

# Effects of relaxation breathing exercise on fatigue and cortisol level among Indonesian gynecological cancer patients undergoing chemotherapy: a pilot study<sup>†</sup>



Original article

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**Abstract:** **Objective:** This study aimed to determine the effect of the relaxation breathing exercise (RBE) on fatigue and cortisol levels among Indonesian women with gynecological cancer undergoing chemotherapy.

**Methods:** This pilot study consecutively recruited 44 gynecological cancer patients to receive RBE (22) or usual care (22). Cortisol level was measured before and after completion of the intervention (day 8). Fatigue was measured using the Piper Fatigue Scale (PFS). Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) at the baseline days of the study for days 1, 4, and 8. The obtained data were analyzed using Fisher's exact test, the independent *t*-test, and the Mann-Whitney *U* test.

**Results:** There were significant increases in cortisol levels within the groups, either the intervention or control groups, respectively (*P*-value = 0.0003 and 0.001). Despite there being no statistical significance between the intervention and control groups, there were noticeable differences in the cortisol levels, indicating the extreme increase in cortisol levels in the control group (Median [IQR1–IQR3]: 2.30 [0.99–9.09]; Min–Max: 0.43–23.38) compared with the intervention group (Median [IQR1–IQR3] = 2.97 [1.26–5.18]; Min–Max = 0.39–6.91).

**Conclusions:** RBE helps prevent a significant increase in cortisol levels that can alleviate fatigue for women with gynecological cancer. Further research was recommended to compare several intervention modalities for fatigue and cancer-related symptom management based on cortisol level changes.

**Keywords:** anxiety • cortisol • fatigue • gynecological cancer • relaxation breathing exercise

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## 1. Introduction

Globally, cancer has become one of the leading causes of premature death and disability, with approximately 10.0 million cancer-related deaths expected by 2020,

or 1 in 6 deaths, particularly in women.<sup>1,2</sup> Gynecological cancer ranks fourth among women worldwide.<sup>3</sup> In Indonesia, around 40% of malignancies in women are

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caused by gynecological cancer,<sup>4</sup> and the incidence of the cancer types is also similar to the global trend in which the most common types are cervical and ovarian cancers, which are around 13.3% of all cancer cases.<sup>4,5</sup> Gynecological cancers do not show early signs and symptoms. Thus, cancer patients sometimes seek healthcare providers or services after advanced stages, leading to poor outcomes.<sup>6,7</sup> Chemotherapy is one of the most common treatments for advanced cancer and has effectively treated cancer. However, the treatment can cause serious side effects that can severely influence the quality of life of cancer patients.<sup>8,9</sup>

Several studies have highlighted common adverse effects of chemotherapy on the physical, psychological, and social levels such as fatigue, pain, hair loss, infection, anemia, nausea, and vomiting.<sup>8,10–12</sup> Another study found that fatigue was the most common effect of chemotherapy in gynecologic cancer patients, experienced by around 53% of gynecological cancer patients, in which cervical cancer patients rank the highest proportion, followed by ovarian cancer patients.<sup>13</sup>

Cancer-related fatigue is a subjective and multidimensional condition that is caused by many factors, such as demographic, genetic, medical, psychosocial, behavioral, and biological.<sup>14,15</sup> Another possible cause of fatigue is a disturbance in the hypothalamic–pituitary–adrenal (HPA) axis, which causes a decrease in cortisol levels in patients with chronic fatigue syndrome.<sup>16–18</sup> It is hypothesized that cancer or undergoing cancer treatments alter the function of the HPA axis.<sup>18</sup> This alteration causes changes in the endocrine function that contribute to fatigue.<sup>14</sup> Research conducted by Morrow et al.<sup>19</sup> found a significant decrease in serum cortisol immediately after chemotherapy drug infusion (cisplatin and carboplatin) in gynecologic cancer patients. However, a study by Limberaki et al.<sup>20</sup> found differences in a significant decline in the antioxidant capacity and increased cortisol concentrations in chemotherapy patients.

