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1 **Loss of smell in lung cancer patients undergoing chemotherapy:**
2 **prevalence and relationship with food habit changes**
3

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22 **Abbreviations list**

23 **T0:** Time 0 (before the beginning of the treatment)

24 **T1:** Time 1 (six weeks after th beginning of the treatment)

25 **ETOC:** European Test of Olfactory Capabilities

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32 **Abstract**

33 **Background and Objectives.** Cancer patients undergoing cytotoxic chemotherapies exhibit a
34 series of adverse side effects including smell and taste alterations, which can have a significant
35 impact on their food behavior and quality of life. Particularly, olfactory alterations are often
36 underestimated, although declared as frequent by cancer patients. In the present study, we set
37 out to examine loss of smell in lung cancer patients undergoing chemotherapy and its
38 relationship to food habits.

39 **Material and Methods.** Forty-four bronchial cancer patients receiving cisplatin and 44
40 controls age and gender matched participants were tested for olfactory and gustatory functions
41 using the European Test of Olfactory Capabilities and the Taste Strips test. Participants reported
42 their food and dietary habits by filling a self-administered questionnaire. Patients were tested
43 under two different sessions: i) before the beginning of the treatment, and ii) 6 weeks later, after
44 2 cycles of chemotherapy. Controls were tested under the same protocol with two sessions
45 separated by 6 weeks.

46 **Results and Conclusions.** The results highlighted decreased smell and taste abilities in almost
47 half of the lung patients' group even before the exposition to Cisplatin. On a perceptual level,
48 patients rated typical food odors as less edible compared to controls. Moreover, within the
49 patients' group, hyposmics reported using more condiments, possibly as a compensatory
50 mechanism to their decreased sensory abilities. Taken together, these findings showed that loss
51 of smell is prevalent in lung cancer patients and is related to changes in dietary practices
52 including seasoning. Future studies will provide a better understanding of these sensory
53 compensation mechanisms associated with olfactory loss and their effects on food pleasure in
54 this patient population.

55 **Key words:** Bronchial cancer, Cisplatin chemotherapy, Smell, Taste, Food habits.

56 **Introduction**

57 Cancer patients undergoing cytotoxic chemotherapies exhibit a series of adverse side effects
58 including modifications in smell and taste perception [1]–[6]. The methodological and
59 individual differences among studies examining smell and taste alterations in cancer patients
60 undergoing chemotherapy [7] resulted in a wide range of prevalence of taste and smell
61 alterations (taste alterations found in 45 to 84% and smell alterations in 5- 60% of cancer
62 patients undergoing chemotherapy) [8]. Although smell alterations are declared frequently by
63 cancer patients, they are often underestimated [9]. Differences in the types and severity of
64 olfactory disturbances are reported or diagnosed in cancer patients, including quantitative
65 alterations, expressed as partial or total loss of smell called hyposmia and anosmia respectively
66 [9]. How these two types of olfactory loss are prevalent in cancer patients remains unclear.

67 Moreover, smell alterations are observed in patients with different types of cancers and
68 chemotherapy regimens, but certain molecules are more likely to induce this side effect than
69 others [8], [10]. Cisplatin chemotherapy is known to induce distressing side effects comprising
70 qualitative and quantitative chemosensory perception disturbances [11]–[16]. It is a common
71 part of the treatment for several cancer types such as lung, ovary, testicle, bladder, and some
72 types of digestive cancers. With 2.21 million cases in 2020, lung cancer is the second most
73 common cancer diagnosed worldwide and there is therefore a clear need to better understand
74 and manage olfactory alterations induced by cisplatin-based chemotherapy.

75 Another important aspect of smell loss in lung cancer patients is in relation to changes in food
76 habits. Indeed, the literature examining the interaction between cancer, chemotherapy, smell
77 and taste abilities, and food behavior suggests that before and/or during chemotherapy
78 treatment, the sensitivity of a patient to olfactory stimuli is likely to modulate patient's food
79 habits [17]–[22] [2] [18] [19]. However, these studies often analyze smell without dissociating

80 it from taste [23], [25]. They also use self-reported questionnaires [17], [18], [20]–[22], and
81 focus on reporting annoyance caused by odors, rather than smell perception ability [9]. Given
82 the influence of smell alterations on quality of life, especially related to food behavior [9] [10],
83 smell alterations induced by cancer and chemotherapy need to be further studied for a better
84 quantification, diagnosis and management of this side effect. Whereas some previous studies
85 examined patients' food behavior during chemotherapy [24], [28]–[30], the relationship
86 between smell alterations and food habits in lung cancer patients undergoing chemotherapy is
87 less explored.

88 The aim of the present study was threefold. We first set out to characterize olfactory function
89 in lung cancer patients undergoing Cisplatin-based chemotherapy. Second, we explored how
90 food habits were altered in these patients. Third, we examined how patients' olfactory loss can
91 be related to changes in food habits. To this end, we combined objective psychophysical tools
92 for olfactory assessment with self-reported questionnaire-based methods for food habits
93 assessment. The olfactory information is processed at different levels, from stimulus detection
94 at the peripheral level, to identification and perceptual characterization at the central level.
95 Therefore, here we further aimed to examine how cancer and chemotherapy affect these
96 different stages of odor processing by assessing detection and identification abilities of patient,
97 and estimating four perceptual dimensions including odor intensity, familiarity, edibility and
98 more importantly odor pleasantness because of its known relation to food appreciation [31].
99 Moreover, as olfactory alterations during chemotherapy are commonly accompanied by
100 changes in taste perception, we further examined how cancer and chemotherapy influence
101 gustatory function.

