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ADOLESCENT PHYSICAL ACTIVITY AND BREAST CANCER RISK

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RENEE C. BLOOME

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ADOLESCENT PHYSICAL ACTIVITY AND BREAST CANCER RISK

By

Renee C. Bloome

A THESIS

Submitted to
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ABSTRACT

ADOLESCENT PHYSICAL ACTIVITY AND BREAST CANCER RISK

By

Renee C. Bloome

Breast cancer (BC) is a global problem. While inheritance only accounts for a small portion of BC cases, research speculates that some difference in incidence can be explained by exposures from lifestyle factors. Adolescence has been hypothesized to be a critical time when lifestyle factors can effect BC risk. We aim to assess the relationship between adolescent physical activity (PA) and BC risk in 422 women from the Polish Women's Health Study. Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). Women with increased adolescent PA ($\geq$55.7 MET-h/day) had decreased risk of BC overall (OR=0.56; 95%CI: 0.34-0.95). Premenopausal women expending $\geq$55.7 MET-h/day, had significantly decreased risk of BC (OR=0.14; 95%CI: 0.04-0.44), while no effect was observed in postmenopausal women. The joint effect of adolescent and adult PA on BC showed decreased premenopausal BC risk in women with PA $\geq$ 55.7 MET-h/day during adolescence regardless of adult PA level.

To the brave and inspiring members of the Pink Ribbon Crew team

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The Organization of this Thesis

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Chapter 1: Introduction

The Burden of Breast Cancer

In 2004, cancers accounted for 29% of all deaths in the United States and specifically cancer of the breast is the most incident cancer (age-adjusted) found in American women (*WCRF/AICR 2007)*. However, the burden of breast cancer is not only confined to the women of the United States, but effects women worldwide. The United States has one of the highest incidences of breast cancer in the world with an overall age-adjusted incidence rate of 126.1 per 100,000 American women according to the Surveillance Epidemiology and End Results (SEER) database (*SEER 2008*).

The demographic make-up of the United States is not as homogeneous as other countries around the globe, thus it is important to note that not all races in America have an equal incidence rates of breast cancer. In America, white women have the highest incidence rate (132.5 per 100,000) followed by African Americans, Hispanics, Asian or Pacific Islanders, and American Indian/Alaskan natives with incidence rates of 118.3, 89.3, 89.0 and 69.8 per 100,000 respectively (*SEER 2008*). The number of new breast cancer cases in the United States will be in excess of 182, 460 in 2008 (*ACS 2007*). Within the last decade, a woman living in America has seen her overall lifetime risk for breast cancer jump from one in every ten women (2000) up to one in every eight women (2007) (*ACS 2007*) .

Increases in incidence rates have been seen across the globe, particularly in other industrialized countries. In Poland, breast cancer incidence rates in Polish native women have been observed to be nearly one third of those in the United States (41.4 per 100,000) (*Bebenek 2007*). Lifestyle differences, such as diet or other environmental risk factors, between women living in the United States and those living in Poland have been suggested to contribute to this almost three-fold difference in incidence between these two countries (*Gronwald 2006 & Dunham 2004*).

While the ever-expanding field of genetics has been able to link certain diseases to specific genes, it has been estimated that the inherited causes of breast cancer (such as genetic mutations in BRCA1, BRCA2, and p53) account for a small proportion of breast cancer estimated to be as little as ten percent of all breast cancers diagnosed each year. This leaves up to 90% of the disease to potentially attributed either environmental or lifestyle risk factors (*Newman 1995 & Irwin 2006*). These findings suggest that primary prevention of breast cancer might be achieved through modifiable factors in a woman's life (*Colditz 2005, Rockhill 1998, & UCCC 2008)*.

Studies performed on women that have migrated to the Unites States provide support to this hypothesis (*Nelson 2006, Colditz 2005, McPherson 2000, & Limer 2004)*. Thus breast cancer prevention might not require drastic and expensive newly developed scientific discoveries; if fact, it may be as simple as modifying a lifestyle factor such as diet or a specific activity. If these hypotheses are correct, the impact of the reduction of the burden of breast cancer worldwide would be significant.

A number of modifiable risk factors for breast cancer have been studied since the disease became a public concern over a century ago. Several potentially modifiable risk factors including aspects of diet, physical activity, and body size have been examined for casual links to breast cancer incidence (*Irwin 2006*). With the observation that increased occupational physical activity decreased overall cancer mortality in Australians, British, and Americans in 1922, physical activity became a highly plausible modifiable risk factor for all cancers (*Kruk 2006*). Since then dozens of studies have been published on breast cancer and physical activity and over 70% of them have observed that women with the highest physical activity level have a lower risk of breast cancer when compared to their inactive counterparts (*Kruk 2006*).

In addition to the identifying risk factors for breast cancer, timing when exposure occurs also plays an important role in the effect size of the risk factor. The younger the age when a woman is exposed to risk factors, such as irradiation, certain foods, alcohol ingestion, and smoking, the greater her later risk of breast cancer in adulthood (*Colditz 1995, Cho 2003, Colditz 2005, & Linos 2008*). This evidence suggests that modification of certain risk factors in adulthood only may be too late and thus not as effective as if such modification occurred earlier in life. Therefore, preventative measures may be most effective in breast cancer risk reduction if they occur between late childhood and early adulthood in a girl's life when her breast tissue develops. Therefore, additional research should be focused on this time period (*Colditz 2005*).

The Source of the Data

This analysis will look at the relationship between physical activity during adolescent years (specifically between ages 12-13) and breast cancer risk in Polish migrant women using data from the Polish Women's Health study. The Polish Woman's Health Study was designed to examine if changes in lifestyle factors of Polish women who immigrated to the United States, might explain the increase in beast cancer risk observed in Polish migrant women. The main aim of the study was to examine the effect of diet and other changes in women who migrated to the United States and compare it to their counterparts who remained in Poland. Additionally, information was also collected on other established and potential risk factors such as reproductive history, physical activity, family history, and occupational histories.

Two parallel case-control studies were conducted; one of women still living in Poland and the other of Polish-born women whom have migrated to the United States before 2000. Data collected from both countries included questions about women's lifestyles during 1985-1989 as well as their lifestyles when the women were aged 12-13 years. The time period of 1985-1989 was chosen in order to capture the traditional Polish diet before introduction of market economy after the fall of Communism in 1989. The analysis for this paper will only include the 422 Polish migrant women residing in the United States.

Study Specific Aim

The specific aim of this study is as follows:

1. To examine the relationship between increased physical activity during adolescence (defined as ages 12-13 years of age) and later risk of breast cancer in a United States population of Polish migrant women. Physical activity will be determined by self-reported, usual total of daily (24-hour) physical activity (summation of inactive, recreational, household, and occupational).

Hypothesis: We hypothesize that increased adolescent physical activity will decrease a woman's risk for breast cancer.

Chapter 2: Background

Definition of Breast Cancer

The American Cancer Society's definition of breast cancer reads as follows: "a malignant (cancerous) tumor that starts from cells of the breast (*ACS 2007)*." There are five stages in the progression of breast cancer: stage 0 (*in situ)* – stage 4 (distant metastasis). *In situ* breast cancer is defined as "cancer cells that remain within the basement membrane of the elements of the terminal duct lobular unit and the draining duct" while invasive breast cancer can be defined as "a dissemination of cancer cells outside the basement membrane of the ducts and lobules [of the breast] into the surrounding adjacent tissue [and distant organs]" (stages one through four) (*Sainsbury 2000*). For this study only women diagnosed with histologically- or cytologically-confirmed invasive breast cancers were included as cases.

Etiology of Breast Cancer

Breast Cancer Risk Factors

Globally, breast cancer is the highest incident cancer in women (*Wu 2006*). Many risk factors for breast cancer have been established and refined over the years that this disease has been studied. These risk factors can be divided into three separate groupings: reproductive or hormonal exposures (such as ages at menarche, first full-term pregnancy, or menopause), lifestyle or environmental exposures (such as physical activity, diet, or irradiation), and genetic predispositions (such as BRCA1 and BRCA2 genes). Based on the

Breast Cancer Detection and Demonstration Project (BCDDP) a Gail Model for prediction of woman's 5-year absolute breast cancer risk was developed (*Chen 2006*). The factors that remained significant predictors of breast cancer risk were included in the Gail model and were current age, age at menarche, age at first full-term pregnancy, family history of breast cancer in first degree relatives, and number of breast biopsies (*Gail 1989*). Based on this model, high risk women were defined as those whose five year breast cancer risk was 1.666% or higher (*Gail 1989*). However, studies have identified numerous additional risk factors for breast cancer that are currently not included in the Gail Model.