Fatigue significantly affects the cancer patient's quality of life and causes the patients to feel too tired of doing daily activities and carrying out their roles.<sup>13</sup> Fatigue can cause cognitive, physical, social, mood changes, and sexual disturbances that impact the quality of life.<sup>21–23</sup> Women who experience fatigue have a lower quality of life than women who are not fatigued in all domains.<sup>24</sup> Therefore, effective nursing interventions are imperative to reduce cancer and treatment-related fatigue and to improve the patient's quality of life.<sup>25</sup> Relaxation techniques or relaxation breathing exercise (RBE) is one of the modalities that is found to effectively alleviate cancer-related fatigue. RBE is a conscious

way or action to regulate deep and slow breathing that causes a relaxing effect.<sup>26</sup> Previous research on RBE only focused on reducing fatigue.<sup>27–29</sup> However, studies investigating the effects of relaxation techniques on cortisol levels in cancer patients who experience fatigue are still limited. Thus, this study aims to determine RBE's effectiveness on the cortisol levels and fatigue scores. We hypothesized that the intervention would increase cortisol levels and decrease fatigue scores by comparing the intervention group with the usual care or control group for gynecological cancer patients undergoing chemotherapy.

## 2. Methods

### 2.1. Research design

This research was a pilot experimental study that was conducted in 2 referral hospitals in the Eastern Region of Indonesia. The primary outcome was to assess changes in cortisol levels at baseline before RBE intervention and after 8 days. In addition, the secondary outcomes were to evaluate fatigue, anxiety, and depression levels before the intervention, on the fourth day, and after the completion of 8 days of intervention.

### 2.2. Setting and participants

The patients were recruited from the chemotherapy units (gynecological oncology wards) in 2 referral hospitals in the Eastern part of Indonesia by using a consecutive sampling technique.<sup>30</sup> Eligible participants were adult patients with gynecological cancer undergoing chemotherapy (aged 18–55 years old), residing approximately 100 km<sup>2</sup> around Makassar city, which is the capital city of South Sulawesi province, who underwent chemotherapy at least once, experienced fatigue, had a range of motion, and were able to give consent. The exclusion criteria were patients with chronic conditions, for example, heart diseases or unstable angina, difficulty breathing at rest, persistent cough, and chronic kidney diseases.

The study recruited 235 gynecological cancer patients (Figure 1). The sample size was calculated using a G\*Power analysis (Computer statistical software version 3.0.10; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; <http://www.gpower.hhu.de/>) with  $\alpha = 0.05$  (one tail), power 0.80, a large effect size.<sup>31</sup> Thus, the sample required at least 15 respondents for each group to be able to identify the statistical significance of the intervention.

### 2.3. Procedure and intervention

Participants were recruited according to the inclusion criteria and then allocated to the intervention or control group. Recruitment of the intervention group was conducted first until the sample was fulfilled. Then, it was followed by recruiting participants in the control group. This sampling technique was applied to prevent the participants in the intervention and control groups from meeting each other during the chemotherapy cycles, which might affect the study result. The research aims and the procedure were explained to the patients, and those who consented to participate signed an informed consent form. The researcher then demonstrated to the participants how to fill out the Piper Fatigue Scale (PFS) and make daily notes. In addition, intervention groups were taught the RBE before the intervention and were given the RBE guidelines.<sup>27,28</sup> The exercise was performed for 30 min, 4 times a day (morning/9 AM, mid-day/1 PM, afternoon/5 PM, and night/9 PM) for 7 days during hospitalization under researcher supervision, and after independently discharged at home it was followed up by phone or message from the researchers. The participants in the control group were treated according to hospital standards during the study and taught the RBE after the post-test on day 8 of the study.

The participants were assessed on the first-day post-chemotherapy at 8 AM. The researchers took saliva samples for cortisol examination and measured both groups' fatigue and anxiety levels as initial data. Then, on the fourth day, the researcher reminded the participants to count fatigue and anxiety questionnaires. Furthermore, on the eighth day, saliva samples would be taken as a post-test to measure fatigue and anxiety levels.

