

HEMOSTATIC ADAPTATIONS FOLLOWING EXERCISE TRAINING IN  
PATIENTS WITH CANCER

A THESIS SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL  
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BY

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## ABSTRACT

**Thesis:** Hemostatic Adaptations following Exercise Training in Patients with Cancer

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**Background:** Thrombosis is a common and critical consequence of cancer. Changes in thrombotic potential were examined after exercise training in patients with cancer.

**Methods:** Eight cancer patients ( $65 \pm 11$  yrs) completed this study, five exercising and three non-exercising controls. Venous blood samples were obtained at baseline and after approximately 12 weeks of study participation. Weekly physical activity was measured using a standard, validated physical activity questionnaire. APTT, PT, fibrinogen and factor VIII were measured before and after the 12-week intervention. **Results:** A time x group interaction trend ( $p=0.067$ ) was observed for fibrinogen. Plasma concentrations decreased in the exercise group ( $355 \pm 49.3$  mg/dL to  $331 \pm 19.5$  mg/dL), but increased in the control group ( $341 \pm 52.4$  mg/dL to  $384 \pm 107.9$  mg/dL). Physical activity significantly decreased over time in both groups. **Conclusions:** Exercise training may reduce coagulation potential in cancer patients more than usual and customary care.

**Key Words:** Thrombosis, venous thromboembolism, coagulation

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## **CHAPTER I**

### **Introduction**

An estimated 1,529,560 new cancer cases were diagnosed in 2010 (105). Cancer is the second most common cause of death in the United States, accounting for nearly one in four deaths (105). Thrombosis, the presence of a blood clot within a vessel, is a frequent problem for cancer patients (5, 18, 42, 43, 115), with the principal contributors stemming from cancer treatment, tumor type, tumor stage and complications arising from treatment (38, 43, 58, 66). Physical activity has been shown to reduce coagulation activity in healthy men and women, and other clinical populations associated with an increased thrombotic risk (28, 31, 32, 92, 118). Therefore, exercise training may be helpful in the prevention of thrombosis in cancer patients.

### **Cancer and Thrombosis**

Evidence of the association between cancer and thrombosis was first identified in the 19<sup>th</sup> century (43). Patients with cancer have an increased risk of venous thromboembolism (VTE) compared to patients without cancer (11, 43). Cancer patients account for 18% of the total burden of VTE (42). Alternatively, VTE is often an early sign of an underlying malignancy (115). Almost one in five cases of all symptomatic

VTEs are thought to be cancer-related (42), while cancer risk is higher in patients with VTE. In the first year after hospitalization for VTE, cancer risk is increased four-fold greater compared to the general population. VTE is also a marker of long-term cancer risk: even within 10 or more years there is a 30% increase in overall cancer incidence (8). VTE represents a leading cause of death in patients with cancer (5, 18), and cancer patients who develop VTE have a significantly worse survival (18, 106).

The primary contributors to VTE in cancer patients include tumor type and stage, along with various cancer treatments (38, 43, 58, 66, 103). The highest rates of VTE are found in patients with cancers of the pancreas, stomach, uterus, kidney, lung, and primary brain tumors (8, 18, 51, 69, 97). Compared with the general population, patients undergoing chemotherapy have a two to six fold increased risk of VTE (12, 43). Among hospitalized patients receiving chemotherapy, the rates of VTE increased 47% from 1995 to 2003 (52). In a population based study, cancer was associated with a 4 fold increase in thrombotic risk, whereas, in patients treated with chemotherapy, the risk increased to 6.5 fold (43, 103). Arising from chemotherapy treatment, cancer patients are shown to develop anemia. To treat this, patients are often given erythropoiesis-stimulating agents (ESAs). A systematic review of 57 trials revealed that 229 of 3,728 patients treated with ESAs had thromboembolic events, compared with 118 events in 3,041 controls (13). Cancer related surgery and the extended postoperative period are well-known high risk settings for VTE. It has been shown that the overall 30 day postoperative VTE rate was 3.5%, with rates ranging with procedure from 1.8-13.2% (38). Hospitalization is also shown to increase the risk of VTE in patients with cancer (58). Furthermore, central

venous catheters (CVC) increase VTE risk, 4.3% of cancer patients with CVCs develop CVC related DVT (66).

Venous thrombosis is generally preceded by changes in blood composition and blood flow that promote the creation of a blood clot (27, 75). The coagulation cascade is a complex process of clot formation that occurs in response to vessel injury in order to prevent excess blood loss (82). Patients with cancer are shown to have shortened clotting times of activated partial thromboplastin time (APTT) and Prothrombin time (PT) compared with individuals without malignancy (2). Plasma markers of clotting activation such as fibrinogen, fibrinogen turnover rate, factor VIII, thrombin-antithrombin complex, prothrombin fragments 1+ 2, and von Willebrand factor, are elevated in patients with cancer (26, 33, 96, 121). High levels of fibrinogen, factor VIII, and von Willebrand factor independently increase thrombotic risk (6, 112). Furthermore, persistent activation of the coagulant pathway is associated with an increased incidence of clinical malignancy (77). Tissue factor (TF), an initiator of blood coagulation, is also commonly expressed in a variety of malignancies (110). Data have shown that cancer patients with high TF expression have a VTE rate of 26.3% (50). High levels of TF expression and factor VIII are shown to be an independent prognostic factor for poor survival in patients with malignancy (57, 73, 114, 116). Moreover, high levels of fibrinogen, factor VIII, and von Willebrand factor independently increase thrombotic risk (6, 112).

In light of the substantial prevalence of thrombosis in cancer patients, anticoagulant medications are generally recommended (49). A systematic review of 11 studies reported a significant decrease in mortality in cancer patients treated with

anticoagulants (59). However, pharmacological anticoagulation introduces the risk of bleeding complications. In the previously described review, significant complications were observed in studies using warfarin (59), and a recent clinical study of oral anticoagulant use by cancer patients reported hemorrhagic episodes in 14.8% of participants (96). Given the risks associated with pharmacological anticoagulation, there is great need for alternative therapies that effectively minimize thrombotic potential without introducing additional risks to the patient.

### **Exercise as an Anticoagulant**

Physical activity has been shown to reduce coagulation activity in healthy men and women, as well as clinical populations associated with an increased thrombotic risk (28, 31, 32, 92, 118). Physical activity has an inverse dose-response relationship on concentrations of factor VII, VIII, and IX, along with fibrinogen, von Willebrand factor, and D-dimer in a healthy population (32, 34, 61, 118). TF is substantially reduced with exercise training in various clinical populations including diabetes, peripheral arterial disease, and patients with coronary artery disease (28, 31, 92).

Aerobic and resistance exercise training results in considerable improvements in physical function, fatigue, mood, and quality of life in cancer patients who are actively receiving treatment or are post treatment (39, 102). Research demonstrates that exercise training is practical, safe, and well-tolerated (56). Through training, cancer patients experience significant health benefits, including increased aerobic capacity, strength, and flexibility, along with decreased distress, enhanced well-being, and improved functioning (47, 56, 81). The literature also reveals resistance exercise increases muscle

size, strength, and power, along with improved mobility in cancer survivors (62). Alternatively, there is an inverse relationship of physical activity to malignancy, physical activity can greatly increase cancer prevention (47, 119).

### **Statement of the Problem**

There is a substantial prevalence and mortality risk of DVT in cancer patients (5, 12, 43). This is primarily due to the type and stage of cancer, along with the treatment received and side effects arising from treatment (12, 13, 43, 103). Anticoagulants are the current recommendation to reduce thrombotic potential in cancer patients, nevertheless, there are several risks associated with pharmacological anticoagulation (49, 59, 96). Regular exercise training results in numerous benefits for the cancer patient and is known to reduce thrombotic potential in healthy individuals and other clinical populations (39, 47, 56, 62, 81, 102, 119); however, there is no research examining potential improvements in thrombotic risk in this population following a period of exercise training.

### **Purpose of the Study**

The purpose of this investigation was to examine the changes in thrombotic potential after a period of structured exercise training in patients with cancer. Based upon previous findings with exercise and hemostasis, it was hypothesized that exercise training would reduce coagulation activity more than usual and customary care.

### **Importance of the Study**

Excessive coagulation is a common and critical consequence of cancer and cancer treatment. Regular exercise training decreases the risk of thrombosis in healthy men and women as well as patients with cardiovascular and metabolic diseases.

However, research that assesses the impact of regular exercise on thrombosis in patients with cancer has yet to be published. Results of this study could yield important information regarding thrombosis in cancer patients. This may provide an alternative therapy for patients with cancer to reduce the risk of excessive coagulation and cardiovascular events.

### **Delimitations**

Ten subjects completed this study, five in an exercising group and three in a non-exercising control group. Participants were men and women at least 18 years of age, at least 110 lbs and non-smokers. Subjects were also free from known cardiovascular or metabolic disease and had an active cancer diagnosis. Subjects were recruited from the patients treated at Ball Memorial Hospital's Cancer Center in Muncie, IN. Use of anticoagulant medications was cause for exclusion from the study. Participants had no physical limitations that prevented them from participating in a light to moderate aerobic exercise program.

### **Definition of Terms**

1. *Hemostatic* – Pertaining to stagnation of the blood.
2. *Coagulation* – The process of blood clot formation.
3. *Thrombosis* – The presence of a blood clot in the circulatory system.
4. *Venous thromboembolism* – The presence of a blood clot within the veins with the potential to break off and travel through the blood stream.
5. *Anticoagulation* – The process of preventing or slowing down coagulation of the blood.

## **Chapter II**

### **Review of Literature**

An estimated 1.6 million new cancer cases will be diagnosed in 2011(1). Cancer is the second most common cause of death in the United States, accounting for nearly one in four deaths (105). Thrombosis, the presence of a blood clot within a vessel, is a frequent problem for cancer patients (5, 18, 42, 43, 115), this is primarily due to the type and stage of cancer, along with the treatment received and side effects arising from treatment (12, 13, 43, 103). Anticoagulant medications are the current recommendation to reduce thrombotic potential in cancer patients, nevertheless, there are several risks associated with pharmacological anticoagulation (49, 59, 96). Regular exercise training results in numerous benefits for the cancer patient (39, 47, 56, 62, 81, 102, 119) and reduces thrombotic potential in healthy men and women as well as various clinical populations (21, 28, 31, 32, 34, 61, 72, 82, 92, 118); however, there is no research examining potential improvements in thrombotic risk in people with cancer following a period of exercise training. Thus, the purpose of this investigation was to examine the changes in thrombotic potential after a period of structured exercise training. Based upon

previous findings with exercise and hemostasis, it was hypothesized that exercise training would reduce coagulation activity more than usual and customary care.

## **COAGULATION**

The coagulation cascade is a complex process of clot formation that prevents excess blood loss in an injured blood vessel (82). Upon damage to a blood vessel, vasoconstriction is first to occur in order to limit blood loss. Platelets then adhere to collagen exposed from the sub-endothelium of the damaged vessel, and become activated. The activated platelets release granules of serotonin, ADP, and thromboxane A<sub>2</sub>. ADP attracts more platelets to the area, while thromboxane promotes vasoconstriction and platelet aggregation. This positive feedback encourages the formation of a platelet plug. Activation of the coagulation cascade is the next step in the process of fibrin clot formation, promoting the development of a more stable fibrin clot.

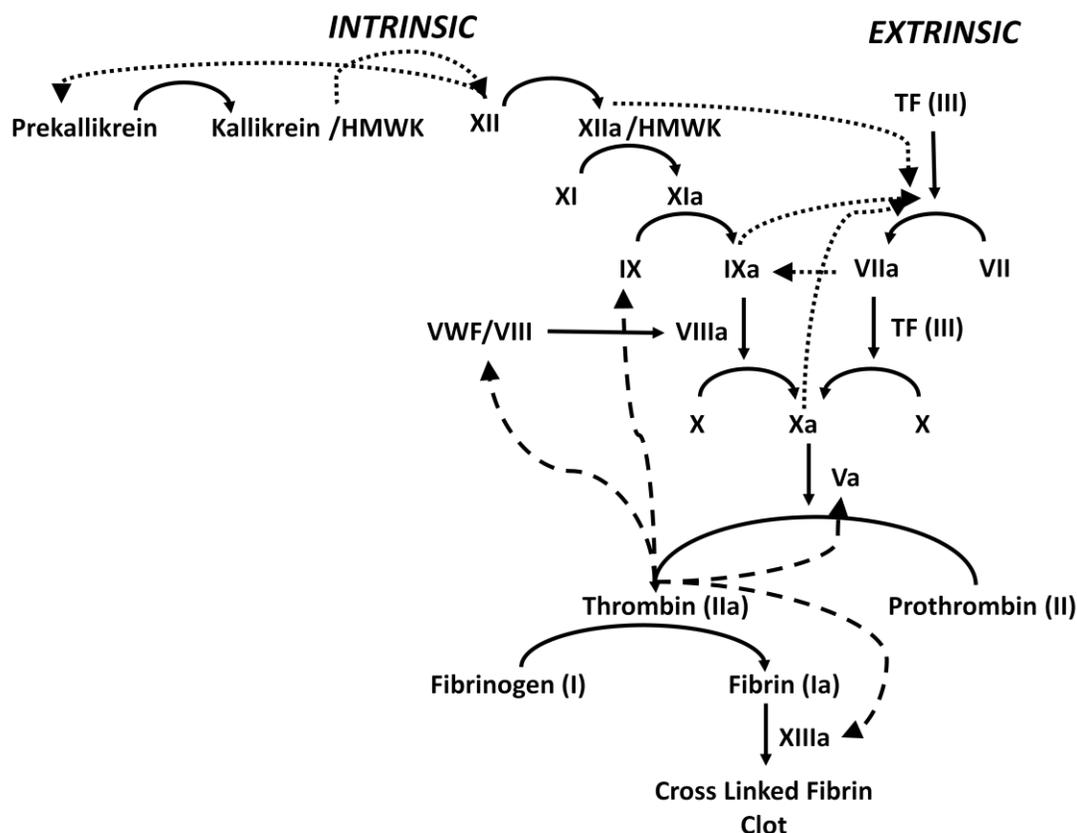
As illustrated in Figure 1, the coagulation cascade consists of three pathways: the intrinsic, extrinsic, and common pathway. In order to be activated, the intrinsic pathway requires components previously contained in the blood stream, while the extrinsic pathway begins with the exposure of tissue factor (TF) from the subendothelium, a cell membrane protein that does not travel in the bloodstream. Both pathways ultimately lead to the activation of factor X, which is the root of the final, common pathway which leads to fibrin clot. Although three pathways exist in the coagulation cascade, they are not mutually exclusive of one another. Certain enzymes from each pathway activate zymogens in another; while a number of enzymes accomplish positive feedback, activating other substrates to stimulate their own formation.