Recently in the context of developing prediction models for breast cancer risk over the next five or ten years, Santen *et al* reviewed and prioritized the additional risk factors that could be used to improve identification of women at high risk for breast cancer (*Santen 2007*). Based on literature review, priority was scored on a scale from one to five. Risk factors with a priority score of one to two and a half were considered high priority and low priority was given risk factors that scored over two and a half. Priority score of 1 was given to the risk factors in the Gail Model parameters, quantitative breast density, free estradiol plasma concentrations, total parity (including number of births in addition to never vs. ever) and age at menopause (*Santen 2007*). High priority risk factors: score of 1.5 was given to BMI and weight gain (ages 20-50 years); priority score 2 was assigned to total estosterone plasma concentrations, paternal and second-degree family history of breast cancer (including their ages of cancer onset) and ovarian cancer; priority score 2.5 was given to waist-hip ratio and height (loss and age final height was attained) (*Santen 2007*). Low priority risk factors, scores greater than 2.5, included alcohol use, breast feeding (number of years), genetic mutation in the BRCA1 and BRCA2 genes (applies to less than ten percent of the population), bone density, IGF plasma concentrations, use of hormone replacement therapies (estrogen-based), physical activity, high fat diet, and oral contraceptive use (*Santen 2007*). Based on the scoring from the expert panel, this report indicates the importance of modifiable risk factors, most of the risk factors listed above, are potentially modifiable with the exception of those that fall under the hereditary-type exposures. Some of the above identified modifiable breast cancer risk factors such as BMI, weight gain, and hormone levels may be effected by level of physical activity.

Some of these modifiable risk factors, both high and low priority, have been hypothesized to be critical not only in adulthood, but even more importantly during adolescence (the years of breast development) (*Colditz 1995, Berkey 1999, & Kodama 1981*). Within the last decade, the focus breast cancer etiology research has been shifting from exposures in adulthood to exposures that happen in utero, childhood and adolescent years (*De Assis 2006 & Okasha 2003*). It has been hypothesized that many of the risk factors that have been inconsistently associated with breast cancer risk when assessed in adulthood may eventually play an important role in breast cancer etiology when assessed at an earlier lifetime period such as adolescence (*Hunter 1993 & Colditz 1995*).

Menopausal Status as a Potential Effect Modifier of Breast Cancer Risk Factors

The timing of breast cancer's onset is often further characterized by the woman's menopausal status (premenopausal and postmenopausal). It has been suggested that pre- and postmenopausal breast cancers could have different etiologies and new evidence on modifiable risk factors suggests that pre- and postmenopausal breast cancer should not be combined into one overall breast cancer disease (*Newman 1995, Irwin 2006, Colditz 2005, & Kruk 2007*[a]). Instead, associations should be examined separately in these two groups or important information regarding breast cancer risks or preventions may be missed (*Enger 2000*). Evidence supporting this theory has been particularly prominent in studies examining body size and energy expenditures (*Reeves 2007*). Additional examples of where differing effects on breast cancer risk are seen by differing menopausal status include overall weight, weight gain, and BMI (*Carmichael 2006 & Shin 2008*). For one example, having an increased BMI prior to menopause (premenopausal) reduces breasts cancer risk; however, increased BMI after menopause (postmenopausal) increases risk (*Cleary 1997 & McPherson* 2000).

However, menopausal status has been inconsistently defined in various studies and sometimes completely omitted when results are reported. At the American Institute for Cancer Research along with the World Cancer Research Fund's recent conference on all cancer sites, the importance of examining pre- and postmenopausal breast cancer separately was heavily emphasized

(*WCRF/AICR 2007*). Given this information and the aim of our proposed study, it is acceptable to hypothesize that we may observe different effect sizes of adolescent physical activity in premenopausal verses postmenopausal women.

Evidence for Importance of Adolescent Physical Activity

In addition to the importance of the timing of the outcome (breast cancer), timing of exposures is critical to assess (*Linos 2008, Friedenreich 2001, Colditz 1995, & De Assis 2006*). While both lifetime and adult physical activity have been studied in regards to breast cancer risk, a new rising topic in this field has been to examine physical activity specifically during the time period of adolescence. To date, research on adolescent physical activity and breast cancer risk has been minimal. However, the number of publications on this topic began to increase in the past decade: over 70% of the studies on adolescent physical activity and breast cancer have been published after 1998.

To date 32 individual studies have been published on adolescent physical activity and breast cancer risk in women. Seven of these studies are cohort (*Maruti 2008, Margolis 2005, McTiernan 2003, Wyshak 2000, Rockhill 1998, Paffenbarger 1987, & Frisch 1985*) and the remaining twenty-five studies (*Sprague 2007, Kruk*[a] *2007, Kruk*[b] *2007, Magnusson 2005, Yang 2003, Steindorf 2003, Dorn 2003, Matthews 2001, Friedenreich 2001, Lee 2001, Adams-Campbell 2001, Verloop 2000, Moradi 2000, Shoff 2000, Levi 1999, Marcus 1999, Carpenter 1999, Gammon 1998, Chen 1997, Hu 1997, McTiernan 1996, D'Avanzo 1996, Taioli 1995, Mittendorf 1995, & Bernstein 1994*) are designed as case-control. In addition, two reviews of this literature have been published (*Lagerros 2004 & Monninkhof 2007*). The first review was Lagerros *et al* based on 23 studies, 19 case-control and 4 cohorts, concluded that moderate to heavy adolescent (defined as under 24 years of age) physical activity significantly decreases a woman's overall risk for breast cancer by 19% (overall OR=0.81; 95%CI: 0.73-0.89) when compared to the lowest level of physical activity reported (*Lagerros 2004*). A similar effect was seen when they summarized studies that reported effects by menopausal status: premenopausal estimates (n=9 studies) – OR=0.85, 95%CI:0.70-1.02; and postmenopausal estimates (n=11 studies) – OR=0.88, 95%CI:0.78-0.99 (*Lagerros 2004*). Similarly, Monninkhof *et* al that included in their review 18 case-control and 3 cohort studies, saw an overall 20% to 80% reduction in postmenopausal breast cancer risk with increasing physical activity (sum of all time periods of activity lumped together), but were unable to make any specific distinctions about the risk for premenopausal women (*Monninkhof 2007*). The two reviews, however, did not include the same studies of the adolescent physical activity and Monninkhof did not summarize adolescent physical activity separately from adult physical activity.

The effect of adolescent physical activity on overall breast cancer risk as observed from cohort studies varies from a slightly protective relative risk (RR) to an effect slightly over 1 (*Maruti 2008, Margolis 2005, McTiernan 2003, Wyshak 2000, Rockhill 1998, Paffenbarger 1987, & Frisch 1985*). Exact summarization of risk from cohort nor the case-control studies is not possible as no single measure of adolescent physical activity was used. In addition, all adolescent physical activity for these studies was recalled in later adulthood. Two cohort studies examined the effect of adolescent physical activity in a population of mostly premenopausal women (*Maruti 2008 & Rockhill 1998*). Maruti found a significant protective effect from increased recreational physical activity (measured in MET-h/wk) (*Maruti 2008*) while Rockhill did not observe any effect of increasing vigorous physical activity per month/year (*Rockhill* 1998). In addition, two cohort studies looked at this effect in postmenopausal women (*Margolis 2005 & McTiernan 2003*), however, neither found conclusive results.

Nearly half of the case-control studies observed a mild to significant decreased risk for breast cancer with increasing adolescent physical activity (*Shoff 2000, Kruk[a] 2007, Dorn 2003, Matthews 2001, Lee 2001, Marcus 1999, Bernstein 1994, Levi 1999, Yang 2003, Verloop 2000, & Mittendorf 1995*). However, similar to the cohort studies, few studies used the same measurement for adolescent physical activity. The fourteen other studies (*Sprague 2007, Carpenter 1999, Steindorf 2003, Friedenreich 2001, Kruk[b] 2007, Adams-Campbell 2001, Moradi 2000, Gammon 1998, Chen 1997, Hu 1997, D'Avanzo 1996, McTiernan 1996, Magnusson 2005, & Taioli 1995)* observed a null or slightly increased breast cancer risk with increasing adolescent physical activity. The age range for these case-control studies was defined in the time period between 0 and 20 years of age (when adolescent ages were specified). Three studies (*Gammon 1998, Marcus 1999, & Verloop 2000*) examined adolescence around the same time that we did for our analyses and the results from these studies showed a small non-significant protective effect from increasing adolescent physical activity.

Only 4 studies (*Dorn 2002, Friedenreich 2001, Matthews 2001, & Hu* 1997) examined the relationship of increased adolescent physical activity on breast cancer risk for both menopausal strata. Overall, results from stratification by menopausal status suggested a different effect between both pre- and postmenopausal women in two (*Friedenreich 200 & Hu 1997*), of the four studies. One study (*Matthews 2001*), observed that the joint effect from exercising as both an adolescent and an adult was statistically significant for all (OR = 0.47 95%CI: 0.36-0.62), premenopausal (OR = 0.57 95%CI: 0.40-0.82), and postmenopausal women (OR = 0.36 95%CI: 0.24-0.55). Kruk also examined a joint effect of ever versus never exercising in adolescence and adulthood with greatest decrease in risk in Polish women who indicated activity for both periods (OR = 0.45 95%CI: 0.28-0.73) (*Kruk*[a] *2007*).