### 2.4. Instruments

The fatigue level of cancer patients was measured using the PFS, a self-administrated questionnaire constructed by Piper et al.<sup>32</sup> The PFS contains 22 questions in numerical scale forms ranging from 0 to 10. There are also 5 open questions for subjective measurement. These instruments have been translated into Bahasa Indonesia with Cronbach's  $\alpha$  coefficient of 0.98.<sup>33</sup>

Hospital Anxiety and Depression Scale-Anxiety (HADS-A) is a scale to measure anxiety and depression that is developed by Zigmond and Snaith.<sup>34</sup> The HADS consists of 14 items and separates 2 subscales (anxiety and depression), with 7 items in each subscale. Each item contains 4 4-point Likert scale (0–3). Scores of HADS were calculated by summing both subscales.<sup>35</sup>

Rudy et al.<sup>36</sup> tested the reliability of the Indonesian version of this instrument and found the interrater agreements for HADS-A and Hospital Anxiety and Depression Scale-Depression (HADS-D) were 0.706 and 0.681, respectively. The value of 0.61–0.80 shows that the Cohen Kappa agreement is reasonable.

Demographic characteristic data were obtained from a questionnaire such as age and education. The participant's medical history, including cancer types, stages, chemotherapy cycle, and treatment history, was obtained from the patient's medical records.

Specimens were collected by enumerators who had been trained before the intervention was conducted. The enumerators collected the salivary cortisol on the first day and 8 days after chemotherapy at 8 AM and brought the specimens to the laboratory using a special container filled with ice packs. The samples were analyzed by a laboratory technician blinded to the study participants in the laboratory of Hasanuddin University Hospital. The Salimetrics Cortisol Enzyme Immunoassay kit was utilized, with the normal salivary cortisol range for adult women during Ante-Meridiem (AM) time being 0.094–1.515.<sup>37</sup> Salivary cortisol has been used as a biomarker of both physical and psychological stress, including fatigue, as cortisol has been considered to be a reliable measurement of the HPA axis adaptation to stress.<sup>38</sup>

### 2.5. Statistical analysis

Descriptive and inferential statistical analyses were performed using the SPSS version 22.0 software package (SPSS Inc., Chicago, IL, USA). Fisher's exact test and independent *t*-test were used for the homogeneity test of the participants' characteristics between groups,<sup>39</sup> in which a *P*-value >0.05 was considered similar. Mann-Whitney *U* test was applied to determine the significance level between the groups, whereas Wilcoxon signed ranks test and One-way repeated measures Analysis of Variance (ANOVA) test were conducted to compare within groups.<sup>39</sup>  $\alpha \leq 0.05$  was considered statistically significant for these hypothesis testing.

### 2.6. Ethical principle

The study was approved by the Human Research Ethics Committee of the Medical Faculty of Hasanuddin University (permit number 638/H4.8.4.5.31/PP36-KOMETIK/2018). A research permit was also obtained from the hospital research and development departments where the research was conducted. The study followed the Helsinki Declaration. In addition, the

