Effects of music therapy on anxiety of patients with breast cancer after radical mastectomy: a randomized clinical trial

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Abstract

Aim. This paper is a report of a clinical trial of the effects of music therapy on anxiety of female breast cancer patients following radical mastectomy.

Background. There is insufficient evidence on the effects of music therapy on state anxiety of breast cancer patients following radical mastectomy.

Methods. A Hall’s Core, Care, and Cure Model-based clinical trial was conducted in 120 female breast cancer patients from March to November 2009. A randomized controlled design was utilized. The patients were randomly allocated to the experimental group \((n = 60)\) received music therapy in addition to routine nursing care, and the control group \((n = 60)\) only received routine nursing care. A standardized questionnaire and the State Anxiety Inventory were applied. The primary endpoint was the state anxiety score measured at pretest (on the day before radical mastectomy) and at three post-tests (on the day before patients were discharged from hospital, the second and third time of admission to hospital for chemotherapy respectively).

Results. The pretest score revealed that the majority of the patients had a moderate level (77.5%) and 15% had severe level of state anxiety. The repeated-measure ANCOVA model analysis indicated that the mean state anxiety score was significantly lower in the experimental group than those in the control group at each of the three post-test measurements. The mean difference between the experimental and control group together with 95% confidence intervals were 
\(-4.57 (-6.33, -2.82), -8.91 (-10.75, -7.08)\) and 
\(-9.69 (-11.52, -7.85)\) at the 1st post-test, 2nd post-test and 3rd post-test respectively.

Conclusion. Music therapy is found to have positive effects on decreasing state anxiety score.

Keywords: breast cancer, Hall’s model, music therapy, radical mastectomy, state anxiety
Introduction

Breast cancer is the most common cancer in women worldwide (Liao et al. 2010). In China, the incidence rate of breast cancer has increased by 37.6% in the past two decades with an average annual growth rate of 2.3% (Li et al. 2004). The disease itself and treatment (including surgery and other adjuvant therapies) may cause severe psychological disorders for patients, with anxiety being among the most common disorders. As an adjuvant therapy, music therapy has been used successfully in reducing anxiety of various kinds of patients; however, very little information is available on the effects of music therapy on anxiety in female breast cancer patients following radical mastectomy.

Background

Literature review

Breast cancer is prevalent throughout the world and is developing a rapidly increasing trend. Global statistics show that the annual incidence of the disease is increasing occurring more rapidly in countries with a low incidence rate (Vahdaniinia et al. 2010). Data from developed countries indicate that one in every eight women is likely to suffer from breast cancer which is one of the leading causes of cancer death in women between the ages of 35 and 50 (Puig et al. 2006, Avci & Gozum 2009). The incidence of breast cancer is increasing rapidly in China (Mok et al. 2000). In 1972, the number of new cases of breast cancer was 532 (the standardized incidence rate was 18.90 per 100,000) which accounted for 9.7% of all tumours and ranked third. In 1999, the number of new cases was 1651 (the standardized incidence rate was 52.98 per 100,000) and ranked first. In 2007, the standardized incidence rate was already up to 81 per 100,000 (Wu & Dong 2009).

The primary treatment modality for breast cancer is surgery together with other adjuvant therapies such as chemotherapy, radiotherapy and hormonal therapy. However, these advanced cancer treatments were aggressive in nature and increased the exposure of patients to treatment side-effects. Female breast cancer patients especially those who have had radical mastectomy are confronted with indispensable stresses during their lifetime. This includes impaired body image as a result of losing a breast which may lead to experiencing and enduring negative impacts of subsequent unhealthy moods. To this end, cancer and treatment-related symptoms are major factors of stress for female breast cancer patients undergoing treatment for the disease. Of all the symptoms, anxiety is the most prevalent psychological symptom perceived by breast cancer patients with a prevalence rate between 21.1% and 29% in other countries (Payne & Endall 1998, Montazeri et al. 2001, Osborne et al. 2003, So et al. 2010) and between 50% and 86.4% in China (Xiao 2000, Chen et al. 2002, 2009, Wang et al. 2005, Gao et al. 2006, Wang & Yan 2007). The variation may be due to the utilization of different instruments and heterogeneous samples between each of the studies.

