

# The Relationship Between Taste, Olfaction, and Nutrition in the Cancer Population

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**M**alnutrition is a frequently encountered problem in cancer patients<sup>1</sup> and a consistently poor prognostic indicator.<sup>2-4</sup> By implication, nutritional practices and the nutritional management of patients with cancer have a potentially significant impact on patient outcomes.<sup>5</sup>

Good nutritional practices (consuming adequate nutrients within caloric needs; maintaining a healthy body weight; consuming a variety of fruits, vegetables, whole grains, and low-fat dairy products daily; minimizing trans-fatty acid consumption; and decreasing consumption of sodium-rich foods) can reduce or ameliorate the “nutrition impact symptoms” that tend to impede oral intake (eg, gastrointestinal disturbances, dysphagia, sensory changes) and are associated with improved quality of life.<sup>6</sup> Poor nutritional practices, in contrast, are associated with poorer patient outcomes, primarily resulting from an increased incidence and severity of side effects, as well as an increased incidence of infection.<sup>7,8</sup>

Of major importance to a patient’s nutritional status is his or her chemosensory function, particularly the senses of taste and smell.<sup>9,10</sup> This article will review the biology of these two senses in the context of both health and neoplastic disease.

## Biology of Gustation

The so-called chemical senses of taste (or, more formally, gustation) and smell (olfaction) are thought to be the oldest, or most primitive, senses. In common parlance, “taste” often is used interchangeably with “flavor,” the fusion of taste and smell. In the physiologic sense, “taste” is a term applied strictly to sensations

arising from specialized taste receptor cells located on the tongue and oropharynx.<sup>11</sup>

The sense of taste originates within the specialized epithelium lining the tongue’s edges and anterior dorsal surface, the soft palate, and portions of the pharynx and larynx. Within this epithelium are taste receptor cells that synapse with sensory axons carrying sensory information to the brain.

The lifespan of each taste receptor cell is short, lasting an average of 10 days; these cells are continuously regenerated by nearby stem cells.<sup>12</sup> The receptor cells are located in multicellular clusters (“taste buds”). On the surface of the tongue, these taste buds lie within three types of papillae: *fungiform papillae* are mushroom shaped and cover the anterior two thirds of the tongue; *foliate papillae* are located on the posterolateral edges of the tongue, with taste buds tucked inside their folds; and *circumvallate papillae* are large and form an arc on the posterior aspect of the tongue, with taste buds lying in their surrounding moats.<sup>12</sup>

Minor salivary glands known as von Ebner’s glands are located within the surrounding epithelium, producing a serous secretion that fill the folds of the papillae and dissolves taste molecules. Above each taste bud is a taste pore, a small opening in the epithelium that restricts the flow of solute reaching the taste receptor cells to small ions.<sup>12</sup>

The apical end of each receptor cell contains microvilli that are exposed to the oral mucus. Located on the microvilli are taste receptor proteins that allow us to distinguish between four basic tastes: sweet, sour, salty, and bitter. (Some authorities endorse a fifth taste, called umami, that serves to enhance the “savory” qualities of certain foods. It is believed that dysfunction in this taste may be responsive to treatment with amino acid supplementation.<sup>13</sup>) Sweet and bitter chemicals are detected by G-protein-coupled receptor families. Salty and sour chemicals are detected by ion-

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channel ( $\text{Na}^+$ ,  $\text{H}^+$ ) receptors. Different combinations of these taste receptor proteins in individual receptor cells result in varying degrees of sensitivity and specificity to different tastes. Activation of these receptor proteins leads to depolarization of the receptor cell, which, in turn, can interact with neighboring cells or release neurotransmitters to activate nearby neurons located within the taste buds.<sup>12</sup>

The neural fibers located within the taste buds make up parts of cranial nerves VII, XI, and X. The anterior two thirds of the tongue are innervated by the chorda tympani nerve, and the soft palate is innervated by the greater superficial petrosal nerve, both of which are branches of the facial nerve (cranial nerve VII). The posterior third of the tongue is innervated by the glossopharyngeal nerve (cranial nerve XI), and the pharynx and larynx are innervated by the vagus nerve (cranial nerve X).<sup>12,14</sup> These first-order neurons project ipsilaterally to synapses in the nucleus of the solitary tract within the brain stem.<sup>12,14,15</sup> Second-order neurons travel through the thalamus and project primarily to the insular cortex and the operculum, with other areas, such as the orbitofrontal cortex, playing a smaller role.<sup>12,15</sup> Within the central nervous system, information from various senses, including taste, smell, and oral somatosensation, are all integrated to give us the sense and experience of flavor.

## Biology of Olfaction

The sense of smell originates in the superior region of the nasal cavity, where the olfactory epithelium lies. Several important cell types compose this pseudostratified columnar epithelium. At the base is a thin layer of basal cells that divide and differentiate throughout life, regenerating the other cell types.<sup>12,14</sup> Throughout the epithelium are supporting cells that are believed to play a maintenance role, although their exact function remains unclear. Scattered within the olfactory epithelium are specialized glands known as Bowman's glands that secrete a thin, watery mucus that protects the epithelial surface while providing a medium for odorant molecules to act. The majority of cells in this epithelium, however, are the olfactory receptor cells, with an average lifespan of 30 days.<sup>12</sup>

Unlike taste receptor cells, olfactory receptor cells are true first-order neurons and collectively make up cranial nerve I, providing a direct conduit from the olfactory receptor to the central nervous system.<sup>14</sup> From each of these bipolar cells, a dendrite extends apically to the surface of the epithelium, giving rise to an olfactory knob. Long, nonmotile cilia project from these knobs into the nasal cavity, creating a large surface area for odorant molecules to bind to and interact.<sup>12,14</sup>

