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Title: SUBJECTIVE AND OBJECTIVE TASTE AND SMELL CHANGES IN CANCER

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Key Message:

Malnutrition is prevalent in cancer patients and a key predictor of morbidity, mortality, treatment response and toxicity. Taste and smell changes (TSCs) are frequent and may contribute to malnutrition. This paper reviews the assessment of taste and smell and the prevalence and clinical sequelae of TSCs in cancer. Early intervention may support nutritional status, quality of life and survival.

Abstract

Context: Malnutrition is highly prevalent in cancer patients and an important predictor of morbidity, mortality, treatment response and toxicity. Taste and smell changes (TSCs) are common and may contribute to malnutrition. Research has previously focused on patients receiving chemotherapy (CT) or head and neck radiotherapy (RT). However, TSCs may occur pre-treatment, with other treatment modalities, and in cancer survivors. This review evaluates objective and subjective assessment of taste and smell, discusses the prevalence of TSCs in cancer, and reviews the clinical sequelae of TSCs in cancer patients.

Objectives: To critically evaluate objective and subjective assessment of TSCs, and the prevalence and clinical sequelae of TSCs in cancer.

Methods: A literature search was conducted using PubMed, CINAHL and Embase for English-language articles published January 2009-June 2016. Search terms included combinations of the following: chemosensory, taste, smell, cancer, chemotherapy, radiotherapy, hormone therapy, immunotherapy, survivors. Reference lists of articles retrieved were also reviewed.

Results: Variation in objective and subjective assessment methodologies has resulted in difficulties interpreting the literature. TSC prevalence varies depending on stage of disease and treatment regimens, from 16-70% and 50-70% during CT and RT, respectively. TSCs in patients who are treatment-naïve, receiving hormone or immunotherapy treatment, post treatment and cancer survivors have not been adequately studied. TSCs are associated with impaired nutritional status. The relationship between cancer-associated symptoms and nutritional status is not clearly defined.

Conclusion: There is no gold standard assessment tool for TSCs. Heterogeneity in study methods hinders conclusive identification of the most appropriate way to measure TSCs. Subjective measures may reflect the patient experience and more reliably predict changes in dietary behaviour. Evaluation of TSCs should form part of all nutritional assessments in cancer patients. The true prevalence and severity of TSCs at all stages of cancer could then be established.

Keywords: cancer; chemosensory; review; smell; taste

Introduction

The chemical senses of taste and smell are essential to life. They alert us to danger (e.g. gas, fire), prevent ingestion of toxins and support oral nutrition [1]. Together, taste and smell drive flavour perception, i.e. the sensory impression of food [2] and support digestion. Disturbance of these senses can occur for a number of reasons, including disease and medications [4, 5, 6]. Food aversions can develop which can reduce the amount, enjoyment and quality of food consumed [4, 7]. Taste and smell changes (TSCs) may contribute to an increased risk of malnutrition (under or over-nutrition) [8, 9], low mood, diminished social interaction and reduced quality of life [1, 10]. Cachexia occurs in approximately half of all cancer patients and predicts poor prognosis [11, 12]. As TSCs occur in 40-50% of those with cachexia [13], understanding and managing factors which contribute to their development is crucial.

Epstein *et al.* [14], in their recent review, focused on the physiology of taste and provided a comprehensive analysis of objective methods of assessment of taste changes (TCs). Subjective methods to evaluate TCs were not evaluated. Discussion on the impact of TCs in cancer primarily included patients post chemotherapy (CT) or radiotherapy (RT). Smell and changes in smell that occur in cancer were not addressed.

This article aims to critically review objective and subjective assessment of TSCs and provide a thorough evaluation of the literature in relation to prevalence and clinical consequences of TSCs throughout the cancer trajectory.

Physiology of Taste and Smell

Taste perception is mediated by receptor cells in taste buds on the dorsal and postero-lateral tongue surfaces, and on the epithelial surface of the oropharynx and larynx [15]. Taste receptor cells also exist in the gut [16]. Saliva plays a key role in bringing food stimuli in contact with the receptor cells.