Additionally, the World Cancer Research Fund and the American Institute for Cancer Research recently published a report titled "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective (*WCRF/AICR 2007*)." Although not broken out at specific ages, total physical activity was found to be protective both premenopausal (summary OR = 0.97 95%CI:0.95-1.00) and postmenopausal (summary OR = 0.97 95%CI:0.95-1.00) breast cancers (*WCRF/AICR 2007*).

Hypothesized Biologic Mechanisms

While the exact mechanism through which physical activity may act upon breast cancer is unknown, several mechanisms have been proposed. What is known is that physical activity has the ability to alter multiple aspects of a woman's menstrual cycle. Women with increased physical activity have been observed to have a later age at onset of menarche (*Frisch 1981 & Irwin 2006*) as well as reduced total number of ovulations during her lifetime (*Bernstein 1987 & Friedenreich 2002*) especially during strenuous physical activity in adolescence (*Rockhill 1998*). In women of reproductive ages, physical activity has also been observed to reduce the level of circulating estradiol (*Jasienska 2006*). These characteristics involve modifying a woman's exposure to circulating hormones, which have been shown to play an important role in invasive breast cancer both premenopausally and postmenopausally (*Chavez-MacGregor 2008*). Increasing exposure to physical activity will decrease the level of circulating ovarian hormones a woman is exposed to during her reproductive years (*Bernstein 2002*) and the resulting fluctuation may account for the overall protective effect observed between physical activity and breast cancer risk (*Bernstein 2005*).

Another hypothesized hormonal-altering mechanism is that physical activity may alter breast cancer risk through regulating both overall weight and weight gain (*Hoffman-Goetz 1998 & Friedenreich 2001*). Physical activity is very strongly associated with weight through the process of balancing the energy ingested versus expended, known as energy balance (*Friedenreich 2002*). Physical activity may also help to decrease the amount of abdominal fat stored which has been hypothesized to be at an increased metabolic level and possibly associated with increased risk for the development of some cancers including cancer of the breast (*Friedenreich 2002*). Rockhill *et al* notes that weight and/or weight gain may be the culprit for the differing effects of adolescent physical activity seen in pre- and postmenopausal women (*Rockhill 1998*).

Evidence on the importance of exposures during adolescence.

The human breast is the only organ that is not developed (functional) at birth (*Schedin 1997 & Frazier 2004*) . It is not until over a decade of life that this organ even begins to develop and continues its develop for nearly an additional decade (*Shu 2001*). During this developmental period, a woman's breast is believed to be very susceptible to insults that might predispose to breast cancer (*Dirx 1999, Pryor 1989, & Frazier 2004*). While adult breast cells are still susceptible to carcinogenic insults, many studies have shown greater susceptibility of breast tissue during adolescence or childhood than after onset of adulthood (*De Assis 2006*, *Land 2003, & Ronckers* 2005).

The idea that adolescence could be a susceptible time for insult to breast tissue was first induced from observing Japanese women who survived the atomic bomb. The Life-Span Study (LSS) was started on residents of Hiroshima and Nagasaki who were living in the cities on the date the bombs were dropped on these cities (*Land 1995)*. While all women exposed to these high radiation blasts were at an increased risk for breast cancer, women exposed before the age of 20 were at the highest risk and postmenopausal women exposed were at the lowest risk (*Ronckers 2005*). Women who were under the age of 19 at the time of exposure to radiation from the atomic bombings consistently had the highest percentage of radiation-related breast cancers regardless of radiation dose (*Land 1995*). For example, the percentage of radiation-related breast cancer for women exposed to the highest estimated radiation dose of greater than 0.5 sieverts when they were aged 0-19 years, 20-39 years, and greater than 40 years of age were 72.4%, 60.9%, and 39.1% respectively (*Land 1995*). This dose-response relationship became an important observation for estimating a window of susceptibility for breast cancer risk.

Colditz and Frazier review how the importance of timing of exposure is of great importance when dealing with many of the risk factors commonly associated with breast cancer (*Colditz 1995*). Ages at onset of menarche, first live birth, ingestion of certain foods, alcohol consumption, exposure to radiation, and physical activity are some of the important risk factors that have been observed to change the breast cancer risk depending on time of exposure (*Tretli 1996*). Animal exposure to isoflavanones during adolescence have shown increased differentiation in mammary gland development. This is important to breast cancer risk as early differentiation of breast tissues has been found to be protective (*Thanos 2006*).

Other dietary constituents have been shown to have a significant impact on breast cancer risk when ingested during adolescence. In rodent models a significantly reduction in incidences of mammary tumors have been observed after intake of phytoestrogens during their adolescence (*Lamartiniere 1998 & Messina 2001*). Recently, Linos *et al*, based on the Nurses Health Study II, observed that increased red meat consumption was positively associated with later breast cancer risk when consumed during high school (*Linos 2008*). However, no such association was observed in with consumption in adulthood suggesting that adolescence is the more critical time for this particular dietary exposure (*Linos 2008*). Since both diet and activity level are components of the overall energy balance which, as stated above, is a hypothesized risk factor for postmenopausal breast cancer, effects of physical activity may be analogous to observed effects of adolescent dietary exposures.

MET Levels as a Measure of Physical Activity

Physical activity can be measured in three different ways: "intensity (how much energy is expended), duration (refers to the minutes or hours of individual's activity episode), [and] frequency of muscular contractions (e.g. episodes performed per day, week, or month) (*Kruk 2006*)." Survey procedures such as interviews with participants have all three components of physical activity measurement on the basis of which a summary index of average level of physical activity is determined (*Kruk 2006*). One of these summary measures is MET-h per day or week (*Ainsworth 2000*). MET levels, units of metabolic equivalent' calculated "as the ratio of the energy expenditure when performing specific activities to the resting metabolic rate of the subject" calculated from the assumed average adult (*Forsum 2006*). In the literature evaluating the effects of adolescent physical activity and breast cancer risk, most of the recent studies have used the measure of MET-h as the measure of physical activity. Per unit time such as day or week, the higher the calculated MET level represents a higher level of physical activity. In the literature many of the more recent studies do use MET-h to measure physical activity (*Monninkhof 2006*). Additional measures such as hours per day or week, for differing levels of intensity (such as medium or strenuous) have also been reported.

Chapter 3: Methods

Polish Women's Health Study

The Polish Women's Health Study was designed to examine the lifestyle factors that differed between Polish immigrants to United States and Polish native women in Poland that could account for the increased risk of breast cancer after migration to United States. Dietary differences were the focus of the original investigation, however, information on physical activity was collected.

Design of the study to be analyzed - Case-control study

Description of the dataset to be used

The data for this thesis work will be obtained from Dr. Dorothy R. Pathak's Polish Women's Health Study. This case-control study was performed to identify protective factors in the lifestyles of Polish women. Data on breast cancer risk factors, including amount and intensity of physical activity, were collected from two sources of women: those living in one of four cities in Poland (Gliwice, Katowice, Poznan, and Bialystok) and Polish migrants living in the Detroit or Chicago area (United States). Women in both countries provided information on their reproductive risk factors as well as specific exposures (including diet and physical activity) during specific years of their adulthood (1985-1989) as well as their adolescent years, defined as the time a woman was 12-13 years of age. The dataset that will be used to test our hypothesis stated above (Chapter 1) is the U.S. component of the study and includes the Polish migrant women residing in Chicago, Illinois or Detroit, Michigan at the time of the study.

Case Selection

Breast cancer cases were identified from Cook County (Chicago) using the Illinois State Cancer Registry and from Detroit Metropolitan Area using the Surveillance Epidemiology and End Results (SEER) database at Karmanos Cancer Institute in Michigan. Cases who had an unknown country of birth were first screened for race (White), followed by their place of birth.

Inclusion Criteria: Only incident cases identified between January 1st, 1994 and December 31st 2001, histologically-confirmed, ages of 20 to 79 years, and Polish-born were included in the study.

Exclusion Criteria: Women diagnosed with cancer of other sites (except squamous and basal cell skin cancers) were ineligible for the study. Also excluded from the study were cases of breast cancer *in situ* and women who were non-Polish born.

Control Selection

Control selection was population-based and frequency-matched to the cases by the two areas of residence and 5-year age group. Controls under 65 years of age were identified through Random Digit Dialing (RDD). The distribution of Polish-born from the 1990 census was used to calculate sampling fractions for RDD. Controls between the ages of 65-79 years of age were identified from Medicare records of the Health Care Financing Administration. Upon identifying potential controls, women were screened for place of birth and only those who were Polish-born, had no history of breast cancer, and no previous other cancers (except squamous and basal cell skin cancers) were included in the study.

Sample Size

The size of the initial dataset was 443 women, 140 cases and 303 controls. We further restricted our analytical dataset by dropping 6 (2 cases & 4 controls) study participants whose total adolescent physical activity per day was less then 10 hours including sleep time. Upon review of their questionnaires we noticed comments by the interviewer that these women were unable to recall their complete daily physical activity during adolescence. In addition, we defined adulthood as 18 years or older, thus 15 women (all controls) were also excluded from analyses because they were under 18 years of age in 1989 (our proxy for adulthood). The resulting analytic dataset contains 284 controls and 138 cases for a total of 422 women.