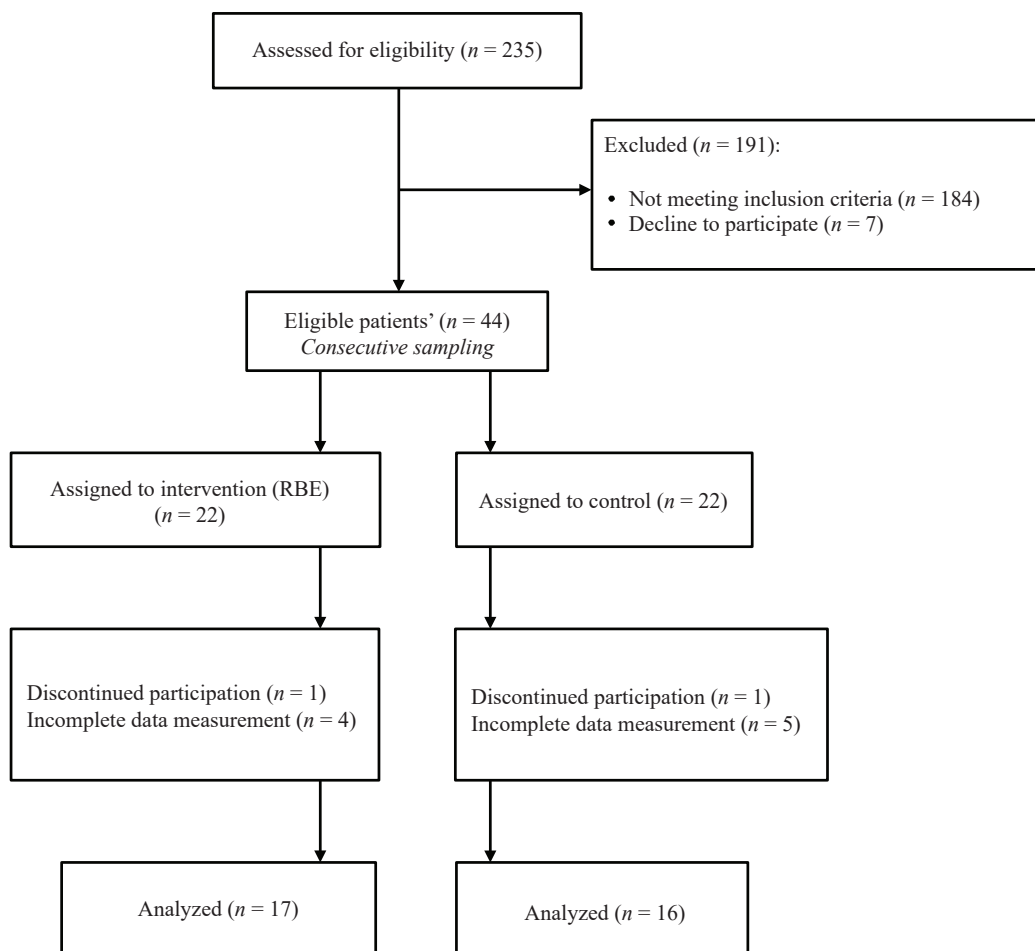
researchers consider informed consent, privacy, freedom, confidentiality, and the right to withdraw from this study of the participants.

### 3. Results

There were 235 potential gynecological cancer patients to approach. Of these, 44 consented and were enrolled in the study, 22 for the intervention group and 22 for the control group. Two participants discontinued participation ( $n = 1$  intervention and  $n = 1$  control) due to lost contact ( $n = 1$ ) and disease progression ( $n = 1$ ). In addition, 9 participants were incomplete in the data measurement, including fatigue score, HADS, and cortisol level. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is presented in Figure 1. Participant socio-demographic and medical characteristics are shown in Table 1.

Table 2 shows median cortisol level scores within and between groups before and after RBE intervention. There were statistical significances in cortisol levels within the groups, either intervention or control groups, respectively ( $P$ -value = 0.0003 and 0.001). In addition, although there was no statistical significance between the intervention and control groups (pretest  $P$ -value = 0.150; post-test  $P$ -value = 0.83), there were noticeable differences in the cortisol levels in terms of the Interquartile Ranges (IQRs) and maximum values, indicating the extreme increment of cortisol level among the participants in the control group and a beneficial effect of the RBE in the intervention group.

Table 3 shows the difference in the fatigue scores before and after RBE in the intervention and control groups. This study found a significant difference that was found in the intervention group ( $P$ -value = 0.012, ES = 0.443). However, there was no difference found



Note: CONSORT, Consolidated Standards of Reporting Trials; RBE, relaxation breathing exercise.