They detect chemical signals which produce taste and stimulate neurotransmitter release onto afferent nerve fibres that convey signals to the brainstem. Taste receptors are renewed every 10 days [15].

Smell perception is also stimulated by chemical signalling. Odour molecules bind to receptors in the cilia of olfactory receptor neurons [17], propagating a nerve impulse, which terminates in the nasal olfactory bulb. Convergence of olfactory bulb impulses generates signals to the primary olfactory cortex and the caudal orbital cortex, where the combination of smell and taste creates the perception of flavour [17]. Perceived flavour is then integrated with texture and temperature in the orbitofrontal cortex to give the overall sensory impression of food [18]. Smell receptors are renewed every 30 days [17].

Basic taste modalities include sweet, sour, salty, bitter and umami (the savouriness of protein-rich foods), and possibly fat and metallic tastes [8, 19]. There are no defined smell modalities; this makes description of smell difficult for patients. Changes to both taste and smell can be classified into three broad categories: change in sensitivity, distorted perception and hallucination.

Taste and Smell Changes in the General Population

In 2008, estimates of the prevalence of taste and of smell changes in the general population were 20% and 21.6%, respectively, according to German data [20]. Common aetiologies include chronic illnesses such as allergic rhinitis, chronic inflammatory middle ear disease and head injury [21, 22] in addition to smoking [20], older age [23], medication [24] and micronutrient deficiencies [23]. Impairments may be temporary or permanent [25].

Reported prevalence of TSCs in cancer is up to 70% [26, 27]. Whilst the aetiologies for TSCs post cancer treatment are relatively well established [10], changes in the treatment-naive are not fully understood. Several mechanisms have been proposed. These include mechanical, e.g. tumour obstruction to chemoreceptor sites [28]; neurological, e.g. tumour interference with neural

transmission [28]; and metabolic, e.g. increased salivary urea concentration due to tissue catabolism (bitter taste) [29].

Methodology

This is a narrative review which aims to evaluate the assessment, prevalence and clinical sequelae of TSCs in the cancer population. A literature search was conducted using PubMed, CINAHL and Embase. Search terms included combinations of the following: chemosensory, taste, smell, cancer, oncology, chemotherapy, radiotherapy, hormone therapy, immunotherapy, cancer survivors. Articles were included if they were available in full text, English language, conducted in patients with cancer and published between January 2009 and June 2016. Non-cancer diagnoses studies were excluded. Reference lists of articles retrieved were also reviewed.

Assessment of Taste and Smell Changes in Cancer

TSCs can be assessed objectively or subjectively [30, 31]. There are two primary outcome measures: detection and recognition. Detection is the awareness of a taste or smell sensation, whereas recognition indicates that a taste or smell quality is acknowledged and can be named (e.g. salty taste, smell of coffee) [8]. Threshold testing determines the minimum stimulus required for detection of a sensation or recognition of a quality. An increased threshold indicates that sensitivity is reduced and vice-versa [8]. Detection thresholds are typically lower than recognition thresholds; test procedures must be standardised to take this into account [8].

1. Objective assessment

Taste

Objective taste assessment methods used in cancer include electrogustometry, liquid tastants and filter paper discs/strips. They are useful for understanding the physiology of TCs, as highlighted by Epstein *et al.* [8,14], though each method has limitations.

Electrogustometry involves the application of an electrode to tongue taste receptors; an electrical current (microampere range) is then released to assess taste detection [30]. Although studies have suggested validity, reliability and reproducibility [32, 33], electrogustometry has limited clinical use due to poor correlation between electrically and chemically induced taste perception (i.e. chemical stimulants in food) [34]. Furthermore, it does not measure taste recognition [31].

The application of liquid tastants of varied strengths and volume can be used to assess whole mouth or localized sensitivity [35]. Forced-choice procedures (where participants must identify tastant among blanks) are often used to avoid confounding [36]. However, this method is time consuming and laborious with great heterogeneity in testing, e.g. one strategy involves applying drops directly to the tongue (~50 µL) while another involves tasting a stimulus added to water (3-5 mL)[32].