As anxiety is one of the known psychological disorders, it may cause other related adverse effects. Some patients may develop symptoms such as fatigue, sleeping difficulties, digestive problems, elevated heart rate, restlessness, muscle tension, sweating and trembling, changes in appetite and weight, and loss of energy. Other patients may show pathological worry, prolonged arousal, lowered immune functioning, feelings of helplessness and pessimism (Sharpley et al. 2009). In this situation, the treatment and recovery of female breast cancer patients may be hindered and in some cases patients may lose confidence in fighting against the disease and the hope of convalescence.

To tackle the problem of anxiety, music therapy has been used in cancer care which focuses on both physical and psychological needs arising from the disease process and from chemotherapy medications and radiation treatments (Daykin et al. 2006). In 2005, the American Music Therapy Association (AMTA) defines music therapy as ‘the clinical and evidence-based use of music experimental to accomplish individualized goals in a therapeutic relationship by a credentialed professional who has completed an approved music therapy programme’. It is used to improve, maintain, remediate or prevent one or more of the clinical issues in patients as specified in their needs for habilitation and rehabilitation (De Niet et al. 2009). In different nursing care settings, music therapy can be carried out not only by professional music therapists, but also unpaid carers, volunteers and performing musicians. Even when music therapists are not available, music has been championed as a nursing procedure (Aldridge 2003).

Studies about the effects of music therapy on cancer patients with various diagnoses have revealed numerous benefits. Listening to relaxing music (one of the commonest methods of implementing music therapy) has been effective in increasing comfort, relaxation, relieving self-reported pain, reducing anxiety, lowering treatment-related distress and decreasing nausea and vomiting. Other related studies also demonstrate that music therapy has been effective in evoking positive emotions and memories, expanding consciousness, improving sense of self, mood, quality of life and sleeping, enhancing psychological well-being and decreasing psychological symptoms (including anxiety, fear, fatigue, worry and diastolic blood pressure) during treatment (Evans...
The efficacy of music therapy in providing these benefits has also been confirmed by cancer patients with well-documented outcomes (Vickers & Cassileth 2001, Cui et al. 2005, Clark et al. 2006, Li et al. 2007, Jin et al. 2008, Lv et al. 2008, Wan et al. 2009). However, few nursing studies have been performed on the use of music therapy in female breast cancer patients following radical mastectomy.

The findings in the literature show that breast cancer incidence in China is high and increased rapidly in age-specific female populations. In addition, those who suffered from the disease were profoundly impacted by anxiety which is one of the common problems faced by the patients. Although previous studies have shown that music therapy has been helpful in cancer care to reduce anxiety, this randomized control will provide further evidence on the effects of music therapy on state anxiety of female breast cancer patients following radical mastectomy.

Conceptual framework

Lydia E. Hall’s ‘Core, Care, and Cure Model’ (Marriner-Tomey 1994) was used as the theoretical framework for the study. In this model, core, care and cure are representing the patient, intimate bodily care and aspect of nursing behaviour such as administration of medications and treatments. The definition of ‘ill’ as described by Hall, is a kind of behaviour which is dictated by feelings both conscious (known feelings) and unconscious (feelings-out-of-awareness). When patients are in the state of unconscious feelings (feelings-out-of-awareness), they have no choice as to their behaviour and the feelings making them act.

Lydia divides the entire treatment process into two stages: the acute and non-acute. When the patients past the acute stage while they receive intensive medical care and multiple diagnostic tests, they enter into the next stage of non-acute recovery phase which is conducive to learning and rehabilitation. Therefore, it is the ideal time for wholly professional nursing care.

Among the core (the patient), care (body) and cure (nursing behaviour), different diseases could cause the patient to suffer from different feelings (behaviours) which required the nurse to carry out appropriate procedures and nursing care in light of these differences. In this clinical trial, female breast cancer patients following radical mastectomy were in the second stage of illness. Anxiety caused by the disease itself and related treatments left patient with many adverse effects, which not only influenced the effects of treatment but also delayed the patient’s convalescence. By implementing music therapy following radical mastectomy to reduce anxiety, patients could control their own feelings, motives, goals and ultimately exert their self potentials to the greatest extent. Thus, the goal of rehabilitation can be achieved successfully.

The conceptual framework chart is depicted in Figure 1.