102 **Methods**

103 **1. *Participants***

104 The study included forty-four patients treated for bronchial cancer and forty-four healthy
105 control participants without any history of cancer and chemotherapy. The protocols used
106 included carboplatin etoposide, cisplatin etoposide, carboplatin paclitaxel, carboplatin
107 pemetrexed, cisplatin pemetrexed and cisplatin vinorelbine. All patients have anti-nausea
108 treatments according to the recommendations of the international societies (MASCC) [32],
109 [33]. Patients' recruitment was conducted in two centers: 22 patients were recruited at Lyon
110 Sud Hospital Center, and 22 patients at Saint-Etienne hospital (France). Inclusion criteria for
111 patients were as follows: patients scheduled for Cisplatin-based chemotherapy for small or non-
112 small cell lung cancers, with no previous chemotherapy treatment, no prior oro-nasal
113 impairment, and no gastrointestinal disorders. Note that stages of cancer in patients were stage
114 IV or neo adjuvant or adjuvant chemotherapy. If radiotherapy was used, it is a palliative
115 radiotherapy which does not concern any mediastinal or vertebral lesion and therefore there is
116 no risk that radiotherapy will cause additional emetic disorders. Control individuals were age-
117 and gender-matched with patients and had no history of oro-nasal impairment and/or neurologic
118 pathology. Patients were recruited during the medical consultation preceding the chemotherapy
119 treatment and after having received an oral and written explanation of the study from their
120 doctor. Controls were recruited via posters and flyers distributed in Lyon area (France). All
121 participants had the full ability to understand the study. The experimental procedure was
122 conducted according to the Declaration of Helsinki and was approved by the local Ethics
123 Committee in Lyon. The protocol was registered on clinicaltrials.gov (NCT02368509) and was
124 explained in detail to all volunteers, who provided written consent prior to participation.

125 **2. *Sample size***

126 The number of patients required for the study was calculated using PASS 2008 software (NCSS,
127 LLC. Kaysville, Utah), based on the rating of odors by bronchial cancer patients in a previous
128 exploratory study (Laville et al., 2010; data not published). The analysis revealed that thirty-
129 nine patients were needed for 80% power, an alpha level of 0.05, and an expected difference of
130 -0.55 points in odor pleasantness rating (standard deviation: 1.2) for cancer patients vs. 0
131 (standard deviation: 0.25) for control subjects. In each group, we recruited five more subjects
132 to remedy a possible discontinuation from the study.

133 **3. Experimental protocol**

134 **3.1. Study design.** The study followed a longitudinal design, with the smell and taste functions
135 and food habits assessed at baseline (T0) before the beginning of chemotherapy, and at a follow-
136 up (T1), six weeks after the first chemotherapy cycle. A group of lung cancer patients
137 undergoing was compared to a control group of age- and gender-matched healthy participants.

138 **3.2. Assessment of olfactory function.** Participants' olfactory performance was assessed at T0
139 and T1, using the European Test of Olfactory Capabilities (ETOC) [34]. Odorous solutions
140 (volume: 5 ml) were dissolved in mineral oil and poured into a 15 ml flask (1.7 cm diameter at
141 opening; 5.8 cm high). Each flask contained a synthetic absorbent (polypropylene) to optimize
142 odor diffusion. The ETOC test is composed of 16 odors: 8 typical food odors (vanilla, apple,
143 garlic, anise, orange, fish, lemon and mint); and 8 less typical food odors (cloves, eucalyptus,
144 cinnamon, fuel-oil, pine, cut grass, rose, thyme). The ETOC was composed of 16 blocks of 4
145 flasks. Only one flask per block contained an odorant. For each block, participants were asked
146 firstly to detect the flask containing the odor, and secondly to identify the detected smell.
147 Identification was assessed by a multiple-choice procedure in which participants select the
148 correct descriptor among 4 options, with the list of 4 descriptors being different for each row
149 of 4 flasks. Detection and identification scores range from 0 to 16 and provide an indicator of
150 olfactory function. To reduce the probability of fortuitous correct identification, only odors that

151 had been correctly detected were considered in the identification score. Then, participants were
152 asked to rate the intensity, pleasantness, familiarity and edibility of each of the 16 odors on a
153 scale from 1 (not at all pleasant/intense/ familiar/ edible) to 9 (very pleasant/intense/ familiar/
154 edible). Olfactory status of participants (anosmia, hyposmia or normosmia – the latter being
155 defined as a normal sense of smell) was defined using ETOC cut-off values defined in Jousain
156 et al. [35].

157 **3.3. Assessment of gustatory function.** Taste detection and identification abilities were
158 assessed at T0 and T1 with a short version of the Taste Strips test [36]. Strips made from filter
159 paper were impregnated with four taste solutions. The length of a taste strip is 8 cm and an area
160 of 2 cm² is impregnated with a taste stimulant (sweet with 0.4 g/mL sucrose, salty with 0.25
161 g/mL sodium chloride, sour with 0.3 g/mL citric acid and bitter with 0.006 g/mL quinine-
162 hydrochloride). The taste strips were presented in a randomized order, and the impregnated part
163 of the strip was placed on the participant's tongue. Then, participants were asked to close the
164 mouth and report whether they detect a taste or not (detection task). An identification task
165 followed, where they asked to identify the detected taste by choosing one of four possible
166 answers (sweet, sour, salty, bitter). Before assessment of each taste strip the mouth was rinsed
167 with water. Detection and identification scores ranged from 0 to 4 and provided an indicator of
168 the gustatory function. After the identification task, participants were asked to rate the
169 pleasantness, intensity, and familiarity of each of the 4 taste stimuli on a scale from 1 (not at all
170 pleasant/ intense/ familiar) to 9 (very pleasant/ intense/ familiar).