Main Exposure: Adolescent Physical Activity

Women in the study were asked to report their non-occupational and occupational physical activity during the time when they were aged 12- 13 years old and during their adulthood years during 1985-89 (see Appendix B). The process for derivation of total hours spent in a given activity was the same for both time periods.

Adolescent Non-Occupational Physical Activity

Average number of hours spent doing activities such as: school athletic participation, other recreational, household, occupational, and inactive/sedentary actives including hours of sleep per day were reported. Women could report the number of hours spent participating in the given activity in terms of per day, per week, per month, and in some types of activities such as sports, per year. For the purpose of these analyses, we converted all answers into hours spent per day. To accomplish this, all hours of activities reported per week were divided by 7, those reported per month were divided by 30.4 (an average number of days/month), and activities reported per year were divided by 365.25. Hours of each activity were then summed up to calculate the total number of hours each woman reported per day. To calculate total MET-hs per day, the hours spent on each type of activity that has its own unique MET value (*Ainsworth 2000*) were multiplied by that value and added together.

Since interviewers were instructed not to question respondent's answers, the derived number of non-occupational hours/day when combined with occupational hours of physical activity to create total hours per day, was both under and over 24 hours. Therefore, the total reported hours per day needed to be standardized to a 24-hour day for each individual. To calculate the adjustment fraction, number of hours reported were divided by 24. Subsequently, the total calculated MET-hs for each individual, were divided by their same unique standardization fraction. This ensured that hours reported for each activity were uniformly adjusted by the inverse of the standardization fraction for each individual.

MET-h from stair climbing were not included in our total daily physical activity variable for the following reason. Literature states that the average person takes about only one second per step to climb stairs (*Bassett 1997*). When this value is multiplied by the amount of stairs (or flights) climbed and converted into a per day measure, MET-hs calculated from hours spent climbing stairs is insignificant compared to all other activities. For example, if a woman were to climb even 6 flights of stairs a day, with an average of 20 stairs per flight, and a MET value for stair climbing set to 8.5, her total MET-hs from stairs contribute less than 0.3 of a MET-h/day. For this reason, we have not included MET-h/d from stair climbing in our total daily MET-hs for either the adult period or the adolescent period collected from our subjects.

Similar process was used to calculate non-occupational daily activity for adulthood.

Adolescent Occupational Physical Activity

Women reported the number of months or years they were employed during adolescence and adulthood. For the time when they were 12-13 years old, the maximum time was reported either as 24 months or 2 years. For adulthood, 1985-1989, it was either 60 months or 5 years. Women had the option of reporting their work activities, either in months or in years. For the adolescent years, women who reported working during the summer, when not in school, were assigned their work duration to be 3 months/year. Women were then asked to report their average number of hours they worked in a given week.

Only 42 women reported being employed when they were 12-13 years old. For the women who reported holding an occupation during their adolescence, the number of hours worked per week ranged from 3 hours per week to 84. It is important to note that for some women, the time period during which they were 12-13 years old overlapped with the years that Europe was involved in World War II. Several of our study participants indicated they had worked in a concentration and/or labor camp during this time period. This often resulted in seemly high reporting of hours worked per week as well as percent of those hours spent in strenuous physical activity.

The typical work and school weeks in Poland prior to 1985 consisted of six school and work days as opposed to the typical five-day work week found in the United States. To incorporate this knowledge, we assumed that any women reporting an adolescent or adult occupation worked this six-day work week thus the number hours reported working per week was divided by 6 instead of 7 as for non-occupational activities.

If a woman reported that she worked a certain number of months during these two time periods, the number of months reported was multiplied by 26.1 to convert the number of months into the number of work days during that time period. The value 26.1 was calculated by multiplying the average number of days in a month, 30.4 by (6/7) to account for the 6 day work week. The result gave us the average number of work days that each woman worked during either the 2 year adolescent time period or during the 5 years in adulthood.

If a woman reported that she worked a certain number of years in either adolescence or adulthood, then the number of years was multiplied by 312 working days per year. The conversion of 312 was calculated by multiplying 52 weeks per year times the number of working days per week, 6. The result gave us an average number of work days during the specific time period.

To calculate the average number of days worked/year, the above calculated number of days was divided by 2 for adolescence and 5 for adulthood. Since respondents were reporting the average number of hours worked/week, that number was divided by 6 to account for the average number of hours worked/day. To calculate the final number of average hours worked per day during the given time period (adolescence or adulthood), the number of working days/year was multiplied by the average hours worked/day and then divided by 365.25.

In the questionnaire, after reporting the number of hours worked per week, women were asked to indicate either the number of hours, or percent of time, they spent each week sitting, standing, walking without lifting, walking with lifting less than 25 pounds, and doing heavy physical work. Each of these occupational activities carries a different MET value. Sitting was assigned a MET value of 1.5, standing was coded at 2.3 MET value, walking without lifting 3.0 MET value, walking with some lifting (less than 11.5 kg or 25lbs) 4.0 MET value, and heavy physical work 7.0 MET value (*Ainsworth 2000*). Percentage of time in each type of activity was then multiplied by corresponding MET-h value. To obtain the total MET-h for the occupational daily activity, the occupational daily hours were weighted by percentage of time spent in that activity times the corresponding MET-h and summed over all types of activities involved in their work day. The standardization fraction that was required to adjust each day to 24 hours and initially calculated by summing the hours of non-occupational and occupational daily activities (described in the non-occupational physical activity section above), was then applied to the total MET-hs calculated for the occupational activity.

Total Physical Activity

After both occupational and non-occupational physical activity converted to MET-hs per day were calculated, all activity for each time period was summed up creating a variable of total daily physical activity for both the adolescent and adult periods.

Creation of Adolescent MET-h/d Tertiles

Tertiles were created using the total daily MET-hs as reported by controls. The adolescent tertiles created from the data were as follows: low = 0-<45.9 MET-h/day, medium = 45.9-<55.7 MET-h/day, and high as greater than or equal to 55.7 MET-h/day.

Creation of Adult MET-h/d Tertiles

Adult physical activity tertiles were calculated by a process similar to those for adolescent physical activity. The adult tertiles were as follows: low = 0 - < 48.8 MET-h/day, medium = 48.8 - <59.6 MET-h/day, and high as greater than or equal to 59.6 MET-h/day.

Joint Levels of Adolescent and Adult Physical Activities

We created nine categories from the tertiles derived for both the adolescent and adult physical activity. The nine categories are with adolescent tertile level followed by the adult in the following notation: low/low, low/med low/high, med/low, med/med, med/high, high/low, high/med, and high/high.

Other Important Breast Cancer Covariates:

Duration of Stay in the United States

During the interview, each woman provided a date when she migrated to the United States (US) from Poland. From this information, a duration of stay variable was created to account for potential participant acculturation. Duration of stay was divided into three categories: women who migrated recently (after 1985), those who migrated before 1985 but have lived in the U.S. less than 10 years, and those migrated before 1985 but have lived in the U.S. for more than 10 years since.

First-degree Family History of Breast Cancer

Women that indicated their mother, sister, or daughter had been diagnosed with breast cancer were considered to have a first-degree family history of breast cancer. This variable was divided into a binary outcome of positive or negative for familial history of breast cancer.

Adult BMI(1985-1989)

Women reported their respective height and weights during 1985-1989 and from this their adult BMI was calculated using the formula - weight (kg)/ $[\text{height}]^2$ (m) (*NHLBI 1998*). Once BMI was calculated, women were further categorized into one of four BMI groups: BMI<18.5 = underweight; BMI 18.5-<25 = normal weight; BMI 25-<30 = overweight; and BMI>30 = obese (*NHLBI 1998*).

Some women could not recall their weight during the time period of 1985-1989 and to include them in the analysis, their weight had to be extrapolated from answers to similar questions. In addition to weight during 1985-1989 weight at age of 18, 30, 40, 50 or 60, were also collected and where appropriate used to calculate the missing BMIs. For example, if a 25 year-old woman did not report weight in 1985-1989 but did report weights for ages 18 and 30, her weight was interpolated between those two values and appropriate BMI was calculated for 1985-1989.

Adolescent Body Size

Height and weight for the time when participants were aged 12 to 13 years were not obtained. Instead, women were asked to identify their closest body size and shape from a series of nine pictures (*Koprowski 2001*). Women selecting one of the first two figures were labeled as 'underweight,' those selecting one of the subsequent three figures were considered 'normal weight," and women reporting a figure of six through nine were grouped into an 'overweight' category (see Appendix C).

Oral Contraceptive(OC) Use

This covariate was divided as a binary variable. Women that had ever used oral contraceptives of any kind were considered 'users;' all other women were considered 'non-users.'

