Exercise as an Intervention for Cancer-Related Fatigue

Cancer-related fatigue (CRF) has been operationally defined by the National Comprehensive Cancer Network (NCCN) as a “persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning.” In people with no known pathology or limitations, fatigue is a universal human experience that is regarded as a basic protective mechanism against the depletion of metabolic energy reserves. With adequate rest, nourishment, and sleep, fatigue in these individuals is self-limiting. However, in contrast to exercise-induced fatigue experienced by these individuals, the fatigue experienced by patients with cancer is of greater magnitude and persistence, tends to remain after rest periods, is more disruptive to activities of daily living, and has a more negative affective impact.

Until recently, medical advice for patients undergoing treatment for cancer was to obtain additional rest and avoid activities that are physically challenging. Currently, the use of exercise as an adjunct therapy for cancer treatment-related symptoms has gained favor in oncology rehabilitation as a promising intervention. The purpose of this update is to examine evidence from recent (since 1997) randomized clinical trials (RCTs) regarding the effectiveness of exercise as an intervention for CRF.

The sources of data included all those RCTs found from MEDLINE and CINAHL literature searches for the selected time period using the key words “exercise,” “fatigue,” and “cancer.” The effects of exercise on fatigue in patients with cancer, both those in intervention programs and survivors (5-year), are summarized in the Table. We present findings from 8 recent RCTs, 6 of which involved patients with breast cancer, and provide suggestions for exercise program protocols and for future research endeavors. The majority of articles in the literature involve patients with breast cancer, and physical therapists should take note of this point when making clinical judgments based on the reported findings. For a comprehensive review of literature on this topic, the reader is directed to Watson and Mock.

Key Words: Cancer, Exercise, Fatigue.

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Incidence
Cancer-related fatigue is one of the most prevalent and stressful sequelae of cancer treatment.\textsuperscript{3–7} It is reported to affect 70\% to 100\% of patients receiving radiation therapy, cytotoxic chemotherapy, stem cell or marrow transplantation, or treatment with biological response modifiers.\textsuperscript{8–12} Better management of formerly predominant sequelae of pain, nausea, and vomiting has led to the increasing distinction of CRF as the most stressful cancer-related symptom.\textsuperscript{11,12} Cancer-related fatigue also can be related to the increase in intensive multimodal cancer treatment, characterized by increased dose density and dose intensity.

Etiology
Cancer-related fatigue is a complex and multifactorial phenomenon that is likely due to a variety of causes and contributing factors.\textsuperscript{13} The exact mechanisms involved in its pathophysiology are unknown.\textsuperscript{14,15} It may be a sequela of the malignancy itself, caused by multimodal cancer treatment, or secondary to treatment-related anemia. Cancer-related fatigue has known contributory physiologic factors, including cachexia, deconditioning, and high levels of certain cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-\(\alpha\).\textsuperscript{14} Psychosocial factors contributing to fatigue include anxiety, depression, and insomnia. Commonly, CRF does not occur as an isolated symptom, but rather among multiple symptoms and, in this circumstance, is correlated with decreased functional status.\textsuperscript{16}

Over 30\% of people with cancer experience anemia and its sequela, fatigue. People are classified as having anemia when hemoglobin levels are lower than 12 g/dL.\textsuperscript{17} Glaspy et al\textsuperscript{18} reported that more than one third of the nearly 4,300 patients in their study became anemic after 3 cycles of chemotherapy. The etiology of cancer-related anemia is multifactorial and includes intrinsic factors such as bone marrow involvement, blood loss, and nutritional deficiencies and extrinsic factors such as the use of radiotherapy and chemotherapy. Summarily, the anemia can be secondary to comorbidities (eg, gastrointestinal bleeding, hemoglobinopathies), to the advancing disease (eg, bone marrow infiltration, diminished nutritional state), or to the cancer therapy (eg, hypoplasia of bone marrow in radiotherapy target areas, bone marrow toxicity due to chemotherapy).\textsuperscript{19}

