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Nicholas J. Ridolfi

Philadelphia College of Osteopathic Medicine, nicholasrid@pcom.edu

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Does physical activity, when combined with androgen deprivation therapy, yield a better quality of life in prostate cancer survivors?

Nicholas J. Ridolfi, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not physical activity, when combined with androgen deprivation therapy, yields a better quality of life in survivors of prostate cancer.

STUDEY DESIGN: Three randomized, controlled trials (RCTs) were found using the PubMed and Cochrane databases. The studies compared regular physical activity in men undergoing androgen deprivation therapy for prostate cancer.

OUTCOMES MEASURED: The outcomes measured were self-reported quality of life surveys at different time intervals.

RESULTS: Two out of the three studies demonstrated statistically significant improvement in reported quality of life during the exercise programs. The third study did not find significant increases in quality of life.

CONCLUSIONS: Based off of the data collected, physical activity seems to be safe and effective in improving quality of life in men undergoing androgen deprivation therapy for prostate cancer.

KEY WORDS: prostate cancer, androgen deprivation therapy, physical activity, quality of life

Introduction

The most common death from cancer in the male population, behind lung cancer, is prostate cancer.¹ Prostate cancer is also the leading cause of cancer in men of all races and ethnicities.¹ Prostate cancer is a very common type of cancer, typically treated with androgen deprivation therapy.^{2,3} Moreover, the diagnosis comes with a treatment plan that often decreases quality of life through adverse side effects. A few of these side effects include gain of fat mass, loss of muscle mass, urinary incontinence, erectile dysfunction, decreased quality of life, bowel dysfunction, and fatigue.^{2,3} Furthermore, males may be receiving long term treatment for up to two decades.² This paper looks at three randomized controlled trials comparing the efficacy of aerobic exercise combined with androgen deprivation therapy in an effort to increase quality of life (QoL) in prostate cancer survivors.

The exact cause of prostate cancer is unknown, though increasing age, high consumption of dietary fat, and family history seem to play a major role.⁴ Although this disease crosses the spectrum of ethnicity, according to the CDC in the years 1999 to 2012, the highest prevalence was seen amongst black men, followed by Caucasian, Hispanic, American Indian, and Asian.⁵ Though symptoms can vary amongst men, most common symptoms of prostate cancer include back pain, urinary hesitancy, and hematuria.⁴

Standard screening measures include digital rectal exams and/or prostate specific antigen levels in the serum, although further research is being conducted about what the best screening method is.⁴ Digital rectal exams are a part of all physical exams for males between the ages of 40-70. Unfortunately, with the current prostate cancer screening methods, false-positives and false-negatives can occur. The usual methods used to treat

this condition include androgen deprivation therapy (ADT), chemotherapeutics, immunotherapy, external beam radiation therapy, brachytherapy, radionuclide therapy, or radical prostatectomy.^{2,3} Overall ADT has excellent outcomes, however, with it comes many associated side effects. This is especially in the elderly (>70), where testosterone may fail to recover fully.³

Prostate cancer statistics are well documented. According to the CDC, the total number of prostatectomy procedures in 2010 was 138,000.⁶ The CDC also reports the number of deaths from prostate cancer in 2013 alone, was 27,682.⁶ However, 2.9 million men in the United States have been diagnosed with prostate cancer at some point in their lives and are still alive.⁷ Prostate cancer is a disease predominantly associated with older men, with the average age being over 65.⁷ However, most prostate cancer survivors are not meeting the guidelines for physical activity.⁸

The cost of the treatment in 2012, averaged per patient per year \$3,205 for prostatectomy, \$2,557 for brachytherapy, with the most costly treatment being the external beam therapy, averaging \$6,412 annually.⁹ In 2013, the cost of androgen deprivation therapy was \$1,100 for a three-month regime.¹⁰

Overall outcomes are good, however we do see a decreased quality of life with both diagnosis and treatment.

Objective

The objective of this evidence based medicine review is to determine whether physical activity, when combined with androgen deprivation therapy, yields a better quality of life in survivors of prostate cancer.

Methods

The studies that were included in this review consist of three randomized controlled trials (RCTs). The population consisted of male survivors of prostate cancer that had undergone or were currently undergoing androgen deprivation therapy. The intervention used was physical activity consisting of both resistance and aerobic exercise. The comparison included sedentary male survivors of prostate cancer that had already undergone or were undergoing androgen deprivation therapy.

The keywords used in the searches were “prostate cancer”, “physical activity”, and “androgen deprivation therapy.” All of the RCTs reviewed were published in peer-reviewed articles, written in English, and found on the PubMed database. The articles were chosen based off relevance to the clinical question and were patient oriented outcomes (POEMs).

