Peer-reviewed | Manuscript received: May 26, 2014 | Revision accepted: October 06, 2014

Olfactory disorders in oncology – an overview

Sabine Chmelar, Mödling/AT, Andreas Temmel, Perchtoldsdorf/AT, Peter Kier, Wien/AT, Herman Toplak, Graz/AT, Elisabeth Pail, Bad Gleichenberg/AT

Summary

Currently olfactory disorders in cancer patients are often seen as a minor matter, but they actually deserve more attention. Literature shows that tumor diseases and their treatment can affect the olfactory perception of the patients. Olfactory disorders impair quality of life, lead to loss of appetite, decreased nutrient intake and therefore are subsequently risk factors in the complex development of malnutrition.

More scientific work is needed for a better understanding of olfactory disorders and their impact on oncological patients, to explore new therapeutic approaches and scientifically reinforce nutritional therapeutic recommendations. As a result of improving the dietary condition, the therapeutic effectiveness as well as the quality of the patients' lives can be improved.

Changes in the perception of odors by patients in oncological care are not only burdensome for those affected, but also pose a challenge for the dietician. This article aims to provide an overview on the latest information concerning this topic.

Keywords: olfactory disorders, oncology, malnutrition, quality of life, diet therapy

Zitierweise:
Chmelar S, Temmel A, Kier P, Toplak H, Pail E (2015) Olfactory disorders in oncology – an overview. Ernahrungs Umschau 62(1): 2–7

This article is available online:
DOI 10.4455/eu.2015.002

The olfactory sense

Besides its function in food intake, olfaction is closely linked to our emotions. On the one hand the classification in good and bad odors is genetically determined, e.g. to recognize spoiled food, on the other hand it is strongly shaped by cultural influences on us. In addition, perception of the body odor of other people fulfills an important social function, such as the newborn's capability of finding the mother's mammilla [1–3].

The human ability of smell perception is dependent on various factors. Advancing age and consumption of tobacco both decrease olfactions. Physiological factors, such as hormonal status or regulatory mechanisms in hunger and satiety, can influence the sense of smell [4, 5]. Whereby in hunger the olfactory function improves and the stimulus threshold for odors declines [6].

Definition of olfactory disorders

◆ Table 1 provides an overview on the different manifestations of olfactory disorders (dysosmia).

Scientific studies focusing on olfactory disorders in patients with an oncological primary disease cover very heterogeneous patients groups in terms of tumor type, stage, therapy, etc. Therefore results are very hard to compare to each other and data, such as the incidence of olfactory disorders, vary considerably [9, 10].

Nutritional relevance

Prevention of malnutrition, accompanying an improvement of the subjective state of quality of life and an increase in effectiveness of the therapy, is a major therapeutic goal in nutrition therapy of oncological patients [11]. Changes in odor perception are – among other symptoms such as alopecia (loss of hair), dysgeusia (alterations of the sense of taste), fatigue, etc. – a strong limiting factor in everyday life of cancer patients [12] and one of many symptoms that affect food intake significantly [13]. A reduced sensitivity or changes in odor and flavor perception are associated with decreased nutrient intake and the development of food aversions [9].

Quantitative odor distortion		
hyperosmia	exaggerated sense of smell	
normosmia	normal sense of smell	
hyposmia	decreased ability to detect odors	
anosmia	total	inability to detect odors
	functional	significant limitation with low residual perception
	partial	significant reduced sensitivity to one or more specific fragrances
Qualitative odor distortion		
parosmia	altered perception of smell in the presence of an odor	
phantosmia	perception of smell without an odor present	
pseudosmia	imaginative reinterpretation of an odor under the influence of strong emotions	
olfactory intolerance	exaggerated subjective sensitivity to fragrances in normal sensitivity	
agnosia	inability to classify or contrast odors, although able to detect odors	

Table 1: **Definition of olfactory disorders** [7, 8]

Currently, odor or taste problems are not routinely questioned or clarified. This might be due to the lack of instruments to investigate in a brief and concise way whether dysosmia is present or not. Furthermore, the different forms of olfactory dysfunction in cancer patients complicate detection. In addition, the current dietary recommendations (such as choose cold food, avoid strong odors, etc.) are of rather trivial nature and scientifically unsubstantiated [13]. Attempts at therapy with zinc also have not shown any positive results [14].