171 **3.4. Assessment of eating habits.** Participants were asked to fill a self-administered
172 questionnaire that focused on cooking, culinary and dietary habits specifically designed for the
173 study. The questionnaire was composed of the following items: (1) Several months ago, who
174 used to cook in your home? (Multiple choice answer: you cook by yourself, your partner cooks,
175 you cook with your partner, your children, another person); (2) Over the last few weeks: who

176 is in charge of cooking in your home? (Multiple-choice answer: you cook by yourself, your
177 partner cooks, you cook with your partner, your children, another person); (3) Do you take food
178 supplements? (Yes/No); (4) Have you modified your food and beverage purchasing habits?
179 (Yes/No); (5) Have you modified any of your dietary habits? (Yes/No); (6) Have you modified
180 any of your culinary habits? (Yes/No); (6) Have you added any food/beverage to your usual
181 diet? (Yes/No); (7) Have you removed any food/beverage from your usual diet? (Yes/No); (8)
182 In general, what do you like to add to your dishes to make them tastier? (a list of 14 condiments
183 commonly used among French consumers was proposed to the participants: *salt, sugar, pepper,*
184 *mustard, ketchup, vinegar, soy sauce, lemon, mayonnaise, butter, oil, cream, herbs, and spices*
185 (several possible answers); the total number of chosen condiments was used for statistical
186 analyses with a possible range from 0 to 14).

187 **4. Data analysis**

188 First, the effect of cancer and chemotherapy treatment on the ability to detect and identify
189 olfactory and gustatory stimuli was examined with a two-way ANOVA with “Group” (Patients
190 vs. Controls) as a between-subject factor and “Time” (T0 and T1) as a within-subject factor.
191 For perceptual ratings of odors and tastes, a three-way ANOVA model was used to examine
192 the effect of cancer and/or chemotherapy on pleasantness, intensity, familiarity and edibility
193 ratings. Here, for both odors and tastes, “Group” (Patients vs. Controls) and “Time” (T0 and
194 T1) were included as respectively between-subject and within-subject factors. “Stimuli type”
195 was added as a within-subject factor for odors (food odors and non-food odors) and for tastes
196 (4: sweet, salty, sour, bitter). For all ANOVAs, the significant effect of group*time or
197 group*stimuli interactions was tested.

198 Second, a descriptive analysis was conducted for patients’ food habits. When the number of
199 individuals that responded positively (i.e. “yes”) to a specific question was of at least 5, a chi-
200 square test was used to examine the dependency between proportions of answers and time of

201 assessment (T0 vs. T1) in patients and controls separately. For item #8 (food seasoning), the
202 number of added condiments was analyzed using a two-way ANOVA with “Group” as a
203 between factor and “Time” as a within-factor.

204 Third, to explore the relationship between olfactory alterations and food habits of cancer
205 patients, we characterized patients’ olfactory status (using odor detection and odor
206 identification scores of the ETOC test; cut-off values were taken from Jouslain et al., 2016) and
207 compared food habits of patients with a normal sense of smell vs. food habits of patients with
208 altered olfaction. Because of its non-binary nature, and its direct relationship with senses, the
209 “number of added condiments” was selected as the dependent variable among the food habit
210 variables of the questionnaire. The statistical analysis used was an ANOVA with “Olfactory
211 status” (2: normosmia, hyposmia) as a between-subject factor and “Time” (2: T0, T1) as a
212 within-subject factor.

213 For all statistical analyses, the alpha level was set at $p < .05$. Statistical analyses were performed
214 using JASP, an open-source project supported by the University of Amsterdam which offers
215 offers standard analysis procedures in both their classical and Bayesian form ([https://jasp-](https://jasp-stats.org)
216 [stats.org](https://jasp-stats.org)). Descriptive statistics are expressed as Mean \pm Standard Deviation (SD) for all
217 variables unless otherwise indicated.

218

219 **Results**

220 *1. Demographics and clinical data*

221 A total of 44 bronchial cancer patients and 44 age- and gender-matched healthy controls were
222 included for the analysis (63,5% men and 36.5% women in each group). The characteristics of
223 participants, including age, gender, smoking status, and body mass index are summarized in

224 *Table 1.* No difference in BMI was observed between the two groups at T0, but patients' BMI
225 was significantly lower in the patients' group at T1 compared to T0 ($p=0.01$).

226 Given that there was a higher proportion of smokers in the patients' group, the main statistical
227 analyses including all participants were accompanied by an additional analysis including only
228 non-smokers patients ($n=26$) and controls ($n=41$).

229 *2. Olfactory abilities*

230 *Figure 1* shows **odor detection and odor identification** scores in both groups as a function of
231 time. Whereas no significant effect of "Time" was observed for odor detection ($F(1,86)=.066$,
232 $p>.050$, $\eta^2_p<.001$) and odor identification ($F(1,86)=.005$, $p>.050$, $\eta^2_p<.001$), a significant effect
233 of "Group" was found for both measures. Patients scored significantly lower than controls for
234 both odor detection ($F(1,86)=7.127$, $p=.009$, $\eta^2_p=.077$) and odor identification tasks
235 ($F(1,86)=12.880$, $p<.001$, $\eta^2_p=.130$). Time*Group interaction was not significant ($p>.050$ in
236 both cases). The complementary analysis considering only non-smokers participants ($n=26$ for
237 patients, $n=41$ for controls), no effect of "Time" was noted ($p>.050$ in all cases), and the above
238 observed effects of "Group" remained significant for odor identification ($F(1,65)=5.610$,
239 $p=.021$, $\eta^2_p=.079$) and of borderline significance for odor detection ($F(1,65)=3.278$, $p=.075$,
240 $\eta^2_p=.048$). Interestingly, a significant Time*Group interaction was observed for odor detection
241 ($F(1,65)=5.465$, $p=.022$, $\eta^2_p=.076$), but paired comparisons (bilateral Student t-tests) revealed
242 no alterations with time in patients ($t(25)=1.683$, $p=.105$) and controls ($t(40)=-1.309$, $p=.198$).