Randomized Clinical Trials Testing Exercise on Patients With Breast Cancer
Using an RCT model, Mock et al\textsuperscript{20} compared patients with breast cancer who were participating in a 6-week walking exercise program with a group of patients with breast cancer who were receiving usual care to determine the effects of exercise on physical functioning and symptom intensity. The subjects (N=46) all had stage I or II breast cancer, were sampled at the beginning of a 6-week radiation therapy program, and were randomly assigned to either a control (usual care) group or an experimental (exercise) group. Control subjects received health care in an outpatient department and were encouraged to remain active during their cancer treatment but were given no instructions regarding an exer-
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<td>Mock et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>*Patients with breast cancer RT/stages I and II N=46</td>
<td>Experimental 2-group</td>
<td>Home-based walking, 4–5×/wk for 30 min</td>
<td>F=VAS and PFS EX=12-Minute Walking Test</td>
<td>↑ Walking ability in exercisers ↓ Fatigue and other symptoms compared with controls</td>
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<td>*Patients with breast cancer CT/RT/stages I–II N=50</td>
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<td>F=PF EX=12-Minute Walking Test</td>
<td>↑ Walking ability in exercisers ↓ Fatigue and other symptoms compared with controls</td>
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<td>*Patients with breast cancer CT/stage II N=61</td>
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<td>F=VAS EX=12-Minute Walking Test</td>
<td>↑ Pretest-posttest walking ability ↓ Fatigue in active exercisers</td>
<td>61% of subjects adhered to program Single-group design</td>
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<td>Schwartz&lt;sup&gt;25&lt;/sup&gt;</td>
<td>*Patients with breast cancer CT/stages I–III N=27</td>
<td>Pre-experimental 1-group</td>
<td>Home-based walking or patient choice, 3×/wk</td>
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<td>Oldervoll et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>**Patients with Hodgkin disease N=24</td>
<td>Experimental 2-group</td>
<td>Home-based brisk walking or patient choice/20 wk, 65%–80% HRmax, 3×/wk for 40–60 min</td>
<td>F=KQ EX=VO&lt;sub&gt;2max&lt;/sub&gt; and SF-36</td>
<td>↑ Maximal aerobic capacity ↓ Physical functioning ↓ Fatigue in active exercisers</td>
<td>Exercise was self-report Demonstrated positive effect of exercise on reducing CRF in 5-year survivors of cancer</td>
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<td>Segal et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>*Patients with prostate cancer ADT N=1.55</td>
<td>Multi-center experimental 2-group</td>
<td>Resistance exercise/12 wk</td>
<td>F=FACT-F EX=leg press, chest press</td>
<td>↓ Fatigue in active exercisers</td>
<td>First to demonstrate positive effect of resistance training on reducing CRF</td>
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<sup>a</sup> CT=chemotherapy, RT=radiation therapy, PBSCT=peripheral blood stem cell therapy, ADT=androgen deprivation therapy, F=fatigue measure, VAS=visual analog scale, EX=exercise, HRmax=maximum heart rate, VO<sub>2max</sub>=maximal oxygen consumption, QOL=quality of life, PFS=Piper Fatigue Scale, SLET=Symptom Limited Exercise Test (oxygen uptake), POMS=Profile of Mood States, FQ=Fatigue Questionnaire, FACT-F=Functional Assessment of Cancer Therapy-Fatigue, SCL-90=Symptom Check List, SF-36=Medical Outcomes Study 36Item Short Form Health Survey, *=receiving cancer treatment, **=survivor, CRF=cancer-related fatigue.
cise program. The experimental group was given an exercise prescription of low- to moderate-intensity exercise (60%–80% of maximum heart rate) and used the Borg Scale for Rating of Perceived Exertion (target rating of 11–13). Subjects from both groups were tested with the 12-Minute Walking Test to determine physical functioning. Fatigue was the most prevalent and distressing symptom reported. The experimental group performed better than the control group on physical functioning, fatigue, anxiety, and difficulty sleeping. Mean fatigue scores on the 100-mm visual analog fatigue scale increased in the usual care group from 25.18 (SD=31.28) to 43.05 (SD=36.37) and in the exercise group from 13.65 (SD=16.06) to 26.12 (SD=20.27) (P=.01). No adverse effects from the aerobic training were recorded. The investigators recommended that exercise be prescribed and monitored for patients with breast cancer undergoing radiation therapy as a low-cost self-care activity to reduce fatigue and improve physical functioning.

