Nausea at the End of Adjuvant Cancer Treatment in Relation to Exercise During Treatment in Patients With Breast Cancer

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Purpose/Objectives: To evaluate the relationship between nausea and exercise during and after adjuvant cancer treatment (chemotherapy and radiation therapy or chemotherapy alone).

Design: Secondary data analysis from a longitudinal, single-blinded, three-arm, randomized controlled trial. The trial failed to show a significant effect of an exercise intervention on nausea control (by intent to treat analysis); therefore, patients were analyzed together to evaluate the relationship between nausea and actual exercise behavior.

Setting: Outpatient cancer treatment clinics.

Sample: 112 female patients with breast cancer who were receiving adjuvant cancer treatment.

Methods: Actual exercise behavior–based analysis was conducted with nausea intensity and the participant's exercise status measured three times during and after adjuvant cancer treatment. Participants were considered exercisers if actual exercise behaviors corresponded to the recommendation of the American College of Sports Medicine: aerobic exercise at a minimum of moderate intensity, 20 minutes per session, and three times per week. Mann-Whitney U tests evaluated the difference in nausea intensity depending on actual exercise status.

Main Research Variables: Nausea intensity and exercise status.

Findings: Exercisers experienced significantly less intense nausea than nonexercisers at the completion of adjuvant cancer treatment.

Conclusions: A moderate level of aerobic exercise is related to less intense nausea at the completion of adjuvant cancer treatment.

Implications for Nursing: A moderate level of aerobic exercise is recommended during adjuvant cancer treatment because of the possibility of reducing nausea intensity as well as alleviating other symptoms from adjuvant cancer treatment.

Key Points . . .

- ➤ Current nausea control with antiemetics continues to be inadequate and requires additional intervention.
- ➤ Studies of exercise for nausea control are limited and provide inconsistent results.
- ➤ A moderate level of aerobic exercise is related to less intense nausea at the completion of adjuvant cancer treatment.

Exercise has been suggested as a possible intervention for cancer-related symptoms (American Cancer Society, 2007). In considering exercise as an intervention for patients with cancer, guidelines provide specifics for the exercise regime, such as the mode, intensity, duration, and frequency. In 1998, the American College of Sports Medicine (ACSM) recommended aerobic exercise of moderate intensity for 20–60 minutes per session, three to five times per week. Exercise has shown positive effects in controlling well-known and prevalent symptoms, such as fatigue, in patients with cancer (Mitchell, Beck, Hood, Moore, & Tanner, 2007; Mock et al., 2001, 2005; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a, 2007b). However, studies of exercise for nausea control are limited and provide inconsistent results.

Winningham and MacVicar (1988) first reported researching the positive effects of exercise on nausea control. Repeated verbal reports from participants about the effects of exercise in controlling their nausea during a pilot trial stimulated the researchers to investigate further. Their randomized clinical trial included 42 women with breast cancer receiving chemotherapy. Participants were randomized to an exercise group, a placebo group, or a control group. Aerobic exercise on a cycle ergometer at a rate prescribed to reach 60%–85% of maximal heart rate was performed by patients in the exercise group three times a week for 10 weeks. The placebo group performed stretching and flexibility exercises but not an aerobic exercise. The control group did not perform any exercise. The 16 participants in the exercise group demonstrated marked improvement with less nausea compared to the placebo and control groups ($p = 0.03$). No antiemetics were administered, although all participants were on moderately emetogenic chemotherapy regimens that included cyclophosphamide, methotrexate, and 5-fluorouracil. Suboptimal control of nausea during this evaluation of exercise effect could raise the question of whether the achieved exercise effect on nausea control could be reproduced when antiemetics were used according to current antiemetic guidelines.

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Mock et al. (1994) conducted a randomized clinical trial with 14 women with breast cancer. The exercise intervention was brisk incremental walking of 10–45 minutes followed by five-minute cool-down period, four to five times a week for four to six months. The exercise intervention was part of a comprehensive rehabilitation program that consisted of a structured exercise program that included walking plus support group meetings for four to six cycles of chemotherapy. A significant difference in the intensity level of the nausea was found at mid-treatment testing (day 15 of every chemotherapy cycle) ($p = 0.02$). No statistically significant difference was found between the exercise group and usual care group when the mean nausea intensity level was compared across all periods of treatment, although the usual care group did report more nausea. Whether the exercise had any time-specific effects in controlling the nausea is questionable. Separating the exercise effect from the comprehensive rehabilitation program is difficult because the intervention was combined with support group meetings. The small sample size of only nine exercisers also is an issue. In addition, antiemetic use was not controlled, although participants received moderately to highly emetogenic chemotherapy.