The inclusion criteria included men at least eighteen years of age that had received or were currently receiving androgen deprivation therapy. The males were also sedentary, meaning that they had not done structured exercise under the oncology guidelines of 150 minutes of aerobic and twice resistance training sessions per week for at least 6 months prior.³ Bourke et al included men receiving long term ADT. Galvao et al sent surveys to subjects asking them to be apart of a study and required prior approval from the subject’s general practitioner (GP). McGowan included only males that lived in Alberta, Canada and were diagnosed between the years 2005 and 2009. Exclusion criteria included men with a comorbid condition that would affect exercise, especially unstable angina, uncontrolled hypertension, recent myocardial infarction, history of pacemaker, any neurologic disorder, and metastasis of primary prostate cancer.² Subjects that were not cleared by their GP were also excluded.³

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# of patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bourke, 2014 (1)	RCT	100	71+/- 6 yrs	Sedentary men, men receiving long term ADT.	Men with unstable angina, unctrolled HTN, recent MI, pacemakers, metastasis of primary CA	32	12-week lifestyle intervention consisting of aerobic and resistance exercise.
Galvao, 2013 (2)	RCT	347	71.9 +/- 5 yrs	Eligible patients that responded to anonymous questionnaire, clearance from their GP,	No response, GP declined, travel constraints, already meeting exercise oncology guidelines, preexisting illness	23	Resistance and aerobic exercise or printed educational material about physical activity
McGowan, 2013 (3)	RCT	423	47-89	At least 18 years of age, must reside in Aleberta, Canada, diagnosed with prostate CA between 2005 and 2009	Patients that did not return completed inventory questionnaire	120	Self-administered implementation intention, telephone assisted intention, standard physical activity recommendation. Data measured at baseline, 1, and 3 months.

Outcomes measured

The primary outcome measured in all three studies was quality of life. Bourke et al used the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaires at 12 weeks and 6 months. Galvao et al utilized the Short Form-36 Health Survey to determine quality of life at baseline, 6 months, and 12 months. McGowan et al utilized both the FACT-P and the Short Form-36 Health Survey.

Results

Bourke 2014 et al utilized 100 male patients, based off of the inclusion/exclusion criteria in Table 1, and implemented a 12-week aerobic and resistance exercise program with a follow up at 6 months. The trial's median age was 71.² Individuals were placed into a group in which they performed exercise under the guidance of an exercise physiologist compared to a usual care group.² The usual care group will not be discussed any further in this paper. The exercise group performed thirty minutes of activity on stationary cycles, rowing ergometers, and treadmills at an intensity of 55-75% of their age predicted maximum heart rate.² The men exercised twice per week for the first six weeks, and then once per week for the remaining six weeks, with recommendation of exercising on their own at least once more per week.² The co-primary outcomes measured in the study were quality of life and change in diastolic blood pressure.² QoL was measured via the FACT-P and FACT-F surveys.² Clinically relevant increases in QoL were seen at the end of intervention, with a mean difference of 8.9 points at 95% confidence interval (CI), although sustained changes in QoL were not persistent at six months with a mean difference at 3.9 points at 95% CI on the FACT-F.²

Table 2. Data between intervention and control groups at 12 weeks and 6 months.²

FACT – F	Control (mean)	Intervention (mean)	Mean Difference	P Value
12 weeks	42.4	45.8	5.3	<0.001
6 months	41.9	43.5	3.9	0.007

In Galvao 2013 et al, three hundred forty-seven men were invited via a letter of invitation from their oncologist to participate in the study. Subjects first needed to be cleared by a physician to participate, along with other inclusion/exclusion criteria in Table 1. The men were divided into two groups of either supervised exercise or physical activity with printed material based off of testosterone levels, age, whether disease relapse occurred, and waist circumference size.³ The supervised exercise group performed resistance and aerobic exercise twice per week for six months using standard weight room equipment (such as dumbbells and leg press machine) and under the supervision of an exercise physiologist.³ This group was also encouraged to exercise at least once per week on their own. Both groups in this study received a pedometer to track their steps. The printed exercise group was recommended one hundred fifty minutes per week of moderate physical activity and received an educational booklet. Quality of life was measured using the Short Form-36 Health Survey at baseline, 6 months, and 1 year. From seven to twelve months was considered “the maintenance phase.”³ Data was analyzed using SPSS v.19; and analysis was intention to treat.³ The tests were two-tailed, with an alpha level of 0.05 and confidence interval of >95%.³ Significant increase in physical functioning at 6 months, with a p value of 0.006 and at 12 months, with a p value at 0.002 for the supervised exercise group were documented.³

TABLE 3. Physical Functioning between groups at 6 months and 12 months.