Hormone Replacement Therapy (HRT) Use

Similar to oral contraceptive users, HRT users were divided into 'users' and 'non-users.' Women that had ever used any type HRT was placed in the 'users' category while all others were labeled as 'non-users.'

Age at Menarche

Women were asked to report the age at which their natural menstruation began. The median age at menarche for all women was about 14 years. Age at menarche was then categorized into 4 different groups: less than 13 years, 13-14, 14-15, and greater than or equal to 15 years. Four women did not report their age at menarche and were assigned the median value of 14 to avoid exclusion.

Age at First Full-term Pregnancy & Parity

Women whose pregnancies reached a gestational age of 24 weeks or greater were considered to have a full-term birth. Women were then divided on the age when they experienced their first full-term birth. The variable for age at first full-term pregnancy was divided into four categories for analysis: nulliparous, under the age of 22 years, 22 to less than 30 years, and 30 years and older.

Menopausal Status and Age at Menopause

Women who did not report natural or surgical menopause were considered premenopausal (n=171). All other women (n=251) were considered postmenopausal. For postmenopausal women, the average age at menopause was 50.5 years. In addition, women who reported stoppage in menstrual cycles, were older than 50 years of age, but did not report their age at menopause were assigned an age at menopause equal to 50 years. Women who had surgeries that removed both of their ovaries were also considered postmenopausal at the age of their surgery.

Women were further divided into three different categories for age at menopause: premenopausal, 50 years of age or less, and over 50 years of age.

Adult Total Caloric Intake

As part of the questionnaire women filled out a Food Frequency Questionnaire (FFQ) to capture usual intakes of certain foods during 1985-89. Calories assigned to an average serving for a specific food were then multiplied by the frequency of consumption standardized to daily consumption. For a few foods including breads, eggs, and alcohol, where the number of servings was also reported, the frequency of consumption was multiplied by number of servings, subsequently multiplied by calories per serving. Total caloric intake was then calculated as the sum of the caloric intake from each food-type in the questionnaire. Tertiles were then formed based on the distribution in controls: less than 2047 calories/day; between 2047 and less than 2660 calories/day; and over 2660 calories/day.

Adult Alcohol Consumption

Three questions in the FFQ asked about alcohol consumption. Intakes of beer, wine, and hard liquor during 1985 -1989 were assessed and subsequently calculated as weekly number of servings. Total number of weekly servings was calculated as the sum of the weekly servings of beer, wine, and hard liquor. Tertiles were formed from the total average weekly alcohol consumption: low =0 – <0.21 serving/week; medium = 0.21 - <1.09 servings/week; and high $\geq$ 1.09 servings/week.

Age in 1989

Controls were matched on to the distribution of age at diagnoses of cases however, case identification ranged from 1994 through 2001. Therefore in 1989, cases were older than controls. This variable was created in order to adjust the models for the potential age difference between cases and controls during 1985-1989. This variable (presented in Table 2) was divided into six categories : < 18 years; 18 - < 35 years; 35 - < 45 years; 45 - < 55 years; 55 - < 65 years; $\geq$ 65 years. Since we used the years between 1985 through 1989 as a proxy for adulthood, women in the < 18 years of age category (n = 15 controls) were excluded from all analyses since they had not started adulthood (defined as $\geq$ 18 years) between 1985 and 1989.

Statistical Analysis

Logistic regression always adjusted for matching variable (age and site) was used to perform all univariate and multivariate modeling to assess the effect the various risk factors on breast cancer risk.

All potential confounders were chosen based on literature review and were all included as adjustment variables in the models. In order to make out results for the effect of adolescent physical activity on breast cancer risk to be comparable to previous studies, none of the potential confounders were eliminated based on the change they had in point estimates for our main exposure. To assess for potential effect modification by all risk factors considered as potential confounders, interaction terms of these risk factors with tertiles of adolescent physical activity were included in the models. The Likelihood Ratio Test comparing the -2logL from the model that did not include specific interaction, with the model that incorporated potential effect modification, was calculated and assessed for significance at a $p<0.05$. If effect modification was observed, analyses of the effect of adolescent physical activity on breast cancer risk were performed in the separate strata of that variable.

Three types of models were run: first in addition to the main exposure of adolescent physical activity, included adjustment for the design matching variables (i.e. age and site); the second model, in addition, included adjustment for all potential confounders, including age in 1989, except adult physical activity, and the final model included all variables in Model 2 plus adjustment for adult physical activity.

Chapter 4: Results

All tables from these analyses can be found in Appendix A. Tables 1 and 2 provide a distribution of the demographic and various risk factors for cases and controls.

Descriptive Characteristics of Women in the Polish Women's Health Study

Upon viewing Table 1, we were able to establish that relative to controls, cases had a significantly higher proportion of first degree relatives with breast cancer (p=0.05); a lower level of physical activity in adulthood (p=<0.01); a higher proportion of later first full-term pregnancies (p=0.02); and a non-significant lower mean age at menarche (p=0.06).

Table 2 provides the distribution of age at diagnosis (reference ages for controls) and age in 1989 for cases and controls by menopausal status. The age distributions did not differ significantly between cases in either premenopausal (*p=0.43*) or postmenopausal (*p=0.29*) women. Over 92% of both cases and controls did not spend their adolescent years (through age 13) in the United States even after stratification by menopausal status.

Assessment of the Effect of Adolescent Physical Activity on Breast Cancer Risk

Table 3 reports three models for the effect of adolescent physical activity on breast cancer risk. In the first model, the odds ratios (OR) and 95% confidence intervals (95% CI) for the effect of adolescent physical activity on breast cancer risk are adjusted only for the matching variables of site and age. The results show that women in the highest intensity group during adolescence (greater than or equal to 55.7 MET-h per day) had a significant 44% reduction of breast cancer risk (OR = 0.56, 95%CI: 0.36-0.95). Reduced, though not significantly, risk was also observed for women who fell in the medium level of physical activity during adolescence (OR = 0.71, 95%CI: 0.43-1.16). Adjusting for known breast cancer risk factors and potential confounders shows very little change in the odds ratio (OR) of women at either medium or high level of adolescent physical activity, however neither of the estimated odds ratios reaches statistical significance; medium: OR=0.77, 95%CI: 0.43-1.35 and high: OR=0.66, 95%CI:0.37-1.19.

Further adjustment for adult physical activity in tertiles does not substantially change the observed effect medium and high adolescent physical activity on breast cancer risk in Model 3 (medium: OR=0.76, 95%CI:0.43-1.37; and high: OR= 0.71, 95%CI: 0.39-1.29). Additionally, we observed that in this model the highest level of adult physical activity also has a significant protective effect (OR=0.51, 95%CI:0.27-0.98) (data not shown).

A test for trend of adolescent physical activity was run for each model. The trend in the first model was statistically significant with OR=0.75; p=0.03. This implies that for each tertile increase in adolescent MET-h per day, a 24% reduction in breast cancer risk is observed. The magnitude of the risk reduction based on linear trend in both of the adjusted models (Model 2 and 3) was in the same direction as to that from the unadjusted model, OR=0.81, p=0.16 and

OR=0.84, p=0.25 Model 2 and Model 3 respectively, however, these estimates did not reach statistical significance at p=0.05.

Each of the potential confounders (listed in Table 1), were assessed for potential effect modification in models evaluating the effect of adolescent physical activity and breast cancer risk. Assessment for potential effect modification by all of the adjustment risk factors included in Models 2 and 3 revealed a significant effect modification of the adolescent physical activity and breast cancer risk relationship by menopausal status (LRT, chi square with 4 degrees of freedom = 13.107 $p<0.05$). Therefore, models assessing the relationship between adolescent physical activity and breast cancer risk were run within each strata of menopausal status. For premenopausal women, a consistent significant reduction across all three models was observed for the highest tertile of adolescent physical activity with a lesser reduction in risk observed in women who were in the medium level of adolescent physical activity. Odds ratios and confidence intervals for premenopausal women with high adolescent physical activity were: Model 1 (OR=0.23, 95%CI:0.09-0.56), Model 2 (OR=0.14, 95%CI:0.04-0.44), Model 3 (OR=0.12, 95%CI:0.04-0.40). The respective odds ratios for medium adolescent physical activity were: Model 1 (OR=0.70, 95%CI:0.33-1.47), Model 2 (OR=0.52, 95%CI:0.21-1.32), Model 3 (OR=0.44, 95%CI:0.17-1.18). The tests for linear trend for all three models in premenopausal women were also statistically significant with the OR for the linear trend in the final fully-adjusted model being OR=0.35, $p<0.001$ indicating

65% reduction in breast cancer risk per tertile increase in adolescent physical activity.

For postmenopausal women, no consistent effect of increasing adolescent physical activity (medium or high compared to low) on breast cancer risk was observed. However, the inclusion of adjustment for adult physical activity, Model 3 (data not shown), shows an increased protection for postmenopausal breast cancer risk for both medium and high levels of adult physical activity: medium – OR = 0.70 95%CI: 0.32-1.55; high – OR = 0.31 95%CI: 0.13-0.77.