Unlike the two previous studies on exercise, Schwartz (2000) did not find an exercise effect on nausea. Eight weeks of home-based progressive aerobic exercise was performed during the first four cycles of chemotherapy. Participants all were receiving moderate to highly emetogenic chemotherapy (doxorubicin and cyclophosphamide or cyclophosphamide, methotrexate, and 5-fluorouracil) as a treatment for breast cancer and were instructed to perform exercise four days a week, with a progressive increase in the duration and intensity of their exercise. Antiemetic use was not controlled. The women who adhered to the program reported walking as the most common activity and exercised an average of 33 minutes per exercise session. Whether the intensity of the exercise was high enough to produce an exercise effect in controlling nausea was not reported in the study.

The most recent exercise study by Andersen et al. (2006) combined six weeks of physical activity with relaxation, massage, and body awareness training. The researchers reported that nausea intensity levels did not change after the intervention among 54 patients with diverse cancer diagnoses. The physical activity of this intervention consisted of 90 minutes of warm-up, heavy resistance training, and fitness activities. The fitness component consisted of 10-minute interval exertions in the form of cycling on stationary bicycles, with an intensity of 80%–100% of the participant's maximum heart rate, three times per week. Interestingly, nausea scores were slightly increased after the exercise intervention, although the change did not reach statistical significance. Whether 10 minutes of cycling as aerobic exercise was long enough to influence the level of nausea or if the high intensity of the aerobic exercise or heavy resistance training had any adverse effect on nausea control is difficult to determine. In addition, because the intervention was packaged, the effect of exercise cannot easily be evaluated. All patients in the trial received antiemetic drugs, including 5-hydroxytryptamine 3 receptor antagoinst, metoclopramide, or prednisone. The exercise could have not been enough to provide additional nausea and vomiting control with these antiemetics.

To summarize, four studies have investigated the effects of exercise on the control of nausea. Two studies supporting the effects of exercise on nausea were limited by small sample sizes and uncontrolled use of antiemetics. Studies that combined exercise with other interventions made the evaluation of exercise effects alone difficult. The findings of the Schwartz (2000) and Andersen et al. (2006) studies contradict reported positive effects of exercise on nausea control; however, the intensity of exercise performed by the participants in the Schartz study likely did not reach the established moderate exercise level to make a difference in the incidence of nausea. The Anderson et al. study had a short duration of a higher-than-moderate level of exercise in combination with heavy resistance training. Further research is required before recommending a moderate level of aerobic exercise to control nausea.

The purpose of the present study was to evaluate the relationship between nausea intensity and a moderate level of aerobic exercise recommended by ACSM (1998) during and after adjuvant cancer treatment (chemotherapy and radiation therapy or chemotherapy alone). The theoretical framework for the study is the University of California, San Fransisco Symptom Management Model (Dodd et al., 2001). The study is focused on nausea as a symptom experience, exercise for its management, and nausea intensity as an outcome.

Methods

Design

The present study is a secondary analysis of data collected as part of a longitudinal, randomized controlled trial that tested the effectiveness of a systematic exercise intervention for cancer-related fatigue and associated symptoms. In the trial, participants were randomized into three groups that were comprised of a group receiving exercise prescription throughout the study period, a group starting to receive exercise prescription after having completed their cancer treatment, and a group receiving usual care throughout the study period. Researchers were blinded as to the participant's group assignment when collecting data. The trial failed to show significant effect of an exercise intervention for nausea intensity control (by intent to treat analysis). Therefore, patients were analyzed together to evaluate the relationship between nausea and actual exercise behavior.

Sample and Setting

Participants were recruited from six outpatient cancer treatment clinics in the counties of the San Francisco Bay Area. Inclusion criteria were women age 18 or older who had a confirmed diagnosis of breast cancer; were beginning their first cycle of chemotherapy; were able to read, write, and understand English; had a Karnofsky Performance Scale (KPS) score of greater than 60; and were mentally able to understand and complete a written informed consent. Participants were excluded from the study if they were receiving concurrent radiation therapy or bone marrow transplantation or had uncontrolled hypertension or diabetes mellitus, a pain intensity rating of 3 or higher on a 0–10 numeric scale, a lytic bone lesion or orthopedic limitations, a history of major depression or sleep disorders, chemotherapy within the past year, a diagnosis of AIDS-related malignancies or leukemia, or absolute contraindications to exercise testing as established by ACSM (1995).