Within the membranes of these cilia are the olfactory receptor proteins, a diverse family of G-protein-coupled receptors encoded by the largest gene family in the human genome. Odorant molecules dissolve within the nasal mucus, then bind to one of these G-protein-coupled receptors. Within the cell, the G-protein  $G_{\text{olf}}$  is activated, and it, in turn, activates adenylyl cyclase III, which converts ATP to cyclic AMP (cAMP). cAMP then binds to cyclic nucleotide-gated ion channels in the ciliary membrane, opening them and allowing  $\text{Ca}^{2+}$  ions

to enter the cell. The resulting depolarization of the cell triggers action potentials. The signal is terminated as the increasing intracellular levels of  $\text{Ca}^{2+}$  and cAMP lead to activation of protein kinases, which, in turn, inactivate the ion channels.<sup>12</sup>

Basally, the action potentials travel through slow unmyelinated axons that extend in fascicles through the cribriform plate to the paired olfactory bulbs.<sup>15</sup> Within the bulbs, the axons synapse with mitral and tufted cells by releasing the neurotransmitter glutamate. These second-order neurons then project ipsilaterally to form the bilateral olfactory tracts that lie in the olfactory sulci of the basal forebrain.<sup>12</sup> They convey olfactory information to multiple areas of the central nervous system that, together, comprise the primary olfactory cortex. These areas consist primarily of the piriform cortex, the amygdala, and the rostral entorhinal cortex.<sup>12,15</sup> From the primary olfactory cortex, higher-order projections extend to form a complex web of connections with other areas of the brain, including the orbitofrontal cortex, thalamus, hypothalamus, basal ganglia, and hippocampus,<sup>12</sup> all of which act together to create the perception of smell.

## The Interaction of Taste and Olfaction

In her landmark work on the effect of chemotherapy on taste and olfaction, Bartoshuk<sup>16</sup> outlined the functional interplay of taste and olfaction from which the sensation of "flavor" arises. Volatile compounds rise from the mouth into the nasal cavity via the olfactory pore, where they interact with olfactory receptors. Unlike taste, which falls into four well-defined classifications (bitter, salt, sour, and sweet), there is no similar classification for olfaction, which is classified on a general object-based model (eg, "minty" or "smoky").

Taste is thought to be an "analytic" sense; that is, its individual components are each sensed simultaneously. Olfaction, on the other hand, is generally thought to be a "synthetic" sense: its individual components *blend*, creating a holistic sensation different from any of the distinct, individual components. Olfactory impairment increases a patient's perception of disability and negatively impacts quality of life. In a 14-year study of approximately 1,400 patients, self-reported "satisfaction with life" was inversely related to degree of subjective (self-graded on a scale from slight impairment to complete anosmia) olfactory loss.<sup>17</sup>

Another fundamental distinction between taste and smell is that of "affect," the pleasurable or unpleasurable associations with a given sensation. Taste-related affect appears to be "hard wired" and generally fixed, whereas olfactory-related affect appears to be learned and is labile. The pairing of an odor with a pleasant sensation, such as a high-calorie meal, or, alternatively, an unpleasant sensation, such as nausea, influences affect.

Nevertheless, taste and smell typically act in tandem with each other and in concert with other properties to form the characteristic referred to as palatability. Yeomans<sup>18</sup> defines palatability as the hedonic (psychologic) evaluation of orosensory food cues under standardized conditions. The sensory properties involved include taste, smell, texture, temperature, visual appearance, sound, and irritative sensations. The literature examining the relationship between palatability and appe-

tite is somewhat mixed, but, in general, increased palatability results in increased oral intake.<sup>19</sup>

### Clinical Implications of Chemosensory Dysfunction

Chemosensory dysfunction in the patient with cancer has a particularly powerful impact. The loss of familiar tastes and smells (as a result of chemotherapy, radiation treatments, or surgery) at such a psychologically taxing time can negatively influence the patient's subjective outlook. Secondary depression—itsself often associated with an anorexia syndrome—will diminish quality of life and possibly affect outcome.<sup>20</sup>

Chemosensory dysfunction is closely linked to diminished oral intake in the cancer population. Given the association between poor nutrition and poor patient outcome, strategies for improving nutritional status could be of critical importance. Taste and olfaction are each complex senses, being derived from both organic (sensory) and psychologic (hedonic) stimulation. The interplay between these two senses potentiates this complexity. It is well recognized that there is a dearth of research on the mechanism of medication-induced chemosensory dysfunction. While this body of research continues to accumulate, oncologists can manage chemosensory dysfunction in a systematic fashion.

After assessing the patient for comorbidities that may affect appetite, such as depression, a basic nutritional screening should be performed on each patient early in treatment. Such screenings have demonstrated efficacy at identifying “at-risk” patients who should then receive a more extensive nutritional assessment. The patient should be informed of the possible chemosensory changes that may be experienced and, moreover, should be encouraged to report any such changes on scheduled visits. The onset of chemosensory dysfunction often portends a higher-risk nutritional status.

Patients should be encouraged to take a proactive approach to managing their own nutrition by varying the appearance, temperature, and texture of meals; by experimenting with new and different types of food; and by using supplemental flavorings in cooking. The cancer patient under active treatment is likely experiencing one of the least pleasant periods of his or her life. Addressing chemosensory dysfunction in a more systematic fashion has significant potential for improving patient quality of life.

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