



26 **ABSTRACT**

27 **Background:** Although positive outcomes are popularly attributed to humor, no previous  
28 randomized controlled trial (RCT) has examined the impact of humor interventions on adult  
29 cancer patients. The Comedy in Chemotherapy (COMIC) Study was an RCT that compared  
30 symptoms, salivary immunoglobulin-A (IgA) and salivary cortisol in oncology outpatients.

31 **Methods:** The COMIC Study was conducted from 2007-2009 in an outpatient oncology clinic at  
32 The Queen's Medical Center (QMC) in Honolulu, Hawaii. Forty-nine participants were  
33 randomly assigned to a humor intervention (N=26) or a non-humor intervention (N=23) while  
34 receiving chemotherapy. Primary outcome measures were symptoms related to cancer and  
35 chemotherapy (Edmonton Symptom Assessment (ESAS) score), anxiety (Spielberger State-  
36 Trait Anxiety Index (STAI-S) score), immune function (salivary IgA level), and stress level  
37 (salivary cortisol level).

38 **Results:** Humor group participants reported: (1) a significant decrease in cancer and  
39 chemotherapy-related symptoms (total ESAS;  $P=0.004$ ) and (2) a significant decrease in  
40 anxiety levels (STAI-S score;  $P<0.001$ ) and (3) a trend toward increased salivary IgA levels  
41 ( $p=0.077$ ). Differences between groups reached borderline statistical significance in the ESAS  
42 ( $P=0.065$ ) and the STAI-S ( $P=0.099$ ) measures. Salivary IgA and cortisol were not significantly  
43 different between groups. In post-intervention interviews, humor group participants described  
44 physiological and psychological improvements.

45 **Conclusion:** Pilot study findings support the use of humor as a low-risk intervention that may  
46 complement pharmacologic therapy for management of symptoms related to cancer and  
47 chemotherapy. Additional study is recommended to more fully assess the efficacy of humor in  
48 cancer and other health conditions.

49 **Trial Registration:** ClinicalTrials.gov NCT01037933 <http://clinicaltrials.gov>

50

51 **INTRODUCTION**

52 As the world's population ages, chronic diseases such as cancer are increasingly common, and  
53 interventions that maximize health and well being in such diseases are receiving greater  
54 attention.[1] The use of humor is one such intervention. Humor has been used to diminish pain,  
55 improve immune function, and decrease stress and has become a popular topic in both  
56 professional and lay literature over the last 20 years as a cognitive-behavioral intervention.[2-6]

57  
58 Humor involves cognitive, behavioral and social aspects, as well as a pleasant emotional state.  
59 [7,8] It can also, however, be degrading or divisive. As a result, for this study the American  
60 Association of Applied and Therapeutic Humor's (AATH) definition of "therapeutic humor" is  
61 used to define humor as "any intervention that promotes health and wellness by stimulating a  
62 playful discovery, expression, or appreciation of the absurdity or incongruity of life's situations  
63 and can be used as a complementary treatment of illness to facilitate healing or coping, whether  
64 physical, emotional, cognitive, social or spiritual." [9]

65  
66 The theoretical models regarding the physiologic impact of humor are the complementary fields  
67 of psychoneuroendocrinology (PNE) and psychoneuroimmunology (PNI), which describe  
68 interactions among autonomic, neuroendocrine and immune systems as well as subsequent  
69 impact upon disease development and progression.[10-12] These models suggest that  
70 hormones such as adreno-corticotropin releasing hormone (ACTH), cortisol and epinephrine  
71 change as a result of physical and emotional stress, which may affect clinical outcomes. Other  
72 neurotransmitters, neurohormones and cytokines can also be affected by stress.[7,8] PNI  
73 research suggests that humor may have positive physiologic effects on immune function by  
74 reducing stress and improving natural killer cell activity.[13-15] Significant cardiac vasodilatation  
75 has been reported in patients who viewed a comedy video, and vasoconstriction in those who  
76 viewed a stressful war video.[16]