In order to activate the extrinsic pathway, blood must be exposed to a negatively charged surface such as collagen or TF. The exposure of TF causes factor VII (FVII) to bind and become activated to factor VIIa, instigating the extrinsic pathway. The FVIIa/TF complex triggers the activation of factor X to factor Xa. In addition to activating FX, the FVIIa/TF complex activates factor IXa in the intrinsic pathway. This occurrence leads to further activation of factor X.

The intrinsic pathway consists of a more complex series of reactions. Exposure of the sub-endothelium to the contact factors (zymogens of FXII, FXI, Prekallikrein, and cofactor HMWK) initiates the intrinsic pathway. Through a series of steps, coagulation factors XII, XI, IX, and VIII along with von Willebrand factor, eventually lead to the activation of FX, the root of the common pathway. Factor VIII in its activated form acts as an accelerator, increasing the activation of FX by several thousand fold.

The activation of FX from both the extrinsic and intrinsic pathways initiates the final, common pathway, eventually leading to fibrin clot formation. Activated FXa, using FVa as a cofactor, cleaves and activates prothrombin (FII) into thrombin (FIIa). To stimulate its own production, thrombin activates cofactors FV and FVIII, as well as FIX, from the intrinsic pathway. Following its activation, thrombin also activates fibrinogen (FI) into fibrin (FIa). To further stabilize the fibrin clot, thrombin activates FXIII, which catalyzes the formation of covalent bonds between fibrin monomers to form fibrin polymers. FXIIIa forms a cross-linked fibrin clot with increased mechanical strength and increased resistance to proteolysis.

Overall, a hemostatic plug, consisting of an accumulation of activated platelets mixed together with fibrin, occurs in response to vessel wall injury. This plug seals the wound even after vasoconstriction discontinues.



**Figure 1.** Diagram of the coagulation cascade illustrating the formation of a fibrin clot. Solid arrows indicate sequential steps in the pathway from the intrinsic, extrinsic and common pathways leading to a fibrin clot. Dotted arrows indicate activation of proteins from one pathway activating proteins in another pathway. Dashed arrows indicate thrombin stimulating its own formation by activating precursor proteins earlier in the pathway.

## EXERCISE AND COAGULATION

Physical activity has been shown to reduce coagulation activity in healthy men and women, as well as clinical populations associated with an increased thrombotic risk (21, 28, 31, 32, 72, 92, 118). Geffken et al. (32) studied the association between physical

activity and inflammation markers on healthy, elderly people. Physical activity was associated with significantly lower markers of inflammation, including C-reactive protein, fibrinogen, factor VIII activity and white blood cell count. Moreover, Connelly, Cooper and Meade (21) interviewed men on the frequency and intensity of their exercise and measured several coagulation factors. They found fibrinogen and factor VII were significantly lower in the men who underwent frequent, strenuous exercise training.

Physical activity has an inverse dose-response relationship on concentrations of factor VII, VIII, and IX, along with fibrinogen, von Willebrand factor, prothrombin fragments 1+ 2 and D-dimer in a healthy population (21, 32, 34, 61, 118). Gris et al. (34) found that three months of physical training significantly decreased levels of FVIII. Through a six month aerobic training program, Lockard et al. (72), found that prothrombin fragments 1 + 2 were significantly reduced in older men and women. Furthermore, TF is substantially reduced with exercise training in various clinical populations including diabetes, peripheral arterial disease, and patients with coronary artery disease (92).

## **EXERCISE AND CANCER**

Aerobic and resistance exercise training results in considerable improvements in physical function, fatigue, mood, and quality of life in cancer patients who are actively receiving treatment or are post treatment (39, 102). Hanna et al. (39) studied 39 patients with 13 different types of cancer as well as cancer survivors. Subjects completed a 16 session comprehensive exercise program of low to moderate intensity aerobic and resistance exercise. Patients reported significantly less fatigue and a significantly elevated

mood upon completion of the exercise program. Total distance walked, as tested by the six minute walk test, was also significantly increased, while perceived exertion remained the same even with an increase in walking distance.

Research also demonstrates that exercise training is practical, safe, and well-tolerated for patients with cancer (56). Through training, cancer patients experience significant health benefits, including increased aerobic capacity, strength, and flexibility, along with an increased quality of life (47, 56, 81). The literature also reveals resistance exercise increases muscle size, strength, and power, along with improved mobility in cancer survivors (62). Kolden et al. (56) had 40 women with primary breast cancer complete an exercise program three times per week for 16 weeks. The program consisted of aerobic, resistance and flexibility exercises. Results of the study showed the exercise program was safe, feasible, and well tolerated. Additionally, the patients ended the program with an increased aerobic capacity, strength, and flexibility, along with decreased distress, enhanced well being, improved functioning and an overall improved quality of life.

Alternatively, there is an inverse relationship of physical activity to malignancy, physical activity can greatly increase cancer prevention (19, 24, 47, 119). John, Koo and Horn-Ross (47) assessed lifetime histories of activity (including, but not limited to: recreation, chores and occupation) in 472 newly diagnosed cases of endometrial cancer compared to 443 controls without. Both higher total lifetime physical activity and moderate intensity activity were associated with reduced cancer risk. Moreover, women with the greatest lifetime activity had the highest reduction in risk. Obese and overweight

women showed a higher risk of cancer. Furthermore, Dosemeci et al. (24) evaluated physical activity based on energy expenditure and sitting hours during work and the risk of cancer. Men and women with cancer in 15 different locations were assessed against men and women without cancer. Cancer risk was elevated in workers with sedentary jobs for cancers of the colon, rectum, melanoma, breast, prostate, and ovary.

## **CANCER AND COAGULATION**

The association between cancer and thrombosis has been established since the 19<sup>th</sup> century (43). Patients with cancer have an increased risk of venous thromboembolism (VTE) compared to patients without cancer (11, 12, 23, 43, 52, 64, 69). A large, population based study of 3,220 cancer patients showed the risk for venous thrombosis is increased seven-fold, dependent on the type and stage of cancer diagnosis (11). Additionally, it is estimated that 15% of cancer patients will develop deep vein thrombosis (23).

Khorana et al. (52) completed a cohort study including hospitalizations at 133 U.S. medical centers between 1995 and 2003. Among 1,015,598 cancer patients, 3.4% were diagnosed with DVT and 1.1% with pulmonary embolism (PE). Levitan et al. (69) analyzed patients with DVT/PE alone, DVT/PE and malignancy, and malignancy alone through the Medicare Provider Analysis and Review Record database. At initial hospitalization, those with malignancy had a higher rate of DVT/PE. Moreover, among patients with DVT/PE and malignancy, the likelihood of death within 183 days of initial hospitalization was greater than those with DVT/PE and no malignancy. Additionally, the

probability of recurrent thromboembolism was higher for patients with DVT/PE and malignancy than those with DVT/PE and no malignancy.

Alternatively, VTE is often an early sign of an underlying malignancy (8, 45, 63, 107, 115). Almost one in five cases of all symptomatic VTE are thought to be cancer-related (42), while cancer risk is higher in patients with VTE. In the first year after admission for VTE, there is a four-fold greater cancer risk over the general population. The incidence of cancer is highest within the first six months of experiencing a VTE, 40% of cases already have metastatic disease at the time of diagnosis (63, 107). VTE is also a marker of long-term cancer risk: even 10 years after the occurrence of VTE, there is a 30% increase in overall cancer incidence (8). Hettiarachchi et al (45) followed 400 patients with deep vein thrombosis (DVT) who were included in a randomized, clinical trial. Seventy of these 400 patients had been diagnosed with malignancy. Among 137 patients with unexplained DVT, 10 new malignancies were diagnosed (7.3%), and 3 new malignancies were diagnosed in 189 patients with secondary DVT (1.6%). Prandoni et al. (88) conducted a study following 250 patients with deep vein thrombosis for two years. Cancer was found in five of the 153 patients with idiopathic venous thrombosis. During follow up, cancer developed in 11 of the 145 patients with idiopathic venous thrombosis, 35 had confirmed recurrent thromboembolism. Of the 35, overt cancer consequently developed in six.

Chew et al. (18), determined the incidence of VTE in cancer patients living in California. Among 235,149 cancer cases, 3,775 were diagnosed with VTE within two years of diagnosis, 463 at the time of cancer diagnosis, and 3,312 subsequently.

Additionally, there was a strong association between metastatic stage cancer at the time of diagnosis and the incidence of thromboembolism. In the cases where thromboembolism was concurrently diagnosed with cancer, 56% were diagnosed with metastatic stage cancer.

Baron et al. (8) assessed cancer incidence during 1989 among 61,998 patients without a previous cancer diagnosis admitted to the hospital between 1965 and 1983 for VTE. They found a large increase in the risk for diagnosis of nearly all cancers at the time of VTE or during the first year after. Moreover, a 30% increase in risk continued in the years to follow. It has also been shown that persistent activation of the coagulation pathway is associated with an increased incidence of malignancy and higher total mortality (77).

VTE represents a leading cause of death in patients with cancer (5, 18, 53, 106, 111), and cancer patients who develop VTE have a significantly worse survival rate than patients who do not experience thrombotic complications (4, 18, 69, 77, 106). Alcalay et al. (4) showed that VTE is a significant predictor of death within one year of cancer diagnosis among patients with local or regional stage disease.

A study was conducted on the Danish Cancer Registry, Danish National Registry, and Danish Mortality Files to obtain data on the survival of patients who received a diagnosis of cancer at the same time as or after VTE (106). Survival rate was compared to matched (cancer, age, sex, year of diagnosis) cancer patients who did not have VTE. Out of 668 patients who had cancer at the time of their VTE, 44% had distant metastasis, compared with 35% of 5371 controls. The one year survival rate was 12% in the group

with cancer at the time of VTE, as compared to 36% in the control group. Therefore, cancer patients with VTE had a 2.2 fold increase in mortality as compared to matched cancer patients without VTE. Furthermore, patients who were diagnosed with cancer one year after the episode of VTE had an increased risk of distant metastasis at the time of diagnosis and a low one year survival rate at one year (38%) compared to the control group (47%).

In addition, Trujillo-Santos et al. (111) assessed the 30 day outcome in all women with active cancer in the RIETE registry. Enrolled were 2,474 women with cancer and acute VTE. Of the 13% of patients who passed away within the thirty days, 3% died of pulmonary embolism. It was also concluded that fatal PE was more common in women with breast, colorectal, lung and pancreatic cancer.

Patients with cancer who develop VTE are also at higher risk for recurrent thrombotic complications than VTE patients without malignancy (41, 46, 69, 89). Levitan et al. (69) showed that patients with malignancy and DVT or PE have a threefold higher risk of recurrent thromboembolic disease and death than patients with DVT or PE without malignancy. Patients with malignancy while also receiving chemotherapy have a more than 4 fold increased risk of recurrence (41).

### ***Primary Contributors to Clotting in Cancer Patients***

The primary contributors to VTE in cancer patients include tumor type and stage, along with various cancer treatments (38, 43, 58, 66, 69, 103). The highest rates of VTE are found in patients with cancers of the pancreas, breast, stomach, uterus, kidney, lung, and primary brain tumors (8, 18, 51, 69, 97, 99). Advanced stages of malignancy also

leads to higher risk for VTE (12, 89). Patients with distant metastases have an approximate 2 fold increased risk of venous thrombosis than patients without distant metastases (12). Furthermore, the risk for VTE recurrence is higher in patients with more advanced disease, in patients with metastases there is a five-fold higher recurrence rate, compared to a two to threefold higher risk in patients with local tumors (89).

One treatment approach to cancer is chemotherapy. Chemotherapy drugs work by attacking reproducing cells in the body. There are three possible goals for chemotherapy treatment: cure, control or palliate. Chemotherapy is different from radiation therapy and surgery in that it can be used systemically, to treat cancer throughout the body rather than one specific location. Chemotherapy is an independent risk factor for VTE (43, 54, 58, 67). Compared with the general population, patients undergoing chemotherapy have a two to six fold increased risk of VTE (12, 43, 99). In a population based study, cancer was associated with a 4 fold increase in thrombotic risk, whereas, in patients treated with chemotherapy, the risk increased to 6.5 fold (43, 103). Khorana et al. (53) analyzed causes of death in cancer patients receiving chemotherapy. Among non-cancer causes of death, thrombosis was a leading contributor, responsible for 9.2% of deaths out of 141 people. It has also been shown that the risk of VTE declines after completion of chemotherapy (68). Levine et al. (68) compared 12 weeks of hormonal therapy with 36 weeks of chemotherapy in women with breast cancer to women with breast cancer not undergoing these treatments. Of these patients, 6.8% experienced thrombosis as opposed to no thrombotic events in patients without therapy.

Hormone therapy is another form of treatment for cancer patients. Hormone therapy consists of drugs that are sex hormones or hormone like drugs that change the action or production of female or male hormones. They may slow the growth of certain cancers that respond to natural hormones in the body. Hormonal therapy is yet another contributor to venous thrombosis (12, 67, 68). Hormonal therapy leads to a 1.6 fold increased risk of venous thrombosis (12). Studies also show that the combination of chemotherapy and hormonal therapy is associated with more thromboembolic complications than chemotherapy alone or hormonal therapy alone (99).