	Mean change over 6 months	Mean change over 12 months
Physical Functioning	M - 2.4 P value = 0.006	M - 3.5 P value = 0.002

There were few severe adverse effects observed in the trial. Two participants dropped out due to back and knee pain, respectively. One participant died from lung cancer, during the maintenance phase although the cause of death was not associated with exercise. Another participant had a nonfatal myocardial infarction, also during the maintenance phase, and made a full recovery.

McGowan 2013 et al incorporated 1,500 prostate cancer survivors residing in Alberta, Canada and diagnosed between 2005 and 2009. These participants were mailed questionnaires, and pending response, participated in the study.⁸ Subjects were placed into one of three groups; standard physical activity recommendation (SR), self-administered implementation intention (SA), and telephone assisted (TA); using a computer generated, Graphpad Software program.⁸ Measures include medical characteristics such as date of diagnosis, disease stage, and current status of treatment.⁸ Quality of life was measured using the short-form36 health survey.⁸ Analysis of covariance was used to examine differences in groups at month 3.⁸ Demographic and medical factors such as age, marital status, body mass index, education, and employment were documented as these indicators were all thought to play a role in physical activity behavior.⁸ The outcomes were measured at the third month only. In this study, there were no significant differences reported by subjects in quality of life between groups and no correlation between the factors listed above.

Table 4. Patient oriented outcomes between groups at month 3-post intervention.⁸

Between group Comparisons at 3 months	P value
TA vs SR	0.585
SA vs SR	0.226
TA vs SA	0.512

Discussion

Although previous data has shown that resistance training can improve quality of life in younger men on short term ADT, Bourke et al was the first to study older sedentary men with similar increases in QoL.⁸ As many cancer survivors do not meet the standard exercise recommendations, the population studied is ideal because it represents the general public.² Further evidence suggests, that ADT can cause cardiovascular disease, and physical activity could act as a preventative measure.²

The study by Bourke et al, is to date the largest lifestyle intervention RCT of sedentary men with advanced prostate cancer on ADT.² The study found that tapered exercise as an intervention measure showed important changes in disease specific QoL. Although previous data has shown that resistance training can improve quality of life in younger men on short term ADT, Bourke et al was the first to study older sedentary men with similar increases in QoL.^{2,11}

Galvao et al shows two important findings in their study. The first, six months of supervised exercise showed several important prognostic factors, which included improved cardio respiratory fitness, lower body physical function, self reported physical

functioning, mental health and muscle strength.³ The second important finding, was that these findings were largely sustained in the following six-month home maintenance programs.³ This study showed that the findings of long-term prostate cancer survivors who were previously treated with ADT, showed improvements that had been observed at six months were also sustained at twelve months through home based maintenance programs.³ The discussion addressed that ADT can negatively affect muscle strength. This study showed muscle strength gains across a twelve month period with significant improvements for the exercise group.³ Although it is known that ADT causes adverse effects, this is the first study that demonstrates long-term prostate cancer survivors previously treated were able to increase their skeletal muscle with supervised exercise training.³ The study targeted a well-defined population, of long term older prostate cancer survivors, a group that has been difficult to enroll in such exercise research.³ Also included was a comprehensive series of physical fitness markers. A limitation of this study was the inclusion of men who were motivated to embark in an exercise program, this may not be representative of older men in this population.

McGowan et al concluded that their hypothesis was supported for the intention group. This group reported a significantly greater increase in physical activity compared to standard physical activity at a one-month interval. However the telephone-assisted group, did not show improvement. A similar limitation to Galvao et al was that the subject group seemed overwhelmingly interested in participating. The telephone assisted group received print materials but did not report better QoL during a six-month intervention period. A limitation of the telephone group, was some of the subjects after agreeing to participate, explained that they were unable to fulfill their agreement. Lastly

the physical activity was conducted over a very short time, therefore they were unable to show significance.

In conclusion of the discussion two out of the three studies found that not only does the intervention of physical activity seem effective, but also it is relatively inexpensive, and with prior clearance from a healthcare provider, it is safe as well. Exercise is not covered under many insurance plans, however exercise is accessible to anyone at their home with proper instruction.

Currently, androgen deprivation therapy is mainly used only for prostate cancer treatments. There are no relative black box warnings, but some studies have shown correlations between fatal cardiovascular events such as myocardial infarcts in long-term studies.¹²

Conclusion

This selective EBM review investigated three randomized controlled trials comparing quality of life and exercise in men who had received or were currently receiving androgen deprivation therapy. In conclusion, this systematic review demonstrates that physical activity is effective in improving the quality of life in patients that had undergone androgen deprivation therapy. Two out of the three studies included have shown clinically significant data proving that routine physical activity increases quality of life. Based off of these statistics, physical activity should be strongly considered for those receiving androgen deprivation therapy to increase their quality of life.

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