Mock et al21 used similar study methods in a pilot project to test the feasibility of exercise as intervention for CRF in a multi-institutional setting, which consisted of 5 university teaching hospital cancer centers. Patients with breast cancer who were taking part in a walking exercise program were compared with a group of patients with breast cancer who were receiving usual care to determine the effect of exercise on fatigue, physical functioning, emotional distress, and quality of life. The subjects (N=50) were receiving either chemotherapy or radiation therapy and were randomly assigned to either a control (usual care) group or an experimental (exercise) group. Subjects from both groups were tested with the 12-Minute Walking Test, the Profile of Mood States (POMS), the Piper Fatigue Scale (PFS), the Symptom Distress Scale (SDS), and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Because 50% of the control group were actively exercising independently during the study period and 30% of the experimental group were unable to maintain a regular exercise regimen, analysis was modified from intention-to-treat to an explanatory compliance cohort model. Comparisons were then made between low-exercise and high-exercise groups. Study findings indicated that a home-based walking exercise program can decrease CRF and emotional distress while improving physical functioning and quality of life. The mean scores on the fatigue subscale of the POMS scale (POMS-F) decreased in patients in the high-exercise group from 5.04 (SD=5.20) to 4.35 (SD=4.54) during intervention, while mean scores increased in the low-exercise group from 7.18 (SD=4.82) to 9.81 (SD=5.91) (P=.00). No adverse effects from the aerobic training were recorded. Exercise recommendations were expanded by the investigators to include patients with breast cancer undergoing chemotherapy in addition to those receiving radiation therapy. Because this study was not a true RCT, a limitation of the study is that subjects who exercised may initially have felt better than those who did not exercise.

Use of exercise as an effective measure for controlling or reducing CRF was extended from patients with stage I and II breast cancer to include patients with other types of solid tumors and hematologic malignancies in the following studies. Dimeo et al22 studied patients (N=32) with solid tumors (breast carcinoma, sarcoma, non-small-cell lung carcinoma) or non-Hodgkin lymphoma who had recently completed chemotherapy and autologous peripheral blood stem cell transplantation (PBSCT) to examine the effect of physical activity on fatigue. Patients participated in the 6-week exercise program after having recently completed their cancer treatment. The experimental group walked on a treadmill daily on weekdays for 6 weeks, and the control group did not exercise. During the first week, the exercise was 5 sets of 3 minutes of continuous walking. Exercise during week 2 progressed to 4 sets of 5 minutes of continuous walking, then to 3 sets of 8 minutes of continuous walking for week 3, to 3 sets of 10 minutes of continuous walking for week 4, and to 2 sets of 15 minutes of continuous walking in the fifth week. During the sixth week, the exercise was 30 minutes of uninterrupted treadmill walking. During week 7, the training group was observed to have better (P<.05) maximum physical performance (X=8.3 km/h [SD=1.6] for training group; X=7.5 km/h [SD=1.3] for control group) on the treadmill. At that time, none of the subjects in the training group reported fatigue in daily activities, whereas 4 of 16 control subjects reported daily activities limited by fatigue.

Similarly, Dimeo et al23 examined the effect of exercise on fatigue in patients (N=63) with solid tumors (breast carcinoma, sarcoma, seminoma, small-cell lung carcinoma) or non-Hodgkin lymphoma who were receiving chemotherapy and autologous PBSCT during their hospital stay. The POMS-F was the measure utilized for scoring fatigue. The experimental group used a bed ergometer daily for 30 minutes (15 sets of 1 minute of continuous cycling, with 1-minute rest periods) until hospital discharge, and the control group did not exercise. At the time of hospital discharge, subjects in the control group had increased fatigue scores (P=.02) from 9.2 (SD=10.2) on the POMS-F at admission to 11.5 (SD=8.6). In contrast, the training group demonstrated no change (P=.28), from 9.6 (SD=10.0) on the POMS-F at admission to 11.7 (SD=8.9) at discharge.