Cancer patients sometimes develop anemia due to cancer treatment. To treat this, patients are often given erythropoiesis-stimulating agents (ESAs). These agents have been shown to increase thrombotic events in patients with cancer (13, 44). Published from a systematic review of 57 trials, 6% of cancer patients treated with ESAs had thromboembolic events, compared with 3% of controls (13). Moreover, medication with erythropoietin leads to an overall significantly poorer cancer outcome (44, 70). Henke et al. (44) studied 351 patients with head and neck cancer undergoing radiation therapy. Subjects were randomly assigned to take either placebo or epoetin  $\beta$  throughout radiation treatment to correct for anemia. Anemia was taken care of in the patients taking erythropoietin; however, overall cancer outcome was worse in these individuals. Tumor progression and death was higher in patients medicated with epoetin  $\beta$  than in patients taking placebo.

Hospitalization is another independent risk factor for VTE (43, 58). Khorana et al. (52) reviewed hospitalization records in cancer patients between 1995 and 2003. During

hospitalization, venous thromboembolic events were reported in 41,666 patients (4.1%). Mortality was significantly greater among patients who developed VTE compared with patients who did not over the course of the study (16.3% vs. 6.3%). Shen and Pollock (101) evaluated 578 patients who had fatal or nonfatal PE in patients with malignancy and patients without malignancy. PE occurred in 17% and was fatal in 14% of cancer patients, as compared to 13% and 8% in noncancer patients. They found that one of every seven hospitalized cancer patients died due to PE. Hospitalized patients with cancer have twice the incidence of VTE, PE and deep venous thrombosis as those without (108).

Surgery is the oldest form of cancer treatment and is done for many reasons in cancer patients. Some of the various surgeries include: prophylactic, diagnostic, staging, curative and palliative. Cancer related surgery and the extended postoperative period are well-known high risk settings for VTE (43). It has been shown that the overall 30 day postoperative VTE rate is 3.5%, with rates ranging by type of surgery performed from 1.8-13.2%, example surgeries included were pulmonary resection, nephrectomy and prostatectomy (38). Patients who undergo surgery are at a twofold higher risk for postoperative VTE compared with noncancer patients undergoing the same procedure (3, 43, 87). Agnelli et al. (3) studied cancer patients undergoing either general, urologic or gynecologic surgery. Clinically overt VTE affected 2.1% of patients. Moreover, VTE was the most common cause of death at 30 days after surgery, responsible for 43% of deaths (3).

Furthermore, central venous catheters (CVC) are an independent risk factor for VTE (9, 14, 43, 66, 91). Central venous catheters are used for numerous reasons in

patients with cancer. Examples include: long term therapy, the ability to give several drugs at one time and continuous infusion therapy. Almost 5% of cancer patients with CVCs develop CVC related DVT (66). Revel-Vilk et al. (91) reported CVC in children and young adults significantly increases risk for thrombosis and this risk increases by catheter type, insertion point and family history. Peripherally inserted central catheters lead to a higher risk of DVT over Hickman catheters or Port-a-Caths. Catheters inserted in the superior vena cava lead to higher risk of DVT over catheters inserted at the right atrium. Catheters inserted in the angiography suite also lead to higher risk of DVT over insertion in the operation room.

### ***Changes in Hemostasis that may lead to Clotting***

Venous thrombosis is generally preceded by changes in blood composition and blood flow that promote the creation of a blood clot (27, 75). High levels of fibrinogen, factor VIII, and von Willebrand factor independently increase thrombotic risk (6, 112). Tsai et al. (112) assessed adults with no history of VTE, cancer or warfarin use to see whether higher levels of coagulation markers were risk factors for VTE. In subjects who developed VTE (within an average of eight years from baseline assessments), elevated factor VIII and von Willebrand factor levels were common, independent, and dose-dependent risk factors for venous thromboembolism, and an elevated factor VII level was a possible risk factor.

Patients with cancer commonly experience these changes in blood composition and blood flow. Plasma markers of clotting activation such as fibrinogen, fibrinogen turnover rate, factor VII, factor VIII, thrombin-antithrombin complex, prothrombin

fragments 1+ 2, d-dimer, and von Willebrand factor, are elevated in patients with cancer (26, 33, 55, 93, 96, 112, 121). Moreover, high levels of d-dimer, prothrombin fragments 1 + 2, and factor VIII independently predict VTE in patients with cancer (7, 116). Furthermore, a prolonged prothrombin time and elevated levels of prothrombin fragments 1 + 2 indicate a more advanced cancer stage (60). Goldenberg, Kahn and Solymoss (33) evaluated coagulation markers in (a) cancer patients with acute DVT, (b) non-cancer patients with acute DVT and (c) cancer patients with no thrombosis. They found that levels of thrombin-antithrombin III complex, prothrombin fragments 1+ 2 and von Willebrand factor antigen were significantly higher in the DVT + cancer group than the cancer control or DVT control groups. Additionally, Palumbo et al. (84) have shown that the absence of fibrinogen strongly diminishes the metastatic potential of an aggressive tumor. Moreover, higher levels of fibrinogen and d-dimer are associated with a poor prognosis (16).

Furthermore, persistent activation of the coagulant pathway is associated with an increased incidence of clinical malignancy, especially in the digestive tract (77). Miller et al. (77) studied healthy men to investigate the connection between the coagulant pathway and cancer incidence. Persistent activation of the coagulation pathway was classified as exceeding the upper quartiles of the population distribution of prothrombin fragments 1 + 2 and fibrinopeptide A on two consecutive annual exams. Cancer incidence rates in men developing persistent activation were compared to men without this condition. They found that persistent activation of the hemostatic pathway was associated with activation through the coagulation pathway. In patients with persistent coagulation activation, total

mortality was almost double that in other men, this finding was attributed to a higher death rate from all cancers combined.

Tissue factor (TF), an initiator of blood coagulation, is also commonly expressed in a variety of malignancies, including glioma, breast cancer, lung cancer, leukemia, colon cancer and pancreatic cancer (22, 35-37, 48, 79, 100, 110, 113, 114). Data have shown that cancer patients with high TF expression have a VTE rate of 26.3% (50). High levels of TF expression are shown to be an independent prognostic factor for poor survival in patients with solid tumors (57, 73, 114, 117). The plasma and breast cancer tissue of women with breast cancer were examined to evaluate the significance of TF expression in malignancy (114). The concentration of plasma TF was associated with tissue TF expression in both the tumor and stroma. Tumor TF expression, established by a multivariate analysis, is an independent prognostic indicator for overall survival.

Vrana et al. (117) found that the recruitment and/or activation of TF expressing stromal cells is an early event to invasive breast cancer. It has also been shown that tumor cells often induce the local expression of soluble hemostatic factors or their receptors in adjacent stromal cells (90). Mueller et al. (78) demonstrated that cell surface expression of TF contributes to melanoma progression by allowing metastatic cells to provide essential signals for prolonged adhesive interactions and/or movement of tumor cells across the endothelium, resulting in successful tumor metastases.

Cancer patients may also have abnormal clotting times, although research on these measures produces inconsistent results (2, 16, 55). Kirwan et al. (55) found that before chemotherapy, patients with breast cancer have prolonged clotting times of

activated partial thromboplastin time (APTT) and prothrombin time (PT). However, after chemotherapy treatment began (within 24 hours of receiving chemotherapy and up to three months thereafter) patients showed a significant shortening of APTT. Conversely, PT was prolonged further in patients after chemotherapy. Moreover, research has also shown that a prolonged PT is associated with poor prognosis (16, 55). On the contrary, some studies show a prolongation in APTT and a shortening in PT (17, 86), while other investigations show no change in either APTT or PT (76).

### **Pharmacological Anticoagulant Treatment**

In light of the substantial prevalence of thrombosis in cancer patients, anticoagulant medications are generally recommended (49). Studies of the use of anticoagulant drugs, however, produce inconsistent results and reflect the risks associated with such a treatment. A systematic review of 11 studies evaluating the impact of pharmacologic anticoagulation in cancer patients revealed a significant decrease in mortality in patients treated with anticoagulants (59). However, major bleeding complications were observed with anticoagulant use, only reaching statistical significance in warfarin studies (59). A recent clinical study of oral anticoagulant use by cancer patients reported hemorrhagic episodes in 14.8% of participants (96).

Palareti et al. (83) reported the effects of anticoagulants on patients who had cancer versus those without malignancy. The rates of major, minor and total bleeding were significantly higher in cancer patients, as well as an increased risk of recurrent thrombosis. Although, Lee et al. (65) compared the effects of a low molecular weight heparin (LMWH) with an oral anticoagulant in thrombosis prevention in patients with

cancer. While the significant risk of major bleeding in both groups was the same, the probability of recurrent thrombosis (17% vs. 9%) and mortality rate (39% vs. 49%) was lower in the LMWH group than the oral anticoagulant. This suggests LMWH reduce the risk of recurrent thromboembolism without increasing the risk of bleeding. Prandoni et al. (89) found that the 12 month incidence of recurrent thromboembolism in cancer patients taking anticoagulants is 20.7% compared to 6.8% in patients without cancer. They also found that cancer patients are more likely to develop major bleeding during anticoagulation treatment than those without malignancy, at 12.4% and 4.9% respectively. Bona, Hickey and Wallace (15) demonstrated the rate of recurrent thrombosis is sixfold higher in patients with cancer when treated with anticoagulants.

Given the risks associated with pharmacological anticoagulation, there is great need for alternative therapies that effectively minimize thrombotic potential without introducing additional risks to the patient.

## **SUMMARY**

There is a substantial prevalence and mortality risk of DVT in cancer patients (5, 12, 43). This is primarily due to the type and stage of cancer, along with the treatment received and side effects arising from treatment (12, 13, 43, 103). Anticoagulants are the current recommendation to reduce thrombotic potential in cancer patients, nevertheless, there are several risks associated with pharmacological anticoagulation (49, 59, 96). Regular exercise training results in numerous benefits for the cancer patient (39, 47, 56, 62, 81, 102, 119); however, there is no research examining potential improvements in thrombotic risk in this population following a period of exercise training. Thus, the

purpose of this investigation was to examine the changes in thrombotic potential after a period of structured exercise training. Based upon previous findings with exercise and hemostasis, it was hypothesized that exercise training would reduce coagulation activity more than usual and customary care.

## **CHAPTER III**

### **Methodology**

The purpose of this study was to examine the hemostatic adaptations following exercise training in patients with cancer compared to a matched group of patients receiving usual and customary care. All procedures were reviewed and approved by the Institutional Review Boards at Ball State University and IU Health Ball Memorial Hospital.

### **Subject Sample**

Subjects were recruited from the patients treated at IU Health - Ball Memorial Hospital's Cancer Center. Participants were men and women with an active cancer diagnosis who were at least 18 years of age, non-smokers, and who weighed at least 50 kg . Subjects were also free from known cardiovascular or metabolic disease. Use of anticoagulant medications was cause for exclusion from the study. Upon joining the study, subjects chose to participate in either the 12 week exercising group or a non-exercising, 12 week control group. Participants had no physical limitations that prevented them from participating in the aerobic exercise program described below. Ten subjects volunteered for this study, five in the exercise group and five in the non-exercising

control group. Two participants passed away from the disease during the course of the study and were not included in the final analyses.

### **Experimental Design**

All participants completed a written informed consent, and general health history questionnaire. Participants also signed a HIPPA document for the release of health information for research purposes related to this study. Prior to, and 24 hours after completion of the program, the subject was interviewed about the number of hours spent asleep and the amount of time spent engaged in physical activity using a standard, validated physical activity questionnaire (98). The subject was further asked to describe the intensity of activity as Light, Moderate, Hard or Very Hard. Average physical activity during the prior seven days was quantified in kilocalories per kilogram of body weight per day. A venous blood sample was also obtained at this time.

#### Control Group:

The non-exercising control group completed a 12 week period of usual and customary care that did not include the exercise program.

#### Exercise Group:

The exercise group completed training which lasted 12 weeks. Two sessions per week were completed for each of the first two weeks, after which patients participated in 3 sessions per week for a total of 34 exercise sessions. Data from subjects who participated in fewer than 80% of the prescribed sessions or who required more than 16

weeks to complete 34 sessions were not included in final analyses. Aerobic exercise consisted of walking in a hallway or on a treadmill, or seated activity on a recumbent cross-training machine (Nu-Step® TRS 4000). Each patient's exercise prescription was tailored to the individual based on current fitness level as determined by the 6-minute walk test (71) and any limitations to exercise. Severely deconditioned patients were given a target heart rate range associated with 30-45% of heart rate reserve (HRR), which equates to light to moderate intensity. Less sedentary, more fit patients were given appropriate HR ranges within 45-60% of HRR (moderate intensity). Using the Borg 6-20 category-ratio scale (80), subjective ratings of perceived exertion were used as an adjunct to target HR ranges to determine appropriate exercise intensity. Exercise duration gradually progressed by adding 3-5 minutes per session as tolerated until the patient was able to exercise continuously for 40 minutes. Intensity was likewise increased over the 12 weeks of training through small increases in walking speed or resistance on the recumbent stepper, as tolerated by the patient. Exercise progression was carefully monitored by CEP staff, and was determined on a session by session basis for each individual patient.

Each exercise session began with acquisition of resting heart rate, blood pressure and oxygen saturation. Oral temperature was taken if the patient reported unusual symptoms related to fever or other illness. Exercise participation was prohibited if oral temperature exceeded 100°F, oxygen saturation was <88%, resting systolic blood pressure was >200 mmHg or diastolic BP was >110 mmHg.

All training sessions were conducted in the Cancer Exercise Program (CEP) in the Cancer Center at Ball Memorial Hospital in Muncie, IN. The CEP is a structured exercise program that is directly supervised by a Registered Nurse and staffed by master's trained exercise physiologists with expertise in cancer and exercise prescription. All exercise sessions were monitored by CEP personnel.

### **Participant Benefits**

Voluntary educational opportunities were provided to each study participant. Classes covering different topics such as fatigue and pain, stress management and nutrition were offered each week. Upon completion of the study, each participant was compensated \$30. Subjects were also given any information collected as part of their participation in the project.

### **Blood Sampling and Assays**

Venous blood samples were obtained at baseline and after approximately 12 weeks (34 exercise sessions) of study participation. Each patient's blood samples were obtained at the same time of day to control for diurnal variations in coagulation. Blood samples were collected after a 12 hour fast and 24 hours without caffeine, alcohol or exercise. Platelet-poor plasma was isolated within 60 min of collection by centrifugation at 1,500 g for 20 min at 4°C. Plasma aliquots were frozen and stored at -80°C until assayed.