Assessment of the Joint Effect of Adolescent and Adult Physical Activity on Breast Cancer Risk

The differing effects of adolescent and adult physical activities by menopausal status motivated the evaluation of the joint effect of both adolescent and adult physical activity on breast cancer risk by menopausal status. The ORs in Table 4 are from fully-adjusted models within each menopausal strata (see Table 3 - Model 2). Table 4 shows that high levels of physical activity during both adolescence and adulthood relative to women with low levels of activity during both time periods, provide a significant protection in premenopausal women (OR = 0.11, 95%CI:0.02-0.67) and a non-significant protection in postmenopausal women (OR = 0.36, 95%CI:0.08-1.58).

For the combination of medium adolescent physical activity with high adult physical activity, although point estimates were protective for both premenopausal and postmenopausal women, statistical significance was reached only in premenopausal women. The ORs were: premenopausal (OR=0.13, 95%CI:0.02-0.95); postmenopausal (OR=0.27, 95%CI:0.05-1.59).

When the level of adolescent physical activity was low, no significant protection from increasing high physical activity in adulthood was observed. Results in Table 4 suggest that the greatest reduction in breast cancer risk is achieved from the combination of high physical activity during both adolescence and adulthood. However, high adult physical activity does not reduce breast cancer risk when the individual had low level of adolescent physical activity. These observations jointly imply that greatest reduction in overall breast cancer risk can be achieved by increasing adolescent physical activity.

Chapter 5: Conclusions & Discussion

Discussion

This study provides evidence that increased physical activity (both medium and high relative to low) during the adolescent years (specifically ages 12-13 years) even after adjustment for physical activity during adulthood, provides significant reduction in risk for breast cancer in premenopausal women. We observed no such protective effect among postmenopausal women. However, in analyzing the joint effect of adolescent and adult physical activity shows that women who had medium or high adolescent activity as well as high adult activity had significant reduction in risk irrespective of menopausal status. Women with low physical activity in adolescence did not gain significant breast cancer risk reduction due to increased levels of activity in adulthood. Our findings point to the importance of increased levels (medium or high) of physical activity during adolescence in reducing breast cancer risk especially in premenopausal women.

Physical activity throughout life may modify a woman's lifetime exposure to circulating hormones therefore altering her breast cancer risk, however this is only one hypothesis (*Bernstein 1987 & Friedenreich 2002*). The exact biological mechanisms of adolescent physical activity on breast cancer risk are still not completely understood. Further research on physical activity and breast cancer risk is needed especially for different life periods (including adolescence) as hormone levels change throughout a woman's lifetime (*Friedenreich 2001*).

Findings from our analysis add to the hypothesis that increased adolescent physical activity decreases risk of breast cancer in women especially for premenopausal women. Few studies, however, have examined the effect of adolescent physical activity on breast cancer risk across menopausal strata (*Monninkhof 2007*). Results similar to our findings in premenopausal women (decreased breast cancer risk with increased physical activity during adolescence) have been previously observed in both cohort (*Wyshak 2000 & Maruti 2008*) as well as case-control studies (*Bernstein 1994, Dorn 2002, & Verloop 2000*) on populations comprised of a majority of premenopausal women. Our results, however, did not corroborate study findings from four other case-control studies (*Chen 1997, Gammon 1998, Friedenreich 2001, & Steindorf 2003*) and one cohort (*Rockhill 1998*) on populations containing large numbers of premenopausal women. Measures such as higher number of episodes of adolescent physical activity as well as increased adolescent MET-h of active (sum of recreation, occupational, and household) physical activity were seen to have inconclusive or increased findings on breast cancer risk when compared to the least active group(s) (*Rockhill 1998, Chen 1997, Gammon 1998, Friedenreich 2001, & Steindorf 2003*). Only one review (*Lagerros 2004*) observed a protective effect of increased adolescent physical activity on premenopausal breast cancer risk.

Although not significant, our findings also suggest a null effect of increasing adolescent physical activity on postmenopausal breast cancer risk. Three other case-control studies (*McTiernan 1996, Carpenter 1999, Moradi 2000*) have also found null effects of increasing adolescent physical activity on postmenopausal breast cancer risk. However, six other case-control studies examining the effect of adolescent physical activity, showed a decreasing risk of postmenopausal breast cancer (*Levi 1999, Mittendorf 1995, Taioli 1995, Friedenreich 2001, Dorn 2002, & Shoff 2000*). But measures of adolescent physical activity have not been consistent between these studies. Similar to our methods, one previous case-control study (*Friedenreich 2001*) examined adolescent physical activity using MET-h. In that study, a significant protective effect of the highest versus the lowest levels of adolescent physical activity was observed (OR = 0.73 95%CI:0.54-0.98). Both reviews of adolescent physical activity literature found a reduced risk for postmenopausal women (*Lagerros 2004 & Monninkhof 2007*).

In addition, the results from our analyses are comparable to other published data on Polish women. Although employing the use of hospital-based controls and having low response rates for both cases (49.2%) and controls (41.4%), Kruk observed a decreased overall breast cancer risk with increasing physical activity (measured in MET-h/week/year) at ages 14 to 20 years old: OR: 0.37 95%CI: 0.23-0.60 (*Kruk 2007*). However, unlike our analyses, these results were not provided specifically by menopausal strata.

Another component of our analyses, the joint effect of adolescent with adult physical activity, has also been previously explored. Two studies examining dichotomous responses (yes/no or ever/never) to participating in both adolescent and adult physical activities have observed significant reduction in overall breast cancer risk among women whom were active during both periods when compared to women inactive in both periods: OR = 0.46, 95%CI:0.28-0.73 (*Kruk 2007*), OR = 0.47, and 95%CI:0.36-0.62 (*Matthews 2001*). Three studies

(*Verloop 2000, Matthews 2001, & Maruti 2008*) further examined this joint effect by menopausal strata. Similar to the results from our analyses, all three studies found significant reduction in risk for premenopausal breast cancer when comparing exercisers in both adolescence and adulthood with women who were low or non-exercisers in both time periods: OR = 0.68, 95%CI: 0.53-0.87 (*Verloop 2000*), RR = 0.70 95%CI: 0.53-0.93 (*Maruti 2008*), & OR = 0.57 95%CI: 0.40-0.82 *(Matthews 2001*). Although our results for postmenopausal breast cancer risk of high adolescent and adult physical activity (when compared to low for both) were not significant (OR = 0.36 95%CI: 0.08-1.58; cases = 4; controls =27) possibly due to small sample size, were similar to a previous statistically significant postmenopausal joint effect (OR 0.36 95%CI:0.24-0.55) which was based on a larger sample size (cases = 43; controls = 95)(*Matthews 2001*).

However direct comparison of our results to all other studies on adolescent physical activity and breast cancer risk poses a challenge. Only about 50% of the previously published literature uses the measure of MET values (*Carpenter 1999, Chen 1997, Lee 2001, Gammon 1998, Kruk 2007, Kruk 2007, Mittendorf 1995, Matthews 2001, Marcus 1999, Friedenreich 2001, Steindorf 2003, & Maruti 2008)* to assess adolescent physical activity while other use additional methods such as ever vs. never (*Wyshak 2000 & Mctiernan 2003),* episodic (*Shoff 2000 & Yang 2003*) , hourly (*McTiernan 1996, Bernstein 1994, Levi 1999, Moradi 2000, & Dorn 2002*), energy expenditure (*Hu 1997)* or comparisons to peers (*Frisch 1985, Paffenbarger 1987, & Verloop 2000*). Along with the measure of the adolescent physical activity, physical activity can be further categorized into several different subtypes allowing each individual researcher focus on one specific type of activity such as recreational, occupational, or household. To date, our analyses appear to be unique in their measurement of total daily adolescent physical activity (in MET-h/day) which includes inactive as well as sleep time in the daily MET-h calculation.

As indicated in the hypothesized biological mechanisms above, energy balance may play an important role in how adolescent physical activity effects breast cancer risk. Data on both body size and usual daily dietary consumption were also captured in this questionnaire and thus allowed us to make adjustments for them.

Limitations

Limitations in this thesis are similar to ones seen in other case-control studies on adolescent physical activity and breast cancer risk. Even cohort studies examining this association of adolescent physical activity and breast cancer risk rely on recalled data of adolescent physical activity due to the large lag time between adolescence and breast cancer occurrence. This limitation was minimized by using memory prompts (i.e. picture cards and reference dates) during the data collection for this study.

While two different time periods were captured for this data, one was determined by a specific age (adolescent years of between ages 12-13) and the other time period was assessed between stationary calendar years (adulthood 1985-1989) during which ages ranged from 18 to 72 years. As stated previously in the methods section in Chapter 3, women whose period of adolescence (defined as < 18 years) overlapped with the second time period (1985-89), were eliminated from analyses to prevent multiple reporting between the two time periods and to ensure more appropriate captures of adolescent and adulthood exposures. Although the adult physical activity was captured for different ages in 1985-1989, the information on all other variables that could be related to energy expenditure, such as diet and BMI, were also recorded for this same time period (1985-1989) to make appropriate adjustments in our models.