Hypotheses

The study had two hypotheses: (1) Patients in the experimental group will have a reduction score of state anxiety in comparison with patients in the control group after music therapy; (2) The treatment effect changes with follow-up time, i.e. there is an interaction effect between treatment group and follow-up time.

The study

Aim

The aim of the study was to examine the effects of music therapy on state anxiety in female breast cancer patients following radical mastectomy in a Chinese setting.

Design

A randomized, controlled clinical trial was conducted, with a between-group comparison of female breast cancer patients – the intervention group receiving music therapy in addition to routine nursing care and the control group receiving only routine nursing care. Because of the specificity of the study, no blinding was used.

Participants

This clinical trial was conducted in the oncology centre of a general hospital in Xian, China. Target population consisted of patients with breast cancer who were admitted to the hospital. A convenient sample of breast cancer patients was recruited in the study according to the inclusion criteria: female aged between 25 and 65 with a pathological diagnosis of breast cancer requiring radical mastectomy [including

![Figure 1 Conceptual framework chart.](image-url)
modified radical mastectomy and extensive radical mastectomy (ERM)]. Patients were excluded if they were allergic to sound or had the voice sensitivity of epilepsy, or did not prefer music listening.

Sample size and randomization
One hundred and twenty female breast cancer patients were recruited to the study. The randomization procedure was performed with 120 random numbers produced by a computer program (Ni & Dai 2002) and all patients were randomly allocated to two groups: an experimental group \((n = 60)\) and a control group \((n = 60)\). The sample size was calculated based on the parameters of state anxiety (measured by SAI) in other related studies on cancer patients among which the largest sample size was selected (Shi et al. 2007, Deng et al. 2008, Lu 2008, Wan et al. 2009). It was calculated that 100 patients (50 in each group of the study) were needed to detect the difference of five state anxiety score between the two groups with a power of 80% at the 5% level of statistical significance. The sample size was increased to 120 patients to allow for a 20% drop-out rate.

Data collection
Data were collected by the researchers from March to November 2009.

Instruments
Data were collected by using a standardized demographical data questionnaire and the State Anxiety Inventory (SAI). The demographical data questionnaire includes a total of 15 items, such as age, occupation, education level, residence, monthly income, marital status and age of first suffering from breast cancer.

The Chinese version of the SAI was used to evaluate anxiety in female breast cancer patients in the study. The SAI is one of the most widely used self-reporting measures of anxiety and consists of a 20-item scale designed to assess anxiety as an emotional state using a four-point Likert format \((1 = \text{not at all, } 4 = \text{very much so})\). It is a well-established scale used extensively in research and clinical settings and in Chinese populations (Shek 1993, Taylor-Piliae & Chair 2002). Possible scores range from 20 to 80, with higher scores indicating greater anxiety (low anxiety = 20–39, moderate anxiety = 40–59, high anxiety = 60–80) (Barnason et al. 1995). The validity coefficient is 0.88 (Shek 1993), the test–retest reliability coefficient is 0.72 (Wong et al. 2001). The Chinese version of SAI has also been applied to many studies, the test–retest coefficient of SAI is 0.88 (Lin et al. 2003). The Cronbach’s Alpha reliability coefficient of SAI is 0.90 in this clinical trial.

Both of the two groups completed the demographical data questionnaire and the pretest of SAI before radical mastectomy. The three post-test SAI were conducted on the day before patients were discharged from hospital (1st post-test) and the second (2nd post-test) and third (3rd post-test) time admitted to hospital for chemotherapy. As a result of different modes of chemotherapy, the intervals between tests were 14, 21 and 28 days [average 18.9 (7.1) days] respectively. All patients were asked the items on the questionnaire and the answers were documented by the data collectors who were trained on how to complete the questionnaires and had no information about the group allocation. The primary endpoint was the scores of state anxiety at the follow-up visits. The flow chart of the clinical trial procedure is depicted in Figure 2.

Interventions

The experimental group
Patients in the experimental group were given an introduction of the music name and type of music stored in the music media library which had been copied onto the MP3 players. Music therapy was delivered by the researchers. Patients selected their preferred music, controlled the music volume and listened through a headphone connected to the MP3 player. The total experimental time involving hospital stay following radical mastectomy was 13.6 (2.0) days and the two chemotherapy periods were 18.9 (7.1) days. Music therapy was twice a day (30 minutes per session), once in the early morning (6 a.m.–8 a.m.) and once in the evening (9 p.m.–11 p.m.). Patients who did not adhere to music listening during postoperative hospital stay gained the assistance and encouragement from the researchers, when discharged from hospital, they would be followed-up by the researchers through telephone interviews so that they could complete the experiment as the study required.