77

78 The autonomic nervous system appears to affect immune function, and salivary IgA is a marker  
79 of immune competence.[17] Humor has been shown to have a significant impact on the  
80 immune system, and a positive correlation between salivary IgA levels and sense of humor has  
81 been suggested.[18] Laughter may increase immunoglobulin levels for as long as 12 hours.[19]  
82 Several studies have demonstrated a significant correlation between humor or laughter and  
83 increased salivary IgA.[19,20], and IgA also appears to be especially responsive to an  
84 individual's emotional state. [21] Positive and/or relaxing experiences may correspond with IgA  
85 increases, while stress may correspond with IgA decreases.[18] Cortisol, a hormone often  
86 associated with emotional stress [22] may also be implicated in the therapeutic aspects of  
87 humor. Decreases in cortisol secretion during episodes of mirthful laughter have been  
88 reported.[23]

89

90 Humor videos have also been shown to increase patients' discomfort level thresholds and  
91 decrease their pain perception.[5,6,24] Children have demonstrated significantly greater pain  
92 tolerance while viewing humorous videos immediately before or after a painful task.[25] Women  
93 with breast cancer identify humor as a means of spiritual coping and stress reduction.[26] A  
94 study of patients with head and neck cancer suggested that sense of humor scores at diagnosis  
95 predicted quality of life at follow-up.[27] Humor-associated laughter has been demonstrated to  
96 modulate and potentially optimize appetite hormones.[28] The occasional use of humor is  
97 ranked by patients with metastatic cancer as one of the top ten "hope-giving" behaviors  
98 demonstrated by oncologists.[29]

99

100 In summary, humor has been reported to show promise for physical, psychological, spiritual and  
101 social benefits in a variety of healthcare settings. However, despite its conceptual popularity,  
102 there is still limited research on humor-based interventions.[7, 30] Studies in oncology practice

103 are scant. We know of no RCT conducted in adult cancer outpatients where symptomatology,  
104 salivary IgA or salivary cortisol were measured as outcome variables before and after a humor  
105 intervention.

106

## 107 **METHODS**

108 The COMIC study was an RCT conducted in the outpatient oncology clinic at The Queen's  
109 Medical Center in Honolulu, Hawaii from 2007-2009. Eligible participants were  $\geq 18$  years old,  
110 could see and hear, and were able to speak English. Participants were excluded if they had  
111 severe mucositis or a diagnosis of head or neck cancer with a resulting decrease in salivary  
112 flow. The Institutional Review Boards at The Queen's Medical Center and the University of  
113 Hawaii approved this trial. Written informed consent was obtained from all participants and co-  
114 participants prior to study entry.

115

### 116 **Randomization and Study Interventions**

117 After completion of baseline assessments, eligible participants were randomized to study arm  
118 using statistical software. Participants viewed either a 45-minute humorous DVD or 45-minute  
119 non-humorous DVD. Since no optimal "dose" of a humorous film is known, 45 minutes was  
120 chosen as a mid-range film length used in comparable studies.[5-7,13,14,16,19,24,28,31] The  
121 DVD "Bananas Bunch" (Guardian Studios) was chosen based upon the definition of therapeutic  
122 humor[9] referenced above, and because it included the work of six individual comedians with  
123 different performance styles and comedic content.

124

125 The non-humorous DVD was "The A to Z of Steam Railways," a British documentary on trains  
126 powered by steam engines. While other studies have used videos such as war movies, this film  
127 was selected because it was mildly engaging without being alarming. The film also included no  
128 music or nature scenes, either of which might have had an impact on participant response.

129

130 To minimize noise from the environment, all participants individually viewed the humorous or  
131 non-humorous DVD using portable DVD players and headsets. If the participant was  
132 accompanied by someone, that person had the option of consenting to be a co-participant in the  
133 study. All participants and co-participants received a \$25 gift certificate for being part of the  
134 study.

135

### 136 **Participant Demographics and Medical History**

137 Participant interviews and medical chart reviews were conducted by a research nurse to obtain  
138 pertinent demographic and clinical information such as age, gender, ethnicity, type of primary  
139 cancer, type and cycle of chemotherapy, comorbidities, Karnofsky performance status, and use  
140 of opioids, anti-emetics, anxiolytics and steroids.

141

142 **Humor Styles Questionnaire (HSQ).** In order to compare participant self-report of receptivity to  
143 humor, the self-enhancing subscale of the HSQ [32] was used. The subscale consists of 8  
144 items. Responses were rated on a 7-point scale, ranging from “totally disagree” to “totally  
145 agree.” Higher scores indicated a greater tendency to use humor to cope with stress. The  
146 summary score was used to compare groups.