**Figure 1.** CONSORT study flow diagram.

| Variables                  | Intervention ( <i>n</i> = 17) |       | Control ( <i>n</i> = 16) |       | <i>P</i> -value |
|----------------------------|-------------------------------|-------|--------------------------|-------|-----------------|
|                            | <i>n</i>                      | %     | <i>n</i>                 | %     |                 |
| Age in years (mean, SD)    | 47.06                         | 8.45  | 45.31                    | 9.81  | 0.587           |
| Educational level          |                               |       |                          |       | 1.000           |
| High                       | 10                            | 30.30 | 10                       | 30.30 |                 |
| Low                        | 7                             | 21.20 | 6                        | 18.20 |                 |
| Cancer type                |                               |       |                          |       | 0.656           |
| Ovarian                    | 4                             | 12.10 | 2                        | 6.10  |                 |
| Cervical                   | 13                            | 39.40 | 14                       | 42.40 |                 |
| Cancer stage               |                               |       |                          |       | 0.296           |
| Early                      | 8                             | 24.20 | 11                       | 33.30 |                 |
| Advanced                   | 9                             | 27.30 | 5                        | 15.20 |                 |
| Chemo cycle                |                               |       |                          |       | 1.000           |
| ≤3                         | 12                            | 36.40 | 12                       | 36.40 |                 |
| >3                         | 5                             | 15.10 | 4                        | 12.10 |                 |
| Regimen                    |                               |       |                          |       | 1.000           |
| Platinum                   | 15                            | 45.50 | 15                       | 45.50 |                 |
| Non-platinum               | 2                             | 6.00  | 1                        | 3.00  |                 |
| PFS Score day 1 (mean, SD) | 4.29                          | 1.75  | 3.54                     | 1.68  | 0.220           |
| HADS day 1 (mean, SD)      | 1.37                          | 0.29  | 1.42                     | 0.38  | 0.622           |

Note: Statistically significant at  $\alpha \leq 0.05$  with independent *t*-test and Fisher Exact Test; HADS, Hospital Anxiety and Depression Scale; PFS, Piper Fatigue Scale; SD, Standard Deviation.

**Table 1.** Socio-demographic and medical characteristic bases (*n* = 33).

| Variable                     | Intervention ( <i>n</i> = 17) |           | Control ( <i>n</i> = 16) |            | <i>P</i> -value <sup>a</sup> |
|------------------------------|-------------------------------|-----------|--------------------------|------------|------------------------------|
|                              | Median (IQR1-IQR3)            | Min–Max   | Median (IQR1-IQR3)       | Min–Max    |                              |
| Cortisol level               |                               |           |                          |            |                              |
| Day 1                        | 0.38 (0.31–0.64)              | 0.25–0.88 | 0.51 (0.38–0.70)         | 0.20–2.35  | 0.15                         |
| Day 8                        | 2.97 (1.26–5.18)              | 0.39–6.91 | 2.30 (0.99–9.09)         | 0.43–23.38 | 0.83                         |
| <i>P</i> -value <sup>b</sup> | 0.0003*                       |           | 0.001*                   |            |                              |

Note: <sup>a</sup>Statistically significant at  $\alpha \leq 0.05$  with Mann–Whitney *U*; <sup>b</sup>Statistically significant at  $\alpha \leq 0.05$  with Wilcoxon signed ranks test.

**Table 2.** Comparison of median cortisol level within and between the 2 groups (*n* = 33).

| Variables/groups              | Time            |             |                  | <i>P</i> -value | Effect size (ES) |
|-------------------------------|-----------------|-------------|------------------|-----------------|------------------|
|                               | Day 1 (pretest) | Day 4       | Day 8 (posttest) |                 |                  |
| PFS Score (mean, SD)          |                 |             |                  |                 |                  |
| Intervention ( <i>n</i> = 17) | 4.29 ± 1.75     | 5.03 ± 1.99 | 3.52 ± 1.52      | 0.012*          | 0.443            |
| Control ( <i>n</i> = 16)      | 3.54 ± 1.68     | 4.65 ± 2.01 | 3.57 ± 1.90      | 0.152           | -                |
| HADS Score (mean, SD)         |                 |             |                  |                 |                  |
| Intervention ( <i>n</i> = 17) | 1.37 ± 0.29     | 1.34 ± 0.25 | 1.28 ± 0.36      | 0.767           | -                |
| Control ( <i>n</i> = 16)      | 1.42 ± 0.38     | 1.42 ± 0.35 | 1.46 ± 0.35      | 0.793           | -                |

Note: Statistically significant at  $\alpha \leq 0.05$  with one-way repeated measures ANOVA test; HADS, Hospital Anxiety and Depression Scale; PFS, Piper Fatigue Scale.