243 For **odor perceptual ratings**, Table 2 summarizes all descriptive data including mean and
244 standard deviation, for each type of rating (intensity, pleasantness, familiarity, edibility),
245 according to "Group" (Patients and Controls) and "Time" (T0 and T1). "Stimuli" effects were
246 observed for all 4 perceptual ratings reflecting that 'Food odors' were rated as more intense
247 ($F(1,86)=31.790$, $p<.001$, $\eta^2_p=.266$), pleasant ($F(1,86)=62.686$, $p<.001$, $\eta^2_p=.426$), familiar

248 (F(1,86)=491.740, $p < .001$, $\eta^2_p = .373$), and edible (F(1,86)=518.217, $p < .001$, $\eta^2_p = .850$) than
249 ‘Non-food odors’. Effects of “Time” were expressed as follow: odor intensity (F(1,86)=10.649,
250 $p = .002$, $\eta^2_p = .110$), odor pleasantness (F(1,83)=.004, $p > .050$, $\eta^2_p < .001$), odor familiarity
251 (F(1,83)=3.746, $p = .060$, $\eta^2_p = .041$) and odor edibility (F(1,83)=1.087, $p > .050$, $\eta^2_p = .013$)
252 reflecting that odors were perceived as more intense (and marginally more familiar) in T0 than
253 T1. Besides the “Odor type” and “Time” effects, effects of “Group” were significant for odor
254 familiarity (F(1,83)=6.243, $p = .014$, $\eta^2_p = .070$), odor edibility (F(1,83)=4.132, $p = .045$, $\eta^2_p = .047$)
255 but not odor intensity (F(1,86)=.797, $p > .050$, $\eta^2_p = .009$) and odor pleasantness (F(1,83)=2.807,
256 $p > .050$, $\eta^2_p = .033$) reflecting lower odor familiarity/edibility ratings in patients compared to
257 controls. Interestingly, for odor edibility, the effect of “Group” was accompanied by a
258 significant “Stimuli*Group” interaction (F(1,83)=8.616, $p = .004$, $\eta^2_p = .094$) reflecting that
259 compared to controls, patients perceived ‘Food odors’ as less edible ($t(84) = 3.028$, $p = .003$)
260 whereas no difference between groups was observed for ‘Non-food odors’ ($t(84) = .413$, $p > .050$).
261 When the same analyses were conducted by considering only non-smoker individuals, the
262 effects of “Group” on odor familiarity (F(1,63)=2.058, $p > .050$, $\eta^2_p = .032$) and odor edibility
263 (F(1,63)=.996, $p > .050$, $\eta^2_p = .016$) were not significant. However, as for the main analysis, the
264 “Stimuli*Group” interaction was significant for odor edibility ratings (F(1,63)=5.325, $p = .024$,
265 $\eta^2_p = .014$) reflecting that compared to controls, patients perceived ‘Food odors’ as less edible
266 ($t(64) = 1.988$, $p = .051$) whereas no difference between groups was observed for ‘Non-food
267 odors’ ($t(64) = -.410$, $p > .050$).

268 3. *Gustatory abilities*

269 Similar to odor detection and odor identification, whereas no significant effect of “Time” was
270 observed neither for taste detection (F(1,86)=.989, $p > .050$, $\eta^2_p = .011$) nor for taste identification
271 (F(1,86)=.677, $p > .050$, $\eta^2_p = .008$), the analysis revealed a significant effect of “Group” for taste
272 detection (F(1,86)=7.891, $p = .006$, $\eta^2_p = .084$) and taste identification (F(1,86)=19.160, $p < .001$,

273 $\eta^2_p=.182$) showing that patients exhibited lower scores of both taste detection and taste
274 identification than controls (Figure 2). For both detection and identification, the Time*Group
275 interaction was not significant ($p>.050$ in all 2 cases).

276 Considering only non-smoker participants, there was no effect of “Time” ($p>.050$ in all cases),
277 but there was a trend towards a “Group” effect on taste detection ($F(1,65)=3.015$, $p=.087$,
278 $\eta^2_p=.044$) and a significant effect for taste identification ($F(1,65)=14.360$, $p<.001$, $\eta^2_p=.181$).
279 The “Group” effect for taste identification was accompanied by a significant Time*Group
280 interaction ($F(1,65)=6.359$, $p=.014$, $\eta^2_p=.089$) showing trends towards a decrease in taste
281 identification from T0 to T1 ($t(25)=-1.886$, $p=.071$) in patients and a trend towards an increase
282 in taste identification from T0 to T1 ($t(40)=1.777$, $p=.083$) in controls.

283 For taste perceptual ratings, statistical analyses showed no significant effect of “Time” and
284 “Group” factors and no significant interactions involving the “Group” factor for any of the three
285 perceptual ratings (pleasantness, intensity, familiarity) ($p>.050$ in all cases). However, as for
286 odors, significant main effects of “Stimuli” were observed for familiarity ($F(3,213)=49.982$,
287 $p<.001$, $\eta^2_p=.412$), intensity ($F(3,216)=17.232$, $p<.001$, $\eta^2_p=.192$) and pleasantness
288 ($F(3,213)=94.880$, $p<.001$, $\eta^2_p=.572$) showing that the four studied taste modalities were rated
289 differently along the 3 perceptual ratings (see Table 3 for descriptive statistics). Note that these
290 significant effects of “Stimuli” remained significant when the analyses considered only non-
291 smoker participants ($p<.001$ for all three perceptual ratings).

292 **4. Food habits**

293 Considering the first item of the questionnaire (« Several months ago, who used to cook in your
294 home? »), responses were comparable across patients and controls, and in T0 and T1: 45% to
295 50% of the participants declared cooking by themselves, 23% to 32% declared that their partner
296 used to cook and 18% to 30% declared cooking with their partner (0% to 2% for the other

297 options). For the second item (« Over the last few weeks who is in charge of cooking in your
298 home? ») a similar pattern emerged: 46% to 48% declared cooking by themselves, 18% to 36%
299 declared that their partner cooks, and 11% to 34% declared that they cook with their partner (
300 0% to 2% for the other options). Results based on items #3 to #7 are displayed in *Figure 3*
301 showing the percentages of patients and controls who answered “yes” to each item at T0 and
302 T1. On a descriptive level, controls exhibited very few variations in their dietary/culinary habits
303 at T0 and T1 (0% to 11% depending on the items and time of assessment), compared with
304 patients (5% to 39%). The distribution of participants’ responses allowed to conduct a chi-
305 square analysis for 4 out of 5 items, and only in patients: Patients modified their dietary habits
306 from T0 to T1 ($\chi^2=4.140$, $p=.040$) and removed some food / beverage from their usual diet at
307 T1, after 6 weeks of treatment ($\chi^2=4.520$, $p=.030$). The analysis considering only non-smokers
308 was not performed for these qualitative variables because of an inadequate sample size given
309 that some items has not been selected, and were consequently filled by a small number of
310 participants.

