EXAMINING THE RELATIONSHIP BETWEEN LEISURE-TIME PHYSICAL ACTIVITY AND THE RISK OF COLON AND BREAST CANCER: A METHODOLOGICAL REVIEW AND META-ANALYSES

by

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ABSTRACT

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Purpose: The objective of this study was to review the methodology and analyze the existing data examining the relationship between leisure-time physical activity and the risk of colon and breast cancer. **Methods:** Methodological differences (participant characteristics, length of time physical activity was measured, categorizations of quantified physical activity, and assessment instrumentation used to record activity) among studies of activity and cancer risk were reviewed and potential confounding was estimated by calculating the percent difference between multivariate-adjusted effect measures and unadjusted effect measures. A series of meta-analyses were completed. Studies quantifying activity using the *Compendium of Physical Activities* were included in the primary meta-analyses of colon and breast cancer risk. Subjects from all studies were combined and categorized into low, moderate, and high amounts of weekly activity. Moderate and high groups were compared to the low reference group. **Results:** Percent differences between adjusted and unadjusted effect measures ranged from 0-31% across all physical activity categories for colon cancer studies and 0-21% for breast cancer studies, with one study reporting a larger difference for each set of analyses (Tang et al., 1999 – 93%; Patel et al., 2003 –64%, respectively). Combined effect measures for

high versus low activity ranged from 0.524 (95% CI = 0.348-0.788; $p = 0.002$; Males) to 0.673 (95% CI = 0.474-0.956; $p = 0.027$; females) for colon cancer risk. For breast cancer risk, effect measures for high versus low activity were 0.832 (95% CI = 0.747-0.926; $p = 0.001$) for pre- and postmenopausal females combined, 0.820 (95% CI = 0.584-1.151; $p = 0.251$) for premenopausal females, and 0.868 (95% CI = 0.754-0.999) for postmenopausal females. **Conclusions:** Higher amounts of leisure-time physical activity were associated with a reduced risk of male and female colon cancer and postmenopausal breast cancer. Future studies of the relationship between physical activity and cancer risk should adhere to a standardized questionnaire for assessing types of activity, standard time frame for measuring activity, and quantification of the amount of activity likely to be protective, to develop a better understanding of the effects of leisure-time physical activity on cancer risk throughout the lifespan.

Chapter I

Introduction

Cancer is defined as a group of diseases that generate from most cell types in the body. It is characterized by uncontrolled cellular proliferation and unregulated cell growth, as well as the spread of abnormal cells, leading to invasiveness of normal body tissue [1]. Malignant tumors differ from their benign counterparts, as malignancies are more invasive, have a faster growth rate, are undifferentiated, and often metastasize. Solid, malignant tumors known as carcinomas are responsible for the majority of cancers originating in body tissues, including the colon and breast. Carcinomas often originate from hyperplasia, which is defined as increased local tissue size due to abnormal cellular proliferation, which often leads to unregulated cell growth.

Three classes of genes are involved in cancer initiation and progression: DNA repair genes, tumor-suppressor genes, and proto-oncogenes [2]. DNA repair genes are not directly involved with cellular replication and growth, but proto-oncogenes are non-mutated alleles of genes associated with normal cellular replication and growth, while tumor-suppressor genes prevent abnormal cellular growth. A mutation of DNA repair genes leads to additional mutations of tumor-suppressor genes and proto-oncogenes, resulting in the initiation and progression of cancer [3]. Specifically, the *p53* gene is an important tumor-suppressor gene whose mutation is associated with approximately

50% of all human cancers, including colon and breast [4]. Both two acquired mutations or one inherited and one acquired mutation of DNA repair gene or tumor-suppressor gene alleles can inactivate the mechanisms that inhibit abnormal cell growth. This is known as the "two-hit theory of carcinogenesis" [5, 6]. Typically, mutations of proto-oncogenes into oncogenes combined with the deactivation or deletion of tumor-suppressor genes leads to an unregulated growth of cancerous cells. The progression of cancer is usually described according to the tumor-node-metastasis (TNM) system, which accounts for the size of the primary tumor, surrounding lymph node involvement, and presence of metastasis [7]. Most cancers are classified in stages I through IV – tumor limited to tissue of origin, spread of tumor into local surrounding tissue, invasive legion with lymph node involvement, and metastasis, respectively.

Cancer recently surpassed heart disease as the leading cause of death among Americans under age 85 since 1999, as 556,902 Americans died of cancer in 2003 and over 564,000 individuals are projected to die from cancer in 2006 [8]. In the United States (U.S.), the total economic burden of cancer is nearly $190 billion, including approximately $65 billion in direct health care expenditures and over $100 billion in indirect costs due to lost productivity (2003 U.S. dollars) [9]. According to the American Cancer Society, the lifetime probability of developing cancer is approximately 46% for males and 38% for females in the U.S. Furthermore, the incidence rate for cancer of all sites was 553.3 per 100,000 males and 413.5 per 100,000 females between 1998 and 2002, and over 1.4 million new cancer diagnoses are expected for 2006. For the first time since 1930 (the first year of recorded cancer records), the total amount of annual

deaths from cancer decreased (-369 deaths), although this was reported only in males (-778), as cancer-related female deaths continued to increase (409).

In addition to the sex differences in cancer related mortality in the United States, there are incidence and mortality differences among races. African American males have a 23% higher incidence rate and 40% higher mortality rate for all cancer sites compared to their White counterparts. Although African American females have a 7% lower incidence rate for all cancer sites, their mortality rate is still 18% higher compared to U.S. White females. Such disparities in survival rates may be related to inequitable access to quality health care, and biological factors such as the development of different cancer-related comorbidities, but the precise impact of these factors remains unclear [10]. However, it appears that access to quality health care may be the most important factor in survival, as recent research reported African Americans have similar survival rates as Whites when similar cancer treatment and care is received [11]. Specifically, access to early detection through appropriate screenings is essential for survival. In addition to the lower survival rate among nearly all U.S. minorities, these populations are also more likely be diagnosed at a later stage than U.S. Whites [12].

In summary, cancer consists of a sequence of events that eventually lead to abnormal cellular growth. It is a leading cause of death in the U.S. and further exploration of risk factors associated with the prevention of cancer is necessary as the relationship between lifestyle risk factors such as physical activity and cancer risk remains largely unclear. Two cancers that are among the most prevalent and fatal are breast cancer and colorectal cancer, and physical activity is thought to provide some degree of a protective effect on each of these cancers.

Colorectal Cancer

A multi-step carcinogenesis model is a widely accepted model for colorectal cancer progression [13]. Adenomatous polyps, which are usually adenocarcinomas, are an established precursor of colon cancer, often becoming colon tumors. Within a normal epithelium, there is initial DNA damage in the form of an *APC* gene mutation, which leads to a hyper-proliferative epithelium, an early adenoma and eventually an intermediate adenoma after further genetic mutations. At the point of the intermediate adenoma, a mutation of the *K-RAS* oncogene, a gene responsible for cellular proliferation and the regulation of cellular growth becomes mutated. Eventually, the presence of a late adenoma occurs, which causes a loss of the *p53* tumor suppressor gene. The loss of *p53* allows for oncogenic growth and for the late adenoma to develop into a carcinoma, which has the potential to metastasize with other alterations.