**Table 3.** Difference in PFS and HADS mean scores within the 2 groups (*n* = 33).

in the control group. In addition, both groups have no significant difference in anxiety scores.

## 4. Discussion

This study aimed to determine the effectiveness of RBE on the cortisol levels of gynecological cancer within 8 days post-chemotherapy. The results indicate that the cortisol levels on day 1 was normal in both the intervention and control groups and increased on day 8. However, the cortisol levels in the control groups increased significantly. Regarding the PFS scores, the average fatigue scores before RBE intervention were at moderate levels for both groups. Then, it increased slightly on day 4 and decreased significantly on day 8 for the intervention group. The fatigue score in the control group was only slightly reduced on day 8.

Similar to these findings, a study by Schmidt et al.<sup>40</sup> found that physical fatigue experienced by breast cancer patients undergoing chemotherapy was relevant to the increase in cortisol levels. This finding is similar to other studies that found cortisol levels increased after chemotherapy.<sup>20,41,42</sup> On the contrary, our results were quite different from a survey by Morrow et al.<sup>19</sup> that found a decline in cortisol levels immediately after the infusion of chemotherapy drugs.

In addition, this study did not find anxiety and depression in any group, meaning the increase in cortisol levels was not caused by anxiety. Following this finding, it can be argued that autoregulation disorders in HPA axis function are hypothesized to be due to cancer-related fatigue mechanisms.<sup>17,40</sup> The HPA axis plays a vital role in the neuroendocrine system that regulates processes in the body, including emotional reactions, the immune system, and energy storage. Physical stress reactions cause the hypothalamus to produce corticotropin-releasing factors, thereby triggering the pituitary gland to produce adrenocorticotrophic hormone (ACTH). ACTH then will stimulate the increase of cortisol secretion from the adrenal glands into the blood.<sup>43</sup>

Although the intervention group in this study experienced increased cortisol levels, the rate was not as high as in the control group. These results are consistent with Ma et al.,<sup>44</sup> who found that the effect of diaphragmatic breathing on attention in adult health found lower cortisol levels after intervention than in the control group. Another study by Jones et al.<sup>45</sup> found that guided imagery

was more effective than muscle relaxation in reducing cortisol levels for human immunodeficiency virus (HIV) patients. This study also found that the self-assessment of fatigue using the PFS showed that the intervention group had a significant difference from the control group, similar to the previous study.<sup>28</sup>

This study has a limitation which was the potential for bias due to the possibility that the participants from the intervention and control groups were able to meet during chemotherapy schedules. This condition caused difficulties to perform randomized samplings, which is a gold standard of interventional studies. Thus, the researchers applied the consecutive sampling method to minimize the risk.

Finally, since this research is a pilot study, a future study with a larger sample size is imperative to support the findings and the efficacy of RBE. Thus, RBE can be suggested as an evidence-based intervention to relieve fatigue, especially in women with gynecological cancer undergoing chemotherapy.

## 5. Conclusions

Cancer and treatment-related fatigue, such as chemotherapy, are associated with increased cortisol levels. Although there is an increase in the cortisol levels in both groups, RBE intervention helps alleviate fatigue and decrease cortisol level to the normal range. Overall, the result of this study shows the effectiveness of RBE on the cortisol levels and fatigue scores.

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## Ethical approval

The study was approved by the Human Research Ethics Committee of the Medical Faculty of Hasanuddin University (permit number 638/H4.8.4.5.31/PP36-KOMETIK/2018).

## Conflicts of interest

All contributing authors declare no conflicts of interest.

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