311 Considering food seasoning (item #8), the analysis revealed that patients used less condiments
312 than controls (3.6+/-2.4 and 4.8+/-2.6, respectively). There was no effect of “Time” ($F(1,86)$
313 $=1.272$, $p>.050$, $\eta^2_p=.015$) and “Time*Group” interaction ($F(1,86)=0.001$, $p>.050$, $\eta^2_p<.001$).
314 Note that the effect of “Group” increased in significance when only non-smokers were
315 considered (mean+/-SD= 2.731+/-1.996 for patients and 4.561+/-2.498 for controls; $F(1,65)=$
316 9.920 , $p=.002$, $\eta^2_p=.132$).

317 **5. Olfactory alterations and food habits in lung cancer patients**

318 Regarding olfactory status, 48% of the patients were hyposmics at T0 and 52% at T1, with 10
319 out of 44 patients changing their olfactory status from T0 to T1 (6 from normosmia to hyposmia,
320 4 from hyposmia to normosmia). Thus, the analysis was conducted on the 34 patients that did
321 not change olfactory status from T0 to T1 (17 normosmics, 17 hyposmics). Note that while the

322 prevalence of hyposmia was 16% at T0 and 20% at T1 in controls (3 controls moving from
323 normosmia to hyposmia, 1 from hyposmia to normosmia), hyposmia was significantly more
324 prevalent in patients than in controls at both T0 ($\chi^2=10.270$, $p=.001$) and T1 ($\chi^2=9.620$,
325 $p=.002$).

326 We further examined the effects of “Olfactory status” (2: normosmia, hyposmia; between-
327 subject factor) and “Time” (2: T0, T1; within-subject factor) on the number of added
328 condiments by patients. The results revealed a significant effect of “Olfactory status”
329 ($F(1,32)=5.092$, $p=.031$, $\eta^2_p=.137$) reflecting that lung cancer patients with hyposmia (mean+/-
330 SD: 4.706+/-2.750) added significantly more condiments than lung cancer patients without
331 olfactory loss (mean+/-SD: 2.853+/-1.974). This influence of hyposmia on food behavior was
332 independent of chemotherapy: no significant effect of “Time” ($F(1,32) =.395$, $p>.050$,
333 $\eta^2_p=.012$) and no significant “Time*Olfactory status” interaction ($F(1,32)=.551$, $p>.050$,
334 $\eta^2_p=.017$) were observed. Finally, smoking status could not explain these effects since there
335 was no dependencies between smoking and olfactory status ($\chi^2=2.431$, $p>.050$).

336

337 **Discussion**

338 The **first aim** of the present study was to examine the effect of cancer and chemotherapy
339 on odor and taste perception by comparing olfactory and gustatory scores before and after 2
340 cycles of cisplatin-based chemotherapy in lung cancer patients. Using psychophysical tests, we
341 showed a decreased sensitivity to taste and smell in patients’ group compared to controls. For
342 olfaction, almost half of the patients (48%) had a reduced ability to perceive odorant stimuli
343 (hyposmia). Smell and taste disturbances were observed even before commencing
344 chemotherapy, suggesting that the alteration of chemosensory perceptions may be related to the
345 cancer itself before the exposition to cisplatin. Rare cases of olfactory [37] and gustatory [38]

346 dysfunctions in lung cancer patients were previously reported, and our study is the first
347 longitudinal case-control study to highlight chemosensory alterations in a group of
348 chemotherapy-naive lung cancer patients. Given the possible impact of smoking status on smell
349 and taste abilities [39], we systematically run additional analyses by considering only non-
350 smokers. Similar pattern of results with very minor exceptions was observed in the main
351 analyses conducted in all subjects relative to the analyses in only non-smokers. For instance,
352 when the main analysis showed a decrease in patients vs. controls in a series of variables (odor
353 detection, odor identification, odor familiarity, edibility of food odors, taste detection, taste
354 identification), the analysis that considered only non-smokers showed nearly the same findings
355 with few significant differences changed to tendencies (significant effects: decrease in odor
356 identification, edibility of food odors, taste identification; borderline significance: decrease in
357 odor detection, taste detection). It should be noted, however, that our analysis included never
358 smokers and quitters in the nonsmoking group. It will be important in future assessments of
359 function in cancer patients to distinguish between these two subgroups because we cannot
360 exclude the hypothesis that the duration since complete cessation of smoking on the one hand,
361 and the number of pack-years on the other, may have an influence on olfactory abilities.

362 Contrary to a series of studies that showed a negative impact of cisplatin on olfactory and
363 gustatory perceptions, our result reported no effect of cisplatin chemotherapy after six weeks
364 of treatment. In a longitudinal study, Ijpma et al. [24] showed decreased olfactory and gustatory
365 sensitivities especially for salty taste in a group of 21 testicular cancer patients at their fourth
366 cycle of cisplatin chemotherapy. Wallizcek-Dworschak et al. [15] explored the influence of
367 cisplatin on olfactory function and showed a significant decrease of olfactory threshold in a
368 small group of 17 testicular cancer patients on day 90 of chemotherapy. In a longitudinal
369 preliminary case-control study, Jousain et al. [40] showed a decrease in the pleasantness and
370 familiarity ratings of food odors in patients compared to controls after 2 cycles of

371 chemotherapy. In line with our results, another longitudinal study that considered a
372 heterogeneous group of cancer patients (bronchial, ovary and breast) did not show any effect
373 of cisplatin on olfactory and gustatory perceptions after 3 cycles of chemotherapy [41]. Factors
374 explaining discrepancies between studies are multiple and include among others: 1/ sample size
375 (some investigations were conducted on small samples [15], [24], [40]), 2/ sample
376 heterogeneity (when sample size was large, the sample was heterogeneous [41]), 3/ absence of
377 control group (only two studies included a healthy control group [24], [40]).