Filter paper discs/strips impregnated with taste solution are applied directly to the tongue. Although validated, thresholds may differ according to where on the tongue the stimulus is applied [37]; adequate salivary output, often compromised following cancer treatment [8], is required.

Smell

Objective methods to assess smell in cancer include 'Sniffin Sticks', inhalation of solutions and the University of Pennsylvania Smell Identification Test (UPSIT).

'Sniffin' Sticks' (US Neurologicals, Washington) are pen-like odour dispensing devices for identification (16 sticks), discrimination (48 sticks in 16 triple sets) and threshold (48 sticks: 32 blanks and 16 dilutions of N-butanol) testing [38, 39]. They have been validated in various populations [40, 41] and are cost-effective [39] but may be prone to learning effects. This may reduce their value in the clinical setting [42].

Techniques involving inhalation of solutions to determine detection threshold, for example, phenyl methyl-ethyl-carbinol [43, 44] or phenethyl and menthol [44] solutions, have significant within- [45], across-subject [45] and day-to-day variability [46]. The UPSIT uses cards impregnated with specific odours, to assess odour recognition. The cards are scratched with a pencil to release the odour and

the odour recognised is chosen from four options [47]. A strength of this method is that normative data from 4000 individuals are available [48]. Unfortunately, this test cannot measure smell detection thresholds [47].

Although electrogustometry, to assess taste, and 'Sniffin' Sticks', for the evaluation of smell, have the most evidence to support their use, inconsistent results continue to be reported from studies within and across cancer populations, using these methods (Tables 1-4). This may reflect varied study design. As outlined earlier, their use in clinical practice is also limited and patients may be burdened by TSCs not identified by objective testing [49]. Further research is needed before one objective assessment method can be recommended.

2. Subjective assessment

While objective methods are best for determining the physiology of TSCs, and assessing taste and smell acuity [8], subjective data more accurately describe cancer patients' experiences of TSCs and more reliably predict changes in dietary behaviour [26].

Differences in assessment strategies used in objective and subjective studies have led to inconsistent results. This is likely due to differences in measurement technique, variability in study design and other disease-related factors such as primary tumour site or treatment regimen [50, 51]. The literature has not taken adequate account of these factors. Self-report measures may avoid many of the limitations of objective testing of TSCs [4, 26, 30, 50] and could be more clinically valuable. A key limitation is that there is no internationally validated questionnaire for this purpose [31], despite a number of instruments being available.

Goldberg's eight-item 'Chemosensory Questionnaire' [52] has good construct validity and is time-efficient. However, it is only validated in head and neck (H&N) cancer and does not assess the characteristics of TSCs. A Swedish 33-question tool [26] includes information on CT regimens and cycles but has been used by only one research group. A 41-item US questionnaire [53] has established content validity but published results of its use are sparse. Similarly, a recently developed

chemotherapy-induced taste alteration scale [54] has high reliability, validity and a favourable response rate, yet is infrequently cited in the literature and solely assesses taste.

The 'Taste and Smell Survey' [5] characterises quality and severity of TSCs and is time efficient, but has been amended numerous times [55-57] and requires validation. It has been used most frequently to assess TSCs in cancer and other disease states, facilitating direct comparison between studies. However, differences in study design and length of follow-up must be acknowledged. Its ease of use in a clinical setting makes it a convenient measure of subjective TSCs. Nonetheless, it must be validated before firm recommendations can be made on its use.

Prevalence of Taste and Smell Changes in Cancer

Estimates of the prevalence of TSCs are difficult to determine given the variation in methodology, confounders such as diverse use of anti-emetics and analgesics and combined prevalence figures reported using both subjective and objective assessment (Tables 1-4). Furthermore, much of the literature has focused on TSCs related to CT or RT of the head and neck. Nonetheless, there is consensus that the prevalence of TSCs in cancer is underestimated [58, 59]. A study in 1998 concluded that TCs were under-recognised by medical oncologists in 36% of cases [59]; similar findings were reported more than 10 years later [60]. Patients may be aware of TSCs [61], but consider them trivial or are unable to articulate their taste and smell sensations [62] and so changes may go unreported. Staff and patients communicate less about symptoms they believe are untreatable [62], as few effective interventions are available [10]. This may exacerbate the under-recognition of TSCs.