147

### 148 **Outcome Measures**

149 Outcomes were measured before and immediately after the intervention. Primary  
150 measurements included symptom scores, anxiety ratings, salivary IgA, and salivary cortisol.  
151 Secondary outcomes included perceptions of participants, co-participants and nurses regarding  
152 the overall intervention experience. All assessments were conducted by a research nurse who  
153 was not involved in the direct care of the participant.

154

155 **Edmonton Symptom Assessment Scale (ESAS).** The ESAS is a validated tool that measures  
156 nine symptoms in patients with cancer or chronic illness.[33] The intensity of each symptom was  
157 rated on a 10-point scale; 0 indicated “no symptom” and 10 indicated “worst possible symptom.”  
158 A global ESAS intensity score was calculated by totaling the nine symptom responses. Total  
159 scores were compared within arms using the Wilcoxon signed rank sum test and differences  
160 (post- minus pre-) between arms using the Wilcoxon-Mann-Whitney test.

161  
162 **State-Trait Anxiety Index (STAI-S).** The STAI-S is a validated scale designed to measure state  
163 and trait anxiety.[34] The “state” or “S” portion of the scale consisted of 20 statements. Each  
164 item was given a score of 1 to 4, from “not at all” to “very much so.” Scores were totaled for the  
165 20 items, with higher scores indicating more anxiety.

166  
167 **Salivary IgA and Cortisol.** Salivary IgA and cortisol were collected by means of a polyester roll  
168 or sorbette (Salimetrics, LLC, State College, PA). Participants were instructed to eat no food  
169 within 30 minutes prior to specimen collection. Each participant rinsed his/her mouth with water  
170 10 minutes before sample was collected, then placed one sorbette in each cheek for three  
171 minutes. The sorbettes were placed in a sterile collection device, and stored in a  $-70^{\circ}$  freezer  
172 until completion of enrollment. At the end of the study, salivary samples were packaged with  
173 dry ice and shipped via express carrier to a laboratory at the University of Washington for  
174 analysis.[35]

175  
176 **Perceptions of Participants and Caregivers.** Following the collection of post-intervention  
177 ESAS, STAI-S, salivary IgA and cortisol measurements, all participants were asked five open-  
178 ended statements or questions regarding their experience watching the DVD to gather their  
179 overall impressions of the intervention (**Table 1**). Interviews were tape-recorded and  
180 transcribed verbatim.

181

## 182 **Statistical Analyses**

183 Student's t, chi-square ( $\chi^2$ ), or Wilcoxon-Mann-Whitney tests were used to compare  
184 characteristics of participants between the two groups at baseline. Non-parametric statistical  
185 tests were used on outcome variables as distributions were asymmetric and because of the  
186 small sample size. Wilcoxon signed rank sum tests were used to assess potential differences in  
187 outcomes within groups (baseline and post-intervention). Wilcoxon-Mann-Whitney tests were  
188 used to assess potential differences between groups post-intervention (humorous and non-  
189 humorous groups). All tests were two-tailed with P-values < 0.05 considered statistically  
190 significant. Statistical analyses were carried out with the use of SAS software, version 9.1 (SAS  
191 Institute). The standardized Cronbach's coefficient alpha indicated an acceptable lower bound  
192 for the reliability coefficient for the HSQ (0.80), ESAS (0.91), and STAI-S (0.76).

193

194 For the qualitative data, all transcripts were reviewed by three members of the research team  
195 and recurring phrases or concepts from the transcripts were identified and labeled with codes  
196 done by topic coding. Similar concepts were then grouped into categories by analytic coding.  
197 The data were then analyzed for emerging themes using the identified concepts and  
198 categories.[36]

199

200 A sample size of 50 participants was selected for this pilot feasibility study based on an  
201 estimated number of patients receiving chemotherapy in the outpatient oncology clinic.