378 An important question to raise here is that of the mechanisms involved in these gustatory
379 and olfactory alterations in the lung cancer patients. Different hypotheses can be put forward.
380 First, although the above mentioned gustatory and olfactory losses may be related to an
381 alteration in the functioning of the sensory receptors resulting from cancer-related inflammation
382 [42] and perhaps the brain regions involved in these two forms of perception, we cannot rule
383 out the possibility of an involvement of the respiratory system for the olfactory modality.
384 Indeed, as odorant molecules are diffused in the ambient air, they are dependent on the
385 respiratory tract to reach the olfactory receptors located on the ceiling of the nasal cavity [43].
386 Breathing, thus allows the outside air loaded with oxygen but also with odorants to penetrate
387 the body via the nasal cavity. Therefore, by disturbing the respiratory capacities of the patients,
388 it is possible that the lung cancer also disturbs the sampling of the odorant molecules at the
389 level of the olfactory epithelium. This could lead to an alteration of the olfactory function of
390 the patients. Second, recent studies identified gustatory and olfactory receptors in bronchial
391 tissue, specifically in human airway smooth muscle, which has led to interesting work on a
392 novel olfactory-like chemosensory network in human airway smooth muscle cells [44], [45]. If
393 these chemosensory cells contribute to gustatory and olfactory perception, and if they are
394 altered by bronchial cancer, then this could also partly explain the decreased sense of smell and

395 taste in patients tested. This hypothesis is speculative at this stage and requires further testing
396 in future work to be validated.

397 Third, it is also possible that the olfactory alterations are of cognitive origin. Indeed, our data
398 show a decrease in odor familiarity and identification, as well as the perceived edibility of food
399 odors. These results argue for an alteration of the olfactory process at a cognitive stage of
400 processing. Although our data only show an effect of cancer on olfactory alterations, others
401 have shown chemotherapy-induced cognitive impairments [46], [47]. In accordance with our
402 study, Von Ah et al. reported cognitive changes including difficulties to recognize words and
403 pictures in newly diagnosed breast cancer patients [48]. Thus, the effect of cancer and/or
404 chemotherapy is likely to go beyond the peripheral level and respiratory system, possibly
405 affecting conduction and integration of the olfactory/gustatory information. Interestingly, the
406 finding with odor edibility was specific to food odors and it was not observed to non-food
407 odors, which supports the link between chemosensory disturbances and patients' food behavior
408 [7].

409 In the second and third **aims**, we explored how patients' food habits were altered and how
410 they were related to olfactory alterations. It is common that cancer patients undergoing
411 chemotherapy exhibit modification in food behavior, mainly modifications in food intake [19]
412 food preferences [22], [23], and culinary practices [3], [14]. Here, significantly more patients
413 declared modifying their dietary habits and removing some foods or beverages from their diet
414 after only six weeks of chemotherapy. These changes were not observed in the control group.
415 Furthermore, differences in food habits items between patients and controls were observed even
416 before the chemotherapy, suggesting that patients' relationship with food is modified at the
417 point of diagnosis. Newly diagnosed patients tend to change their dietary habits, with the aim
418 to contribute to the fight against the disease and the improvement of treatment's efficiency [49].
419 Considering food seasoning, patients declared adding less condiments than controls at both T0

420 and T1. Adding condiments to enhance flavor and complement the dish in order to meet sensory
421 expectations could be interpreted as an eating behavior modification related to food
422 appreciation and subsequent pleasure derived from its consumption. However, cancer diagnosis
423 and chemotherapy treatments are usually accompanied by a decrease in appetite and a lack of
424 motivation to eat, because of physiological [50] or psychological [51] reasons. The fact that
425 patients are less involved in the food experience, and experiment a decreased food enjoyment
426 [52] may explain why they report using less condiments. Interestingly, within the patient group,
427 hyposmics used more condiments, suggesting a sensory deficit compensation by seasoning in
428 order to meet sensory expectations.

429 The study presents some limitations that are worth to be discussed. Firstly, the effect of
430 chemotherapy on sensory perceptions may be observed after more than six weeks of treatment,
431 by reaching a given cumulative dose of cisplatin, thus, a longer-term study would be more
432 informative. Furthermore, by choosing to assess patients' chemosensory function three weeks
433 after the administration of their chemotherapy, we possibly missed the instant effect of
434 chemotherapy that was shown to be cyclical and more severe right after the treatment
435 administration [24], [25]. Third, our patient group included both small cell and non-small cell
436 bronchial cancers. Whether this factor introduced significant heterogeneity in our group of
437 patients can be questioned. Here, given that both histological types have the same risk factors
438 (smoking), similar median age, similar therapy, as well as the same types of smoking-related
439 comorbidities, it is probably not a major factor that introduces heterogeneity in our group.
440 Nevertheless, in future studies it will be important to make the sample of interest as
441 homogeneous as possible. Finally, the understanding of patients' food behavior changes could
442 be further improved by using more detailed questionnaires such as the Food Frequency
443 Questionnaire, 24 hour recalls, [53], or real eating context studies for more accurate dietary
444 information.

445 However, our study was designed to circumvent the methodological heterogeneity found in the
446 literature and have therefore numerous strengths from a methodological point of view. Firstly,
447 its longitudinal design that includes a baseline measurement allowed to observe an effect of
448 cancer on smell and taste before and after six weeks of cisplatin treatment. Moreover, our study
449 is one of the few studies with a homogenous cancer localization and chemotherapy regimen,
450 reducing sources of variability between patients. The enrolment of an age- and gender- matched
451 control group enabled to distinguish the effect of the pathologic state from the effect of ageing
452 on sensory abilities [54]. Finally, the use of psychophysical approach for the sensory assessment
453 ensured an objective evaluation of participants' perceptive abilities.