Fibrinogen was measured as a percent relative to normal pooled plasma using a coagulometer (Start4®, Diagnostica Stago; Parsippany NJ) and according to

manufacturer instructions. Clotting time assays (activated partial thromboplastin time, prothrombin time) were determined using standard methods according to manufacturer specifications (Start4®, Diagnostica Stago; Parsippany NJ). Factor VIII was measured by ELISA (VisuLize™; Affinity Biologicals; Ancaster, ON, Canada).

### **Statistical Analysis**

Changes in each variable across time and differences between groups were assessed using two-factor analyses of variance (ANOVA). Subsequent pairwise comparisons were made using Tukey's HSD method. A priori statistical significance for all analyses were set at  $\alpha=0.05$ .

## **CHAPTER IV**

### **Research Manuscript**

**This manuscript was prepared in accordance with the instructions for authors for  
the journal: Medicine and Science in Sports and Exercise**

## ABSTRACT

**Background:** Thrombosis is a common and critical consequence of cancer. Changes in thrombotic potential were examined after exercise training in patients with cancer.

**Methods:** Eight cancer patients ( $65 \pm 11$  yrs) completed this study, five exercising and three non-exercising controls. Venous blood samples were obtained at baseline and after approximately 12 weeks of study participation. Weekly physical activity was measured using a standard, validated physical activity questionnaire. APTT, PT, fibrinogen and factor VIII were measured before and after the 12-week intervention. **Results:** A trend ( $p=0.067$ ) was observed with fibrinogen, concentrations decreased in the exercise group ( $355 \pm 49.3$  mg/dL to  $331 \pm 19.5$  mg/dL), but increased in the control group ( $341 \pm 52.4$  mg/dL to  $384 \pm 107.9$  mg/dL). Physical activity significantly decreased over time, exercise:  $18 \pm 31\%$  and control:  $55 \pm 50\%$ . **Conclusions:** Regular exercise may reduce coagulation potential in cancer patients more than usual and customary care.

**Key Words:** Thrombosis, venous thromboembolism, coagulation

## INTRODUCTION

There is a substantial prevalence and mortality risk of deep venous thrombosis (DVT) in cancer patients (1, 5, 17). Evidence of the association between cancer and thrombosis was first identified in the 19<sup>th</sup> century (17). Patients with cancer have an increased risk of venous thromboembolism (VTE) compared to patients without cancer (4, 17). Alternatively, VTE is often an early sign of an underlying malignancy (50). Almost one in five cases of all symptomatic VTEs are thought to be cancer-related (16), while cancer risk is higher in patients with VTE.

Heightened rates of VTE transpire in cancer patients attributable to multiple causes (14, 17, 24, 28, 45). The highest rates of VTE are found in patients with cancers of the pancreas, breast, stomach, uterus, kidney, lung, and primary brain tumors (2, 7, 20, 30, 41, 43). Compared to cancer patients without distant metastases, patients with distant metastases have an approximate 2 fold increased risk of venous thrombosis (5). Chemotherapy, central venous catheters, and hospitalization are independent risk factors for VTE in patients with cancer (3, 5, 17, 21, 24, 28, 29, 36). Compared with the general population, patients undergoing chemotherapy have a two to six fold increased risk of VTE (5, 17, 43). Additionally, hormonal therapy leads to a 1.6 fold increased risk of venous thrombosis, compared to cancer patients who do not undergo hormonal therapy (5). Cancer related surgery and the extended postoperative period are also well-known high risk settings for VTE (17).

Because of the magnitude and serious nature of thrombotic risk in cancer patients, clinicians have sought to reduce thrombotic risk in cancer patients. Anticoagulant medications are now commonly prescribed to both hospitalized and ambulatory cancer patients. Nevertheless, there are several risks, particularly bleeding complications, associated with pharmacological anticoagulation (19, 25, 40). Regular exercise training results in numerous benefits for the cancer patient and is known to reduce thrombotic potential in healthy individuals and other clinical populations (15, 18, 23, 27, 34, 44, 52); however, there is no research examining potential improvements in thrombotic risk for cancer patients following a period of exercise training. Therefore, the purpose of this investigation was to examine the changes in thrombotic potential after a period of structured exercise training in patients with cancer. It was hypothesized that exercise training would reduce coagulation activity more than usual and customary care.

## **METHODS**

All study procedures were reviewed and approved by the Institutional Review Boards at Ball State University and IU Health Ball Memorial Hospital. Prior to participation, each subject provided written informed consent.

### *Participants*

Subjects were recruited from the patients treated at IU Health - Ball Memorial Hospital's Cancer Center. Participants were men and women with an active cancer diagnosis who were at least 18 years of age, non-smokers, and who weighed at least 50 kg. Subjects were also free from known cardiovascular or metabolic disease. Use of anticoagulant medications was cause for exclusion from the study. Upon joining the

study, subjects chose to participate in either the 12 week exercising group or a non-exercising, 12 week control group. Participants had no physical limitations that prevented them from participating in the aerobic exercise program described below. Ten subjects volunteered for this study, five in the exercise group and five in the non-exercising control group. Two participants passed away from the disease during the course of the study and were not included in the final analyses. Physical characteristics of the subjects are shown in Table 1 and characteristics of cancer type and treatment are shown in Table 2.

### *Experimental Design*

All participants completed a written informed consent, and general health history questionnaire. Participants also signed a HIPAA document for the release of health information for research purposes related to this study. Prior to, and 24 hours after completion of the program, the subject was interviewed about the number of hours spent asleep and the amount of time spent engaged in physical activity using a standard, validated physical activity questionnaire (42). The subject was further asked to describe the intensity of activity as Light, Moderate, Hard or Very Hard. Average physical activity during the prior seven days was quantified in kilocalories per kilogram of body weight per day. A venous blood sample was also obtained at this time.

*Control Group:* The non-exercising control group completed a 12 week period of usual and customary care that did not include the exercise program.

*Exercise Group:* All training sessions were conducted in the Cancer Exercise Program (CEP) in the Cancer Center at IU Health - Ball Memorial Hospital in Muncie, IN. The exercise group completed 34 exercise sessions, designed to transpire over 12 weeks. Two sessions per week were completed for each of the first two weeks, after which patients participated in 3 sessions per week for a total of 34 exercise sessions. Data from subjects who participated in fewer than 80% of the prescribed sessions or who required more than 16 weeks to complete 34 sessions were not included in final analyses. Each exercise session began with acquisition of resting heart rate, blood pressure and oxygen saturation. Aerobic exercise consisted of walking in a hallway or on a treadmill, or seated activity on a recumbent cross-training machine (Nu-Step® TRS 4000). Each patient's exercise prescription was tailored to the individual based on current fitness level as determined by the 6-minute walk test (31) and any limitations to exercise. Severely deconditioned patients were given a target heart rate range associated with 30-45% of heart rate reserve (HRR), which equates to light to moderate intensity. Less sedentary, more fit patients were given appropriate HR ranges within 45-60% of HRR (moderate intensity). Using the Borg 6-20 category-ratio scale (33), subjective ratings of perceived exertion were used as an adjunct to target HR ranges to determine appropriate exercise intensity. Exercise duration gradually progressed by adding 3-5 minutes per session as tolerated until the patient was able to exercise continuously for 40 minutes. Intensity was likewise increased over the 12 weeks of training through small increases in walking speed or resistance on the recumbent stepper, as tolerated by the patient. Exercise progression was carefully monitored by CEP staff, and was determined on a session by session basis for each individual patient.

### *Blood Sampling and Assays*

Venous blood samples were obtained by clean venipuncture with minimal stasis at baseline and after approximately 12 weeks (34 exercise sessions) of study participation. Each patient's blood samples were obtained at the same time of day to control for diurnal variations in coagulation, and after 20 minutes of seated rest. Blood samples were collected after a 12 hour fast and 24 hours without caffeine, alcohol or exercise. Platelet-poor plasma was isolated within 60 min of collection by centrifugation at 1,500 g for 20 min at 4°C. Plasma aliquots were frozen and stored at -20°C until assayed.

Fibrinogen was measured as a percent relative to normal pooled plasma using a coagulometer (Start4®, Diagnostica Stago; Parsippany NJ) and according to manufacturer instructions. Clotting time assays (activated partial thromboplastin time, prothrombin time) were determined using standard methods according to manufacturer specifications (Start4®, Diagnostica Stago; Parsippany NJ). Factor VIII was measured by ELISA (VisuLize™; Affinity Biologicals; Ancaster, ON, Canada).

### *Statistical Analysis*

Statistical analyses were done using IBM SPSS v20.0. Changes in each variable across time and differences between groups were assessed using two-factor analyses of variance (ANOVA). A priori statistical significance for all analyses were set at  $\alpha=0.05$ .

## RESULTS

Activated partial thromboplastin time (APTT) significantly decreased from baseline to completion of the 12 week protocol in exercise ( $37.4 \pm 3.8$  s to  $33.9 \pm 1.5$  s) and control ( $34.6 \pm 4.4$  s to  $31.5 \pm 2.3$  s) groups, ( $p < 0.05$ ). However, there were no significant differences between groups and no time x group interaction.

Prothrombin time (PT) significantly decreased from baseline to completion of the 12 week protocol in both exercise ( $13.2 \pm 0.5$  s to  $11.9 \pm 0.5$  s) and control ( $14.7 \pm 0.8$  s to  $12.2 \pm 1.2$  s) groups ( $p < 0.05$ ). However, there were no significant time x group interactions.

Fibrinogen levels were not significantly different between groups and there was no main effect of time ( $p > 0.05$ ). Although the time x group interaction did not rise to the level of statistical significance, a trend was observed ( $p=0.067$ ) and the associated effect size was very high ( $\eta^2 = 0.70$ ). Figure 1 indicates the exercise group experienced a decrease in fibrinogen levels from baseline to post test measurements; whereas, the control group experienced an increase in fibrinogen levels from baseline to post test measurements.

There were no significant differences found with Factor VIII activity between group and no time x group interactions ( $p < 0.05$ ).

As shown in Figure 2, a significant main effect of time was observed for physical activity, indicating both groups became less active during the study period ( $p=0.05$ ).

However, there were no significant differences between groups ( $p < 0.05$ ) and no time x group interaction.

## **DISCUSSION**

The purpose of this study was to examine the changes in thrombotic potential after a period of structured exercise training in patients with cancer. The main finding from this investigation was that physical training appeared to reduce fibrinogen concentration in patients with cancer whereas fibrinogen concentration increased in patients participating in the control group. This finding supports the hypothesis that exercise training would reduce thrombotic potential. Earlier studies have found that exercise training reduces coagulation activity in healthy individuals as well as other clinical populations (8, 12, 13, 32, 37, 51). Specifically, among other coagulation measures, fibrinogen is shown to decline (8, 12, 51). In the present study, the small sample size may have limited statistical power, thus precluding the ability to observe statistically significant changes. However, the interaction trend and effect size suggest that exercise training provoked a potentially clinically important decrease in fibrinogen that was not observed in the control group. Fibrinogen is an acute phase protein, whose plasma concentrations will increase or decrease in response to inflammation. Research demonstrates that physical activity mitigates inflammation (9). Thus the decrease in fibrinogen levels in the exercise group may have resulted from a reduction in inflammation due to the exercise training regimen.

Other findings from the present study do not corroborate the fibrinogen results. There were no significant differences between groups observed for APTT and PT.

Surprisingly, there was a significant shortening in clotting times observed with both groups over time, possibly indicating changes in the blood that favor thrombotic development. Studies of clotting times in patients with cancer have produced inconsistent results (6, 22, 35). A possible explanation for the overall reduction in clotting time is related to seasonal changes in hemostatic activity. Increased plasma concentrations of fibrinogen, factor VII, d-dimer, von Willebrand factor and thrombin are seen in the winter months (10, 38, 39, 47, 53). In the present study, participants completed baseline measurements in the fall, (August through November), and post test measurements for all subjects were completed in the winter months (December through February). On the other hand, van den Burg et al. (49) showed the unfavorable seasonal changes in hemostatic markers are negated by exercise training, which may also explain the fibrinogen findings discussed above.

The present study observed no significant differences in coagulation factor VIII for either group. Earlier studies show regular exercise is associated with reductions in thrombotic potential, including coagulation factor VIII (11, 12, 37, 51). There is an inverse dose-response relationship of exercise intensity with hemostatic and inflammatory variables (46, 51). Exercising at higher intensity decreases serum levels of fibrinogen, factor VII and factor VIII more than exercise at a lower intensity (46). Wannamethee et al. (51) demonstrated a significant and inverse dose-response relationship of physical activity to hemostatic measures of fibrinogen, plasma and blood viscosity, platelet count, coagulation factors VIII and IX, von Willebrand factor and D-dimer. In the present study, participants in the exercise group performed mainly light

with some moderate intensity exercise. Thus, the exercise regimen may not have been strenuous enough to affect factor VIII as well as the clotting times.

Another potential explanation for the lack of significant findings with regard to PT, APTT and factor VIII is related to overall physical activity. Previous studies indicate physical activity is correlated to reduced levels of hemostatic markers such as fibrinogen, coagulation factors VIII and X, von Willebrand factor and d-dimer (12, 26, 51). Participants in both groups of the present study decreased overall weekly physical activity levels from baseline to conclusion of the investigation. One might predict that subjects who participated in a supervised exercise training program would therefore increase physical activity levels. However, we suspect that the seasonal change from fall to winter months throughout the 12 week protocol may have affected the physical activity levels of the participants.

One limitation of this study was the small sample size, which may have hindered our statistical power. Controlling for or limiting the medications used by our patients was another constraint. Also, as described above, the light intensity of exercise in the present study may have resulted in the non-significant findings of APTT, PT and factor VIII. Future research is warranted to examine the changes in thrombotic potential after a period of structured exercise training in patients with cancer using higher exercise intensity ranges and a sufficient sample size. Future research should also take seasonal variation on hemostatic measures and physical activity into account.

In conclusion, the present study indicates a formal exercise training program may reduce coagulation potential in cancer patients more than usual and customary care. It is

speculated that more intense exercise programs that also increase overall physical activity are likely to induce even greater reductions in thrombotic risk. Results of this study may be important for medical and exercise professionals who work with individuals with cancer.

