

The multi-dimensional features of TSAs and the lack of clarity in what is understood and described have important implications for future research and in the clinical management of TSAs and other symptoms. In English the word flavour is often used synonymously with the word taste making it difficult to



differentiate these components. Furthermore, in Swedish there is no one word to describe the concept of flavour. The reduced enjoyment of food is a further dimension of TSAs. It is therefore important that in research regarding prevalence of TSAs and in the clinical situation where advice and interventions are matched to patients' symptoms that communication regarding what is actually being talked about is made clear through the use of a consistent vocabulary by researchers and clinicians.

Energy intakes were seen to decrease with increasing TSS scores and mean weight loss was greater in patients reporting both TSAs and loss of appetite. It is however not clear to what extent food hedonics plays a role in the impact of TSAs on energy intake. It is also not clear what social and emotional consequences the patient's reduced enjoyment of food may have for the patient, their family and friends.

## 7 CLINICAL AND RESEARCH IMPLICATIONS

### 7.1 CLINICAL IMPLICATIONS

Care of the patient who has been diagnosed with lung cancer focuses on treating the disease and managing symptoms that the patient experiences. Symptoms are the patients' perception and interpretation of problems, so a mutual understanding and good communication between patients and dietitians and healthcare staff are fundamental to the development of supportive care strategies.

Although there is a lack of evidence-based guidelines for the identification and management of TSAs, patients and family care-givers may have found strategies for self-management of TSAs. Helping patients and family care-givers articulate and interpret their problems may therefore lead to a better understanding of methods to cope with TSAs which could provide a basis for the development of evidence-based guidelines for identification and advice.

It is important that dietitians and other healthcare staff ask questions about the patient's eating, TSAs and other symptoms in order to help both patients and their family care-givers differentiate and verbalise characteristics of changes and to fully penetrate the complexities of the perceived TSAs. The interplay of TSAs with other symptoms seen in this study may also make it difficult for patients with lung cancer, their family care-givers and healthcare staff to determine the nature of the problem being experienced by the patient. In-depth assessment to identify the characteristics of TSAs and other symptoms is necessary to be able to make individualised suggestions to match patient-reported symptoms with appropriate advice and interventions. Important questions therefore need to be asked regarding characteristics of a patient's TSAs relating to:

- increased intensity of any of the basic tastes
- decreased intensity of any of the basic tastes
- other changes in general taste or general intensity of taste
- changes in sense of smell
- particular foods that taste or smell differently
- other symptoms e.g. loss of appetite, nausea, early satiety
- changes in food enjoyment

In this context it is important to consider that men and women may experience, interpret and assign importance to TSAs and other symptoms differently and may therefore have differing needs, abilities or readiness to talk about their perceptions.

The time-point when patients reported the highest number of TSAs during the study period was seen to vary, occurring at different stages of the treatment trajectory. This indicates that an understanding of the patient's experience of TSAs requires follow up throughout the course of disease to be able to evaluate the effectiveness and benefit of nutritional intervention to the patient.

The perception of TSAs poses a challenge regarding nutritional care of patients with lung cancer both in and out of hospital. Hospital menus are not adapted to cope with patients' changes in taste and smell function. For example desserts on hospital menus are invariably sweet which is not of benefit to patients who have a heightened sensitivity to sweet taste. Equally patients with altered perception of salt may prefer to season their food themselves. The heightened sensitivity to smells some patients reported may also be a factor to consider in the logistics of hospital meal-times and the smell of hospital food as it is served on the wards. Consideration should therefore be given to TSAs in the planning of hospital menus and meal service. Furthermore, the range of tastes within commercial oral nutritional supplements available to patients with lung cancer requires increased versatility so that they can be more easily tailored to different characteristics of TSAs.

## **7.2 IMPLICATIONS FOR FUTURE RESEARCH**

Taking into account the variation in how TSAs are defined and reported by patients with lung cancer, the gender differences in characteristics of TSAs perceived and the complex interplay with other symptoms, future research studies in this area are warranted. After reflecting over the results from study II, it was useful to consider their implications for the TSS as an instrument for assessing TSAs. Whilst confident that the translation of the TSS had produced a robust instrument in Swedish comparable with the English version, it is now apparent that there are definite possibilities to extend and improve its content in both languages. In order to fully explore both sensory and hedonic aspects of TSAs more specific questions regarding these different dimensions could be included. The interplay of TSAs with other symptoms such as loss of appetite, early satiety and nausea that appear to influence patient perceptions of TSAs may therefore require the addition of questions that better tease out the nature of the actual problem being reported. These reflections provide incentives for future study to further develop the TSS in both English and Swedish to provide an instrument which addresses these wider dimensions of TSAs both for future

research and in particular the assessment of self-reported TSAs in the oncology clinic.

It would therefore be of clinical importance to investigate how patients with lung cancer, their family caregivers and healthcare staff experience interrelationships between TSAs, loss of appetite, early satiety, nausea and to what extent these symptoms are able to be distinguished from one another. Furthermore, the gender differences seen in study II justify further investigation of the differences and similarities in how women and men with lung cancer reason about and verbalise their perception and experiences of TSAs and their effects on food intake. With a lack of evidence-based advice and interventions it seems pivotal to investigate if patients with lung cancer, their family caregivers and healthcare staff have strategies or advice that they have found helpful in enabling patients to cope with TSAs and/or other symptoms impacting on food intake. This may then contribute vital information which could form the foundation of a clinical intervention study alongside other methods that are recommended, for example the FASS (fat, acid, salt and sweet) method developed by Rebecca Katz [57] which uses four basic ingredients to enhance the flavour of food. An intervention study could test which strategies really work for which particular problems.

The hypothesis developed from this explorative data that increasing TSS scores are associated with decreasing energy intakes should be followed up with a larger study in the lung cancer population. It would also be particularly useful to explore how both sensory and hedonic aspects of TSAs impact on nutritional intake and the social aspects of eating.

Since patients report TSAs in terms of sensory and/or hedonic changes, it seems imperative to be able to match patient descriptions of TSAs to a framework of clinical definitions in order to improve the communication between patients and healthcare staff. This could better enable the diagnosis, assessment, management and evaluation of care of the different components of TSAs. One approach would be to develop terms and definitions for TSAs which can be incorporated into the International Dietetics and Nutrition Terminology (IDNT) [2]. This is a standard terminology developed by the Academy of Nutrition and Dietetics in the United States for the nutritional care process, which has been translated into Swedish and is used by Swedish dietitians [1]. A nutritional diagnosis of TSAs could be included in the clinical category of diagnoses and the characteristics of TSAs then described in terms of signs and symptoms.

Further research building on the work in this thesis could lead to a structured evidence-based approach to the identification, discrimination and management of TSAs and their impact on eating. This would enable dietitians and healthcare staff to better advise patients with lung cancer experiencing TSAs and support their family care-givers so that food and mealtimes can be enjoyed which in turn may help maintain nutritional status.

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