The flavor of chemotherapy

Changes in smell and taste during treatment with chemotherapy are well-known problems in adult cancer patients. However, little was known if and how chemotherapy impacts smell and taste function in children with cancer. Therefore, the general aim of the present dissertation was to assess smell and taste function in children with cancer receiving treatment. Do smell and taste typically change during treatment, and if so, how bothersome are these treatment symptoms? Are experienced changes in smell and taste associated with eating problems? To answer these questions (and more), it was first necessary to gain further insight into children's taste function, how it develops, and how to measure it (chapters 2 and 3). Next, I studied smell and taste function in children with cancer through analyzing questionnaire data, measuring smell and taste function, and interviewing childhood cancer patients (chapters 4 – 7).

In this chapter, I will first give an overview of the main findings in this thesis. Subsequently, the findings regarding changes in smell and taste in children with cancer are discussed in the wider context of previous research. Next, implications of the main findings for both research and clinical practice are discussed, and the methodological strengths and limitations are considered. Finally, I conclude that changes in smell and taste are prevalent, bothersome, and relevant but that these changes can include either increased or decreased chemosensory function.

SUMMARY OF MAIN FINDINGS

Chapter 2 reviews available evidence regarding taste dysfunction in children and methods for assessing such taste dysfunction. The review indicates that there is clear evidence for various medical conditions (e.g., cystic fibrosis, diabetes mellitus, kidney disease, autism, asthma, et cetera) negatively affecting children's taste function. However, the number of tools to adequately measure taste function in a pediatric clinical setting was small. Most studies reporting taste dysfunction in pediatric patients relied on taste tests conducted in controlled laboratory settings, tests that are largely unsuitable for point-of-care (or bedside) testing. Only one standardized and commercially available taste test (i.e., "Taste Strips"; Burghart, Wedel, Germany) that can be used in a pediatric clinical setting was found, although it lacked age-related normative data [1].

In **Chapter 3**, we measured taste function in a large cohort of healthy children (aged 6 – 15 years) using the Taste Strips test to obtain age-related normative values for this test. "Taste Strips" are filter-paper strips impregnated with a taste solution to determine sweet, sour, salty, and bitter taste scores, using four concentrations of each taste quality. This chapter further describes the association of age, gender, and PROP taster status with children's taste function (as measured with the Taste Strips test).

We found that taste function increases with age, which allowed us for distinguishing three meaningful age groups (6 – 7, 8 – 9, and 10 – 15 years). Further, the total Taste Strips score was higher in girls compared to boys. This study then resulted in age- and sex-specific cut-off values for the Taste Strips test scores to distinguish children's normal taste function from a reduced sense of taste using the 10th percentile, thereby extending the utility of the Taste Strips test to children in a clinical setting. In addition, this study revealed that PROP-tasters (sometimes referred to as supertasters) had higher Taste Strips scores compared to non-tasters, which might indicate the validity of the Taste Strips test when measuring taste function in children. However, children's self-reported impression of how well they can taste did not correlate with the Taste Strips scores [2].

The study described in **Chapter 4** identified the presence and severity of nausea and nausea-related symptoms in children with cancer during the first year of treatment and its relationship with health-related quality of life (HRQoL). In addition, potential risk factors for the outcomes of interest were described. For this study, retrospective data of the PedsQL Cancer Module (i.e., nausea, pain, treatment anxiety, and worry scales) and PedsQL 4.0 Generic Core Scales (generic total HRQoL score) was available from 781 patients (between 2 and 21 years old). These questionnaires are offered every three months during treatment prior to a doctor's appointment in the outpatient clinic, using the online portal KLIK (Kwaliteit van Leven In Kaart, Dutch acronym for Quality of Life in Clinical Practice). For this study, we focused on data from the nausea scale which consist of the following items assessing nausea-related symptoms: nausea during medical treatment, food not tasting good, nausea while thinking of medical treatment, being too nauseous to eat, and nausea caused by food/smells. Data included proxy-report (i.e., parent report for children 2 - 7 years old) or self-report (i.e., children > 7 years old).

The presence of nausea during medical treatment was highest at 6 months after diagnosis. The symptom "food not tasting good" was reported most frequently (range 51.6%-62.8%), followed by "nausea caused by food/smells" (range 33.6%-48.1%). Pain, treatment anxiety, and worry were significantly associated with reported nausea in all children. Additionally, male gender, a solid tumor, and BMI were associated with self-reported nausea in patients aged 8-21 years. Lastly, the occurrence of nausea-related symptoms was negatively associated with average HRQoL scores. In other words, experienced nausea – especially in relation to tasting and smelling food – is common and negatively impacts quality of life in children with cancer [3].