## REFERENCES

1. Ambrus JL, Ambrus CM, Mink IB, and Pickren JW. Causes of death in cancer patients. *J Med.* 1975;6(1):61-4.
2. Baron JA, Gridley G, Weiderpass E, Nyren O, and Linet M. Venous thromboembolism and cancer. *Lancet.* 1998;351(9109):1077-80.
3. Beckers MM, Ruven HJ, Seldenrijk CA, Prins MH, and Biesma DH. Risk of thrombosis and infections of central venous catheters and totally implanted access ports in patients treated for cancer. *Thromb Res.* 2010;125(4):318-21.
4. Blom JW, Doggen CJ, Osanto S, and Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293(6):715-22.
5. Blom JW, Vanderschoot JPM, Oostindier MJ, Osanto S, van der Meer FJM, and Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66 329 cancer patients: results of a record linkage study. *J. Thromb. Haemost.* 2006;4(3):529-35.
6. Buccheri G, Ferrigno D, Ginardi C, and Zuliani C. Haemostatic abnormalities in lung cancer: prognostic implications. *Eur J Cancer.* 1997;33(1):50-5.
7. Chew HK, Wun T, Harvey D, Zhou H, and White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med.* 2006;166(4):458-64.
8. Connelly JB, Cooper JA, and Meade TW. Strenuous exercise, plasma fibrinogen, and factor VII activity. *Br Heart J.* 1992;67(5):351-4.
9. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology.* 2002;13(5):561-8.
10. Frohlich M, Sund M, Russ S, Hoffmeister A, Fischer HG, Hombach V, and Koenig W. Seasonal variations of rheological and hemostatic parameters and acute-phase reactants in young, healthy subjects. *Arterioscler Thromb Vasc Biol.* 1997;17(11):2692-7.
11. Gardner AW, and Killewich LA. Association between physical activity and endogenous fibrinolysis in peripheral arterial disease: a cross-sectional study. *Angiology.* 2002;53(4):367-74.
12. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, and Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol.* 2001;153(3):242-50.
13. Gris JC, Schved JF, Feugeas O, Aguilar-Martinez P, Arnaud A, Sanchez N, and Sarlat C. Impact of smoking, physical training and weight reduction on FVII, PAI-1 and hemostatic markers in sedentary men. *Thromb Haemost.* 1990;64(4):516-20.
14. Hammond J, Kozma C, Hart JC, Nigam S, Daskiran M, Paris A, and Mackowiak JI. Rates of Venous Thromboembolism Among Patients with Major Surgery for Cancer. *Ann Surg Oncol.* 2011.
15. Hanna LR, Avila PF, Meteer JD, Nicholas DR, and Kaminsky LA. The effects of a comprehensive exercise program on physical function, fatigue, and mood in patients with various types of cancer. *Oncol Nurs Forum.* 2008;35(3):461-9.
16. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, and Melton LJ, 3rd. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med.* 2002;162(11):1245-8.

17. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, and Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000;160(6):809-15.
18. John EM, Koo J, and Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev.* 2010;19(5):1276-83.
19. Khorana AA. The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: strategies for improving VTE prophylaxis in hospitalized cancer patients. *Oncologist.* 2007;12(11):1361-70.
20. Khorana AA, and Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol.* 2009;27(29):4839-47.
21. Khorana AA, Francis CW, Culakova E, and Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer.* 2005;104(12):2822-9.
22. Kirwan CC, McDowell G, McCollum CN, Kumar S, and Byrne GJ. Early changes in the haemostatic and procoagulant systems after chemotherapy for breast cancer. *Br J Cancer.* 2008;99(7):1000-6.
23. Kolden GG, Strauman TJ, Ward A, Kuta J, Woods TE, Schneider KL, Heerey E, Sanborn L, Burt C, Millbrandt L, Kalin NH, Stewart JA, and Mullen B. A pilot study of group exercise training (GET) for women with primary breast cancer: feasibility and health benefits. *Psychooncology.* 2002;11(5):447-56.
24. Kroger K, Weiland D, Ose C, Neumann N, Weiss S, Hirsch C, Urbanski K, Seeber S, and Scheulen ME. Risk factors for venous thromboembolic events in cancer patients. *Ann Oncol.* 2006;17(2):297-303.
25. Kuderer NM, Khorana AA, Lyman GH, and Francis CW. A meta-analysis and systematic review of the efficacy and safety of anticoagulants as cancer treatment: impact on survival and bleeding complications. *Cancer.* 2007;110(5):1149-61.
26. Lakka TA, and Salonen JT. Moderate to high intensity conditioning leisure time physical activity and high cardiorespiratory fitness are associated with reduced plasma fibrinogen in eastern Finnish men. *J Clin Epidemiol.* 1993;46(10):1119-27.
27. LaStayo PC, Marcus RL, Dibble LE, Smith SB, and Beck SL. Eccentric exercise versus usual-care with older cancer survivors: the impact on muscle and mobility- an exploratory pilot study. *BMC Geriatr.* 2011;11:5.
28. Lee AY, Levine MN, Butler G, Webb C, Costantini L, Gu C, and Julian JA. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. *J Clin Oncol.* 2006;24(9):1404-8.
29. Levine MN. Prevention of thrombotic disorders in cancer patients undergoing chemotherapy. *Thromb Haemost.* 1997;78(1):133-6.
30. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, and Rimm AA. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore).* 1999;78(5):285-91.
31. Lipkin DP, Scriven AJ, Crake T, and Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J (Clin Res Ed).* 1986;292(6521):653-5.
32. Lockard MM, Gopinathannair R, Paton CM, Phares DA, and Hagberg JM. Exercise training-induced changes in coagulation factors in older adults. *Med Sci Sports Exerc.* 2007;39(4):587-92.

33. Noble BJ, Borg GA, Jacobs I, Ceci R, and Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc.* 1983;15(6):523-8.
34. Oliveira MM, Souza GA, Miranda Mde S, Okubo MA, Amaral MT, Silva MP, and Gurgel MS. [Upper limbs exercises during radiotherapy for breast cancer and quality of life]. *Rev Bras Ginecol Obstet.* 2010;32(3):133-8.
35. Pectasides D, Tsavdaridis D, Aggouridaki C, Tsavdaridou V, Visvikis A, Tsatalas K, and Fountzilas G. Effects on blood coagulation of adjuvant CNF (cyclophosphamide, novantrone, 5-fluorouracil) chemotherapy in stage II breast cancer patients. *Anticancer Res.* 1999;19(4C):3521-6.
36. Revel-Vilk S, Yacobovich J, Tamary H, Goldstein G, Nemet S, Weintraub M, Paltiel O, and Kenet G. Risk factors for central venous catheter thrombotic complications in children and adolescents with cancer. *Cancer.* 2010;116(17):4197-205.
37. Rigla M, Fontcuberta J, Mateo J, Caixas A, Pou JM, de Leiva A, and Perez A. Physical training decreases plasma thrombomodulin in type I and type II diabetic patients. *Diabetologia.* 2001;44(6):693-9.
38. Rudez G, Meijer P, Spronk HM, Leebeek FW, ten Cate H, Kluft C, and de Maat MP. Biological variation in inflammatory and hemostatic markers. *J Thromb Haemost.* 2009;7(8):1247-55.
39. Rudnicka AR, Rumley A, Lowe GDO, and Strachan DP. Diurnal, seasonal, and blood-processing patterns in levels of circulating fibrinogen, fibrin D-dimer, C-reactive protein, tissue plasminogen activator, and von Willebrand factor in a 45-year-old population. *Circulation.* 2007;115(8):996-1003.
40. Sallah S, Husain A, Sigounas V, Wan J, Turturro F, Sigounas G, and Nguyen NP. Plasma coagulation markers in patients with solid tumors and venous thromboembolic disease receiving oral anticoagulation therapy. *Clin Cancer Res.* 2004;10(21):7238-43.
41. Sallah S, Wan JY, and Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost.* 2002;87(4):575-9.
42. Sallis JF, Haskell WL, Wood PD, Fortmann SP, Rogers T, Blair SN, and Paffenbarger RS, Jr. Physical activity assessment methodology in the Five-City Project. *Am J Epidemiol.* 1985;121(1):91-106.
43. Saphner T, Tormey DC, and Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. *J Clin Oncol.* 1991;9(2):286-94.
44. Sherman KA, Heard G, and Cavanagh KL. Psychological effects and mediators of a group multi-component program for breast cancer survivors. *J Behav Med.* 2010;33(5):378-91.
45. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, and Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158(6):585-93.
46. Siscovick DS, Fried L, Mittelmark M, Rutan G, Bild D, and O'Leary DH. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. *Am J Epidemiol.* 1997;145(11):977-86.
47. Stout RW, and Crawford V. Seasonal-Variations in Fibrinogen Concentrations among Elderly People. *Lancet.* 1991;338(8758):9-13.

48. van den Burg PJ, Hospers JE, Mosterd WL, Bouma BN, and Huisveld IA. Aging, physical conditioning, and exercise-induced changes in hemostatic factors and reaction products. *J Appl Physiol.* 2000;88(5):1558-64.
49. van den Burg PJ, Hospers JE, van Vliet M, Mosterd WL, Bouma BN, and Huisveld IA. Effect of endurance training and seasonal fluctuation on coagulation and fibrinolysis in young sedentary men. *J Appl Physiol.* 1997;82(2):613-20.
50. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood.* 2007;110(6):1723-9.
51. Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, and Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation.* 2002;105(15):1785-90.
52. Wolin KY, Yan Y, and Colditz GA. Physical activity and risk of colon adenoma: a meta-analysis. *Br J Cancer.* 2011;104(5):882-5.
53. Woodhouse PR, Khaw KT, Plummer M, Foley A, and Meade TW. Seasonal-Variations of Plasma-Fibrinogen and Factor-Vii Activity in the Elderly - Winter Infections and Death from Cardiovascular-Disease. *Lancet.* 1994;343(8895):435-9.

**Table 1.** Physical characteristics of the study subjects

	Exercise (n=5)	Control (n=3)
% Female	100	66
Age, yrs	65.8 ± 9	63.7 ± 18
Height, cm	163.1 ± 8	164.3 ± 14
Weight, kg	82.4 ± 47	76.5 ± 12
Body Mass Index	30.4 ± 17	28.4 ± 3.6

Values are represented as mean ± SD.

**Table 2.** Cancer type and treatment of the study subjects

	Exercise (n=5)	Control (n=3)
Cancer Type	Breast (5)	Breast (2), Lymph Node (1)
Chemotherapy	3	2
Radiation	5	3
Surgery	4	2
Hormonal Therapy	5	2

Values are represented as number of subjects who underwent treatment.

Figure 1.

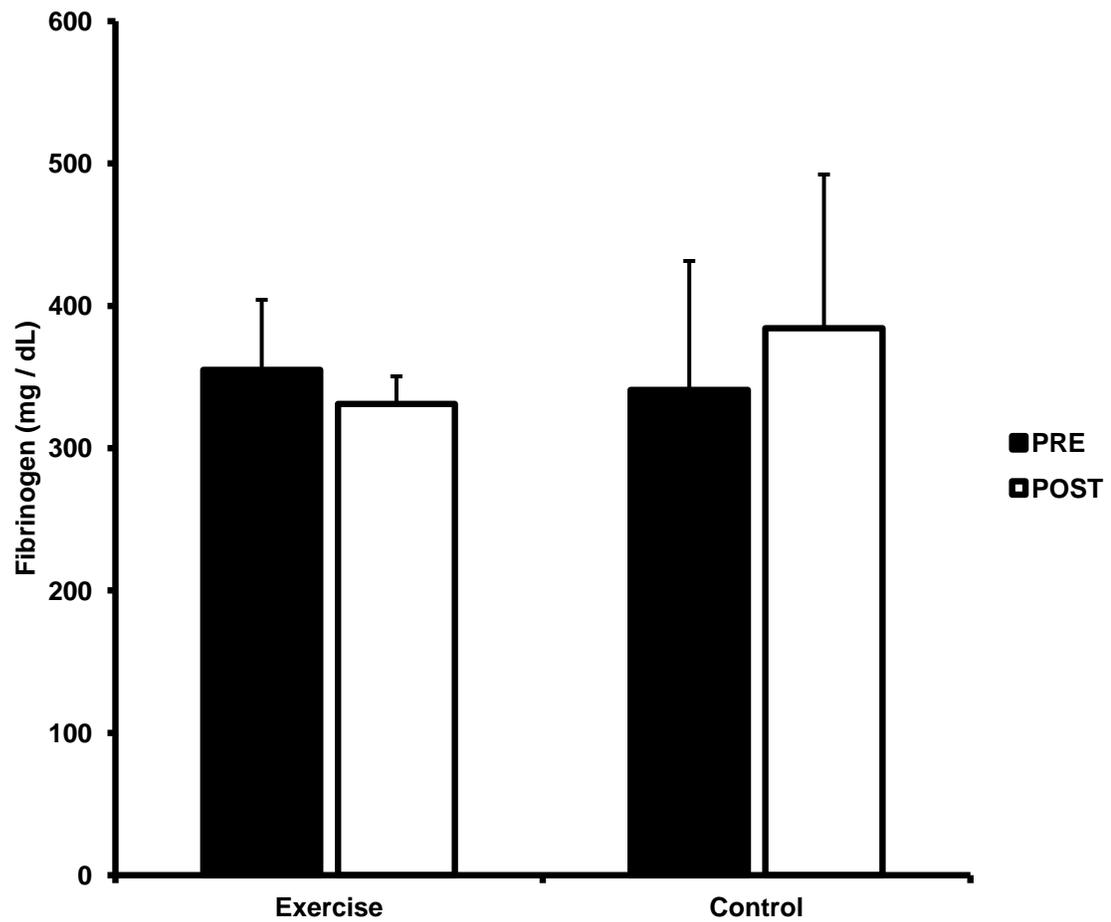
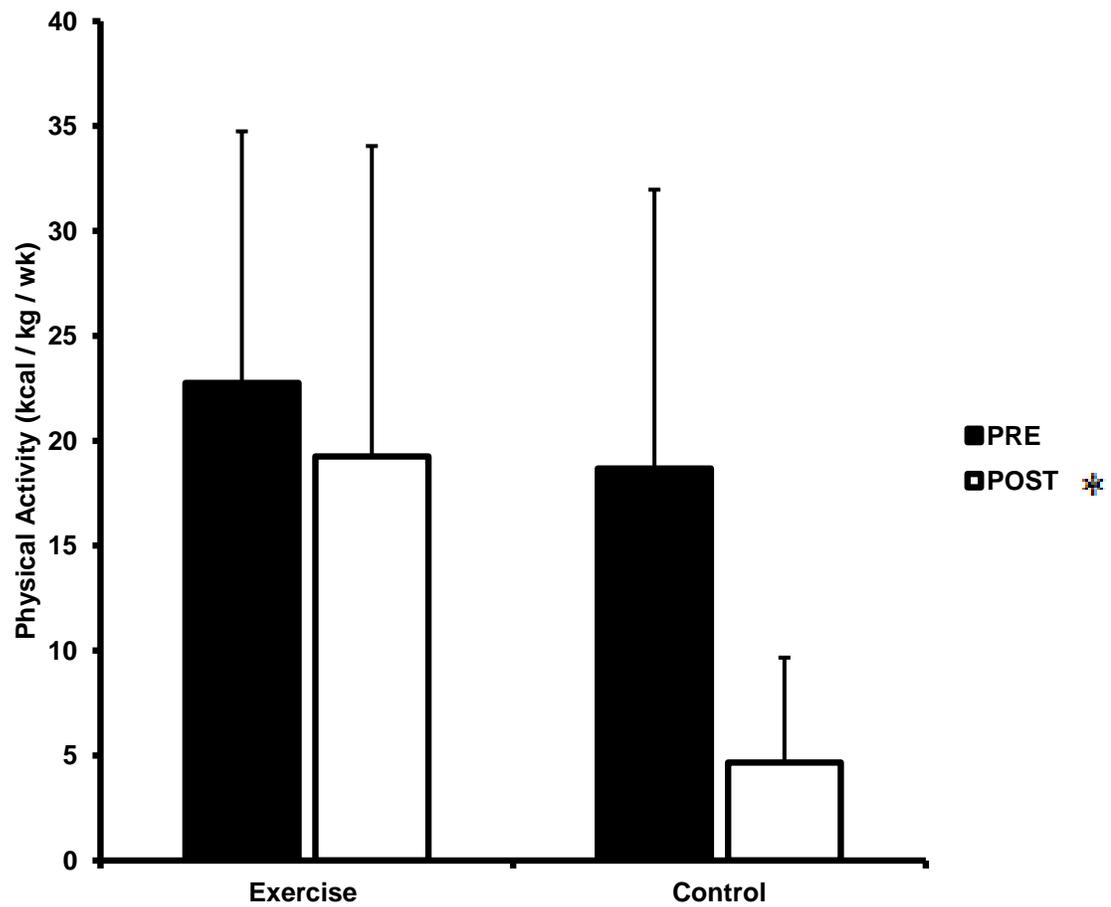