Currently, colorectal cancer is the second most prevalent cancer among both sexes combined, and the third most prevalent cancer for each sex, as over 72,000 male cases and 75,000 female cases are predicted for 2006. This is equivalent to 10% and 11% of all cancer cases, respectively [8]. Colorectal cancer is the second most fatal cancer among males, and 27,870 deaths are predicted for 2006, which is equivalent to 10% of all cancer deaths in males - slightly more than the predicted deaths due to prostate cancer. Colorectal cancer is responsible for 10% of all cancer deaths in females, and only lung and breast cancer cause more deaths. The mortality rate for colorectal cancer (death rate per 100,000 population) remained relatively stable between 1950 and 2002, but has decreased to below 30% in the past ten years. Meanwhile, the mortality rate among females slowly, but steadily decreased between 1950 and 2002, and is currently under

20% [8]. Recent trends (1998-2002) indicated a decrease in the incidence rate of colorectal cancer by 1.8% (both sexes), 2.5% (males), and 1.5% (females) per year. Additionally, annual trends during the same time period show a decrease in deaths attributable to colon cancer by 2.0% for males [14]. African-American males and females have higher colorectal cancer incidence and mortality rates compared to U.S. Whites. Higher mortality rates among African Americans may be due to later screening and diagnosis in this population [12]. Additionally, there may be biological disparities such as different comorbidities and higher presence of various risk factors between the two populations.

While no association between physical activity and rectal cancer has been reported, the association between physical activity and colon cancer risk reduction is very consistent among epidemiologic studies for occupational, leisure-time, and total activity. Prior studies have reported a dose-response effect of physical activity on colon cancer risk at higher exercise levels [15-19]. The biological plausibility of the positive effect of physical activity on colon cancer development consists of several primary mechanisms including a reduction in body fat [20], improved gastrointestinal transit time [21], and a reduction in circulating hormone levels, including estrogen [22].

Prior research has shown little alteration in the relationship between physical activity and colon cancer after adjustment for other potential confounders. Confounding factors are variables other than the exposure (in this case physical activity) that can potentially impact the association between the exposure (physical activity) and colon cancer risk [18, 19, 23-25]. However, some effect modification, defined as the "variation in magnitude of a measure of exposure across levels of another variable" may be present

in the form of higher fiber intake [24]. Fiber intake has a similar impact on the gastrointestinal transit rate, as well as BMI, which can also affect colon cancer risk, regardless of physical activity level [18].

In addition to physical inactivity, primary risk factors for colon cancer include a diet that is low in fiber and vegetables while high in meat intake, obesity, and tobacco smoking. Such lifestyle factors may provide some explanatory evidence for why the U.S. and other western countries having some of the highest colorectal cancer incidence rates in the world [26]. Consumption of specific foods and nutrients may play a role in the development of colon cancer. The "western diet", which is high in saturated fats including red meat while low in fiber, fruits, and vegetables has long been suspected to be a risk factor for colon cancer [27]. While the data remain inconsistent, research reports a modestly lower risk for colon cancer with a higher consumption of vegetables and fruits [16, 28]. The precise relationship between fiber and colon cancer risk also remains unclear. However, prior research indicated a colon cancer risk reduction with a higher intake of dietary fiber [29, 30]. Additionally, folic acid, Vitamin E, calcium, and overall multivitamin supplementation have been associated with a reduction of colorectal cancer or adenomas [31-33]. Mounting evidence suggests an elevated risk of colon cancer with meat eating, but the findings remain inconsistent [17, 34].

Most epidemiologic studies report that obesity increases the risk of colon cancer, especially in males. Males in the highest quintile for body size have a doubled risk of colon cancer [16]. Most studies report a positive linear relationship between body mass index (BMI) and colon cancer [28]. Females who were in the highest BMI quintile had a 40% higher risk of colon cancer compared to their lowest quintile counterparts, although

this relationship is not as clear in older females. However, for most males and females, a strong linear relationship is typically reported in the obese (BMI > 30 kg/m^2) [28]. Recent studies have reported that an early onset and long history of cigarette smoking may be a risk factor for colon cancer because tobacco is a major source of carcinogens, including heterocyclic amines, which cause tumor-suppressor gene mutations in rats [35, 36]. Prior research also reported an elevated risk between smoking and colorectal adenomas [35].

Colon cancer becomes symptomatic with the obstruction and bleeding of the bowel. Changes in bowel habits, blood in the stool, and anemia are typical symptoms. As the cancer progresses, fatigue, anorexia, pain, weight loss, and jaundice can occur. Compared with cancers at other sites, screening is relatively effective at detecting colon cancer at earlier stages through stool testing for blood, sigmoidoscopies, and colonoscopies. The American Cancer Society recommends a colonoscopy or flexible sigmoidoscopy every five years in addition to an annual fecal occult blood test (FOBT), and over half of all individuals aged 50 years and older have had a FOBT, colonoscopy, or sigmoidoscopy [37]. Detection of colon cancer is usually through one of the aforementioned screening tests along with a biopsy, and treatment is usually through radical surgical removal of the primary lesion whenever possible. Treatment often only includes removal of the tumor but may include chemotherapy and/or radiotherapy. At the present time, chemotherapy following surgery has been established only as an effective treatment in stage III colon cancer, and current evidence suggests this therapy can prevent some colon cancer deaths [15].

Physical activity appears to provide a protective effect on colon cancer among males and females. Relative to other risk factors, the relationship between physical inactivity and the development of colon cancer is understood because physical activity appears to specifically have a positive impact on the colon through various mechanisms including an improved gastrointestinal transit rate, positive hormonal alterations, and a reduction in body fat. The relationship between physical activity and colon cancer risk is discussed in greater detail later in this chapter.

Breast Cancer

Breast cancer is the most prevalent form of cancer in females, affecting more females than the next two most prevalent cancers (lung and colorectal) combined [8]. Over 175,000 new cases of invasive breast cancer were expected in 2007, which is approximately 31% of all new female cancer cases. Additionally over 40,000 female breast cancer deaths are expected this year. This is equivalent to approximately 15% of all cancer deaths in females, second only to lung cancer. Since 1980, breast cancer incidence has been steadily climbing, albeit more slowly in the past few years [8]. This could be because more females are surviving breast cancer through early detection and use of mammograms, however, an increased obesity among U.S. females, and use of postmenopausal hormone therapy are also possible reasons for the increase in breast cancer [8, 38]. Between 1930 and 1990, the mortality rate for breast cancer (per 100,000 population) remained slightly above 30%. Since 1990, the mortality rate has begun to slowly decrease [8]. The incidence rate for female breast cancer is much higher among U.S. Whites compared to African Americans (141.1 per 100,000 vs. 119.4 per 100,000,

respectively). This is likely due to a later age at first birth and increased use of mammograms and hormone replacement therapy among White females [10]. Additionally, African American females are less likely to be screened and diagnosed with breast cancer at an early stage compared to White females [12].

Both genetic and environmental factors influencing the development of breast cancer have been extensively studied in epidemiologic research [39]. Approximately 5% to 10% of all breast cancer cases and over 30% of cases among females under age 30 years can be attributed to direct germline mutations [40]. Specific genes that have been linked to the presence of breast cancer include the Breast Cancer Genes 1 and 2 (*BRCA1* and *BRCA2*, respectively). While the exact function of these genes is not known, it appears that these two genes act as tumor-suppressors [41]. Mutations of these suspected tumor-suppressor genes are responsible for an estimated 2% to 5% of breast cancer cases and are more strongly associated with breast cancer incidence among younger females. Individuals under age 40 years with *BRCA1* are approximately 20 times more likely to develop breast cancer and have a lifetime risk of 60% to 85%, and this gene is more commonly found in Ashkenazi Jewish females [41, 42]. Another tumor-suppressor gene associated with the development of breast cancer is the *p53* gene, which also is associated with colorectal and many other forms of cancer. Germline mutations of *p53* can occur in females with rare familial cancer, but this is quite infrequent in the population [41, 42]. More commonly, *p53* mutations may also be associated with breast tumor progression [42].

Many risk factors, including family history in a first degree relative, later menopausal onset (>54 years), high endogenous estrogen levels, postmenopausal

hormone use, early age of menarche (<12 years), later age of first birth (> 30 years), nulliparity, and obesity have an established relationship with breast cancer [39]. Additionally, oral contraceptive use probably is associated with the disease, but the relationship is not as strong [43]. It is generally reported that physical activity decreases the risk of breast cancer [44], however, the precise protective effect of physical activity in pre- and post-menopausal females remains unclear and is discussed in further detail later in this chapter.