Smell and taste changes have a fundamental impact on the lives and the diet of the persons affected. It is not solely about the nutrient intake and food selection, but also about the social component of the food environment, subsequently affecting the quality of life. Early detection of smell and taste disorders would be necessary for the timely prevention of malnutrition.

Explanatory theories for olfactory disorders in cancer

Based on animal studies, the average lifetime of olfactory neurons is estimated at 30 or 90 days [8, 15].
The cytotoxic effects of chemotherapy might interfere with the regeneration of the olfactory neurons from the basal cells [16], although the reasons for this are yet not fully understood. Suitable explanations would be a reduced number of receptor cells through destruction or a negative effect on cell renewal, changes in cell structure or changes in receptor surface or interruption of neural coding [9, 17].
Substances for tumor therapy, in studies repeatedly associated with smell and taste disorders, are doxorubicin, methotrexate, cisplatin, carmustine and vincristine [17, 18].
A Japanese study by Suga et al. with 136 patients showed that a wide variety of chemotherapeutics have a negative effect on olfactory performance. 31 % of patients who received docetaxel and fluorouracil, 22 % of patients with a paclitaxel therapy and 23 % treated with the HER-2-antibody trastuzumab reported an olfactory dysfunction [19].
A recent work by Steinbach et al. examined the impact of carboplatin-containing chemotherapy drugs on the senses of smell, taste and hearing. During therapy the sense of smell decreases significantly and – as confirmed in other studies [20, 21] – is recovered after about three months [22].
In addition, Schiffmann supports the theory that the presence of the tumor leads to metabolic changes that affect the sensory perception, or complications such as stomatitis (inflammation of mucous lining of any of the structures in the mouth), dry mouth and infection might also play a role [17]. Additionally a pre-existing malnutrition of the patient concerned could be the cause of odor and flavor changes [18].

Methodological problems in the identification of olfactory disorders

Patients' interviews confirm that smell and taste disorders are perceived quite differently in terms of severity, effects, etc. and that patients show both: either a decreased or an increased sensitivity to odors. One reason for the different results is the methodology of the detection of olfactory dysfunction. Patients may not be able to distinguish between taste and smell when explaining their subjective impressions, or by a change of olfaction they understand that smells smell different than before, but not that the odor threshold changes [21, 23].

Reference	Patients		Methods
	n	Characteristics	
Ovesen et al. 1991 [27]	51	cancer of the lung, ovary or breast	determination of olfactory detection thresholds by the method of Amoore and Ollmann
Epstein et al. 2002 [28]	50	high-dose chemotherapy and allogeneic stem cell transplantation	90–100 days post transplantation QOL-questionnaire (QLQ-C30)
Yakirevitch et al. 2005 [29]	21	chemotherapy including cisplatin	Sniffin' Sticks odor identification test kit before beginn motherapy, after each course and 3 weeks after the la
Yakirevitch et al. 2006 [30]	42	oncological patients in hospital treatment	Sniffin' Sticks odor identification test kit
Hutton et al. 2007 [31]	66	patients with advanced cancer (locally recurrent or metastatic)	three-day dietary record targeted interviews questionnaire about self-perceived smell and taste f Functional Assessment of Anorexia/Cachexia Therap CT)
Bernhardson et al. 2008 [24]	518	cancer patients receiving chemotherapy (≥ 6 weeks)	questionnaire
Brisbois et al. 2011 [32]	192	advanced cancer patients (locally recurrent, locally advanced or metastatic)	questionnaire about self-perceived smell and taste function three-day dietary record Edmonton Symptom Assessment Scale (ESAS) Functional Assessment of Anorexia/Cachexia Therapy (FAACT) Patient Generated Subjective Global Assessment (PGSGA)

Tab. 2: **Overview of study results on olfactory disorders in cancer patients**

Current study results

According Brisbois et al., smell and taste changes are observed in 50–90 % of advanced stage cancer patients. The characteristics can be of both quantitative (e.g. altered sensitivity) as well as of qualitative nature (e.g. phantom smells) [13]. Additionally, patients often describe odors during or immediately after a dose of chemotherapy, which can be explained by the diffusion of the drug from the capillaries in the nasal mucous into the olfactory receptors [16].