Figure 2.



**FIGURE LEGENDS**

- Figure 1.** Measures of fibrinogen before and after 12 weeks of exercise training or usual and customary care (control). Data are presented as mean  $\pm$  SD. A linear trend of time  $\times$  group was observed with fibrinogen ( $p=0.067$ ).
- Figure 2.** Weekly physical activity levels before and after 12 weeks of exercise training or usual and customary care (control). Data are presented as mean  $\pm$  SD. \* $p=0.05$ .

## **CHAPTER V**

### **Summary**

The purpose of this study was to examine the changes in thrombotic potential after a period of structured exercise training in patients with cancer. The main finding from this investigation was that physical training may influence fibrinogen in patients with cancer. A trend in fibrinogen levels was observed in this investigation ( $p = 0.067$ ). A reduced level of fibrinogen from baseline to post measurements was seen in patients participating in the exercise group, whereas fibrinogen concentration increased in patients participating in the control group. This finding supports our hypothesis that exercise training would reduce thrombotic potential. Earlier studies have found that exercise training reduces coagulation activity in healthy individuals as well as other clinical populations (21, 32, 34, 72, 92, 118). Specifically, among other coagulation measures, fibrinogen is shown to decline (21, 32, 118). In the present study, the small sample size may have limited statistical power, thus precluding the ability to observe statistically significant changes. However, the interaction trend suggests fibrinogen changed in the exercise group differently than the control group. Fibrinogen is an acute phase protein, whose plasma concentrations will increase or decrease in response to inflammation. Research demonstrates that physical activity mitigates inflammation (29). Thus the

decrease in fibrinogen levels in the exercise group may have resulted from a reduction in inflammation due to the exercise training regimen.

Other findings from the present study do not corroborate the fibrinogen results. There were no significant differences between groups observed in clotting times APTT and PT. Surprisingly, there was a significant shortening in clotting times observed with both groups over time. Studies measuring clotting times of the coagulation pathways in patients with cancer produce inconsistent results (16, 55, 86). A possible explanation for the overall reduction in clotting time is related to seasonal changes in hemostatic activity. Increased plasma concentrations of fibrinogen, factor VII, d-dimer, von Willebrand factor and thrombin are seen in the winter months (30, 94, 95, 109, 120). Frohlich et al. (30) measured rheological and hemostatic markers in 16 volunteers monthly over the course of a year. Seasonal variation with peak values in the winter months was found in plasma viscosity, whole blood viscosity, fibrinogen, plasminogen activator inhibitor, LDL cholesterol and triglyceride levels. Rudnicka et al. (95) measured circulating levels of hemostatic markers in 9377 men and women aged 45 years. Levels of fibrinogen, d-dimer and von Willebrand factor were all significantly higher in the winter months. In the present study, participants completed baseline measurements in the fall, (August through November), and post test measurements for all subjects were completed in the winter months (December through February).

The present study observed no significant differences in coagulation factor VIII for either group. Earlier studies show regular exercise is associated with reductions in thrombotic potential, including coagulation factor VIII (31, 32, 92, 118). There is an

inverse dose-response relationship of exercise intensity with hemostatic and inflammatory variables (104, 118). Exercising at higher intensity decreases serum levels of fibrinogen, factor VII and factor VIII more than exercise at a lower intensity (104). Wannamethee et al. (118) demonstrated a significant and inverse dose-response relationship of physical activity to hemostatic measures of fibrinogen, plasma and blood viscosity, platelet count, coagulation factors VIII and IX, von Willebrand factor and D-dimer. In the present study, participants in the exercise group performed mainly light with some moderate intensity exercise. Thus, the exercise regimen may not have been strenuous enough to affect factor VIII as well as the clotting times.

Another potential explanation for the lack of significant findings with regard to PT, APTT and factor VIII is related to overall physical activity. Previous studies indicate physical activity is correlated to reduced levels of hemostatic markers such as fibrinogen, coagulation factors VIII and X, von Willebrand factor and d-dimer (32, 61, 118). Panagiotakos et al (85) assessed the relationship between self reported physical activity and hemostatic markers in over 3000 men and women. Participants classified as physically active had lower levels of hemostatic and inflammatory markers, including C-reactive protein and fibrinogen than those classified as sedentary. Participants in both groups of the present study decreased overall weekly physical activity levels from baseline to conclusion of the investigation. One might predict that subjects who participated in a supervised exercise training program would therefore increase physical activity levels. However, we suspect that the seasonal change from fall to winter months throughout the 12 week protocol may have affected the physical activity levels of the

participants. Research indicates that overall physical activity levels are higher in the spring, summer and fall than in winter (10, 20, 25, 40, 74). Ma et al. (74) followed 593 participants aged 20- 70 for one year. Seasonal differences were found in quantity of physical activity, levels were highest in spring and lowest in winter. Hechler et al. (40) surveyed women from Australia and Germany. They found that 73% of participants perceived themselves to be less active in winter. Lastly, the limited statistical power due to the small sample size may have also precluded a significant change in factor VIII.

One limitation of this study was the small sample size, which may have hindered our statistical power. Controlling for or limiting the prescriptions of our patients was another constraint. The medications of the patients in the present study may have hindered the results. Also, as described above, the light intensity of exercise in the present study may have resulted in the non-significant findings of APTT, PT and factor VIII. Future research is warranted to examine the changes in thrombotic potential after a period of structured exercise training in patients with cancer using higher exercise intensity ranges and a sufficient sample size. Future research should also take seasonal variation on hemostatic measures and physical activity into account.

In conclusion, the present study indicates a formal exercise training program may reduce coagulation potential in cancer patients more than usual and customary care. However, this conclusion is speculative, and results of this study may have been obfuscated by the small sample size and likely seasonal fluctuations in hemostasis.

## REFERENCES

1. Cancer Facts & Figures 2011. *Atlanta: American Cancer Society*. 2011.
2. Abudoureyimu S, Zhang HL, Aizezi R, Jin W, and Upur H. [Changes of prethrombotic state indexes in patients with malignant cancer]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2007;32(6):973-7.
3. Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E, Moia M, Parazzini F, Rossi R, Sonaglia F, Valarani B, Bianchini C, and Gussoni G. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. *Ann Surg*. 2006;243(1):89-95.
4. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, and White RH. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. *J Clin Oncol*. 2006;24(7):1112-8.
5. Ambrus JL, Ambrus CM, Mink IB, and Pickren JW. Causes of death in cancer patients. *J Med*. 1975;6(1):61-4.
6. Ariens RA. Elevated fibrinogen causes thrombosis. *Blood*. 2011;117(18):4687-8.
7. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, Quehenberger P, Wagner O, Zielinski C, and Pabinger I. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol*. 2009;27(25):4124-9.
8. Baron JA, Gridley G, Weiderpass E, Nyren O, and Linet M. Venous thromboembolism and cancer. *Lancet*. 1998;351(9109):1077-80.
9. Beckers MM, Ruven HJ, Seldenrijk CA, Prins MH, and Biesma DH. Risk of thrombosis and infections of central venous catheters and totally implanted access ports in patients treated for cancer. *Thromb Res*. 2010;125(4):318-21.
10. Beighle A, Alderman B, Morgan CF, and Le Masurier G. Seasonality in children's pedometer-measured physical activity levels. *Res Q Exercise Sport*. 2008;79(2):256-60.
11. Blom JW, Doggen CJ, Osanto S, and Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-22.
12. Blom JW, Vanderschoot JPM, Oostindier MJ, Osanto S, van der Meer FJM, and Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66 329 cancer patients: results of a record linkage study. *J. Thromb. Haemost*. 2006;4(3):529-35.
13. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, Trelle S, Weingart O, Bayliss S, Djulbegovic B, Bennett CL, Langensiepen S, Hyde C, and Engert A. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst*. 2006;98(10):708-14.
14. Bona RD. Thrombotic complications of central venous catheters in cancer patients. *Semin Thromb Hemost*. 1999;25(2):147-55.
15. Bona RD, Hickey AD, and Wallace DM. Warfarin is safe as secondary prophylaxis in patients with cancer and a previous episode of venous thrombosis. *Am J Clin Oncol*. 2000;23(1):71-3.
16. Buccheri G, Ferrigno D, Ginardi C, and Zuliani C. Haemostatic abnormalities in lung cancer: prognostic implications. *Eur J Cancer*. 1997;33(1):50-5.
17. Canobbio L, Fassio T, Ardizzoni A, Bruzzi P, Queirolo MA, Zarccone D, Di Giorgio F, Rosso R, and Santi L. Hypercoagulable state induced by cytostatic drugs in stage II breast cancer patients. *Cancer*. 1986;58(5):1032-6.

18. Chew HK, Wun T, Harvey D, Zhou H, and White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med.* 2006;166(4):458-64.
19. Chow WH, Dosemeci M, Zheng W, Vetter R, McLaughlin JK, Gao YT, and Blot WJ. Physical activity and occupational risk of colon cancer in Shanghai, China. *Int J Epidemiol.* 1993;22(1):23-9.
20. Clemes SA, Hamilton SL, and Griffiths PL. Summer to Winter Variability in the Step Counts of Normal Weight and Overweight Adults Living in the UK. *J. Phys. Act. Health.* 2011;8(1):36-44.
21. Connelly JB, Cooper JA, and Meade TW. Strenuous exercise, plasma fibrinogen, and factor VII activity. *Br Heart J.* 1992;67(5):351-4.
22. Contrino J, Hair G, Kreutzer DL, and Rickles FR. In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease. *Nat Med.* 1996;2(2):209-15.
23. Deitcher SR. Cancer-related deep venous thrombosis: clinical importance, treatment challenges, and management strategies. *Semin Thromb Hemost.* 2003;29(3):247-58.
24. Dosemeci M, Hayes RB, Vetter R, Hoover RN, Tucker M, Engin K, Unsal M, and Blair A. Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes Control.* 1993;4(4):313-21.
25. Dunton GF, Whalen CK, Jamner LD, and Floro JN. Mapping the social and physical contexts of physical activity across adolescence using ecological momentary assessment. *Ann Behav Med.* 2007;34(2):144-53.
26. Edwards RL, Rickles FR, Moritz TE, Henderson WG, Zacharski LR, Forman WB, Cornell CJ, Forcier RJ, O'Donnell JF, Headley E, and et al. Abnormalities of blood coagulation tests in patients with cancer. *Am J Clin Pathol.* 1987;88(5):596-602.
27. Eppihimer MJ, and Schaub RG. P-Selectin-dependent inhibition of thrombosis during venous stasis. *Arterioscler Thromb Vasc Biol.* 2000;20(11):2483-8.
28. Estelles A, Aznar J, Tormo G, Sapena P, Tormo V, and Espana F. Influence of a rehabilitation sports programme on the fibrinolytic activity of patients after myocardial infarction. *Thromb Res.* 1989;55(2):203-12.
29. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology.* 2002;13(5):561-8.
30. Frohlich M, Sund M, Russ S, Hoffmeister A, Fischer HG, Hombach V, and Koenig W. Seasonal variations of rheological and hemostatic parameters and acute-phase reactants in young, healthy subjects. *Arterioscler Thromb Vasc Biol.* 1997;17(11):2692-7.
31. Gardner AW, and Killewich LA. Association between physical activity and endogenous fibrinolysis in peripheral arterial disease: a cross-sectional study. *Angiology.* 2002;53(4):367-74.
32. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, and Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol.* 2001;153(3):242-50.
33. Goldenberg N, Kahn SR, and Solymoss S. Markers of coagulation and angiogenesis in cancer-associated venous thromboembolism. *J Clin Oncol.* 2003;21(22):4194-9.
34. Gris JC, Schved JF, Feugeas O, Aguilar-Martinez P, Arnaud A, Sanchez N, and Sarlat C. Impact of smoking, physical training and weight reduction on FVII, PAI-1 and hemostatic markers in sedentary men. *Thromb Haemost.* 1990;64(4):516-20.