Given the close physiological relationship between taste and smell, expert opinion suggests that the two senses should be assessed together [63]. Both increased and decreased detection and recognition thresholds for basic tastes have been noted [4, 42, 64, 65]. Bitter, chemical, metallic or nauseating tastes are also common post CT and RT [8, 57]. For example, metallic taste has been reported in 32% of individuals with breast, colorectal, H&N, lung, stomach, and other cancers following CT and/or RT in one study [59] and in 16% of those with lung cancer in another [66].

Objectively and subjectively elevated salt thresholds have also been documented during and following CT in advanced cancer [2, 67].

Increased and decreased smell thresholds have also been described [68], although the literature available is limited. In cancer, regardless of tumour site, qualitative changes in smell perception, such as altered recognition, predominate [8]. Distorted smell perception is frequently termed as rancid [69], though standardised terms do not exist for smell quality, as previously discussed. Smells are processed in the limbic system which also handles memories and emotions [70]; hallucinations that occur during strong emotional experiences, e.g. a chemical smell occurring during CT due to anxiety [71], may contribute to smell changes (SCs).

Prevalence of Taste and Smell Changes with Chemotherapy

CT causes TSCs via cytotoxic damage to rapidly dividing taste and smell receptors [10]. CT can also cause a bitter taste by entering the mouth through gingival sulcus fluid or diffusing from capillaries to receptor cells [72]. Disruption to saliva and mucous production can affect taste through development of oral mucositis, dry mouth and dental caries [28]. Cytotoxic drugs can also have an independent effect on smell by inducing a smell of their own or affecting the central and/or peripheral nervous systems [72].

TCs have been reported in 20-70% and SCs in 16-49% of those on CT (Table 1). The discrepancy in reported prevalence may be due to the difference in turnover rate of smell and taste receptors (mean 30 days v mean 10 days) with possible further variation occurring as a consequence of CT damage [73]. The olfactory epithelium is also more robust and may, therefore, be less susceptible to damage [74].

Interpretation of reported findings is problematic given the heterogeneity observed in most study populations. Variability in disease severity, treatment regimens, use of different assessment methods and timing of data collection with respect to treatment administration all pose problems [26]. Hyper- and hypogeusia for salt and sweet tastes occur most frequently [26, 62], though changes to bitter and

sour sensation have been reported [42, 75, 76]. Metallic taste has also been noted [53]. There is no consensus on the relative prevalence or severity of TSCs following CT in one cancer type versus another [26, 42]. Taxane-based [42] and irinotecan CT [60] appear to have the greatest effect on TCs and gemcitabine the least effect [26, 60]. However, TSCs have also been noted with cyclophosphamide, folinic acid antagonists, methotrexate and platinum agents [26].

Timing of onset of TSCs following CT can vary. Some subjects reported that TCs began during or shortly after their first CT administration [26], while others reported an onset after the second or third cycle [53]. Cyclical effects of adjuvant chemotherapy on taste function have also been reported [77] with reduced function early in the cycle, recovery later in the cycle and resolution 8 weeks following CT completion.

Frequently cited SCs were reduced sensation [42, 78] and distorted perception of the smell of cleaning products, perfumes, cooking and body odour [26, 62]. Although no discrepancy in the effect on smell with different CT agents is generally reported [42, 79], one recent study noted that changes in smell threshold following CT were significantly greater with 5-fluorouracil and capecitabine compared to cisplatin and carboplatin [78].

Prevalence of Taste and Smell Changes with Radiotherapy

RT can damage sensory receptors depending on the field of administration [74]. Salivary gland function may be compromised in head and neck RT. This can cause hypo-salivation and dry mouth, which may reduce taste due to limited delivery of chemical stimulants to receptors [80]. Research on TSCs during RT has predominantly focused on H&N cancer (Table 2) though a recent study included patients with glioma [81]. In this study, TCs occurred in up to 70% and SCs in 50% of patients.