The control group
Patients in the control group took part in the pre- and the three post-tests. They were not offered any information of music therapy during the study period in case of bias and only received routine nursing care which included the perioperative nursing care of breast cancer and chemotherapy nursing care.

Music media library
The music media library was established by the researchers and experts based on the effects of different types and modes
of music in treatments (Cai 2000, Fang & Gao 2000) and according to the characteristics of Pentameter Therapy Principle and different tonality (Liu 2003). Two hundred and two music were selected in the study which included Chinese classical folk music, famous world music, the music recommended by American Association of Music Therapy (AAMT) and Chinese relaxation music. All of the music files were copied into the MP3 players which would be given to the patients of the experimental group. Patients chose their preferred music and listened to it repeatedly.

**Ethical consideration**

The study was reviewed and approved by the appropriate Human Research Ethics Committee. All participants received an explanation of the study before participating and gave written informed consent before voluntary participation.

**Data analysis**

All data were entered into the database established using EPI DATA (version 3.1; the EpiData Association, Odense, Denmark). Frequencies and percentages were used to summarize categorical variables, and mean and standard deviation to summarize continuous variables. The two sample t-test and chi-square test were applied to detect the differences of the baseline data between the two groups. Repeated measurement ANCOVA model was employed for the data analysis with treatment, follow-up time, interaction between treatment and follow-up time as fixed effects, baseline measurement of state anxiety score as covariate, and the patient as random effect. The group difference together with its 95% confidence interval at each follow-up time point was derived from the ANCOVA model. A value of \( P < 0.05 \) was considered as statistically significant. Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

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**Figure 2** Flow chart of the study.
Results

A total of 120 participants were recruited and underwent the pretest with 60 patients in each group. None of the participants in the experimental and control groups was lost at the first post-test. Fifty-four participants remained in the experimental group (six participants lost) and 51 participants remained in the control group (nine participants lost) at the second and third post-tests, respectively. A total of 15 patients (12.5%) were lost to follow-up.

Demographic characteristics

In Table 1, the characteristics of the female breast cancer patients in the two groups are shown. There were no statistically significant between-group differences in relation to demographical features.

Of the 120 patients, the mean age was 44.88 (9.37) years and 45.13 (9.48) years for the experimental and control groups respectively. The majority of the patients were workers [30.0% (experimental group) and 28.3% (control group)], lived in the city [71.7% (experimental group) and 76.7% (control group)] and had a high school education [28.3% (experimental group) and 45.0% (control group)]. In terms of monthly income, 53.3% (experimental group) and 58.3% (control group) of the patients had a moderate level of monthly income (1000–3000 RMB/month). The main terms of payment for hospitalization and treatment were classified as other types (85.0%) for both groups. This included Rural Cooperative Medical Care (22.6%), Residents Cooperative Medical Care and Medicare (77.4%).

The majority of the patients were married [91.7% (experimental group) and 85.0% (control group)] with 56.4% (experimental group) and 40.4% (control group) having a better spousal relationship. The majority of the patients had one child [58.3% (experimental group) and 60.0% (control group)] with best ‘parent-child’ relationship accounting for 81.4% (experimental group) and 79.3% (control group) of the patients. Most of the patients received Modified Radical Mastectomy [95.0% (experimental group) and 91.7% (control group)] with 93.3% (experimental group) and 83.3% (control group) receiving chemotherapy immediately after surgery. Sixty per cent (experimental group) and 56.7% (control group) of the patients suffered from breast cancer for the first time with a mean age of approximately 42 years for both groups.

Pretest and comparison of state anxiety

The pretest of the state anxiety score for all patients was found to be 51.99 (8.60) with 93 (77.5%) moderate level cases and 18 (15.0%) severe level cases. The state anxiety score of the experimental group and control group were 51.97 (8.50) and 52.02 (8.76) respectively. The two sample t-test showed that there was no statistically significant difference between the two groups in terms of state anxiety scores (t = −0.03, P = 0.98 > 0.05). The two groups were comparable for these baseline measures.