Instruments

Nausea intensity, exercise status, and KPS score were measured through participant self-report. Nausea intensity was measured using a 0–10 numeric scale (patients were asked how much they were experiencing nausea at the time of data collection). The nausea intensity scale was derived from the symptom checklist of 25 commonly experienced symptoms. The symptom checklist has been used to collect data about concurrent symptoms. The 0–10 numeric scale has been tested in parallel with the use of a well-known nausea instrument, the Index of Nausea, Vomiting, and Retching (INVR) (Rhodes & McDaniel, 1999), in studies of chemotherapy-induced nausea and vomiting and has yielded high correlations ($r = 0.75–0.95$) with the INVR nausea experience score (Dibble, Chapman, Mack, & Shih, 2000; Dibble et al., 2007; Lee, Dibble, Pickett, & Luce, 2005). Exercise status was measured as the type of exercise (mode), intensity of exercise (intensity), time per session (duration), and number of days per week (frequency). Functional status was measured by KPS scores (0–100).

Procedures

Actual exercise behavior-based analysis was conducted with nausea intensity and the participant's exercise status measured three times during and after adjuvant cancer treatment. The three data-collecting time points were between completion of the first cycle and the start of the second cycle of chemotherapy (T1), at the end of adjuvant cancer treatment (T2), and at the end of the study (T3, approximately one year after the start of chemotherapy). Participants were regarded as performing exercise (exerciser) if actual exercise behaviors measured at each time point by the mode, intensity, duration, and frequency of exercise corresponded to the recommendation of ACSM (1998): engaging in aerobic exercise at a minimum of moderate intensity for 20 minutes per session three times per week. The intensity of the exercise was regarded as more than moderate if the exercise rating on the Borg Scale (Borg, 1998) was equal to or higher than 12. The Borg Scale measures perceived exertion upon physical activity. Exercise is considered a physical activity of moderate intensity when the Borg Scale rating is between 12–14, which is interpreted as somewhat hard.

Data Analysis

Data were analyzed with descriptive statistics, Mann-Whitney U test, t test, and chi-square test at alpha of 0.05 using SPSS® version 14.0. The Mann-Whitney U test was used because the scores for nausea intensity were relatively low and skewed in their distribution.

Results

A total of 112 women with breast cancer participated in the study. The mean age of participants was 50 years (SD = 9.31) and most were Caucasian (73%). Participants' education level was high ($\overline{X}$ = 16 years, SD = 2.76). Forty-four percent of participants worked either full-time (33%) or part-time (11%).

Table 1. Number of Exercisers and Nonexercisers

Time	Exercisers	Nonexercisers	Missing
1	52	52	8
2	45	52	15
3	67	26	19

N = 112

Table 2. Nausea Intensity of Exercisers and Nonexercisers

	Exerciser		Nonexerciser		All (N = 112)	
Time	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD
1	1.55	2.49	1.69	2.08	1.60	2.26
2	0.47	1.31	1.40	2.31	0.96	1.94
3	0.38	0.91	0.32	0.69	0.35	0.83

Most were married or partnered (68%). The stage of breast cancer ranged from I–III. Ninety-eight participants (88%) received doxorubicin and cyclophosphamide as a chemotherapy regimen, and 59 (53%) received radiation therapy immediately after finishing chemotherapy. Antiemetics were used with chemotherapy; however, only 30 participants provided information about their use of antiemetics. Ondansetron, granisetrion, dexamethasone, metochlopromide, and lorazepam were used but not in a standardized fashion. No participant received antiemetics at the time of the three assessments.

The number of exercisers according to the ACSM recommendation at T1 was 52 (see Table 1). The number decreased to 45 at T2, and increased to 67 at T3. The average length of time between T1 and T2 was 169.72 days (SD = 65.09) and the time between T2 and T3 was 165.64 days (SD = 61.72). Some participants dropped out over the course of the study period. Significantly more participants who dropped at T2 ($p = 0.01$) or T3 ($p = 0.05$) did not receive radiation therapy after chemotherapy. However, exercisers and nonexercisers at T2 or T3 were not different in whether they received radiation therapy after chemotherapy or not. Among exercisers, up to 88% of the women chose walking as their exercise, and 33% chose bicycling either by cycle ergometer or bicycle; some participants chose more than one form of exercise. Exercisers and nonexercisers did not differ in age, stage of breast cancer, KPS, whether they received doxorubicin and cyclophosphamide as a chemotherapy regimen, or whether they received radiation therapy immediately after their chemotherapy.