Increased detection threshold of all basic tastes has been noted [79, 82, 83]. It has been suggested that the minimum radiation dose capable of causing TCs is 15-30 Gray [84]. No significant differences have been found between conventional and hyper-fractionated RT [82], although parotid-

sparing intensity modulated RT has been associated with improved food intake post-treatment [85]. This may reflect better maintenance of salivary function and taste during RT.

There is no consensus on whether SCs occur during RT. One study documented loss of smell subjectively [81], while another, using objective smell assessment, reported that it was unaffected [85]. No studies have attempted to characterise the severity of TSCs during RT.

Prevalence of Taste and Smell Changes in Treatment-Naïve Patients

For the treatment-naive, the literature is limited and at times contradictory. Considerable variation in TSC prevalence is noted (Table 3). Different methods of assessment of TSCs and varied study design may be contributing to these discrepancies.

Although pre-treatment TSCs might be expected in H&N cancer, studies have reported conflicting findings [86-88] and the mechanisms for pre-treatment TSCs remain poorly understood [4, 30]. Neither severity nor duration of TSCs in these patients has been determined. Interpretation of study results and identification of the aetiology of TSCs is difficult given these limitations.

One small study (*N*=12), using objective assessment, found no significant difference in taste thresholds between patients with untreated oesophageal cancer and controls [29]. Similarly, a more recent study, using the 'Taste and Smell Survey' [5] in a group of patients under investigation for lung cancer (*N*=117), found no difference in reported TSCs, between those who were diagnosed with lung cancer and those who were not [50]. Contrary to this, and also using the 'Taste and Smell Survey', our research group showed that almost half of treatment-naive patients with solid tumours (mainly breast or prostate cancer; *N*=40) reported TSCs prior to CT or RT [89].

Prevalence of Taste and Smell Changes with Hormone Therapy and Immunotherapy

No research to date exists on the impact of hormone and/or immunotherapy on TSCs in cancer. However, previous studies have suggested that impaired smell is associated with congenital and

post-menopausal hypogonadism [90, 91] and is improved with hormone replacement therapy [90]. Hormone therapy could, therefore, cause TSCs in cancer. Given that both hormone and immunotherapy are increasingly being used as cancer treatments [92], more research is needed to assess their effects on taste and smell.

Prevalence of Taste and Smell Changes in Patients who have Recently Completed Treatment and Long-term Cancer Survivors

Although taste and smell receptor cells are renewed regularly, cancer treatments may cause permanent damage to these cells due to alterations in receptor cell structure, reduction in number, nerve damage or damage to salivary glands causing hyposalivation [10].

Despite limited research, short- and long-term TSCs have been reported after cancer treatment; reported prevalence ranges from 9-100% [93, 94] and 12-18% [95, 96], respectively. The frequency of TSCs appears to decline with time post-treatment [97, 98] (Table 4). Increased detection threshold for bitter and salty tastes are reported most commonly in this cohort [93, 99], though changes to other basic tastes, including umami [100], have also been noted. TSCs experienced by this group, therefore, contrast with those receiving CT, where sweet and salty tastes are most affected.

Most research focuses on the long-term effects of RT for H&N cancer. The severity of TSCs in cancer survivors after treatment has not been characterised in studies and conflicting evidence exists on the recovery time for chemosensory function after all treatment modalities(Table 4). Although one study reported a similar prevalence of TSCs at 3 months and at 28 years post CT, RT and/or surgery [101], most studies report the greatest extent of TC after 3-8 weeks of treatment [80, 82, 84, 97]. Recovery to baseline appears to take 6-12 months generally, but this depends on disease severity [80, 82, 84, 97]. Smell is less affected by RT than taste [82] and is capable of recovery over a 6-9 month period post RT [28].

Clinical Sequelae of Taste and Smell Changes in Cancer

TSCs can contribute to patient distress. They can interfere with the hedonic value of food and can cause food aversion [10]. This may occur pre- or post-treatment, inhibiting food intake [26, 89, 102]. Social interactions can be negatively impacted as food plays a central role in societal activities [72]. Overall quality of life may, therefore, be reduced.