35. Guan M, Jin J, Su B, Liu WW, and Lu Y. Tissue factor expression and angiogenesis in human glioma. *Clin Biochem.* 2002;35(4):321-5.
36. Guan M, Su B, and Lu Y. Quantitative reverse transcription-PCR measurement of tissue factor mRNA in glioma. *Mol Biotechnol.* 2002;20(2):123-9.
37. Hair GA, Padula S, Zeff R, Schmeizl M, Contrino J, Kreutzer DL, de Moerloose P, Boyd AW, Stanley I, Burgess AW, and Rickles FR. Tissue factor expression in human leukemic cells. *Leuk Res.* 1996;20(1):1-11.
38. Hammond J, Kozma C, Hart JC, Nigam S, Daskiran M, Paris A, and Mackowiak JI. Rates of Venous Thromboembolism Among Patients with Major Surgery for Cancer. *Ann Surg Oncol.* 2011.
39. Hanna LR, Avila PF, Meteer JD, Nicholas DR, and Kaminsky LA. The effects of a comprehensive exercise program on physical function, fatigue, and mood in patients with various types of cancer. *Oncol Nurs Forum.* 2008;35(3):461-9.
40. Hechler T, Chau JY, Giesecke S, and Vocks S. Perception of seasonal changes in physical activity among young Australian and German women. *Med J Aust.* 2004;181(11-12):710-1.
41. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, and Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med.* 2000;160(6):761-8.
42. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, and Melton LJ, 3rd. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med.* 2002;162(11):1245-8.
43. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, and Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000;160(6):809-15.
44. Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, and Frommhold H. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet.* 2003;362(9392):1255-60.
45. Hettiarachchi RJK, Lok J, Prins MH, Buller HR, and Prandoni P. Undiagnosed malignancy in patients with deep vein thrombosis - Incidence, risk indicators, and diagnosis. *Cancer.* 1998;83(1):180-5.
46. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, and Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol.* 2000;18(17):3078-83.
47. John EM, Koo J, and Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev.* 2010;19(5):1276-83.
48. Kakkar AK, Lemoine NR, Scully MF, Tebbutt S, and Williamson RC. Tissue factor expression correlates with histological grade in human pancreatic cancer. *Br J Surg.* 1995;82(8):1101-4.
49. Khorana AA. The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: strategies for improving VTE prophylaxis in hospitalized cancer patients. *Oncologist.* 2007;12(11):1361-70.
50. Khorana AA, Ahrendt SA, Ryan CK, Francis CW, Hruban RH, Hu YC, Hostetter G, Harvey J, and Taubman MB. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. *Clin Cancer Res.* 2007;13(10):2870-5.

51. Khorana AA, and Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol.* 2009;27(29):4839-47.
52. Khorana AA, Francis CW, Culakova E, Kuderer NM, and Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer.* 2007;110(10):2339-46.
53. Khorana AA, Francis CW, Culakova E, Kuderer NM, and Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J. Thromb. Haemost.* 2007;5(3):632-4.
54. Khorana AA, Francis CW, Culakova E, and Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer.* 2005;104(12):2822-9.
55. Kirwan CC, McDowell G, McCollum CN, Kumar S, and Byrne GJ. Early changes in the haemostatic and procoagulant systems after chemotherapy for breast cancer. *Br J Cancer.* 2008;99(7):1000-6.
56. Kolden GG, Strauman TJ, Ward A, Kuta J, Woods TE, Schneider KL, Heerey E, Sanborn L, Burt C, Millbrandt L, Kalin NH, Stewart JA, and Mullen B. A pilot study of group exercise training (GET) for women with primary breast cancer: feasibility and health benefits. *Psychooncology.* 2002;11(5):447-56.
57. Koomagi R, and Volm M. Tissue-factor expression in human non-small-cell lung carcinoma measured by immunohistochemistry: correlation between tissue factor and angiogenesis. *Int J Cancer.* 1998;79(1):19-22.
58. Kroger K, Weiland D, Ose C, Neumann N, Weiss S, Hirsch C, Urbanski K, Seeber S, and Scheulen ME. Risk factors for venous thromboembolic events in cancer patients. *Ann Oncol.* 2006;17(2):297-303.
59. Kuderer NM, Khorana AA, Lyman GH, and Francis CW. A meta-analysis and systematic review of the efficacy and safety of anticoagulants as cancer treatment: impact on survival and bleeding complications. *Cancer.* 2007;110(5):1149-61.
60. Kwon HC, Oh SY, Lee S, Kim SH, Han JY, Koh RY, Kim MC, and Kim HJ. Plasma levels of prothrombin fragment F1+2, D-dimer and prothrombin time correlate with clinical stage and lymph node metastasis in operable gastric cancer patients. *Jpn J Clin Oncol.* 2008;38(1):2-7.
61. Lakka TA, and Salonen JT. Moderate to high intensity conditioning leisure time physical activity and high cardiorespiratory fitness are associated with reduced plasma fibrinogen in eastern Finnish men. *J Clin Epidemiol.* 1993;46(10):1119-27.
62. LaStayo PC, Marcus RL, Dibble LE, Smith SB, and Beck SL. Eccentric exercise versus usual-care with older cancer survivors: the impact on muscle and mobility-an exploratory pilot study. *BMC Geriatr.* 2011;11:5.
63. Lee AY. Thrombosis and cancer: the role of screening for occult cancer and recognizing the underlying biological mechanisms. *Hematology Am Soc Hematol Educ Program.* 2006:438-43.
64. Lee AY, and Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation.* 2003;107(23 Suppl 1):I17-21.
65. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, and Gent M. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349(2):146-53.

66. Lee AY, Levine MN, Butler G, Webb C, Costantini L, Gu C, and Julian JA. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. *J Clin Oncol.* 2006;24(9):1404-8.
67. Levine MN. Prevention of thrombotic disorders in cancer patients undergoing chemotherapy. *Thromb Haemost.* 1997;78(1):133-6.
68. Levine MN, Gent M, Hirsh J, Arnold A, Goodyear MD, Hryniuk W, and De Pauw S. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. *N Engl J Med.* 1988;318(7):404-7.
69. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, and Rimm AA. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore).* 1999;78(5):285-91.
70. Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol.* 2003;4(8):459-60.
71. Lipkin DP, Scriven AJ, Crake T, and Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J (Clin Res Ed).* 1986;292(6521):653-5.
72. Lockard MM, Gopinathannair R, Paton CM, Phares DA, and Hagberg JM. Exercise training-induced changes in coagulation factors in older adults. *Med Sci Sports Exerc.* 2007;39(4):587-92.
73. Lykke J, and Nielsen HJ. The role of tissue factor in colorectal cancer. *Eur J Surg Oncol.* 2003;29(5):417-22.
74. Ma Y, Olendzki BC, Li W, Hafner AR, Chiriboga D, Hebert JR, Campbell M, Sarnie M, and Ockene IS. Seasonal variation in food intake, physical activity, and body weight in a predominantly overweight population. *Eur J Clin Nutr.* 2006;60(4):519-28.
75. Mackman N. Triggers, targets and treatments for thrombosis. *Nature.* 2008;451(7181):914-8.
76. Mielicki WP, Tenderenda M, Rutkowski P, and Chojnowski K. Activation of blood coagulation and the activity of cancer procoagulant (EC 3.4.22.26) in breast cancer patients. *Cancer Lett.* 1999;146(1):61-6.
77. Miller GJ, Bauer KA, Howarth DJ, Cooper JA, Humphries SE, and Rosenberg RD. Increased incidence of neoplasia of the digestive tract in men with persistent activation of the coagulant pathway. *J Thromb Haemost.* 2004;2(12):2107-14.
78. Mueller BM, Reisfeld RA, Edgington TS, and Ruf W. Expression of tissue factor by melanoma cells promotes efficient hematogenous metastasis. *Proc Natl Acad Sci U S A.* 1992;89(24):11832-6.
79. Nakasaki T, Wada H, Shigemori C, Miki C, Gabazza EC, Nobori T, Nakamura S, and Shiku H. Expression of tissue factor and vascular endothelial growth factor is associated with angiogenesis in colorectal cancer. *Am J Hematol.* 2002;69(4):247-54.
80. Noble BJ, Borg GA, Jacobs I, Ceci R, and Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc.* 1983;15(6):523-8.
81. Oliveira MM, Souza GA, Miranda Mde S, Okubo MA, Amaral MT, Silva MP, and Gurgel MS. [Upper limbs exercises during radiotherapy for breast cancer and quality of life]. *Rev Bras Ginecol Obstet.* 2010;32(3):133-8.
82. Owens AP, 3rd, and Mackman N. Tissue factor and thrombosis: The clot starts here. *Thromb Haemost.* 2010;104(3):432-9.

83. Palareti G, Legnani C, Lee A, Manotti C, Hirsh J, D'Angelo A, Pengo V, Moia M, and Coccheri S. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. *Thromb Haemost.* 2000;84(5):805-10.
84. Palumbo JS, Potter JM, Kaplan LS, Talmage K, Jackson DG, and Degen JL. Spontaneous hematogenous and lymphatic metastasis, but not primary tumor growth or angiogenesis, is diminished in fibrinogen-deficient mice. *Cancer Res.* 2002;62(23):6966-72.
85. Panagiotakos DB, Pitsavos C, Chrysohoou C, Kavouras S, and Stefanadis C. The associations between leisure-time physical activity and inflammatory and coagulation markers related to cardiovascular disease: the ATTICA Study. *Prev Med.* 2005;40(4):432-7.
86. Pectasides D, Tsavdaridis D, Aggouridaki C, Tsavdaridou V, Visvikis A, Tsatalas K, and Fountzilas G. Effects on blood coagulation of adjuvant CNF (cyclophosphamide, novantrone, 5-fluorouracil) chemotherapy in stage II breast cancer patients. *Anticancer Res.* 1999;19(4C):3521-6.
87. Prandoni P. Cancer and thromboembolic disease: how important is the risk of thrombosis? *Cancer Treat Rev.* 2002;28(3):133-6.
88. Prandoni P, Lensing AW, Buller HR, Cogo A, Prins MH, Cattelan AM, Cuppini S, Noventa F, and ten Cate JW. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med.* 1992;327(16):1128-33.
89. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, and Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100(10):3484-8.
90. Pyke C, Kristensen P, Ralfkiaer E, Grondahl-Hansen J, Eriksen J, Blasi F, and Dano K. Urokinase-type plasminogen activator is expressed in stromal cells and its receptor in cancer cells at invasive foci in human colon adenocarcinomas. *Am J Pathol.* 1991;138(5):1059-67.
91. Revel-Vilk S, Yacobovich J, Tamary H, Goldstein G, Nemet S, Weintraub M, Paltiel O, and Kenet G. Risk factors for central venous catheter thrombotic complications in children and adolescents with cancer. *Cancer.* 2010;116(17):4197-205.
92. Rigla M, Fontcuberta J, Mateo J, Caixas A, Pou JM, de Leiva A, and Perez A. Physical training decreases plasma thrombomodulin in type I and type II diabetic patients. *Diabetologia.* 2001;44(6):693-9.
93. Rohsig LM, Damin DC, Stefani SD, Castro CG, Roisenberg I, and Schwartzmann G. von Willebrand factor antigen levels in plasma of patients with malignant breast disease. *Brazilian J. Med. Biol. Res.* 2001;34(9):1125-9.
94. Rudez G, Meijer P, Spronk HM, Leebeek FW, ten Cate H, Kluft C, and de Maat MP. Biological variation in inflammatory and hemostatic markers. *J Thromb Haemost.* 2009;7(8):1247-55.
95. Rudnicka AR, Rumley A, Lowe GDO, and Strachan DP. Diurnal, seasonal, and blood-processing patterns in levels of circulating fibrinogen, fibrin D-dimer, C-reactive protein, tissue plasminogen activator, and von Willebrand factor in a 45-year-old population. *Circulation.* 2007;115(8):996-1003.
96. Sallah S, Husain A, Sigounas V, Wan J, Turturro F, Sigounas G, and Nguyen NP. Plasma coagulation markers in patients with solid tumors and venous

- thromboembolic disease receiving oral anticoagulation therapy. *Clin Cancer Res.* 2004;10(21):7238-43.
97. Sallah S, Wan JY, and Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost.* 2002;87(4):575-9.
98. Sallis JF, Haskell WL, Wood PD, Fortmann SP, Rogers T, Blair SN, and Paffenbarger RS, Jr. Physical activity assessment methodology in the Five-City Project. *Am J Epidemiol.* 1985;121(1):91-106.
99. Saphner T, Tormey DC, and Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. *J Clin Oncol.* 1991;9(2):286-94.
100. Sawada M, Miyake S, Ohdama S, Matsubara O, Masuda S, Yakumaru K, and Yoshizawa Y. Expression of tissue factor in non-small-cell lung cancers and its relationship to metastasis. *Br J Cancer.* 1999;79(3-4):472-7.
101. Shen VS, and Pollak EW. Fatal pulmonary embolism in cancer patients: is heparin prophylaxis justified? *South Med J.* 1980;73(7):841-3.
102. Sherman KA, Heard G, and Cavanagh KL. Psychological effects and mediators of a group multi-component program for breast cancer survivors. *J Behav Med.* 2010;33(5):378-91.
103. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, and Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158(6):585-93.
104. Siscovick DS, Fried L, Mittelmark M, Rutan G, Bild D, and O'Leary DH. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. *Am J Epidemiol.* 1997;145(11):977-86.
105. Society AC. Cancer Facts & Figures 2010. *American Cancer Society.* 2010.
106. Sorensen HT, Mellemkjaer L, Olsen JH, and Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med.* 2000;343(25):1846-50.
107. Sorensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, and Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med.* 1998;338(17):1169-73.
108. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, and Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. *Am J Med.* 2006;119(1):60-8.
109. Stout RW, and Crawford V. Seasonal-Variations in Fibrinogen Concentrations among Elderly People. *Lancet.* 1991;338(8758):9-13.
110. Tesselaar ME, Romijn FP, Van Der Linden IK, Prins FA, Bertina RM, and Osanto S. Microparticle-associated tissue factor activity: a link between cancer and thrombosis? *J Thromb Haemost.* 2007;5(3):520-7.
111. Trujillo-Santos J, Casa JM, Casado I, Samperiz AL, Quintavalla R, Sahuquillo JC, and Monreal M. Thirty-day mortality rate in women with cancer and venous thromboembolism. Findings from the RIETE Registry. *Thromb Res.* 2011;127 Suppl 3:S1-4.
112. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N, and Folsom AR. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). *Am J Med.* 2002;113(8):636-42.
113. Ueda C, Hirohata Y, Kihara Y, Nakamura H, Abe S, Akahane K, Okamoto K, Itoh H, and Otsuki M. Pancreatic cancer complicated by disseminated