202

## 203 **RESULTS**

204 Fifty participants were enrolled in the study (**Figure 1**). None withdrew due to adverse effects;  
205 however, one participant consented to be in the study but was hospitalized and died prior to  
206 completion of baseline measurements. Therefore, a total of 49 participants (humor group: N=26,

207 non-humor group: N=23) completed the study. Demographic and clinical information of the 49  
208 patients are summarized in **Table 2**. The only significant demographic difference between the  
209 groups was age: the humor group averaged 56 years old while the non-humor group averaged  
210 63 years old ( $P = 0.047$ ). The majority of participants in both groups were highly functional with  
211 a Karnofsky performance status of  $\geq 90$  (humor group=76.9%, non-humor group=65.2%). Most  
212 participants had been medicated with dexamethasone for their chemotherapy, but there was not  
213 a significant difference in the mean dose taken between the humor group (13.8 mg) vs. the non-  
214 humor group (12.1 mg). The groups did not significantly differ in their self-reported use of  
215 humor to cope with stress (HSQ).

216

### 217 **Primary Outcomes**

218 For the cancer and chemotherapy symptom scores, participants in the humor group had a  
219 significant decrease from baseline in the median intensity of their symptoms (ESAS score -4.5:  
220  $P = 0.004$ ; Wilcoxon signed rank sum test). Those in the non-humor group had a non-  
221 significant increase in median intensity of their symptoms from baseline (ESAS score 2.0;  $P =$   
222  $0.80$ ; Wilcoxon signed rank sum test) (**Table 3**). While the humor group had lower post-  
223 intervention symptom intensity scores compared to the non-humor group, the difference in  
224 intensity between the two groups was of borderline significance ( $P = 0.07$ ; Wilcoxon-Mann-  
225 Whitney test).

226

227 Participants in the humor group showed significant improvement in their anxiety from baseline  
228 ( $P = <0.001$ ). Participants in the non-humor group showed a non-significant decrease from  
229 baseline ( $P = 0.17$ ) (**Table 3**). There was a borderline difference in anxiety post-intervention  
230 between the two groups ( $P = 0.099$ ).

231

232 Salivary IgA level increases from baseline approached statistical significance within the humor  
233 group (15.6 mcg/mL,  $P = 0.08$ ), but not for the non-humor group (10.9 mcg/mL,  $P = 0.44$ ). There  
234 was not a significant difference in salivary IgA levels between the two groups ( $P = 0.65$ ). There  
235 were no significant differences in salivary cortisol levels within or between groups (**Table 3**).

236

### 237 **Secondary Outcome**

238 The overall perception of participants in the humor group was that the intervention had positive  
239 physiological and psychological effects. In contrast, none of the participants in the non-humor  
240 group reported positive changes.

241

242 Psychological effects of participants in the humor group included feeling “happier” as well as  
243 experiencing decreased stress and anxiety. The humorous DVD also provided distraction from  
244 treatment and cancer. Comments included “It kind of made me forget where I was;” “Receiving  
245 chemotherapy made me very sad and the video helped me block it out and relax;” “It takes your  
246 mind off what’s going on and it makes you happy;” and “The comedy blocked thoughts about my  
247 disease and cancer recurrence.” In contrast, participants who viewed the non-humorous DVD  
248 made no statements about distraction from chemotherapy and cancer.

249

### 250 **COMMENT**

251 Overall, research findings about humor and its impact on healing have been tentative, and more  
252 studies are needed in order to determine whether humor and laughter have a positive effect on  
253 long-term health outcomes. Research sample sizes in some studies have been small, and  
254 findings have been inconsistent,[37] including those that have examined the actual physiologic  
255 impact of humor.[30]

256

257 While some studies support the use of humor as a stimulus for salivary IgA , other studies do  
258 not find a correlation.[37] In addition, humor conceptualizations and methodologies vary. Some  
259 researchers focus on a humor stimulus, others focus on the behavior of laughter (with or without  
260 a stimulus), and still others focus on sense of humor and its cognitive component. There is  
261 often little distinction in the literature between socially inclusive humor and humor that may be  
262 sarcastic or cynical, and therefore potentially harmful. Some studies have only enrolled young  
263 healthy males, and many studies do not have a control group. No studies have investigated the  
264 effectiveness of humor on adults with symptoms of cancer and cancer-related treatment.  
265 Though at least one study found enhanced natural killer cell activity in healthy subjects after a  
266 humor intervention,[13] it is not known what impact this would have on patients with a cancer  
267 diagnosis.