Finally, the questionnaire's assessment of physical activity (for both adolescent and adults) used in this analysis has not yet been validated in a United States or Polish population; however, it was developed at the National Institutes of Health specifically for this study. The dietary component, however, has been validated in a United States population (unpublished data).

Strengths

Physical activity assessment in the Polish Women's Health Study questionnaire captured data from two separate time periods: during adolescence (ages 12-13) and adulthood (years between 1985-1989). We were able to assess the effect of physical activity during two different time periods (adolescence and adulthood) as well as the joint effect between physical activities in the two separate life periods. The questionnaire also captured a wide range of non-physical activity information including most, if not all, other breast cancer risk factors. By having access to information on all of these breast cancer risk factors allowed us to account and adjust for them, thus giving us a more accurate estimation of adolescent physical activity's true effect on breast cancer risk.

The Polish Women's Health Study questionnaire captured all daily activity, both inactive times (such as sleeping and sitting) as well as active times (such as recreational and household physical activity). Since women were asked to report hours for each activity, MET-h/day were able to be assigned for all recreational, household, inactive, as well as occupational activity. To date this study appears to be the first to analyze total daily MET-h of adolescent physical activity on breast cancer risk. In addition, using our unique population, we captured considerable heterogeneity in adolescent physical activity exposure ranging from 27 MET-h/day – 89 MET-h/day. Some of the high reporting of MET-h/day can be attributed to the overlapping of World War II with the years some of the women were aged 12 to 13 years. As previously mentioned several women included in our dataset reported being in a labor and or concentration camp during their adolescent years. This information was reported in the adolescent occupational physical activity portion of the questionnaire. This resulted in some women reporting extremely high levels of adolescent physical activity (up to about 82 MET-h/day).

Conclusions

In conclusion, these results enhance the current limited findings in the literature about the effect of adolescent physical activity and breast cancer risk;

however, given that the majority of the women were not residing in the United States during their adolescent years (ages 12-13), it will be imperative to compare these results with those from the Polish component of the Polish Women's Health Study.

Given little evidence for harmful effects of adolescent physical activity on breast cancer risk and the growing evidence for beneficial effects encourage this topic to be further explored and findings implemented. This analysis suggests that there should be more campaigns to increase the level of physical activity in girls under the age of 21. In addition, to encourage adolescent physical activity, maintenance of higher levels of physical activity should be of equal importance to gain the largest benefit from physical activity on breast cancer risk reduction.

APPENDICES

APPENDIX A

Tables 1 – 4

Table 1: Descriptive Characteristics of Women in the Polish Women's Health Study

	Cases (n=138)	Controls (n=284)	*P-Value*
Site			
Detroit	21%	24%	
Chicago	79%	76%	
Duration of Stay in the U.S.			
Recent move	44%	45%	*0.15*
< 10 years	24%	25%	
≥ 10 years	32%	30%	
1st Degree Family Relative with Breast Cancer	14%	8%	***0.05***
Adolescent Physical Activity (MET-h/day)			
Low (0 - < 45.9)	43%	33%	*0.08*
Medium (45.9 - < 55.7)	30%	33%	
High (≥ 55.7)	26%	34%	
Adult Physical Activity (MET-h/day)			
Low (0 - < 48.8)	43%	33%	***<0.01***
Medium (48.8 - < 59.6)	38%	34%	
High (≥ 59.6)	19%	33%	
BMI 1985-89			
Underweight	4%	6%	*0.69*
Normal	65%	59%	
Overweight	24%	26%	
Obese	7%	9%	
Adolescent Bodysize			
Underweight	59%	59%	*0.13*
Normal	36%	32%	
Overweight	4%	9%	
Oral Contraceptive Use	17%	12%	*0.27*
HRT Use	12%	12%	*0.59*
Age at Menarche	13.5	13.8	*0.06*
Age at First Full Term Pregnancy/Parity			
Nulliparous	12%	9%	***0.02***
< 22 years	22%	29%	
22 - < 30 years	50%	54%	
≥ 30 years	17%	8%	
Age at menopause			
Premenopausal	46%	39%	*0.77*
≤ 50 years	26%	30%	
> 50 years	28%	31%	
Adult Total Caloric Intake (calories/day)			
< 2047	40%	33%	*0.34*
2047 - < 2660	33%	34%	
≥ 2660	28%	33%	
Adult Alcohol Consumption (servings/week)			
0 - < 0.21	27%	33%	*0.62*
0.21 - <1.09	38%	34%	
≥ 1.09	35%	33%	

Table 2: Age Characteristics of Women in the Polish Women's Health Study

	Premenopausal		Postmenopausal	
	Cases (n=62)	Controls (n=109)	Cases (n=76)	Controls (n=175)
Age at Diagnosis				
20 - < 35 years	10%	15%	0%	0%
35 - < 45 years	42%	39%	0%	0%
45 - < 55 years	47%	44%	20%	18%
55 - < 65 years	2%	3%	36%	25%
65 - < 75 years	0%	0%	36%	38%
≥ 75 years	0%	0%	9%	19%
	p=0.86		p=0.06	
Age in 1989*				
18 - < 35 years	47%	58%	0%	0%
35 - < 45 years	48%	40%	20%	21%
45 - < 55 years	5%	2%	32%	33%
55 - < 65 years	0%	0%	33%	39%
≥ 65 years	0%	0%	16%	7%
	p=0.43		p=0.29	
Adolescence spent in US (%)	2%	3%	7%	2%

* Excludes 15 controls who were adolesents (<18 years of age) during 1985-89

Table 3: Unadjusted & Adjusted Models for Adolescent Physical Activity (PA) in Total MET-h/day & Breast Cancer Risk

	Model 1 (adjusted for site & age)			**Model 2** (adjusted [1])		**Model 3** (Model 2 + Adult PA[2])	
	Ca/Co	OR	95% CI	OR	95% CI	OR	95% CI
Overall -Total MET-h/day							
Adolescent							
Low (0 - < 45.9)	60/95	1.00	Ref	1.00	Ref	1.00	Ref
Medium (45.9 - < 55.7)	42/92	0.71	(0.43-1.16)	0.77	(0.43-1.35)	0.76	(0.43-1.37)
High (≥ 55.7)	36/97	**0.56**	**(0.34-0.95)**	0.66	(0.37-1.19)	0.71	(0.39-1.29)
Linear trend		**0.75**	**(0.58-0.97)**	0.81	(0.60-1.09)	0.84	(0.62-1.14)
p-value for trend test		*p=0.03*		*p=0.16*		*p=0.25*	
Premenopausal							
Adolescent							
Low (0 - < 45.9)	30/31	1.00	Ref	1.00	Ref	1.00	Ref
Medium (45.9 - < 55.7)	23/36	0.70	(0.33-1.47)	0.52	(0.21-1.32)	0.44	(0.17-1.18)
High (≥ 55.7)	9/42	**0.23**	**(0.09-0.56)**	**0.14**	**(0.04-0.44)**	**0.12**	**(0.04-0.40)**
Linear trend		**0.50**	**(0.33-0.77)**	**0.39**	**(0.22-0.68)**	**0.35**	**(0.19-0.64)**
p-value for trend test		*p<0.01*		*p<0.001*		*p<0.001*	
Postmenopausal*							
Adolescent							
Low (0 - < 45.9)	30/64	1.00	Ref	1.00	Ref	1.00	Ref
Medium (45.9 - < 55.7)	19/56	0.66	(0.33-1.32)	0.78	(0.33-1.82)	0.78	(0.33-1.87)
High (≥ 55.7)	27/55	0.88	(0.45-1.71)	1.24	(0.55-2.83)	1.41	(0.60-3.31)
Linear trend		0.93	(0.67-1.31)	1.11	(0.73-1.68)	1.18	(0.77-1.81)
p-value for trend test		*p=0.68*		*p=0.63*		*p=0.45*	

[1] Adjusted for: age (20-<35, 35-<45, 45-<55, 55-<65, 65-<75, ≥75), site (Chicago, Detroit), age at menarche (<13, 13-<14, 14-<15, ≥15), adult BMI (underweight, normal, overweight, obese), adolescent bodysize (underweight, normal, overweight), first degree family history of breast cancer (yes, no), weekly alcohol consumption (0-<0.21 servings, 0.21-1.09, ≥1.09), oral contraceptive use (ever, never), HRT use (ever, never), age at first full-term pregnancy (nulliparous, <22 years, 22-30 years, ≥30 years), age at menopause (premenopausal, ≤50 years, >50 years), duration of stay in the United States (recent move, <10 years, ≥10 years), age in 1989 (18-<35, 35-<45, 45-<55, 55-<65, 65-<75) and daily caloric intake (<2047, 2047-<2660, ≥2660); [2] Adult PA (<48.8, 48.8-<59.6, ≥59.6);