Sixty-six percent of women experienced nausea during the study period. Nausea intensity generally was low and decreased over time. Mean nausea intensity was lower in exercisers at T1 and T2, whereas nonexercisers had a little less nausea at T3 (see Table 2). Nausea intensity for exercisers at T2 was significantly lower than for nonexercisers ($p = 0.03$) as shown in Table 3. Baseline (T1) and T3 nausea intensity scores did not differ significantly between exercisers and nonexercisers. The intensity of nausea in exercisers had declined at T2 so as to produce significantly lower nausea intensity scores compared to nonexercisers. Exercisers had almost no nausea at T2, whereas nonexercisers had significantly higher nausea intensity and decreased levels similar to those of exercisers at T3 (see Figure 1). T2 had two groups of exercisers. Some participants were regular exercisers at the time of recruitment and continued to exercise during adjuvant cancer treatment (n = 27). Other participants were not exercisers when they enrolled in study but became exercisers during cancer treatment (n = 12). At T2, the regular exercisers who continued their exercise during adjuvant cancer treatment experienced less intense nausea ($\overline{X}$ = 0.37) than did the participants who became exercisers during cancer treatment ($\overline{X}$

Table 3. Mann-Whitney U Comparison of Nausea Intensity of Exercisers and Nonexercisers

Time	Z Score	p
1	–1.06	0.29
2	–2.18	0.03*
3	–0.09	0.93

* $p < 0.05$

= 0.83). However, the difference was not statistically significant. This suggests no accumulative effect of exercise in relation to nausea intensity.

Discussion

Reported levels of nausea intensity in this study generally were low. Although a significant difference was found at T2, the level of nausea intensity in nonexercisers did not reach the level generally considered to be significant nausea (i.e., ≥ 25 on a 0–100 scale). However, the nausea level experienced by exercisers at T2 generally is considered to be no nausea (i.e., < 5 on a 0–100 scale) (Herrstedt et al., 2005; Hesketh et al., 2003; Poli-Bigelli et al., 2003; Schmoll et al., 2006; Warr, Grunberg, et al., 2005; Warr, Hesketh, et al., 2005).

The exercise intervention of Winningham and MacVicar (1988), which involved aerobic exercise on a cycle ergometer of moderate intensity three times a week for 10 weeks, was similar to the exercise performed by the defined exerciser in the present study, and both studies found a significant relationship between nausea and exercise. However, the Winningham and MacVicar study did not use antiemetics, even with moderately emetogenic chemotherapies. The participants in the present study did not take any antiemetics at each time point (T1, T2, and T3), however, nonstandardized antiemetic regimens were used during chemotherapy based on reports from 30 participants. Nonuse or nonstandardized use of antiemetics during the chemotherapy intervention raises the question of whether the suggested exercise effect could be reproduced after use of standard antiemetics.

In a study by Mock et al. (1994), the participants were categorized as an exerciser if their duration of exercise was more than 20 minutes. Mock et al. (1994) found an exercise effect at the middle of treatment (15 days of each chemotherapy cycle) but not in overall nausea scores. The nausea difference found in the present study occurred after the completion of adjuvant cancer treatment (T2) but not at other time points. Although both studies suggest time-specific effects of exercise in nausea control, the time points of the present study do not correspond with the points of Mock et al. (1994). Further research is required to reach better conclusions about any time-specific effects of exercise on nausea control because the present study did not evaluate nausea while patients were receiving adjuvant cancer treatment.

The two other exercise studies (Andersen et al., 2006; Schwartz, 2000) that investigated aerobic exercise as an intervention for nausea control were different in the content of their exercise programs (i.e., suboptimal intensity or duration) and did not demonstrate a significant exercise effect on nausea control. Whether different results were derived within a different exercise context needs further investigation.

Participants in other exercise studies performed exercise while undergoing chemotherapy, whereas participants in the present study also exercised after the treatment (i.e., during the follow-up). This enables further evaluation about the need of exercise during additional periods of time. The present study and other exercise studies that describe positive effects on nausea control support exercising during adjuvant cancer treatment.

The mechanisms by which exercise improves the control of nausea have not been established. Proposed mechanisms of nausea development, such as involvement of the central nervous system (Leslie & Reynolds, 1993; Miller, Rowley, Roberts, & Kucharczyk, 1996) by an increase in vasopressin secretion and activation in autonomic nervous system (Stern, 2002) need further investigation. Evidence that exercise may decrease levels of vasopressin (Braith, Welsch, Feigenbaum, Kluess, & Pepine, 1999) and symphathoexcitation (Gademan et al., 2007) at rest in patients with chronic heart failure suggests a possible link between nausea and exercise through vasopressin and the autonomic nervous system regulation in the central nervous system.