The first study by Dimeo and colleagues22 showed that exercise reduced CRF and improved physical performance in patients with solid tumor or lymphoma follow-
ing high-dose chemotherapy and PB SCT. The second study by Dimeo and colleagues23 showed that exercise prevented the typical CRF experienced by patients receiving high-dose chemotherapy and PB SCT. No adverse effects from the exercise training were reported.

Schwartz and colleagues24,25 gave additional support for the use of exercise as an effective intervention in patients with breast cancer who are receiving chemotherapy in the following 2 studies that utilized a one-group pretest-posttest design. These 2 studies provided additional insights into CRF daily intensity patterns and the need for regular exercise. Schwartz et al24 found an inverse relationship between exercise duration and subsequent reduction of CRF in patients using an accelerometer (physical activity monitor) during an 8-week exercise program. Subjects (N=61) exercised between 15 and 30 minutes, 5 to 4 days per week, and kept exercise and fatigue diaries to document daily activity duration and symptoms experienced. Outcome measures included the 12-Minute Walking Test, activity level recorded with accelerometers, and fatigue diaries. The diary was completed at night and utilized the 100-mm visual analog scale of fatigue (VAS-F), which recorded the level of fatigue on 4 levels: (1) fatigue at its worst in last 24 hours, (2) fatigue at its least in last 24 hours, (3) fatigue on average over last 24 hours, and (4) fatigue right now. Schwartz et al found CRF to be consistently reduced on the same day as exercise, with approximately a 1-day carryover effect. Specifically, fatigue scores using the VAS on exercise days (X=31.65, SD=1.15) were lower (P<.001) than on nonexercise days (X=36.90, SD=1.06). They reported the amount of exercise correlated with the post-exercise fatigue level; in general, the longer a woman exercised, up to a maximum of 60 minutes a day, the less fatigue she felt on that day. The effect of exercise was shown to be immediate and to have no more than a 1- to 2-day carryover effect.

The daily fatigue pattern and the effect of an 8-week program of exercise on CRF were studied by Schwartz25 in women with breast cancer (N=27) who were receiving the first 3 cycles of chemotherapy. A one-group pretest-posttest design was used. Measures included the 12-Minute Walking Test, activity level recorded with accelerometers, exercise logs, and fatigue diaries. The exercise program was adopted by 60% (n=16) of the women. The fatigue pattern most commonly seen in subjects, both exercisers and nonexercisers, was a sharp increase in symptoms in the first 24 to 48 hours after chemotherapy. Women who adopted the exercise program generally had less CRF, whereas women who did not adopt the exercise program had more days of high fatigue and fewer days of low fatigue. Subjects in the exercise group had more “good days” (number of days below baseline VAS-F=67%) than nonexercisers (number of days below baseline VAS-F=16%). Average fatigue scores were decreased with each chemotherapy cycle in 63% of exercisers, compared with 9% of nonexercisers (P=.005). No adverse effects from the aerobic training were recorded.

Randomized Clinical Trial Testing Exercise on Patients With Hodgkin Disease

Use of exercise as an effective intervention for reducing CRF was investigated in patients with Hodgkin disease in the following RCT. Oldervoll et al26 studied the effects of a 20-week aerobic exercise program on fatigue measures in fatigued and nonfatigued people with Hodgkin disease. Using the Fatigue Questionnaire (FQ), they identified fatigued individuals with disease (n=15) who were matched on sex and with non-fatigued individuals with Hodgkin disease (n=15). The mean time since cancer treatment was 79 months for the fatigued group and 59 months for the nonfatigued group. Outcome measures were aerobic capacity (maximal oxygen consumption), fatigue (FQ), and physical functioning (SF-36). The aerobic program consisted of 40 to 60 minutes of continuous exercise (65%-80% of target heart rate) 3 times per week for 20 weeks. Patients used an exercise diary to record their perception of the intensity of the exercise session. Of the 15 fatigued subjects who agreed to participate, 12 attended the medical examination and exercise test. None of the 12 subjects gave their consent to enter the intervention program and finished the program. Specific activities were brisk walking, jogging, bicycling, aerobics, cross-country skiing, and swimming. Maximal aerobic capacity improvement was observed as maximal oxygen consumption increased (P=.04) from a mean of 33.9 mL·kg⁻¹·min⁻¹ (SD=36.0) and maximal walking time increased (P=.04) from a mean of 11.3 to 13.2 minutes. Physical functioning improvement was demonstrated as the SF-36 scores increased from 82.2 to 89.4 (P=.04). Fatigue also was improved after the intervention, as FQ scores dropped from 21.5 to 12.1 (P=.001). No adverse effects from the aerobic training were noted.