A substantial decrease in Calorie intake (430-1100 kcal/day) associated with severe TSCs has been reported in advanced cancer [1, 4, 6]. Average energy intake in these patients (19 kcal/kg BW/day) [4] is reported to be significantly below basal metabolic rates (22-24 kcal/kg/day) [103]. Not only is energy intake reduced, but a limited range of foods, some nutritionally inferior, may be consumed. In one study, up to 55% experienced an unpleasant smell and a bitter taste with high-protein foods, especially red meat, and so avoided them [102]. This may compound the dysregulated protein metabolism observed in cancer and potentiate muscle wasting and malnutrition [103].

Malnutrition has been identified in 40-50% of hospitalized cancer patients, regardless of disease stage [11, 12, 104], and in up to 90% of those with advanced cancer [105, 106]. It is associated with irreversible lean body loss [107]. This can lead to poor cancer treatment tolerance [108], increased frequency and severity of CT [109] and RT toxicity [109, 110] and post-operative complications [111]. Impaired quality of life and reduced survival frequently ensue [112]. The clinical consequences of TSCs in cancer highlight the importance of identifying and managing such symptoms.

It has been noted that people who have no obvious mechanical cause for malnutrition experience cancer-associated symptoms which could negatively affect nutritional status [113]. Clinical experience and research suggest that many of these symptoms, including TSCs, dry mouth, anorexia and weight loss are interrelated and occur together in groups or clusters [114, 115]. Symptom clusters can interfere with appetite and ability to eat [4, 116] and may be a factor in the cancer anorexia-cachexia syndrome [13] which significantly affects nutritional status [117]. Currently, there is no agreement about what constitutes a symptom cluster [118], whether symptoms share a common pathophysiology or whether one symptom cluster can potentiate another [115]. In an attempt to address this, one research group recently described a symptom cluster as “a stable group of two or more symptoms that predictably co-occur and are independent of other clusters” [119]. Seven

clusters have been proposed [115], with taste change included in the fatigue/anorexia-cachexia cluster. The relationship between these symptoms requires greater scrutiny prior to cancer treatment [4], as symptom clusters may not correlate with tumour burden [118]. Correct categorisation of clusters is likely to be therapeutically important, particularly if management of one symptom is influenced by another in the cluster [120] e.g. taste changes and anorexia.

Addressing the association between TSCs, other symptoms of cancer and dietary intake may enable improvement or maintenance of the nutritional status of cancer patients. For example, a previous study showed that, in older people, sensory enhancement of food can increase dietary intake [121], resulting in improved functional status. Early recognition of malnutrition and contributory symptoms such as TSCs, e.g. through use of a screening tool incorporating assessment of TSCs, is therefore vital.

Conclusions

TSCs can contribute to malnutrition, an important predictor of morbidity, mortality, treatment response and toxicity in cancer. TSCs have been reported before, during and after cancer therapy although much of the research relates to patients undergoing CT or RT. Prevalence estimates range from 16-70% in the former and 50-70% among the latter. There is limited research into TSCs in cancer patients who are treatment-naïve, undergoing hormone therapy, immunotherapy, those who recently completed treatment and long-term cancer survivors.

The complex nature of the chemical senses suggests that taste and smell should be assessed together. Objective measures can help to evaluate the physiology of TSCs but subjective measures may be more valuable in a clinical setting. No gold standard assessment tool has been identified and future research is needed in this area. Some studies have assessed either taste or smell while others have combined prevalence values using subjective and objective TSC assessment methods. This variation in the methodologies used is reflected in the findings of the published studies and makes estimation of the true prevalence of TSCs difficult.

Moreover, many studies failed to consider factors such as appetite, environment and food texture and few have investigated the impact of TSCs on quality of life. Interventions cannot be designed or tested until TSCs are accurately defined. Further research is needed to address these limitations and the effect of TSCs on the overall patient experience. Routine evaluation of TSCs should be part of all nutritional assessment in cancer patients. Implementing this change in clinical practice would help demonstrate the true prevalence and severity in this population. A greater understanding of these abnormalities would encourage the development of interventions and inform clinical management.

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