Prior research reports a consistent relationship between age at menopause and breast cancer risk later in life [45]. Specifically, breast cancer risk increases approximately 3% per year of delayed menopause [45]. The increased risk associated with a delayed onset of menopause likely is due to a prolonged circulation of steroid hormones [45]. Specifically, elevated levels of estradiol, a type of active endogenous estrogen is associated with increased breast cancer risk, and adipose tissue is the major source of estrogen following menopause, making obese postmenopausal females with higher levels of endogenous estrogen at an especially higher risk for breast cancer [46]. The relationship between estradiol levels and breast cancer risk among postmenopausal females is among the most consistent in epidemiologic literature [47]. Furthermore, many studies reported postmenopausal estrogen hormone use was associated with an elevated breast cancer risk, and a positive linear association existed between duration of use and level of risk [48].

Other reproductive factors are associated with breast cancer risk. Age at menarche is somewhat associated with both pre- and post-menopausal breast cancer risk, and risk is reduced 5% to 20% per year of delayed onset of menarche [45]. This is most

likely due to the "cyclic hormonal changes that result in ovulation, menstruation, and cellular proliferation in the breast" that commence with menarche [39]. Nulliparous females typically have a higher risk for breast cancer compared to parous females. However, the relationship varies over time and depends on the number of childbirths [45]. For the first 10 to 20 years after delivery, the woman's breast cancer risk is higher compared to a nulliparous woman of a similar age [49]. However, parous females have long-term reduction in risk later in life compared to their nulliparous counterparts, and multiparous females have an even greater risk reduction [50]. The earlier risk among parous females is likely due to the relationship between elevated hormone levels and a pre-existing malignant condition, while the later protective effect from one or more childbirths is likely due to various positive changes including differentiation of the epithelium and ductal system of the breast [51]. Additionally, females who are younger at the time of their first childbirth experience a protective effect independent of parity, as fewer breast cells have been initiated prior to the aforementioned differentiation in the breast epithelium [45]. Prior research only reports a slight increase in breast cancer risk associated with long-term oral contraceptive use, and this relationship generally appears to be stronger among females under the age of 35 years. A slightly higher risk for breast cancer may exist among current and recent users of oral contraceptives, but this risk appears to be attenuated over time after stopping the use of oral contraceptives [52].

The relationship between body mass index (BMI) and breast cancer risk is dependant on the female's menopausal status and use of postmenopausal hormones. A higher BMI typically is not a risk factor for premenopausal females, but is positively, albeit inconsistently, associated with breast cancer risk in postmenopausal females [53].

Following menopause, adipose tissue becomes the primary source of plasma estrogens, creating a positive relationship between estrogen levels and BMI among these females, and making it difficult to determine a strong relationship between BMI and breast cancer risk. Because higher levels of estrogen also are associated with postmenopausal hormone use, determining the relationship between BMI and breast cancer risk among postmenopausal females using hormone replacement therapy is difficult. While a positive relationship between BMI and breast cancer risk was not reported among females with past or current hormone use, a positive relationship between BMI and breast cancer risk was observed among postmenopausal females who did not utilize hormone replacement therapy [54].

Epidemiologic evidence consistently reports some degree of association between physical activity and breast cancer risk [55]. However, this relationship remains relatively unclear compared to the association between physical activity and colon cancer because the biological associations between physical activity and breast cancer are more complex, making it difficult to assess the biologic and epidemiologic evidence [44]. Also, much of the breast cancer risk is influenced by reproductive factors throughout the woman's lifespan that are not easily altered, which makes it difficult to assess the relationship between breast cancer risk and a lifestyle risk factor such as physical activity [56]. A variety of biologic mechanisms have been hypothesized to link breast cancer with physical activity [57]. However, while such underlying mechanisms remain unclear, it is widely accepted that moderate to vigorous physical activity is reportedly associated with a reduction in breast cancer risk for both premenopausal and postmenopausal females [58].

Research has primarily focused on the role of hormonal mechanisms, energy balance, and the relationship between the two as key factors mediating the relationship between physical activity and breast cancer risk. Increased levels of estrogen from a high BMI are often found in postmenopausal females. Additionally, a high BMI often is associated with lower levels of physical activity. Postmenopausal females with a high BMI often have higher levels of circulating testosterone, which is associated with increased levels of estradiol, and therefore increased breast cancer risk [59]. Contrarily, increased levels of physical activity are associated with lower BMI among postmenopausal females. However, increased amounts of physical activity also have been reportedly associated with lower serum estradiol and androgen hormone concentrations in postmenopausal females, independent of the level of body fatness [60, 61]. Prior studies examining the association between physical activity and breast cancer have considered many issues of methodology specific to this relationship. Specifically, prior research reported little confounding, which is present when a variable is associated with both the exposure and the disease, in the relationship between physical activity and breast cancer, but reported total caloric intake and BMI may be an effect modifier of the activity-breast cancer association, especially in postmenopausal females [55, 59, 62]. The potential effects of confounding among studies of physical activity and cancer risk are further addressed in Chapter II. The effect of physical activity on breast cancer risk reduction through alterations in energy balance and profile of endogenous hormone hormones must continue to be considered in order to better understand the role of activity in reducing breast cancer risk throughout the lifespan [55]. Also, appropriately measuring and reporting all components of physical activity is important, as variability can exist

between various modes, frequencies, intensities, and durations of activity. Prior research reported that highly validated instruments providing complete information on the aforementioned four primary components of physical activity are essential for epidemiological studies of the relationship between physical activity and breast cancer [63].

Currently, many breast cancers are diagnosed before the female is symptomatic through mammography, and early detection can prevent spreading to axillary lymph nodes and metastasis [39]. The American Cancer Society recommends that females aged 20 years and older begin breast self-examination, while females aged 20-39 years should complete a clinical breast examination approximately every three years. Females aged 40 years and older should receive both a clinical breast exam and a mammography annually [37]. Nearly 60% of females over the age of 40 years receive mammograms, but many females remain unscreened due to lack of health insurance [37]. When breast cancer is detected via the aforementioned methods pathological reports confirm the need for appropriate treatment. Presently, surgery that preserves as much of the breast as possible combined with post-operative radiation therapy and possible chemotherapy or tamoxifen is the typical treatment protocol [39].

Breast cancer is one of leading cancer-related causes of death among females [8]. The physiological mechanisms associated with the positive effect of physical activity on breast cancer risk remain somewhat unclear compared to that of physical activity and colon cancer. However, consistent activity during the lifespan appears to provide a protective effect on breast cancer risk, especially among postmenopausal females, by

positively impacting some of the hormonal and energy balance mechanisms associated with breast cancer risk.

Physical Activity and Cancer Risk

In recent years, the association between physical activity and cancer risk has been widely published. Studies have examined the relationship between physical activity and a potential reduction in all-cancer risk as well as site-specific cancer risk. Currently, a consistent protective effect from physical activity has only been associated with cancer of the colon, and to a lesser extent, cancer of the breast. While many studies have focused on the role of specific quantifications of physical activity in the prevention of these cancers, relatively fewer publications have provided specific assessments of physical activity and its impact on overall cancer risk. Comprehensive reviews of the association between physical activity and risk of colon and breast cancer are provided later in this chapter.