Randomized Clinical Trial Testing Exercise on Patients With Prostate Cancer

Use of exercise as an effective intervention for reducing CRF has also included resistance training. In a multicenter RCT, Segal et al27 examined the effects of resistance training exercise on fatigue in men who were receiving androgen deprivation therapy for prostate cancer. Subjects were randomly assigned to either a waiting-list control group (n=73) or an experimental group (n=82) who participated in a resistance exercise program consisting of 9 strength-training exercises (60%-70% of one-repetition maximum), 3 times per week for 12 weeks. The exercise program was carried out under supervision of a certified fitness consultant.
Fatigue was measured using the 13-item Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale. FACT-F score changes greater than 0 represent an increase in fatigue. Control subjects had a mean baseline FACT-F score of 42.5 (SD=8.5), which decreased to 40.3 (SD=9.4), a mean change of −2.2 (SD=5.8). The mean baseline FACT-F score of 40.8 (SD=10.6) in the intervention group increased to 41.6 (SD=10.5), a mean change of 0.8 (SD=5.8). The mean change in the positive direction represented reduced fatigue (P=.02). Muscular fitness was measured using a standard load test for chest press and leg press. In the control group, mean chest press repetitions decreased by 2.6, compared with the 13.1 increase in repetitions seen in the intervention group (P=.009). Similarly, in the control group, mean leg press repetitions decreased by 1.6, compared with an 11.8 increase in the repetitions in the intervention group (P<.001). Subjects in the experimental group had less interference from fatigue during activities of daily living as well as higher levels of muscular fitness on the load tests compared with subjects in the control group. No adverse effects were reported from the resistance training. This is the first study to demonstrate that resistance training, rather than aerobic exercise, has a benefit of reducing CRF.

In the 8 studies reviewed, across all training regimens, whether inpatient or outpatient (supervised or community-based), exercise was found to have a positive effect on CRF. Among the 8 studies reviewed, no adverse effects were reported from the exercise programs. However, patients with serious comorbidities such as cardiac and respiratory disease were excluded from the studies.

**Recommendations for Exercise Programs for Patients With CRF**

Findings from the studies sampled lead to the following recommendations for physical therapists. The exercise program should:

1. Begin when patients start their cancer treatment protocol and last throughout the treatment period. Patients undergoing cancer therapy for CRF should be screened using the NCCN Fatigue Practice Guidelines. According to the easy-to-follow algorithm, which flows from patient screening to primary examination to interventions, patients are asked to rate their fatigue on a 0 to 10 rating scale or as mild, moderate or severe. Reported symptoms of moderate or severe intensity are referred for primary examination. The primary examination seeks to identify the cause of moderate to severe fatigue, with emphasis placed on 7 primary factors (pain, emotional distress, sleep disturbance, anemia, nutritional deficiencies, deconditioning, and comorbidities). If none of these factors are identified, a more comprehensive assessment is performed. An individualized exercise program is stressed as the nonpharmacological intervention with the strongest supporting evidence for efficacy. Additionally, education and counseling are recommended.

2. Be of low to moderate intensity (50%–70% of maximum heart rate, or rating of 11–13 on the Borg Scale for Rating of Perceived Exertion).