Table 4: The Adjusted[1] Joint Effect of Adolescent & Adult Physical Activity on Breast Cancer Risk by Menopausal Status

Physical Activity (MET-h/d)	Physical Activity (MET-h/day) Adolescent								
	Low (0 - < 45.9)			Medium (45.9 - < 55.7)			High (≥ 55.7)		
Adult	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Premenopausal									
Low (0 - < 48.8)	13/14	1.00	Ref	4/10	0.28	(0.05-1.58)	1/10	**0.03**	**(0.002-0.39)**
Medium (48.8 - < 59.6)	10/10	0.70	(0.15-3.25)	16/16	0.71	(0.19-2.69)	5/15	**0.15**	**(0.03-0.85)**
High (≥ 59.6)	7/7	0.72	(0.14-3.75)	*3/10*	**0.13**	**(0.02-0.95)**	3/17	**0.11**	**(0.02-0.67)**
Postmenopausal									
Low (0 - < 48.8)	17/32	1.00	Ref	11/17	1.97	(0.56-6.96)	14/11	3.00	(0.82-10.94)
Medium (48.8 - < 59.6)	7/17	1.29	(0.34-4.91)	5/21	0.54	(0.13-2.32)	9/17	1.96	(0.54-7.10)
High (≥ 59.6)	6/15	1.22	(0.30-4.94)	3/18	0.27	(0.05-1.59)	4/27	0.36	(0.08-1.58)

[1] Adjusted for: age (20-<35, 35-<45, 45-<55, 55-<65, 65-<75, ≥75), site (Chicago, Detroit), age at menarche (<13, 13-<14, 14-<15, ≥15), adult BMI (underweight, normal, overweight, obese), adolescent bodysize (underweight, normal, overweight), first degree family history of breast cancer (yes, no), weekly alcohol consumption (0-<0.21 servings, 0.21-1.09, ≥1.09), oral contraceptive use (ever, never), HRT use (ever, never), age at first full-term pregnancy (nulliparous, <22 years, 22-30 years, ≥30 years), age at menopause (premenopausal, ≤50 years, >50 years), duration of stay in the United States (recent move, <10 years, ≥10 years), age in 1989 (18-<35, 35-<45, 45-<55, 55-<65, 65-<75) and daily caloric intake (<2047, 2047-<2660, ≥2660).

APPENDIX B

Physical Activity Questionnaire from the Polish Women's Health Study

Physical Activity Questionnaire from the Polish Women's Health Study

I'll start with asking questions about gym and sports during your school years.

H1. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY):

a. ...participating in gym classes as part of your school program?

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

b. ...participating in sports such as basketball, volleyball, soccer, or swimming as part of a competitive team in or outside of school? Please include time spent at practices.

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

Now, I'd like to ask you about recreational activities and transportation...

H2. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY) Then ask: and during 1985- 1989?

a. (SHOW CARD H-1) ... doing activities while you were sitting or reclining, such as eating, watching television, reading, playing cards, sewing or knitting, or just doing nothing? Please include the time you spent sitting in class.

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

b. (SHOW CARD H-2) ... participating in recreational sports, such as softball, soccer, volleyball, skating, swimming, calisthenics, running or jogging, skiing or cross-country skiing. Please do not include time spent training for a competitive sports team or doing aerobics.

____ Hours per
a. Day b. Week c. Month d. Year e. N/A *(circle one)*

c. ... walking to get to places such as school, work or shopping, or for recreation or exercise, including walking with persons, pets?

____ Hours per

a. Day b. Week c. Month d. N/A *(circle one)*

d. ... bicycling to get to places such as school, work or shopping, or for recreation. Please include time you spent exercising on a stationary bike.

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

e. ... dancing or doing aerobic exercise?

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

Next, I will ask you to estimate the number of stairs you walked up on an average day, week, or month. You can give me you answer as the number of stairs climbed in a day, week, or month, or as a number of floors climbed in a day, week, or month. One floor is about 20 steps. Please remember to include stairs in your home, at school, at work, or other places such as where you shop.

H3. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY) Then ask: and during 1985- 1989?

a. Please estimate the number of stairs or floors that you walked up on an average day, week, or month in you home, at, work, or other places.

____ Stairs or Floors (*circle one*) per
a. Day b. Week c. Month d. N/A *(circle one)*

Next, I'd like to ask you about outdoor activities related to unpaid garden or farm work done after regular working hours or another paying job. About outdoor actives related to jobs that you were paid for and outdoor activities related to work on your own or family farm. I will ask later.

H4. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY) Then ask: and during 1985- 1989?

a. (SHOW CARD H-3) ... moderate and heavy chores such as gardening, sweeping, raking, mowing, digging, planting, weeding, shoveling, chopping wood, milking cows, animal pens, feeding and caring for large animals (cow, pigs, horses, etc)?

____ Hours per
a. Day b. Week c. Month d. Year e. N/A *(circle one)*

Next, I'd like to ask you about household activities. Again, please do not include household activities that you may have done as part of a job for which you were paid.

H5. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY) Then ask: and during 1985- 1989?

a. ...light chores such as cooking, cleaning, washing dishes, making beds, sweeping or vacuuming, mopping, doing laundry (by machine)m and light shopping or standing in lines?

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

b. ...moderate or heavy chores such as heavy cleaning, scrubbing, hand washing clothes with a wash-board or using an impeller-type machine, making home repairs, and heavy shopping like caring and lifting groceries?

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

c. ...moderate or heavy chores related to children, others, or small pets such as bathing, dressing , carrying children, and active play with children or pets?

____ Hours per
a. Day b. Week c. Month d. N/A *(circle one)*

H6. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY) Then ask: and during 1985- 1989?

a. ...sleeping? Please include naps taken during the day.

____ Hours per Day

Now I want to ask you just a few questions about your work relate physical activity. Work includes any part-time or full-time jobs, any self-employment or work for a family business, jobs in the military or on you own family farm, and any jobs you may have held during World War II.

H7. ...how many month or years were you employed?

____ Months or Years (*circle one*)

H8. During those months (NUMBER OF MONTHS OR YEARS FROM H7), about how many hours per week did you usually work?

_____ Hours per Week

Now I'd like to know what percentage or how many hours of you time you spent in each of these five kinds of actives. The total should add up to 100% or the total number of hours you worked each week.

H9. When you were 12 and 13 years old, abut how many hours per day or per week did you spend...(READ FIRST.NEXT ACTIVITY) Then ask: and during 1985- 1989?

a. ...sitting?

____ Hours or Percent (*circle one*)

b. ...standing?

____ Hours or Percent (*circle one*)

c. ...walking with no lifting?

____ Hours or Percent (*circle one*)

d. ...walking with some lifting (less than 11.5 kg or less than 25 lbs)?

____ Hours or Percent (*circle one*)

e. ...doing heavy physical work?

____ Hours or Percent (*circle one*)

H10. TOTAL: SHOULD EQUAL 100% OR HOURS PER WEEK FROM H8

____ Hours or Percent (*circle one*)

APPENDIX C

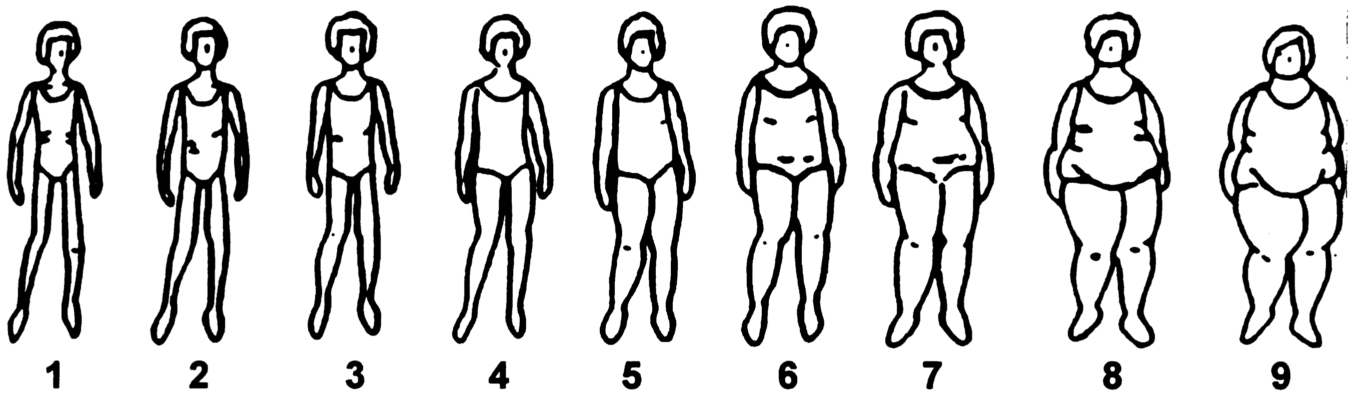
Adolescent Body Size Figures used in the Polish Women's Health Study

Adolescent Body Size Figures used in the Polish Women's Health Study

Card M-1

BODY OUTLINES (ADOLESCENT)

(Please select one)



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