Study Rationale and Broader Impacts

Currently, there are no recommended optimal amounts of physical activity for colon and breast cancer prevention. Established physical activity guidelines may eventually play an important role in disease prevention among high-risk populations. While multiple studies have assessed the effect of physical activity on colon and breast cancer risk, it can be difficult to synthesize the results from all of these diverse studies, as individual studies report different effect measures, energy expenditure amounts, and use different methodology. While prior research has been helpful in establishing a

relationship between physical activity and the risk of colon and breast cancer, it is important to develop an overall, approximate estimate of the effect because individual studies use different methodologies to assess the relationship between activity and cancer risk. Currently, there is no summary estimate for the effect of physical activity on the risk of colon and breast cancer.

Completion of a meta-analysis of both prospective and retrospective studies allows for the development of a quantitative summary estimate from various effect measures. Additionally, including only studies that quantify physical activity using the *Compendium of Physical Activities* allows the summary estimate to be derived from a common metric [64]. Results from this project may be important for researchers studying the role of physical activity in cancer prevention as well as exercise specialists seeking approximate guidelines for prescribing exercise to high-risk patients or clients as part of a comprehensive colon or breast cancer prevention program. Additionally, this project may provide a foundation for more uniform and appropriate energy expenditure categorizations among future studies utilizing the *Compendium* to assess the relationship between physical activity and cancer, eventually leading to established physical guidelines for colon and breast cancer prevention.

Purpose

Many studies have examined the association between physical activity and the risk of colon and breast cancer. Each study presents different methodology (e.g. type of study, effect measure, participant demographics, measurement and categorization of activity, and potential confounding variables studied) and results. It is useful to develop an overall, approximate estimate of published studies examining the potential protective effect of physical activity associated with both colon and breast cancer risk using combined effect measures derived from individual study effect measures. The purpose of this dissertation is to provide a comprehensive review of the existing study methodology to assess potential differences among studies, and to complete a series of meta-analyses to provide a quantitative summary of the overall measure of the effects of leisure-time physical activity on colon and breast cancer risk. Overall effect measures will be developed for the relationship between leisure-time physical activity and colon cancer risk among males and females, and breast cancer risk among pre- and postmenopausal females. The calculated effect measures will help determine whether specific amounts of physical activity are associated with the prevention of colon and breast cancer. Complete study criteria for meta-analysis inclusion, as well as methods used to calculate all individual and pooled effect measures are detailed in Chapter II.

Biological Plausibility for the Relationship between Physical Activity and Colon Cancer

The relationship between physical activity and a reduced risk of colon cancer is 'highly consistent among epidemiologic studies for leisure-time physical activity, occupational activity, and total activity' [15]. While the relationship between physical activity and rectal cancer has not been demonstrated, prior research reported that physical inactivity is a primary risk factor associated with an increased risk of colon cancer, as both case-control and cohort studies reported that higher amounts of physical activity were consistently associated with lower colon cancer risk [15].

It is possible that physical activity provides protection against colon cancer by decreasing the amount of time the colonic contents remain in contact with the epithelium, however, further research needs to be completed [65]. Bingham and Cummings examined the effects of physical activity on large bowel function among 14 previously sedentary subjects beginning a physical activity program [21]. The researchers assessed colonic function by measuring stool rate and colonic transit time. It was reported that overall colonic transit time increased for nine of the 14 subjects, while it decreased in the remaining five, suggesting that this relationship remains unclear. The researchers suggested that physical activity may affect the colon relative to complete inactivity, but also reported that variations in normal physical activity encountered in daily life do not impact colonic function. Further studies are necessary to compare the transit time of individuals completing activities of daily living to those completing higher amounts of leisure-time physical activity in addition to daily living activities. Holdstock et al. (1978) hypothesized that activity throughout the lifespan is essential for optimal control of

colonic transit time [66]. It should be noted that the purpose of this study was not solely to examine the effects of activity on transit time, but rather to compare transit time function among individuals suspected of having irritable bowel syndrome. However, when comparing sedentary versus physically active subjects, the active subjects had a substantial increase in colonic motility after a meal.

Higher physical activity is typically associated with lower insulin, glucose, triacylglycerol levels, and BMI, all of which may play an important role in countering the development of colon cancer [28, 67]. Specifically, elevated serum levels of estrogen, testosterone, and insulin levels may be important factors in determining the effect of physical activity on colon cancer risk, as prior research reported that elevated serum levels of these hormones are associated with a greater risk of neoplastic development in the colon and breast [68, 69]. Obese postmenopausal females may be at a higher risk of developing both cancers, as increased testosterone leads to greater estrogen conversion in the fat cells of such females. It was also reported that prolonged hyperinsulinemia may be associated with colon cancer development, and the effects of physical activity on reducing insulin resistance may be important in the prevention of colon cancer [22, 70].

An established relationship exists between obesity and colon cancer, especially among individuals with greater amounts of abdominal adiposity [20, 23]. The reduction in body fat that often accompanies higher amounts of physical activity may play a role in physical activity's positive effects on colon cancer prevention. However, while it has been reported that confounding may remain an epidemiologic issue in the relationship between physical activity and colon cancer, studies controlling for BMI, diet, and other factors still report a protective effect of physical activity on colon cancer [18].

Physical activity appears to have an independent and important role in the prevention of colon cancer. Slattery et al. (2002) evaluated confounding and effect modification for physical activity for 1993 cases against 2410 controls [18]. Associations between physical activity and colon cancer incidence were examined using responses from case-control studies. No confounding was observed for the physical activity and colon cancer association. However, differences in dietary factors were identified depending on the amount of physical activity completed. The researchers reported that their findings were consistent with prior studies not reporting noticeable confounding in the relationship between physical activity and colon cancer [19, 23, 25, 65]. Specifically, Martinez et al. (1997) reported the association between physical activity and colon cancer risk was slightly modified and remained statistically significant after control for other risk factors such as age, smoking, family history of colorectal cancer, BMI, red meat intake and alcohol consumption (specific findings reported later in this chapter) [23]. Additionally, Ballard-Barbash et al. (1990) reported an increased risk of colon cancer among sedentary males compared to active males, and reported that all findings remained unchanged after adjustment for BMI, height, alcohol, and cholesterol (RR for moderately active = 1.4 (95% CI = 0.8-2.6); RR for least active = 1.8 (95% CI = 1.0-3.2)) [25].

The Effect of Physical Activity on Colon Cancer Risk

Studies have reported a consistent protective effect of physical activity on colon cancer risk for both males and females. Some of the earliest research examining the relationship between physical activity and colon cancer risk reported a protective effect of occupational activity for both sexes [16]. While the specific point in the lifespan where

physical activity may be most effective against colon cancer has not been established, prior studies examining the effects of lifetime occupational activity showed a greater protective effect compared to studies examining activity levels over a shorter period of time (e.g. 2-3 years prior to diagnosis) [71]. Potter et al. (1993) noted that the protective effect of lifetime activity could be because higher amounts of lifetime activity are reported, compared to the amounts reported over a shorter time period, or because individuals reporting consistent activity may truly be more physically active over the course of the lifetime [16]. While the effect of physical activity on site-specific colon cancer risk remains unclear, it is well established that physical activity is not associated with a reduction in rectal cancer risk [71, 72].