3. Be progressive, based on cardiovascular conditioning, building from 15 to 30 minutes of exercise, 3 to 5 days per week. Mock and colleagues instructed subjects to walk as their tolerance to exercise and cancer treatment permitted. Dimeo and colleagues instructed patients to exercise at an intensity that did not provoke symptoms. Oldervoll et al instructed subjects to exercise at an intensity of 65% to 80% of their target heart rate. Segal et al had subjects perform 9 strength training exercises at 60% to 70% of their one repetition maximum, 2 sets of 8 to 12 repetitions.

4. Be predominantly aerobic in nature, although interval training and resistance exercise have been tested and found to be effective.

5. Stress the importance of an exercise diary or log to document the session mode, intensity, duration, target heart rate, symptoms experienced, and so on. Use of an exercise diary has been recommended to document the level of exercise participation and to encourage adherence to the intervention.

Safety is an essential consideration in giving exercise recommendations to individuals who are receiving chemotherapy or other cancer treatment. The patient’s oncologist should provide baseline screening clearance and give instructions about safeguards related to the specific type of cancer treatment. In addition to beginning at a low intensity and progressing slowly, it is important for the clinician to monitor the patient’s response to exercise regularly and adjust the program as indicated. Because the majority of studies described involved patients with breast cancer, it remains to be seen how exercise would affect patients with other forms of neoplasm, such as brain tumors, lymphomas, and sarcomas. Clinicians, therefore, should use caution when recommending community-based exercise programs for these conditions. We recommend that any exercise to be done by those with advanced or recurrent disease should be done under the direct supervision of a physical therapist.
exercise program at a minimum provides guidance to the type of exercise and its intensity, duration, and frequency. Physical therapists are in a unique position to prescribe exercise as well as monitor for adverse changes in patients with cancer, in addition to being able to recognize when exercise may be unsafe in these complex patients (e.g., metastasis to bone).

**Recommendations for Future Research**

The samples studied in this review have been primarily patients with breast cancer, and samples have been limited in regard to ethnicity, socioeconomic status, age, and sex. Little research has focused on exercise for fatigue management in palliative care. Small sample sizes and lack of control groups as well as other forms of methodologic rigor have limited research designs. The need exists to report and control variations in type and intensity of chemotherapy or other cancer treatments that are concurrent with exercise interventions.

Based on these and other identified gaps in current knowledge of exercise interventions for CRF, the following recommendations are suggested for future research in the field:

1. Conducting additional investigations of exercise at all levels but especially at the intervention-testing level.
2. Using more rigorous experimental research designs with larger sample sizes, control groups including individuals with no known pathology or impairments and placebo controls or individuals who receive similar time and attention, and greater standardization of interventions to facilitate replication and increase internal validity.
3. Using more precise and accurate instruments and outcomes to increase validity and reliability (e.g., use of instruments such as accelerometers and actigraphy, which record vectors of activity such as speed or direction changes over time, to measure dose of exercise in home-based programs).
4. Targeting more diverse samples of patients with cancer, especially in regard to ethnicity, socioeconomic status, age, and type of cancer diagnosis.
5. Exploring exercise modifications (aerobic, interval, and resistance training) in recurrent disease and palliative care.
6. Testing exercise interventions across types of cancer treatment, including chemotherapy, radiation therapy, biotherapy, hormonal therapy, and surgery.
7. Reporting study results comprehensively in regard to refusals, withdrawals, adherence rates, and adverse events.
8. Comparing outcomes for supervised laboratory interventions and home-based exercise programs.
9. Beginning investigation of secondary outcomes of exercise interventions such as quality of life, immune function, and survival.

**Conclusion**

The recent body of literature regarding the use of exercise as an adjunct therapy for CRF has established a strong foundation for the oncology rehabilitation team. Specifically, in all studies tested, across all training regimens, exercise was found to be effective in preventing or reducing CRF.

Identified as remarkably underutilized, exercise is one of the few interventions suggested to diminish CRF and other psychosocial symptoms. The positive effect of exercise on CRF should underscore the need for physical therapists’ involvement in the rehabilitation of patients with cancer.

**References**