Post-tests of state anxiety

The summary statistics of state anxiety scores at three post-tests and the inferential statistics generated by the repeated-measures ANCOVA model are shown in Table 2. The model indicates that the mean state anxiety scores of the experimental group were all statistically significantly lower than that of the control group at each of the three post-tests. The mean difference between experimental and control group together with 95% confidence interval was −4.57 (−6.33, −2.82), −8.91 (−10.75, −7.08) and −9.69 (−11.52, −7.85) at the 1st post-test, 2nd post-test and 3rd post-test respectively. The P value for interaction test was <0.001, suggesting that the treatment effect increases with the follow-up time. The above results support the two hypotheses that music therapy can reduce the state anxiety score and the treatment effect changes with the follow-up time.

Discussion

State anxiety of female breast cancer patients

The pretest of state anxiety score in this study showed that the majority of the patients had moderate and severe level anxiety. This was consistent with the results of other related studies on anxiety (Payne & Endall 1998, Montazeri et al. 2001, Osborne et al. 2003, Wang & Yan 2007, Chen et al. 2009, So et al. 2010), which indicate that anxiety is a common psychological disorder in female breast cancer patients. However, the results were different from the study conducted by Wan et al. (2009) who used the same instrument to assess state anxiety of cancer patients. In their study, state anxiety scores before any study procedures in the experimental group was 57.9 (9.5), with the scores of the control group being 58.6 (8.6). In comparison with the published data, state anxiety scores of the patients in this clinical trial were higher. This is most probably due to the fact that patients with different types of cancer, sample size and time and method of data collection were used. Chen et al. (2009) used Self-rating Anxiety Scale (SAS) to test the anxiety levels of breast cancer patients in the study and the results were 39.57% (mild), 13.91% (moderate) and 2.61% (severe). In comparison with the results, anxiety
Table 1 Demographic characteristics of the two group patients (n = 120)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Statistics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), [mean (SD)]</td>
<td>44.88 (9.37)</td>
<td>45.13 (9.48)</td>
<td>t = -0.15</td>
<td>0.89</td>
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<tr>
<td>Occupation</td>
<td></td>
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<td></td>
<td></td>
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<td>14</td>
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<td>17</td>
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<td></td>
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<tr>
<td>Teachers</td>
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<td>9</td>
<td></td>
<td></td>
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<tr>
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<tr>
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<td>&gt; 3000</td>
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<td>5</td>
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<tr>
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<tr>
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<td>14</td>
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<td>21</td>
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<tr>
<td>28</td>
<td>6</td>
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<tr>
<td>First occurrence of breast cancer</td>
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<td></td>
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<td>Yes</td>
<td>36</td>
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<td>Age at first occurrence of breast cancer [mean (SD)]</td>
<td>42.23 (8.78)</td>
<td>42.45 (8.28)</td>
<td>t = -0.14</td>
<td>0.89</td>
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</table>
levels of the patients in this clinical trial were higher in the moderate and severe level. The difference is probably due to the different instrument, sample size and survey methods used. From the comparisons of scores and levels of anxiety in this clinical trial with other related studies, it is clear to see that anxiety is the common psychological disorder in female breast cancer patients.

Effects of music therapy on state anxiety

The researchers anticipated a decrease in the experimental group for state anxiety. There was a statistically significant between-group difference in scores of state anxiety after music therapy. In all cases, patients receiving music therapy reported lower scores of state anxiety than those in the control group at each of the three post-tests. Such results were consistent with other related studies (Palakanis et al. 1994, Chlan 1998, Wong et al. 2001, Liu et al. 2006, Wan et al. 2009), which show that anxiety scores of the experimental group were significantly lower than that of the control group after music therapy demonstrating that music therapy is able to improve anxiety.

Wan et al. (2009) used SAI to test state anxiety score of the experimental group after music therapy for 1 month which was found to be 33.8 (6.5). In this clinical trial, state anxiety score of the experimental group at the 3rd post-test was 30.87 (2.71) after completion of the study including the hospital stay following radical mastectomy [13.6 (2.0) days] and the two chemotherapy periods [each was 18.9 (7.1) days]. This indicated that music therapy can improve state anxiety distinctly and on the other hand, state anxiety scores in this clinical trial were lower than that in the study of Wan et al. (2009). This illustrates that duration of music therapy has certain impacts on the effects of improving state anxiety. With increased time, the state anxiety of patients receiving music therapy is improved significantly.