The study by Andersen et al. (2006) found a slight increase in nausea scores after the exercise intervention, although the increase was not statistically significant. High intensity of exercise (70%–80% of maximal heart rate) is related to higher ratings of nausea (Kondo et al., 2001). The exercise intervention in the study by Andersen et al. might have caused more nausea because 10 minutes on stationary bicycles with an intensity of 80%–100% of maximal heart rate is quite intense exercise. However, the intervention in the Andersen et al. study included several exercise interventions other than 10 minutes of cycling, which increased the difficulty in interpreting the exercise effect.

The number of exercisers increased from T2 to T3. As the parent study was designed to increase the number of participants receiving the exercise prescription between T2 and T3, this increase may be a result of the study design. However, this also may be caused by the women who had recovered after their adjuvant cancer treatment completion being more inclined to exercise regardless of the exercise intervention in the parent study.

The most preferred exercise in this study was walking, which also was true in the studies by Schwartz (2000) and Rogers, Courneya, Shah, Dunnington, and Hopkins-Price (2007). Walking can be easily accepted as an exercise intervention for patients during adjuvant cancer treatment; however, the context of exercise (i.e., mode, intensity, duration, and frequency) is more of a concern. The use of the 1998 ACSM guideline for exercise for patients with cancer was associated

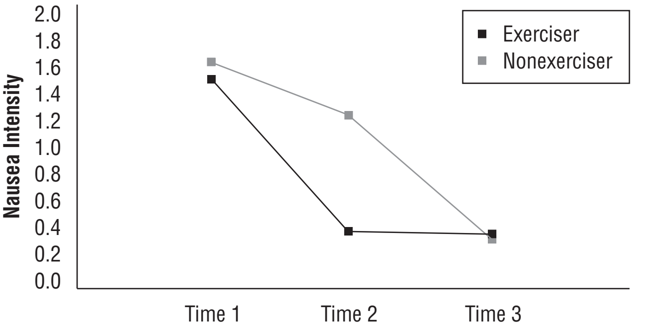

Figure 1. Change in Nausea Intensity

with less intense nausea at T2 of the present study, and the exercise effect in nausea control was found in the study by Winningham and MacVicar (1988) and partly in the study by Mock et al. (1994). Exercise intervention at a minimum criteria set by the ACSM recommendation (1998) is suggested for future exercise studies during adjuvant chemotherapy.

Limitations

The present study has several limitations to consider. First, nausea intensity was not measured during adjuvant therapy, especially during chemotherapy, which is a period of intense nausea. Furthermore, exercise status was determined only at three points (T1, T2, and T3). More frequent data (i.e., daily) would have provided detailed information about the effects of exercise on nausea intensity. Nausea was measured unidimensionally, and other aspects of nausea, such as duration and distress, were not evaluated. Although some studies do support the use of the numeric rating scale as a measure of nausea based on significant correlation with a multidimensional nausea measure from the INVR (Rhodes & McDaniel, 1999), further research is required because some discrepancies have been found between the numeric rating scale and other measures for nausea on a daily basis (Dibble et al., 2000; 2007; Lee et al., 2005). Another issue in nausea measurement occurred at T1. The nausea rating scale used in the study was not phrased to discriminate nausea from the anticipation of the next chemotherapy treatment or nausea that continued after the previous chemotherapy treatment. Wheather nausea at T1 was anticipatory or delayed nausea is difficult to determine.

Finally, as the actual behavior-based analysis was performed, the benefit of randomization was not conserved. A causal relationship between exercise and nausea could not be supported even with the significant difference of nausea intensity according to exercise status, and no difference was found in age, stage of breast cancer, KPS score, chemotherapy regimen or in those receiving radiation therapy after their chemotherapy. Although those who exercised likely had less intense nausea at T2, another possibility is that those who had less nausea were more motivated to perform an exercise program.

Conclusion

Patients with breast cancer who performed a moderate level of aerobic exercise during adjuvant cancer treatment experienced less intense nausea at treatment completion. A moderate level of aerobic exercise is recommended during adjuvant cancer treatment considering its possibility to support a decline in nausea intensity as well as the benefits of alleviating other symptoms from adjuvant cancer treatment. Further study is recommended to evaluate the effect of a moderate level of aerobic exercise, as recommended by ACSM (1998), in addition to antiemetics in controlling nausea during the period of intense nausea, particularly a few days after chemotherapy.

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