Next, in **Chapter 5**, we explored feasibility of psychophysical smell (i.e., Sniffin' Sticks: odor threshold, discrimination, and identification tasks) and taste (i.e., Taste Strips, papillae density) measurements in children with cancer. In addition to feasibility, we investigated smell and taste function before and after a cycle of chemotherapy and compared results with healthy controls. Also, eating behavior was assessed using the Behavioral Pediatrics Feeding Assessment Scale (BPFAS). Thirty-one children with cancer and 24 healthy controls (sibling or friend) between 6 and 18 years old participated in this study.

First, we found that the assessment of smell and taste function was feasible in children with cancer (i.e., completion of tests by ≥ 60% of the patients), although some adaptions (i.e., omitting papillae density measurement and odor discrimination test) were deemed opportune for future studies to limit the risk of overly burdening children. Second, we compared smell and taste function before and after a cycle of chemotherapy and found taste function to be increased in childhood cancer patients, especially for sweet and bitter taste. Thirdly, results were compared against smell and taste scores of healthy controls, showing that the group of children with cancer had lower smell thresholds (i.e., higher sensitivity). Lastly, we found taste function to be correlated with eating behavior, but not with papillae density [4].

Chapter 6 describes a longitudinal study including a cohort of 94 children with cancer (between 6 and 18 years old) undergoing chemotherapy. Smell (i.e., odor threshold and identification) and taste function were assessed at several time points during active treatment (T0-T2) and 3 months after the last chemotherapy (T3). In case of children with acute lymphoblastic leukemia (ALL), the last measurement at T3 was performed during the so-called maintenance phase when children receive a much gentler form

of chemotherapy (typically comprising oral mercaptopurine and methotrexate) that does not require hospital admissions. The aim of this study was to determine the occurrence of smell and taste changes during treatment, whether they resolve after treatment, and to examine which factors are associated to these changes.

Linear mixed models showed that smell sensitivity (i.e., odor threshold) did not change during active treatment but decreased in maintenance phase (children with ALL). The proportion of children showing normal smell sensitivity was not significantly different from expected based on normative values. However, when comparing children with an increased, normal, or decreased smell sensitivity we found differences per diagnosis group, particularly children with myeloid malignancies and lymphoma showed an increased smell sensitivity, whereas a decreased smell sensitivity was hardly present among all diagnosis. Similarly, self-reported smell sensitivity was more often increased than decreased. Interestingly, of all children with an increased or decreased performance on either the odor threshold or odor identification test, only a minority reported as such. Odor identification changed neither during active treatment nor at T3 during maintenance phase or 3 months after treatment, but sex, age, and receiving vincristine were associated with odor identification ability.

Taste Strips test scores did not change during active treatment but increased at T3 in the maintenance phase (for the children with ALL) or 3 months after the last cycle of chemotherapy (for the children with myeloid malignancies, lymphoma, solid tumor, or brain tumor). However, a significantly lower percentage of children than expected scored within a normal range of taste function measured throughout treatment, as taste loss was present among approximately 20% of all children with cancer, and in particular among children with lymphomas and solid tumors. This suggests that chemotherapy affects taste, especially considering that 3 months after the last chemotherapy and during maintenance phase the relative frequency of children with cancer having normal taste function no longer deviated from what one would expect based on established taste function in a general sample of children. Etoposide was found to be negatively associated with taste function, whereas mercaptopurine and corticosteroids were associated with higher taste sensitivity. Interestingly, self-reported taste changes were much more common (range: 60 – 80%) and additionally revealed that taste changes are most often described as “tastes being very different from before” rather than changes in sensitivity [5].

Finally, **chapter 7** describes the results of a qualitative study. Although objectively measuring smell and taste changes is insightful, it does not elucidate what makes these changes so bothersome to children with cancer and what impact changes in smell and taste have on their daily lives. Therefore, children who already participated in the longitudinal SENSORY-2 study described in chapter 6 were asked to be interviewed regarding their experiences with smell and taste changes during treatment. Semi-structured interviews were performed until data saturation was achieved in each age group (6 – 12 years, 13 – 17 years), resulting in 27 participants. Interview data was analyzed through thematic analysis.

We found that changes in smell and taste were common and varied greatly between children. These changes were generally considered bothersome symptoms described as “disappointing” or frustrating”. Children reported various strategies for managing their smell and taste changes such as regularly brushing their teeth and avoiding or masking unpleasant smells. Regarding eating behavior, some children stated adding strong flavors to their food, or frequently trying (new) foods [6].