Chlan (2009) views that anxiety is a state marked by apprehension, agitation, increased motor tension, autonomic arousal and fearful withdrawal. Music can decrease anxiety by occupying attention channels in the brain with meaningful, distractive, soothing auditory stimuli rather than stressful environmental stimuli. In this clinical trial, state anxiety of the experimental group was improved distinctly after music therapy for the postoperative hospital stay and the following two chemotherapy periods. This suggests that it is beneficial to give music therapy as an adjuvant therapy for female breast cancer patients undergoing surgery and chemotherapy so that the issue of anxiety can be addressed.

Use of Hall’s Core, Care, and Cure Model as a guide in music therapy

In the study, Hall’s Core, Care and Cure Model was used as the conceptual framework. Female breast cancer patients in the experimental group were the core of nursing; the corresponding treatments were radical mastectomy with chemotherapy. After the operation, the patients were in the postoperative stage (non-acute recovery phase) and needed more care for their nursing problems, both physically and psychologically. In this clinical trial, anxiety was regarded as the focus of nursing problems and music therapy was used as a nursing experimental procedure. According to the model, the second stage was the appropriate time for patients’ rehabilitation and learning. Therefore, music therapy (music listening) was implemented for the patients in the experimental group and their anxiety was improved significantly.
In clinical nursing practice, music therapy could be used as an alternative nursing measure in caring for the patients in their non-acute recovery stage of illness. For female breast cancer patients who may have different levels of anxiety during the process of diagnosis, treatment and rehabilitation, music therapy has been reported as an effective adjuvant therapy for the problem of anxiety in both clinical and non-clinical environments.

What is already known about this topic
- Breast cancer is one of the leading causes of death for women around the world. The disease itself and the subsequent treatments have a profound physical and psychological impact on patients.
- Reports have shown that patients with breast cancer have a high incidence rate of anxiety during the process of diagnosis, treatment and rehabilitation.
- Music therapy has been reported as an effective adjuvant therapy for the problem of anxiety in both clinical and non-clinical environments.

What this paper adds
- Music therapy was found to have positive effects in reducing state anxiety in female breast cancer patients following radical mastectomy.
- Music therapy has the potential to be used as an alternative form of nursing care in clinical practice.
- The Core, Care and Cure model was noted to be beneficial in implementing music therapy appropriately.

Implications for practice and/or policy
- Music therapy can be used as an alternative way of improving anxiety in female breast cancer patients following radical mastectomy. It will benefit a large number of patients in China if it is generalized in clinical practice and increase their life satisfaction and well-being.
- Music therapy under the instructions of the Core, Care and Cure model could be used as part of the nursing care practice.

Study limitation
In this clinical trial, the data were self-reported and could have been influenced by numerous factors such as defensiveness, misrepresentation, personal emotion and other attitudes. Accordingly, it should be considered in the light of certain limitations. First and foremost, we only collected the quantitative data from the patients; subjective experiences for effects of music therapy need further study. Secondly, no physiological variable was used; therefore, effects of music therapy on physical aspects need further examination. Thirdly, the control group only received routine nursing care; different experimental time and methods of music therapy were noted to be regarded as the control group to further study the effectiveness. Finally, the patients with ERM in the study only accounted for a small part. Thus, effects of music therapy on those patients’ anxiety need further examination.

Conclusion
Music therapy may be of benefit for improving anxiety in female breast cancer patients following radical mastectomy under the guidance of Hall’s Core, Care and Cure model. There is potential in applying music therapy as an alternative nursing procedure in clinical nursing practice for the caring of female breast cancer patients. Further studies on effects of different time and methods of implementing music therapy on anxiety are required.

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Conflict of interest
The authors declare that they have no competing interests.

Author contributions
XL, KZ and HY were responsible for the study conception and design. XL performed the data collection. DW and YZ
performed the data analysis. XL, KZ, HY, DW and YZ were responsible for the drafting of the manuscript. HY, DW and YZ made critical revisions to the paper for important intellectual content. DW provided statistical expertise. XL obtained funding. XL and HY provided administrative, technical or material support. HY supervised the study.

References

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