Patients with smell or taste disorders are more likely to report oral problems, such as dry mouth, aphthous ulcer or mucositis, loss of appetite, nausea and depressive mood than patients without smell and taste changes [24].

Frequent subjective complaints – based on the chemosensory perception – are a bad taste in the mouth, changes in taste and altered sensitivity to odors. The altered sense of olfaction – which, as already shown above, is usually associated with a change in taste – can be expressed by an unpleasant perception of especially food odors, but also by other odors, such as perfume, smell of hospitals, etc. [25].

	Results
	no significant differences in smell thresholds were found between patients with cancer and control patients (n = 29) before chemotherapy and after the third cycle of chemotherapy
	8 % smell decreased 26 % smell sensitivity increased 24 % change in smell Change in smell correlated with change in taste ($p < 0.01$)
ning che- st course	A decrease in olfaction was noted in one patient (4.7 %)
	60 % (n = 25) decreased olfaction – the majority of them (n = 20) were not aware of the problem An earlier chemotherapy or radiotherapy had no significant influence on the olfactory score
unction y (FAA-	86 % (n = 57) reported some type of chemosensory abnormality, of those: - 34 patients (52 %) had both smell and taste complaints - 20 patients (30 %) described only taste complaints - 3 patients (5 %) described only smell complaints patients with severe chemosensory problems showed substantially lower energy intakes (by 900–1100 kcal/d) than patients without chemosensory problems → significant major weight loss in the last 6 months. Smell and taste complaints are followed by a lower quality of life, lack of appetite, nausea and early satiety
	75 % (n = 387) reported some form of chemosensory change, of those: - 213 patients (41 %) had both smell and taste changes - 134 patients (26 %) reported taste changes alone - 40 patients (8 %) reported smell changes alone Taste and smell changes are more prevalent in women than men (79 % vs. 59 %; $p < 0.01$) and showed no association with self-reported weight changes
	26 % (n = 49) no change 42 % (n = 81) stronger sensation overall 18 % (n = 35) weaker sensation overall 14 % (n = 27) mixed sensation compared with patients reporting no chemosensory alterations, patients with smell and taste changes are having: - lower energy intake ($p < 0.01$) - higher weight loss ($p < 0.01$) - lower QOL scores ($p = 0.02$)

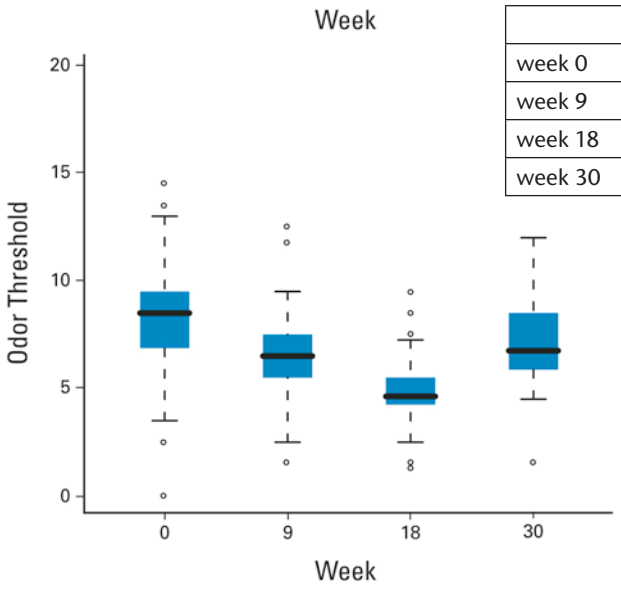
Furthermore, there are individual case reports, such as that of a 63-year-old woman with acute lymphoblastic leukemia and chemotherapy-associated parosmia, which resulted in life-threatening weight loss. The problem was eventually solved temporarily with a nose clip that prevented her from smelling anything at all. After nine months without chemotherapy, the olfactory function had improved in an extent, even without this clip sufficient oral food intake was possible [26].