454 **Conclusion**

455 The present study highlighted decreased smell and taste abilities in almost half of the patients'
456 group even before being exposed to cisplatin treatment. Patients rated typical food odors as less
457 edible compared to healthy controls, possibly involving alterations in odor cognitive processing
458 due to cancer. Despite the sensory deficit, patients declared using less condiments than controls
459 with unaltered chemosensory function. However, within the patients' group, hyposmics
460 reported using more condiments, possibly as a compensatory mechanism to their decreased
461 sensory abilities. Our results confirm the effect of chemosensory alterations on patients' food
462 behavior and underlie the involvement of olfaction in food perception and more specifically,
463 the impact of reduced olfaction on dietary practices including seasoning. Experimental studies
464 are needed to better understand how adapting the sensory properties of food to the patients'
465 sensory abilities may improve their food enjoyment.

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472

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475 manuscript edition, AD and MB contributed to the review and editing of the manuscript, ML,
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477 All co-authors read and approved the final version of the manuscript

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482

483 **Conflict of interest:** None

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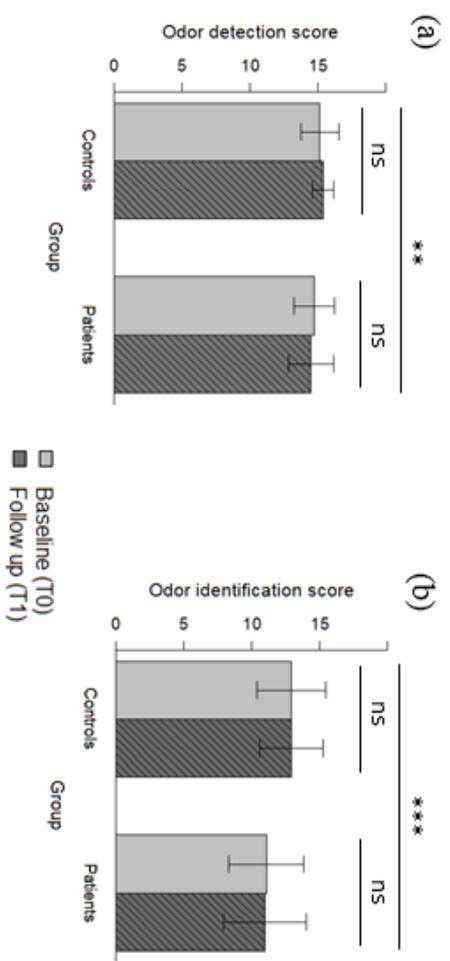
485 6. References

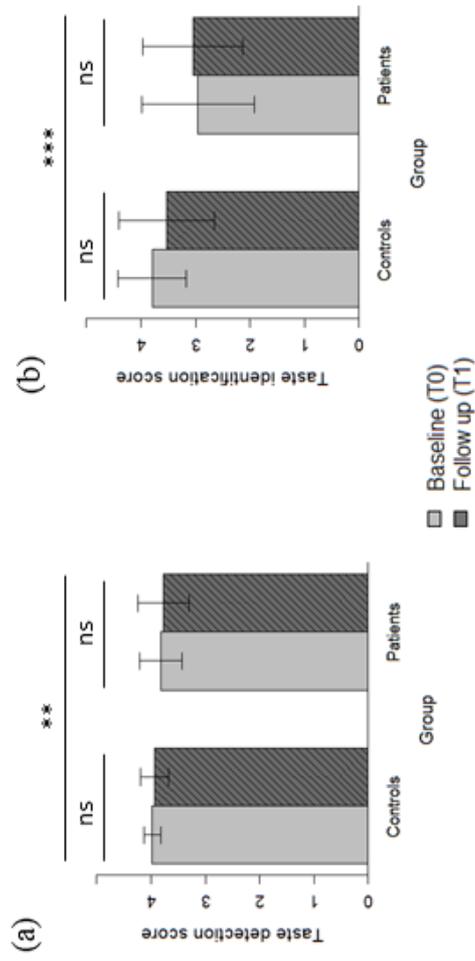
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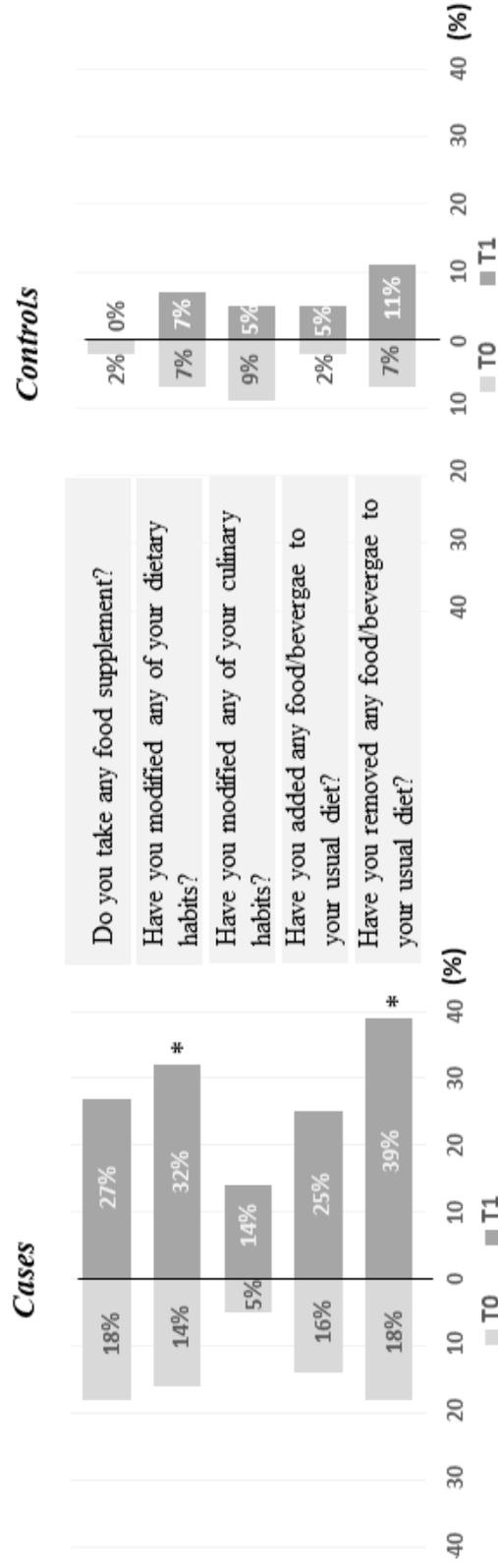