Additional early studies reported a reduced risk with increased amounts of occupational activity for both sexes (OR = 1.6 (95% CI = 0.8-2.9) and RR = 1.3 (95% CI = 1.2-1.5) for sedentary occupations versus active occupations among males and females, respectively) [72, 73]. A few years later, the effects of both occupational and recreational activity on colon cancer risk among both males and females were examined [74]. The study included a cohort of 16,477 Swedes born between 1886 and 1925 and subjects were followed throughout a 14-year follow-up period from 1969-1982. Occupational activities were classified as 'sedentary', 'moderately active', and 'physically demanding', while recreational activity was classified as 'hardly any exercise', 'light exercise', 'regular exercise', and 'hard exercise'. The RR for individuals with moderately active occupations was 1.6 (95% CI = 1.0-2.7) compared with the referent physically demanding occupations group. Furthermore, males with sedentary occupations had an RR of 1.6 (95% CI = 0.8-2.9). A similar association between lower levels of physical

activity and increased colon cancer risk was reported for recreational activity as well, as individuals with 'hardly any exercise' had a RR of 1.3 (95% CI = 0.6-2.6) compared to the referent combined group of 'regular' and 'hard' activity. Additionally, males completing 'light exercise' had a reported RR of 1.7 (95% CI = 1.0-2.8). This study was also one of the first to report a lack of an association between physical activity and rectal cancer risk, as the RR for individuals completing low amounts of occupational and recreational activity were 0.4 (95% CI = 0.1-1.1) and 1.2 (95% CI = 0.7-2.2), respectively. Despite the 95% confidence intervals including a value of 1.0, which indicates no association between the exposure and the outcome, it was concluded that lower amounts of occupational and recreational activity were associated with an increased risk of colon cancer among both males and females. Additionally, the researchers hypothesized that the reported relationship was due to the prolonged gastrointestinal transit time of the stool in the colon, which would increase the amount of contact time between fecal carcinogens and the mucosa [74].

A few years later, Wu et al. (1987) reported that leisure-time physical activity was associated with a reduction in colon cancer risk for both males and females, but was only statistically significant among males (p for trend = 0.008) [75]. Specifically, individuals active less than one hour per day (4,112 subjects and 14,216 person-years of exposure time) were part of the reference group for both sexes. Males exercising one to two hours per day had a RR of 0.89 (95% CI = 0.5-1.6), while females had a RR of 0.72 (95% CI = 0.4-1.3) among 3,979 subjects and 14,377 person-years for combined sexes. Additionally, the most active males (> two hours per day) had a RR of 0.40 (95% CI =

0.2-0.8), while similar females had a RR of 0.89 (95% CI = 0.5-1.6) among 3,487 subjects and 12,747 person-years for combined sexes.

Both cohort and case-control studies have examined the relationship between physical activity and colon cancer risk. Using the physical activity index from the Framingham study, Severson et al. (1989) completed a prospective analysis of physical activity and colon cancer risk and reported a statistically significant, inverse relationship between activity and colon cancer risk (p for trend = 0.027) [76]. The physical activity index is based on multiples of resting activity (which is given a weight of 1.0 in the index), and examples include sedentary (e.g. sitting or standing, index weight 1.1), slight (slower walking on a level surface, index weight 1.5), moderate (e.g. housework, index weight 2.4), and heavy (e.g. shoveling, index weight 5). The total index scores were then divided into tertiles and males in the highest tertile had a RR for colon cancer of 0.71 (95% CI = 0.51-0.99), while those in the second tertile had a RR of 0.56 (95% CI = 0.39-0.80) compared to the lowest (first) referent tertile group.

Whittemore et al. (1990) completed one of the earliest published studies of physical activity and colon cancer risk to study energy expenditure (e.g. a MET equivalent) and account for the intensities of measured activities[77]. The study examined the effects of being sedentary on Chinese individuals residing in the United States and China, and reported a statistically significant increase in colon cancer risk among individuals reporting 5 to 9 and 10+ hours of sitting compared to less than 5 hours of sitting on a daily basis (OR = 2.4 ($P < .05$) and 3.9 ($p < .001$), respectively. When Chinese individuals were analyzed according to sex and geographic residence, the effects of being sedentary on the risk of colon cancer development were especially statistically

significant among Chinese-American males ($p < .001$) and females residing in both parts of the world ($p < .10$). The researchers concluded that a greater duration of exposure to a sedentary lifestyle was generally associated with an increased risk of colon cancer development for individuals of both sexes residing in America and China [77].

Lee and Paffenbarger (1991) examined the effects of physical activity on the risk of colon cancer development among cohorts of college alumni [71]. The researchers examined 17,607 Harvard alumni aged 30-79 who were followed prospectively for the occurrence of colon cancer from 1965 to 1988. 280 of these individuals developed colon cancer. The researchers converted MET values to kilocalories (1 MET is roughly equivalent to one kilocalorie per kilogram body weight per hour). Energy expenditure was estimated for each activity by multiplying its MET score by body weight in kilograms and hours of participation. Physical activity was self-reported in questionnaires and consisted of stair climbing, walking, and sports play. Alumni who expended more than 2,500 kilocalories/week exercising had half the risk of developing colon cancer compared to those who expended less than 1,000 kilocalories/week exercising (RR = 0.19; 95% CI = 0.02-1.52 for >2,500 kcal/wk group versus RR= 0.56, 95% CI=0.29-1.09 for 1,000 kcal/wk group). Alumni who expended between 1,000 and 2,500 kilocalories/week had a reduced risk as well (RR = 0.52; 90% CI = 0.28-0.94). It was concluded that both moderate and high levels of physical activity were effective in preventing the development of colon cancer [71].

A few years later, Longnecker et al. (1995) examined the effects of leisure-time physical activity on colon cancer risk among 163 males with colon cancer and 703 community controls in New England from 1986 to 1988 [78]. The amount of time spent

completing activities with an intensity value > 4 METs was considered vigorous. Subjects were then categorized into four groups according to average time spent at vigorous leisure-time physical activity (0, <1/2, 1, or >2 hours per week). Males exercising vigorously at least 2 hours per week had an odds ratio of 0.60 (95% CI, 0.35-1.00) compared with the referent sedentary group, while individuals completing one hour of vigorous activity per week had an OR of 0.47 (95% CI = 0.16-1.36), and those with a half-hour of activity or less had an OR of 0.73 (95% CI = 0.23-2.29). The researchers concluded physical activity is related to a reduced colon cancer risk (*p* for trend = 0.03).

Thune et al. (1996) completed one of the earliest studies investigating the effects of both recreational and occupational activity on colon cancer risk for both sexes among a cohort over 53,000 males and 28,000 females followed over a six-year period [79]. Females walking or cycling at least four hours per week had a statistically significant reduced colon cancer risk (RR = 0.62; 95% CI = 0.40-0.97; *p* for trend = 0.04), while a similar protective effect was reported for males (*p* for trend = 0.04). Total activity (recreational plus occupational) was also associated with a statistically significant risk reduction (*p* for trend = 0.04), while a non-statistically significant colon cancer risk reduction was associated with solely occupational activity. The researchers reported no association between physical activity and rectal cancer among males or females [79].

Beginning in the mid 1990's, some studies examining the relationship between physical activity and colon cancer began utilizing the *Compendium of Physical Activities* to determine the quantity of total weekly energy expenditure [80]. Giovannucci et al. (1995) completed a prospective cohort study, administering questionnaires about physical activity level with 31,055 respondents [81]. Colon cancer diagnoses occurred in 203

persons, and colon cancer adenomas were diagnosed among 586 individuals. This study was the first to utilize the *Compendium* to determine the quantity of energy expenditure. The reported time spent at each activity per week was multiplied by its typical energy expenditure requirements expressed in METs. Energy expenditure was reported in median MET hours-per-week. The researchers reported that physical activity was independently and inversely associated with risk for colon cancer, as males in the highest quintile of physical activity had approximately half the incidence of colon cancer seen in males in the lowest quintile of activity (age-adjusted RR = 0.44; 95% CI = 0.27-0.71). Also, individuals in the second and third highest energy expenditure quintile had a RR of 0.67 (95% CI = 0.44-1.02) and 0.83 (95% CI = 0.56-1.23), respectively. The second lowest activity quintile had a RR of 0.73 (95% CI = 0.48-1.10), so any amount of activity was effective compared to the referent sedentary group (p for trend = 0.03). The researchers concluded that study results supported a strong inverse association between physical activity and the risk of colon cancer [81].