- intravascular coagulation associated with production of tissue factor. *J Gastroenterol.* 2001;36(12):848-50.
- 114.Ueno T, Toi M, Koike M, Nakamura S, and Tominaga T. Tissue factor expression in breast cancer tissues: its correlation with prognosis and plasma concentration. *Br J Cancer.* 2000;83(2):164-70.
- 115.Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood.* 2007;110(6):1723-9.
- 116.Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C, Zielinski C, and Pabinger I. High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. *Arterioscler Thromb Vasc Biol.* 2009;29(12):2176-81.
- 117.Vrana JA, Stang MT, Grande JP, and Getz MJ. Expression of tissue factor in tumor stroma correlates with progression to invasive human breast cancer: paracrine regulation by carcinoma cell-derived members of the transforming growth factor beta family. *Cancer Res.* 1996;56(21):5063-70.
- 118.Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, and Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation.* 2002;105(15):1785-90.
- 119.Wolin KY, Yan Y, and Colditz GA. Physical activity and risk of colon adenoma: a meta-analysis. *Br J Cancer.* 2011;104(5):882-5.
- 120.Woodhouse PR, Khaw KT, Plummer M, Foley A, and Meade TW. Seasonal-Variations of Plasma-Fibrinogen and Factor-Vii Activity in the Elderly - Winter Infections and Death from Cardiovascular-Disease. *Lancet.* 1994;343(8895):435-9.
- 121.Yoda Y, and Abe T. Fibrinopeptide A (FPA) level and fibrinogen kinetics in patients with malignant disease. *Thromb Haemost.* 1981;46(4):706-9.

## APPENDIX A

### **Consent Form:** Hemostatic Adaptations Following Exercise Training in Patients with Cancer.

The purpose of this study is to assess how regular exercise training impacts blood clotting potential in people with cancer.

Blood clotting is a critical and common problem in patients with cancer, contributing to high costs, rates of morbidity and mortality, and complicating usual medical treatments. Current efforts to manage clotting risk often include treatment with medication. This treatment may complicate usual courses of care for cancer and introduces additional risk of bleeding problems. Exercise training has been shown to decrease the likelihood of a blood clot in healthy men and women, and in various clinical populations. However, the effect of regular exercise on clotting risk in patients with cancer is unknown. We are studying clotting activity in the blood of people with cancer who are either participating in a regular exercise program, or who are receiving standard care but are not engaging in regular exercise.

Men and women who have an active cancer diagnosis and who weigh at least 110 pounds and are at least 18 yrs of age may be eligible to participate in this study. Participants in this study must not have cardiovascular disease or diabetes, must not use tobacco or take anticoagulant (*i.e.* “blood thinning”) medications that may influence the results. As part of this study, you will be asked to provide information about your cancer diagnosis, other illnesses and medications that you are taking. Your participation in this study will involve two visits to the Cancer Center at IU Health Ball Memorial Hospital, separated by approximately 12 weeks. You’ll be asked to fast for 12 hours and avoid alcohol and caffeine for 24 hours prior to each visit. During your appointment you’ll rest in a chair for 20 minutes after which a 10-ml (<1 Tbsp) blood sample will be obtained from a vein in your arm. You will also be asked about your physical activities over the past seven days. Your enrollment in this study will be 12 weeks long, but your time commitment to the project is expected to be less than one hour. If you have enrolled in the Cancer Exercise Program at IU Health BMH, we will obtain these blood samples prior to the initiation of your exercise program and immediately after 12 weeks of exercise training as part of that program. The treatment you receive from your physician and/or as part of the Cancer Exercise Program will not be affected by your participation in this study.

Risks of blood drawing may include discomfort, bruising, and, in rare instances, infection, lightheadedness, and fainting. We will use sterile procedures and trained personnel to ensure that there is minimal discomfort with obtaining the blood samples. Emergency medical treatment is available in the event of injury or serious adverse reaction. You will assume responsibility for the costs of medical care that is provided. In the unlikely event of injury or illness of any kind as a result of participation in this research project, Ball State University, IU Health Ball Memorial Hospital, their agents and employees will assume whatever responsibility is required by law.

After you complete the study, you will be paid \$30. You will also be given any information collected as part of your participation in this project (*e.g.* measures of coagulation activity). You may also benefit from the creation of new scientific knowledge regarding future exercise recommendations for patients with cancer.

Your participation in this study is completely voluntary and you are free to withdraw from the study at any time for any reason without penalty or prejudice from the investigators. Your participation or decision to withdraw from the study will not impact the quality of care you receive at IU Health Ball Memorial Hospital. Please feel free to ask any questions of the investigator before signing this Informed Consent form and beginning the study, and at any time during the study. All study materials will be maintained as confidential. Your information will be stored for three years after completion of the study. Data will be stored in a locked filing cabinet in the researcher's office. Electronic files, which will be password protected, will be stored on the principal investigator's computer and preferred backup medium. If you are not eligible to participate in this study your information will not be retained, and will be destroyed by shredding paper files and permanently deleting electronic information.

For one's rights as a research subject, contact the Director, Office of Research Integrity, Ball State University, (765) 285-5070 ( [irb@bsu.edu](mailto:irb@bsu.edu)) or the Institutional Review Board Administrator at IU Health Ball Memorial Hospital at (765) 747-8458.

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I, \_\_\_\_\_, agree to participate in this research project entitled, "Hemostatic Adaptations Following Exercise Training in Patients with Cancer." I have had the study explained to me and my questions have been answered to my satisfaction. I have read the description of this project and give my consent to participate. I understand that I will receive a copy of this informed consent form to keep for future reference.

\_\_\_\_\_  
Participant's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator's Signature

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**APPENDIX B**

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*Hemostatic Adaptations Following Exercise Training in Patients with Cancer*

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Please answer the following questions regarding your personal medical history.

1. What is your current cancer diagnosis (*e.g.* breast, prostate, lung)?

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2. Describe the medical treatment for your cancer (*e.g.* radiation, chemotherapy, surgery). List approximate dates that treatment began and ended (or that it is ongoing).

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3. Please list any other illnesses that you currently have:

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4. Please list the medications that you presently take:

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## APPENDIX C

### AUTHORIZATION FOR THE RELEASE OF HEALTH INFORMATION FOR RESEARCH PURPOSES

Regulations called the “Privacy Rule” issued under the Health Insurance Portability and Accountability Act (“HIPAA”) are designed to protect the privacy of your individually identifiable health information. The Privacy Rule requires your health care provider(s) to obtain your written authorization before they can use or disclose your protected health information<sup>1</sup> for the purposes of the research study entitled “*Hemostatic adaptations following exercise training in patients with cancer*” (referred to as the “research study.”)

By signing this authorization, you are authorizing your treating physician(s), Indiana University Health Ball Memorial Hospital, and other health care providers to disclose your protected health information to Paul R. Nagelkirk, Ph.D. and his/her research staff for purposes of the research study. You are also authorizing Paul R. Nagelkirk, Ph.D. and his/her research staff to disclose your protected health information to the parties listed below.

#### **Protected Health Information to be Used or Disclosed**

Demographic information (*e.g.* name, age) will be used to describe the subject sample.

The following pieces of information will be collected because of their affects on the variables measured in this study: specific cancer diagnosis; recent surgical or medical treatments; other medical conditions; medication use; physical activity habits.

#### **Parties Who May Receive or Use Your Protected Health Information**

- IU Health BMH’s Institutional Review Board
- Government representatives, when required by law
- IU Health BMH representatives if applicable

Your health care providers will use and disclose your protected health information only as permitted by you in this Authorization and as required or permitted by applicable state or federal law.

#### **Right to Refuse to Sign This Authorization**

You do not have to sign this Authorization. If you decide not to sign this Authorization, you will not be allowed to participate in the research study or receive any research related

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<sup>1</sup> Protected health information includes information that relates to your past, present or future physical or mental health or condition, the provision of health care to you, or the past present or future payment for your health care that either identifies you or can be used to identify you.

treatment that is provided through the study. However, your decision not to sign this Authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

### **Right to Revoke**

You can change your mind and withdraw this Authorization at any time by sending a written notice to Paul R. Nagelkirk, HP 215, Ball State University, Muncie IN 47306 to inform the researcher of your decision. If you withdraw this Authorization, your health care providers may only use and disclose your protected health information already collected for the research study. No further health information about you will be used or disclosed for this research study.

### **Potential for Re-disclosure**

Once your protected health information is disclosed under this Authorization, it may be re-disclosed by the recipient and may no longer be protected by HIPAA or the Privacy Rule. Other confidentiality protections may or may not apply. For example, researchers in other studies could use your protected health information collected for this study without contacting you if they get approval from an Institutional Review Board (IRB) and agree to meet certain other confidentiality requirements. Also, there are other laws that may require your protected health information to be disclosed for public purposes. Examples include disclosures for legally mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

This Authorization does not have an expiration date or expires upon completion of the study.

If you have not already received a copy of the IU Health BMH Notice of Privacy Practices, you may request one. If you have any questions or concerns about your privacy rights, you should contact IU Health BMH's Privacy Officer at (765) 747-4457 or [jwelch6@clarianball.org](mailto:jwelch6@clarianball.org).

By signing below, you agree that you have had the opportunity to review and ask questions regarding this Authorization form and that it reflects your wishes. You will receive a copy of this form after it is signed.

\_\_\_\_\_  
Signature of Individual or Legal Representative

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Individual or Legal Representative Authority of Legal Representative

\_\_\_\_\_  
Address of Individual

## APPENDIX D

## The Seven-Day Recall

PAR#: 1 2 3 4 5 6 7 Participant \_\_\_\_\_

Interviewer \_\_\_\_\_ Today is \_\_\_\_\_ Today's Date \_\_\_\_\_

1. Were you employed in the last seven days? 0. No (Skip to Q#4) 1. Yes
2. How many days of the last seven did you work? \_\_\_\_\_ days
3. How many total hours did you work in the last seven days? \_\_\_\_\_ hours last week
4. What two days do you consider your weekend days? \_\_\_\_\_ (mark days below with a squiggle)

## WORKSHEET

## DAYS

SLEEP		1	2	3	4	5	6	7
M O R N I N G	Moderate							
	Hard							
	Very Hard							
A F T E R N O O N	Moderate							
	Hard							
	Very Hard							
E V E N I N G	Moderate							
	Hard							
	Very Hard							
Total Min Per Day	Strength: Flexibility:	_____	_____	_____	_____	_____	_____	_____

- 4a. Compared to your physical activity over the past three months, was last week's physical activity more, less or about the same?

1. More  
2. Less  
3. About the same

## Worksheet Key:

Rounding: 10-22 min. = .25    1:08-1:22 hr/min. = 1.25  
 23-37 min. = .50  
 38-52 min. = .75  
 53-1:07 hr/min. = 1.0

An asterisk (\*) denotes a work-related activity.

A squiggly line through a column (day) denotes a weekend day.

## APPENDIX E

### *Script*

I'm going to ask about your physical activity over the past 7 days. "Physical activity" refers to anything that is at least as hard as your regular walk when you're trying to get somewhere (i.e. not a casual stroll), and is maintained for at least 10 minutes at a time (i.e. stop-n-go at the grocery store doesn't count).

I'll also ask you to classify your physical activity as either "*Moderate*", "*Hard*", or "*Very Hard*." *Moderate* is your normal walk; running would be considered *Very Hard*; and anything in between would be *Hard*.

(Ask questions 1-4 re: employment and weekend days)

I also need to find out how many hours of sleep you get each night. To make it easier, I'll just ask how many hours you were in bed at night. Let's start with yesterday (e.g. Wednesday). What time did you go to bed Tuesday night? And what time did you get up yesterday morning? (Record # of hours) OK, did you do any physical activity in the morning after you got up? How about in the afternoon, between lunch and dinner? What about in the evening, after dinner until you went to bed? Is that everything? OK, let's back up one day. What time did you go to bed Monday night? And what time did you get up Tuesday morning?.....

(Ask question 4a re: PA over the last 3 months)

### ***Quick Reference:***

**Sleep:** Number of hours spent in bed at night (do not include naps)

**Physical Activity:** Minimum intensity is a purposeful walk, or "walking to get someplace" as opposed to strolling.

**Intensity:** "Moderate" = regular walking pace

"Very Hard" = running

"Hard" = somewhere in between

**Time** = Record as decimal

10-22 min = 0.25

23-37 min = 0.5

38-52 min = 0.75

53-1:07 min/hr = 1.0

1:08-1:22 hr = 1.25

Do one day at a time. First record sleep hours, then record PA minutes for same day.

Then move back one day, repeat. Finish with 7 days ago today.

Do not assume they did the same thing every day, and insist on getting their answer to *every* question, even if they say "I always go to bed at 9 and get up at 7." Apologize for the questionnaire if they get irritated, but press on.

Do not give positive or negative reinforcement cues! Smiles, frowns, and comments like "Good" can influence their answers. "OK" is safe.