268

269 The COMIC study was an RCT using a humor intervention to determine impact on symptoms  
270 related to cancer and chemotherapy. To our knowledge, this study is the first RCT to evaluate  
271 the impact of humor vs. non-humor films on the symptoms of adult cancer patients. The study  
272 demonstrates that a humor intervention may be linked to a significant decrease in the intensity  
273 of symptoms related to cancer and chemotherapy, particularly pain, sense of well-being, and  
274 anxiety. While it is not known what long-term impact humor interventions may have on immune  
275 function, there were suggestive effects for increased salivary IgA in participants from the humor  
276 group post-intervention ( $p=0.08$ ). The magnitude of the increase was not significantly greater  
277 than the non-humor group. This was possibly influenced by small sample sizes with limited  
278 power to detect between-group differences. There was no association with salivary cortisol  
279 ( $P=0.24$ ). A larger sample size or the addition of a control group may help resolve whether  
280 humor has detectable clinical differences versus other interventions and might provide further  
281 support for the use of humor interventions with cancer patients.

282

283 Since this was a pilot study, and since it was the first RCT to examine the impact of a humorous  
284 intervention on the symptoms of cancer and chemotherapy, we cannot make solid comparisons  
285 with previous studies. Possible limitations of this study included the absence of a “no  
286 intervention” group (i.e. a “true” control) and the relatively small sample size. There was also no  
287 attempt to measure the frequency or quality of laughter demonstrated by the participants, nor  
288 was a scale used to determine how funny the participants found the humor intervention. As  
289 suggested in at least one study,[31] future research might allow participants to choose a film  
290 that they themselves think is funny, since it might actually be aversive and countertherapeutic  
291 for subjects to lack choice over the film they watch.

292

293 Strengths of this study include the fact that it was an RCT, that it was held in an outpatient  
294 setting with a relatively controlled environment, and that it was conducted with participants who  
295 presented with actual symptoms rather than had a painful stimulus imposed upon them. Such a  
296 setting is similar to what patients might encounter in clinical practice. The interventions were  
297 also very low-risk and no participants dropped out from the study after the study began. In  
298 addition, the chosen humor stimulus contained several comedy styles in order to appeal to  
299 different tastes in humor and the non-humor intervention was felt to be a neutral intervention  
300 that did not contain stressful content, which might induce anxiety or other symptoms. Another  
301 factor important to clinicians is the study design itself, which can be inexpensively replicated in  
302 other settings. Replication would make it possible to compare findings with participants from  
303 other geographic regions, cultures or diagnostic groups. The COMIC study could also be easily  
304 modified to include a third arm, to add a scale for participants to rate the funniness of the film, to  
305 measure laughter response, or to allow patients to choose their own film.

306

307 **CONCLUSION**

308 We compared cancer and chemotherapy-related symptoms as well as immune and endocrine  
309 function between participants who watched either a humorous or non-humorous DVD.  
310 Participants who watched the humorous DVD described an overall decrease in cancer and  
311 chemotherapy-related symptoms as well as decreased anxiety. They also exhibited physiologic  
312 changes consistent with improved immune function as compared to their baseline. Cancer and  
313 chemotherapy-related symptoms, as well as anxiety decreased more in the humor intervention  
314 group than in the non-humor group but were of borderline significance. These findings merit  
315 further study. In conclusion, humor has the potential to be a low-risk complement to  
316 pharmacologic therapy in oncology practice. Further studies are needed with larger numbers of  
317 participants in order to determine to what degree humor and laughter might positively affect both  
318 immediate and long-term health outcomes.

319

320 **Author Contributions:** Ms. Osterlund had full access to all of the data in the study and takes  
321 responsibility for the integrity of the data and the accuracy of the data analysis.

322 Study concept and design: Osterlund, Conde, Itano, Fischberg, Ferrell, Gazmen, Imler, Latimer,  
323 Willcox

324 Acquisition of data: Osterlund, Conde, Baker, Itano, Gazmen, Imler, Latimer

325 Analysis and interpretation of data: Osterlund, Conde, Baker, Itano, Fischberg, Ferrell, Gazmen,  
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329 Itano, Fischberg, Ferrell, Gazmen, Latimer, Willcox,

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426

427 **FIGURE LEGEND**

428 **Figure 1.** Study Schema