White et al. (1996) reported a case-control study of 251 male and 193 female colon cancer cases diagnosed between 1985-1989 who were compared to 233 male and 194 female control subjects, respectively [82]. Physical activity was assessed using a questionnaire to measure frequency and duration of types of recreational and occupational activities over a 10-year period ending 2 years prior to colon cancer diagnosis. Using the *Compendium*, energy expenditure associated with recreational physical activity was categorized into sedentary (0 METs/week; referent group), low (<7.30 METS/week), moderate (7.30-17.88 METs/week), and high (≥17.88 METs/week) groups [80]. Using the aforementioned categorizations, the age-adjusted RR were 1.00,

0.64 (95% CI = 0.38-1.07), 0.59 (95% CI = 0.37-0.96), and 0.69 (95% CI = 0.42-1.13), *p* for trend = 0.05. The researchers also classified activity by designating a MET value of <4.5 for low intensity activities and ≥4.5 for moderate to high intensity activities and comparing expenditure in total hours per week categorizations of 0 (referent group), <1, 1 to <2.5, 2.5 to <4, and ≥ 4 hours per week. Reported age-adjusted relative risks were 1.00, 0.74 (95% CI = 0.41-1.33), 0.50 (95% CI = 0.28-0.88), 0.52 (95% CI = 0.29-0.92), and 0.79 (95% CI = 0.48-1.29), *p* for trend = 0.08. The investigators concluded recreational physical activity, but not occupational activity (effect measures not reported here), was associated with a reduced risk of colon cancer [82].

More recently, Martinez et al. (1997) assessed the relationship between leisure-time physical activity and colon cancer risk among females in a prospective study using the cohort from the Nurses' Health Study [23]. Subjects were administered leisure-time physical activity questionnaires and subjects were followed up every two years. Reported diagnoses of colon cancer were confirmed by review of hospital records and pathology reports. Using the *Compendium of Physical activities*, an energy cost classification instrument that indexes activities by intensity measured in metabolic equivalents (METs), energy expenditure scores were reported in MET hours-per-week. Females who completed more than 21 MET-hours per week of leisure time physical activity had a lower risk of colon cancer (RR, 0.52, 95% CI = 0.33-0.90; *p* for trend = 0.03) compared to the referent group of females who expended less than 2 MET-hours per week [80]. A MET unit is the ratio of the activity metabolic rate to the resting metabolic rate. Both the *Compendium* and METs are further detailed in Chapter II. Additionally, females expending 11-21 MET hours-per-week had an age-adjusted RR of

0.65 (95% CI = 0.42-1.07), and those expending 5-10 MET hours-per-week had a RR of 0.74 (95% CI = 0.50-1.20). Females with a lower amount of energy expenditure (2-4 MET hours-per-week) had a RR of 0.69 (95% CI = 0.44-1.15). The researchers concluded there was a statistically significant inverse association between leisure-time physical activity and colon cancer incidence in females, and that the association was consistent with the inverse association typically reported in males.

Tang et al. (1999) examined the relationship between colon cancer risk and physical activity in a relatively small case-control study (42 male cases, 43 male controls; 27 female cases, 27 female controls) [83]. Using the *Compendium* to classify light, moderate, and heavy activities, leisure-time energy expenditure of both sexes was categorized into sedentary (0 MET hours-per-week), moderate (>0 to <20 MET hours-per-week) and active (≥20 MET hours-per-week) [80]. The OR for colon cancer risk among highly active males was 0.19 (95% CI = 0.05-0.77) compared to the referent sedentary males, while the OR for colon cancer risk among moderately active males was 2.22 (95% CI = 0.68-7.21); *p* for trend = 0.03. In this particular study, no statistically significant reduction was found among active females between the ages of 33 and 80, as the OR for the highly active females was 0.78 (95% CI = 0.19-3.14), while the OR for the moderately active females was 0.79 (95% CI = 0.30-2.08); *p* for trend = 0.73.
It should be noted that energy expenditure categories were rather broad (e.g. three categorizations with a range of 20 MET hours-per-week in the moderately active group). Such a broad range of energy expenditure scores under one category may cause the effect measure to be slightly unclear, as higher values in the category may have a more positive impact on colon cancer risk, while lower values may have less of a negative effect.

While the relationship between physical activity and colon cancer is consistent, it is not fully established. Colbert et al. (2001) reported a greater protective effect of moderate to heavy occupational activity on colon cancer risk (RR = 0.45; 95% CI = 0.26-0.78) compared to leisure-time physical activity (RR = 0.82; 95% CI = 0.59-1.13) [84]. Also contrary to previous findings was the protective effect of physical activity on rectal cancer among individuals completing both light and moderate to heavy occupational activity (RR = 0.71; 95% CI = 0.36-1.37 and RR = 0.50; 95% CI = 0.26-0.97; *p* for trend = 0.04), while no statistically significant association was reported between leisure-time activity and rectal cancer risk. It was concluded that occupational physical activity provides some degree of protection for both colon and rectal cancers, while leisure-time physical activity did not [84]. While these results are consistent with those of most other studies, they provide evidence that the relationship between physical activity and colon cancer requires further study. The lack of a statistically significant association between leisure-time physical activity and colon cancer supports the similar non-statistically significant findings of leisure-time activity and colon cancer reported among a cohort of males in the Physicians' Health Study [85]. Lee et al. (1997) also reported little association for various amounts of vigorous physical activity. Even the most active individuals (> 5 hours per week) had a RR of 1.1 (95% CI = 0.8-1.6; *p* for trend = 0.60) compared to the reference group of individuals exercising vigorously less than one hour per week. The researchers suggested the reason their findings did not support other studies may be due to an increased likelihood that physically active individuals may be more likely to undergo cancer screening [85].

Recent research focused on the association between physical activity and colon cancer risk among females [86]. Calton et al. (2006) examined 31,783 females and reported 243 colon cancer cases over 270,325 person-years of follow-up. Inconsistent with prior findings, the researchers reported no relationship between increasing amounts of physical activity and colon cancer risk. The authors reported only total physical activity in MET hours-per-day, while the quantity of vigorous and moderate leisure-time physical activity was reported in hours-per-day without MET values. Regardless, a reference group of 0 hours per day for vigorous activity was established. Individuals exercising between 0.1 and 1.0 hours-per-day had an adjusted RR of 1.10 (95% CI = 0.85-1.66), while females who were active between 1.1 and 2.0 hours per day had a RR of 0.87 (95% CI = 0.59-1.29). The most active females (>2.1 hours per day) had a RR of 1.10 (95% CI = 0.78-1.55, *p* for trend = 0.77). It was concluded that the results of this cohort study did not support prior findings that physical activity is associated with a reduced colon cancer risk among females [86].

A recent review of the association of physical activity and colon cancer risk was completed and effect measures were pooled in a meta-analysis [87]. Inclusion criteria for the 47 studies (worldwide) that were part of the analyses consisted of study design (cohort or case-control), exposure (leisure-time activity, occupational activity, or both), inclusion of a control (non-exercising) group, and outcomes of colon, rectal, or colorectal cancer. The authors noted that no type of quantitative synthesis of the data could be completed due to the large amount of heterogeneity associated with the selection methods above. While the methods of a meta-analysis are further described in Chapter II, it should be noted that pooled measures were completed using a fixed effect meta-analysis,

except in cases of greater amounts of heterogeneity among the studies, in which case a random effect meta-analysis was performed. Potential examples of heterogeneity include the difference in the relationship between physical activity and colon cancer risk compared to physical activity and rectal cancer risk, or the difference in the relationship between leisure-time activity and cancer risk versus occupational activity and cancer risk. The review did not address the role of potential confounding variables in any of the analyses. Despite the high amount of heterogeneity and non-specific inclusion criteria, a statistically significant protective effect of physical activity on colon caner risk was still reported. A similar effect was reported for both males and females, and the study confirmed prior research that no statistically significant relationship exists between physical activity and cancer of the rectum. The researchers also concluded that future studies should focus on biomarkers related to the insulin resistance and hyperinsulinemia that is hypothesized to be associated with colon cancer development [87].