Figure 1. Mean (\pm SD) of odor detection and identification scores. (a) Odor detection; (b) Odor identification. For each of the assessed parameters, the ANOVA model showed no significant difference between T0 and T1 in patients and controls but patients scored lower than controls in both odor detection and identification at T0 and T1. ** $p < .01$, *** $p < .001$, “ns” means non-significant difference.

Figure 2. Mean (\pm SD) of tastes detection and identification scores. (a) Taste detection; (b) Taste identification. For each of the assessed parameters, the ANOVA model showed no significant difference between T0 and T1 in patients and controls groups but patients scored lower than controls in both taste detection and taste identification at T0 and T1. ** $p < .01$, *** $p < .001$, “ns” means non-significant difference.

Figure 3. Food habit changes in patients (left panel) and controls (right panel) at T0 and T1 (left and right side of the mirror histograms). Horizontal bars represent the percentage of participants answering “yes” to a given item. * means $p < .050$.

Table 1. Characteristics of the participants.

	Patients	Controls	p-value
Age (years)			
Mean (\pm SD)	63.5 (\pm 6.80)	62.4 (\pm 7.53)	> .05
Range	(46-74)	(47-77)	
Gender (n)			
Male	28	28	> .05
Female	16	16	
Smoking status (n)			
Smokers	17	3	.001
Non-smokers	26	41	
Not mentioned	1	0	
BMI (\pm SD)			
Baseline (T0)	23.72 (\pm 3.64)	24.97 (\pm 3.30)	.08
Follow-up (T1)	23.28 (\pm 3.46)	25.11 (\pm 3.10)	.01

Bold font indicates statistical significance

Table 2. Intensity, pleasantness, familiarity and edibility ratings of odors at T0 and T1 in patients and controls (mean \pm SD).

Olfaction	Patients (n=40)		Controls (n=40)	
	T0	T1	T0	T1
Intensity	5.28 \pm 1.28	5.57 \pm 1.3	5.50 \pm 1.26	5.70 \pm 1.73
Food odors	5.48 \pm 1.33	6.01 \pm 1.37	5.61 \pm 1.27	6.12 \pm 1.33
Non-food odors	5.09 \pm 1.38	5.29 \pm 1.44	5.39 \pm 1.4	5.64 \pm 1.42
Pleasantness	5.83 \pm 1.25	5.96 \pm 1.2	6.33 \pm 0.88	6.17 \pm 1.1
Food odors	6.1 \pm 1.38	6.21 \pm 1.16	6.7 \pm 0.85	6.48 \pm 1.17
Non-food odors	5.56 \pm 1.3	5.72 \pm 1.46	5.95 \pm 1.08	5.68 \pm 1.13
Familiarity	5.28 \pm 1.28	6.32 \pm 1.67	5.5 \pm 1.26	6.96 \pm 1.18

Food odors	6.25±1.85	6.6±1.65	7.19±1.08	7.26±1.16
Non-food odors	5.75±1.81	6.04±1.82	6.52±1.34	6.65±1.35
Edibility	5.54±1.63	5.65±1.43	6.08±1.03	6.15±1.01
Food odors	6.86±1.94	6.92±1.69	7.78±1.05	7.83±1.19
Non-food odors	4.20±1.59	4.38±1.38	4.38±1.49	4.46±1.29

Table 3. Intensity, pleasantness and familiarity rating of tastes at T0 and T1 in patients and controls (mean±SD).

Taste	Patients (n=40)		Controls (n=40)	
	T1	T2	T1	T2
Intensity	6.60±1.60	4.87±1.64	6.30±1.51	5.09±1.43
Sweet	6.23±2.41	6.34±1.99	5.72±2.14	6.59±1.72
Salty	7.09±1.63	6.83±1.73	6.68±1.93	6.56±2.03
Sour	7.13±1.87	7.15±1.50	6.81±1.48	7.27±1.63
Bitter	6.23±2.08	6.20±2.38	6.00±2.18	5.87±1.96
Pleasantness	4.70±1.81	6.60±1.56	4.92±1.38	6.57±1.46
Sweet	6.51±2.21	6.95±2.01	6.93±1.56	7.18±1.93
Salty	4.61±2.36	4.68±2.26	4.77±2.15	4.95±2.06
Sour	4.31±2.58	4.80±2.35	4.77±2.07	4.68±2.18
Bitter	3.35±2.38	3.02±2.13	3.20±1.99	3.46±1.97
Familiarity	5.86±1.91	5.69±1.96	6.40±1.73	6.77±1.60
Sweet	7.12±2.35	6.60±2.46	7.15±2.24	7.61±1.89
Salty	6.38±2.54	6.17±2.51	7.13±1.85	7.43±1.79
Sour	6.02±2.65	5.78±2.76	6.45±2.19	6.70±2.40
Bitter	3.89±2.79	4.33±2.46	4.90±2.74	5.36±2.22

Author statement: individual contributions to the paper

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-KD and MB contributed to data collection, analyzed data and drafted the manuscript,

-KD, MB and AG contributed to define the study design, data analysis, and manuscript edition,

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