◆ Table 2 provides an overview of the current study results.

Study results in breast cancer patients

Steinbach et al. in Germany have a special focus on the particular group of breast cancer patients. In 2007, a total of 69 breast cancer patients and 18 patients with other gynecological malignancies were recruited in different hospital centers in order to examine the effects of chemotherapy on olfactory performance. A smell test with Sniffin' Sticks was performed on the patients before, during, directly

after and three months after the end of chemotherapy. Both, the total value and all three subtests (thresholds, identification and discrimination test), showed a significant reduction in olfactory performance during chemotherapy, wherein the threshold test was the most and the identification test the least affected [20]. Three months after chemotherapy, the olfactory performance has recovered, confirming the results from a qualitative study, also showing a recovery time of about 3.5 months after the end of chemotherapy [21]. ◆ Figure 1 presents the thresholds of all patients over time.



	mean (± SD)
week 0	8.1 (± 2.1)
week 9	6.1 (± 1.7)
week 18	4.9 (± 1.3)
week 30	7.1 (± 1.8)

Figure 1: **Box-Whisker-Plot with odor threshold scores for all patients measured before (0 weeks), during (9 weeks), directly after (18 weeks) and 3 months after (30 weeks) chemotherapy.**
There is a significant decrease in the odor threshold score during and directly after chemotherapy (p < 0.001) [20]
SD = standard deviation

In another study, Steinbach et al. re-analyzed the data of 69 breast cancer patients more precisely. From this could be seen that before chemotherapy the total value of the Sniffin' Sticks test decreased significantly with bigger tumor size and with increasing lymph node involvement, whereas with the latter's the patients' age may have played a role as a potential confounder. The presence of metastases, the resection status, or the histological type of breast cancer had no effect on the sense of odor or taste of the patients [10].

This study found no correlation between the smell and taste performance and the hormone receptor status of estrogen and progesterone and the expression of HER-2. This is in contrast to a study conducted in 1985, in which estrogen-positive breast cancer patients had a significantly reduced olfactory performance compared to the matched controls, and these results did not correlate with estrogen-negative subjects [33]. However, this result could be explained by the higher average age in the estrogen-positive group [10].

Conclusion

Current study results on olfactory disorders in oncologic patients are very heterogeneous and raise a lot of questions. Therefore, further studies are necessary to make proper recommendations in the future.

The identification and observation of these symptoms may improve the holistic approach of the medical treatment of oncologic patients, particularly in respect of olfactory disorders being one factor in the development of malnutrition.

Conflict of Interest
The authors declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

Sabine Chmelar, MSc[1]
Univ. Prof. Dr. Andreas Temmel[2]
Dr. Peter Kier[3]
Univ. Prof. Dr. Hermann Toplak[4]
Elisabeth Pail, MSc, MBA[5]

[1]Universitätslehrgang „Applied Nutrition Medicine"
Medizinische Universität Graz
FH Joanneum Bad Gleichenberg
Prießnitzgasse 19/1, 2340 Mödling/Österreich
E-Mail: sabine.chmelar@gmail.com

[2] Medizinische Universität Wien
Brunnergasse 1 9/4/4, 2380 Perchtoldsdorf/Österreich
E-Mail: andreas.temmel@meduniwien.ac.at

[3] SMZ-Ost/Donauspital
Langobardenstraße 122, 1220 Wien/Österreich
E-Mail: peter.kier@wienkav.at

[4] Medizinische Universität Graz
Auenbruggerplatz 15, 8036 Graz/Österreich
E-Mail: hermann.toplak@medunigraz.at

[5] FH Joanneum Bad Gleichenberg
Kaiser-Franz-Josef-Str. 24,
8344 Bad Gleichenberg/Östereich
E-Mail: elisabeth.pail@fh-joanneum.at

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DOI: 10.4555/eu.2015.002