Prior research is consistent for the most part in reporting that physical activity is associated with a decreased risk of developing colon cancer. The most recent study of quantifiable physical activity and colon cancer risk for both sexes concluded that activities with an intensity of 4.5 METs may be more protective than lighter activities (< 4.5 METs), but acknowledged the importance of quantifying total activity in MET hours-per-week when examining a possible protective effect of physical activity [88]. The researchers also noted that while the protective effect associated with an optimal mode, intensity, duration, and frequency of physical activity throughout an individual's lifetime remains unclear, it is likely to be sex, age, and cancer-site specific. The authors noted the "complicated nature of the physical activity variable,

combined with lack of knowledge regarding possible biological mechanisms operating between physical activity and cancer" [88]. Currently, a small proportion of physical activity and colon cancer studies have examined quantity-specific issues such as the total amount, intensity, and duration of physical activity.

Biological Plausibility for the Relationship between Physical Activity and Breast Cancer

Many epidemiologic studies report some degree of association between physical activity and breast cancer risk [55]. However, this relationship is not as well elucidated as the association between physical activity and colon cancer because the biological associations between physical activity and breast cancer are likely more complex [44]. Much of the breast cancer risk is influenced by reproductive factors throughout the woman's lifespan that are not easily altered, which makes it difficult to assess the relationship between breast cancer risk and a lifestyle risk factor such as physical activity because of the potential effects of activity on the hormonal profile of a woman throughout the lifespan [56]. A variety of biologic mechanisms have been hypothesized to link breast cancer with physical activity [57]. While such underlying mechanisms are not fully explained, it is widely accepted that moderate to vigorous physical activity is reportedly associated with a reduction in breast cancer risk for both premenopausal and postmenopausal females [58]. Research primarily has focused on the role of hormonal mechanisms, energy balance, and the relationship between the two as key factors mediating the relationship between physical activity and breast cancer.

Typically, the time periods of a woman's life in which the influence of physical activity on breast cancer risk is measured are separated into 1) infancy through menarche, 2) menarche through first full term pregnancy, 3) first pregnancy through menopause, and 4) post-menopause[57]. The effects of physical activity likely vary according to a woman's age and reproductive phase. Specifically, an early age at menarche (before age 12 years) is associated with nearly a 200% increase in breast cancer risk, supporting

research reporting that the age at menarche is associated with ovarian function for females into their 30s [52, 89]. The protective effect associated with late menarche is likely related to the lower estradiol concentrations associated with a longer time of anovulatory cycles, as higher levels of endogenous steroid production is shown to be associated with elevated breast cancer risk [90]. Additionally, it was reported that increasing amounts of moderate physical activity were associated with a greater amount of anovular menstrual cycles throughout adolescence, even after adjusting for age at menarche [91]. Specifically, this potential mechanism for breast cancer prevention was more closely related to energy expenditure amounts of greater than 750 kilocalories per week, as menstrual cycle length was an average of 2.4 days longer among individuals with lower amounts of energy expenditure [91]. Because higher amounts of physical activity are associated with a delayed menarche among young girls, this may be an important factor in the association between physical activity and a reduction in breast cancer risk, as moderate amounts of physical activity may provide a protective effect against higher estrogen levels over a longer period of time. Regarding the association of physical activity with hormonal mechanisms related to breast cancer risk, it should be noted that prior studies have not considered the relationship between physical activity and hormonal levels impacted by oral contraceptive use, especially over the long term. Such oral contraceptive usage is associated with an increased risk of breast cancer and may act as a type of hormone replacement therapy and directly counter the beneficial endogenous hormone reductions associated with greater amounts of physical activity [57, 92].

Physical activity and energy balance play an important role in the optimal functioning of the hypothalamic-pituitary-ovarian axis, which is responsible for hormonal

regulation. Research reported that the protective effect of physical activity was substantial in younger lean females, whose increased levels of activity are associated with positive alterations in the hypothalamic-pituitary-ovarian function [62, 93]. However, the exact mechanisms leading to a reduction in breast cancer risk remain unknown.

Increased levels of estrogen that are often a result from a high body mass index (BMI) are often found in postmenopausal females. Additionally, a high BMI is often associated with lower levels of physical activity. Postmenopausal females who meet such a description often have higher levels of circulating testosterone, which is a clear precursor to elevated levels of circulating estradiol, and therefore have an increased breast cancer risk. Specifically, there is a greater amount of conversion from androgens to estrogens, which primarily takes place in the fat cells of postmenopausal females [59]. Contrarily, increased levels of physical activity are associated with lower BMI among postmenopausal females. However, increased levels also have been reportedly associated with lower serum estradiol and androgen concentrations in postmenopausal females, independent of the level of body fatness [60, 61].

While energy expenditure in the from of physical activity clearly has some sort of mediating effect on breast cancer, an individual's abnormal energy balance also is associated with breast cancer risk, as studies have reported that the presence of mammary carcinomas is highly correlated with increased energy intake [94, 95]. If energy intake is equal to energy expenditure, energy balance is achieved. However, the association between increased energy intake, obesity, stage of life, hormonal levels, and breast cancer risk remains unclear. For example, a higher BMI associated with increased energy intake and a lack of physical activity actually reduces the risk of breast cancer among younger

females, and premenopausal weight gain is largely unrelated to breast cancer development [53, 96]. However, the same BMI profile is associated with increased breast cancer risk among postmenopausal females, especially among those receiving hormone replacement therapy [54, 97]. Such differences can likely be attributed to the effect of higher body mass on circulating steroid hormone levels at different times throughout the woman's lifetime. Specifically, a lower risk for breast cancer among females with a higher body mass at a younger age may be associated with higher rates of obesity-related anovulation and lower estrogen levels while additional amounts of estrogen over a long period of time may be responsible for an increased risk of breast cancer among postmenopausal females [97]. This may be a reason that the benefits of physical activity are likely greater among postmenopausal females, while the relationship between physical activity and premenopausal breast cancer risk remains less clear.

Physical Activity Assessment Methods for Evaluating Breast Cancer Risk

Prior studies examining the association between physical activity and breast cancer have considered many issues of methodology. Specifically, the effect of physical activity on breast cancer risk reduction through alterations in energy balance and profile of endogenous hormones must be considered [55]. Also, appropriately measuring and reporting all components of the exposure (physical activity) is important, as variability can exist between various modes, frequencies, intensities, and durations of activity. Prior research reported that highly validated instruments providing complete information on these four primary components of physical activity are essential for epidemiological studies of the relationship between physical activity and breast cancer [63]. Additionally,

Friedenreich (1998) notes "because the effect of physical activity on breast cancer risk is likely to be modest or vary throughout life, measurement of physical activity needs to be very accurate to minimize the possibility that an effect will not be observed because of measurement error [55]". Epidemiological studies assessing the effect of physical activity on breast cancer are also limited by missing information on activity quantities throughout the lifespan of an individual.

Many studies of physical activity and breast cancer have assessed key potential confounders, and no studies have reported a confounding of the relationship between physical activity and breast cancer to date. Specifically, while most studies did not control for total dietary caloric intake, among those studies that did, there was minimal or no confounding of the activity-cancer relationship [43, 62, 98]. However, while no direct confounding is present, total caloric intake may act as an effect modifier, as higher caloric intake is associated with overweight individuals who are more likely to be inactive. Additionally, obesity may also act as an effect modifier of the relationship between physical activity and breast cancer, as it is a risk factor for postmenopausal breast cancer that can be reduced by activity [54, 99].

Currently, epidemiologic research has not fully addressed the effects of physical activity on breast cancer risk in the context of other risk factors. Specifically, many studies have not studied individuals of various body sizes and various hormonal profiles throughout the lifespan that would allow for a better understanding of the mechanisms mediating the relationship between physical activity and breast cancer risk. However, research reports that the limitation to such a strategy is ensuring appropriate sample sizes and statistical power within these highly specific subgroups that will allow for further

appropriate interpretation of the relationship between physical activity and breast cancer [55].

Ainsworth et al. (1998) evaluated various assessment methods of physical activity among studies examining the relationship between activity and breast cancer risk [100]. The researchers examined assessment methods of occupational and leisure-time physical activity with an activity recall period of one year to lifetime, and assigned a summarization quality score to each study. The authors reported a great degree of methodological quality variability among the studies and recommended standardized physical activity measurement methods (e.g. uniform activity classification and recall time for studies). The authors also suggested that physical activity be categorized by type and intensity measured in MET units. Intensity classification cut-points could also be standardized if MET units are used to classify light (< 3 METs), moderate (3-6 METs) and vigorous (>6 METs) activity[100]. In addition to mode and intensity classification, it was concluded that future studies should be related to mechanisms mediating the relationship between physical activity and breast cancer, such as body mass, hormonal profile, and menopausal status [100].

The Effect of Physical Activity on Breast Cancer Risk

Physical activity generally appears to provide some degree of protection from breast cancer, although this relationship may be dependent on the physiological factors discussed above. Methodological issues among studies in this area have also contributed to the uncertainty in assessing the effect of physical activity on breast cancer risk.

An early landmark study that examined the relationship between physical activity and breast cancer risk was completed by Thune et al. (1997) [62]. From 1974 to 1978 and 1977 to 1983, over 25,000 females between the ages of 20 and 54 completed questionnaires related to their leisure-time and occupational activity. After adjusting for age, BMI, and other possible confounders, the researchers reported a relative risk (RR) of 0.63 (95% CI = 0.42-0.95; *p* for trend = 0.04) among regularly exercising females compared to their sedentary counterparts. Additionally, risk reduction was greater in regularly active premenopausal females versus postmenopausal females. While the effect of occupational activity was not as great, the effects of risk reduction were once again greater in premenopausal females.

While there appears to be a relationship between greater amounts of physical activity and reduced breast cancer risk, the relationship is not clearly defined, as some prior research did not find an association between leisure-time physical activity and breast cancer at any point in the female's lifespan [32]. This remained true for even the most active females (> 4 hours per week or > 18 METs per week). When activity was assessed over the two years prior to the reference date, females with >18 total METs of activity per week had an OR of 0.95 compared to females with 0 MET hours-per-week of leisure time activity (*p* for trend = 0.85) [32]. It should be noted that the researchers only

assessed activity among females aged 21 to 45 for two years prior to the reference date and between the ages of 12 and 21. Despite this finding, the overall body of evidence suggests that physical activity provides some level of protection against breast cancer. Rockhill et al. (1999) reported females completing at least seven hours of moderate or vigorous activity per week had a RR of breast cancer of 0.82 (95% CI = 0.70-0.97; *p* for trend = 0.004) compared to females exercising less then one hour per week [101]. Also, researchers examining the effects of occupational and leisure-time physical activity on breast cancer risk among European females reported odds ratios for the most active versus the least active females aged 50-59 years to be 0.68 (95% CI = 0.36-1.28; *p* = 0.53) and 0.42 (95% CI = 0.22-0.80; *p* = .001), respectively[102]. Another European study examined the association between physical activity and risk of postmenopausal breast carcinoma among 60,000 females age 55-59 in the Netherlands [103]. Females reported baseline leisure-time physical activity levels as well as their history of sports participation. It was reported that females who participated in leisure-time physical activity sessions of walking, cycling, and gardening had a RR of 0.76 (95% CI = 0.58-0.99; *p* for trend = 0.001) for development of a breast carcinoma compared to females who participated for less than 30 minutes in the aforementioned activities. These results were independent of BMI, energy intake and weight gain during adulthood. Furthermore, there was little association between sports participation (at any point during the lifespan) and breast cancer risk, possibly because any sports participation among these females may have been for only a brief part of the lifespan.

One of the first studies to assess the effects of physical activity at various points throughout the lifespan on breast cancer risk examined females aged 20 to 54 [104]. It

was reported that more active females between the ages of 10 and 12 had an OR of 0.68 (95% CI = 0.49-0.94). Such effects were also reported for females who became active at any given point in the lifespan (OR = 0.70, 95% CI = 0.56-0.88). Additionally, it was reported that females who became active after age 20, even if only becoming consistently active in the last five years, had a similar reduction in breast cancer risk compared to those who were initially active at a younger age and remained active throughout life. It was concluded that while leisure-time physical activity was associated with a breast cancer risk reduction, such a protective effect was not dependent on the point of the lifespan in which one became physically active [104]. Furthermore, Dorn et al. (2003) examined the affects of physical activity in both pre- and postmenopausal females and reported a somewhat protective effect of physical activity (>182 hours per year consistently throughout the lifespan, reported as 2, 10, 20 years ago, at age 16, and adult lifetime total) within both groups of females. The researchers concluded that such "effects appear strongest … among postmenopausal females who were consistently active throughout their lifetime" [105].

European population-based cohort and case-control studies were published at approximately the same time. The Finnish Adult Behavior Study included over 30,000 Finnish females aged 15 to 64 years, and examined leisure-time and occupational physical activity, and breast cancer incidence annually from 1978 to 1993 [106]. However, only a minor protective effect of consistent physical activity for breast cancer incidence was reported. Further study of the role of physical activity in breast cancer prevention was recommended. Moradi et al. (2000) examined the association between breast cancer risk and lifetime leisure-time and occupational activity among Swedish

females aged 50-74 (3347 cases and 3455 controls) [107]. This was one of the earlier studies examining the specific effects of physical activity on females of postmenopausal status. It was reported that females who were sedentary when they were 25-44 years old had a 50% greater risk for developing breast cancer during their postmenopausal years versus females with the highest levels of occupational activity. Only females completing leisure-time physical activity during their postmenopausal years had a reduction of breast cancer risk, and females who had sedentary jobs with no leisure-time physical activity had a 300% higher odds of developing breast cancer. It was concluded "the effects of occupational and leisure-time physical activity on breast cancer risk appear to be effect-modified by reproductive status" [107].

In the United States, one of the first studies examining the effect of long-term leisure-time physical activity on breast cancer risk was an analysis of female participants of the Epidemiological Follow-up Study (NHEFS) of the first National Health and Nutrition Examination Survey (NHANES I) that occurred between 1971 and 1975 [108]. At follow-up, the study reported that among females over the age of 50 between 1982 and 1984, those with higher amounts of leisure-time physical activity had a 67% breast cancer risk reduction (RR = 0.33, 95% CI = 0.14-0.82; p for trend = 0.026) compared to their sedentary counterparts. After controlling for increases in adult BMI or weight, the association between physical activity and breast cancer was not altered. Thus, it was concluded that higher amounts of leisure-time physical activity throughout the lifespan might reduce breast cancer risk in females over age 50 years, independent of the weight history of the woman. For females under age 50 years, no statistically significant

association was reported between physical activity and breast cancer risk, as active females had an RR of 1.19 (95% CI = 0.43 to 3.30; *p* for trend = 0.732).

Many cohort studies have focused on the effects of physical activity on postmenopausal breast cancer risk. One of the first larger studies examined over 37,000 participants in the Iowa Women's Health Study [109]. It was reported that postmenopausal females with the highest level of physical activity had a slightly reduced risk compared to sedentary females (RR = 0.92, 95% CI = 0.80-1.05). Females reporting lesser amounts of activity had a RR of 0.97 (95% CI = 0.87-1.08). Participants reported whether the activity was 'moderate' (bowling, golf, light physical exercise, gardening, long walks) or 'vigorous' (jogging, racket sports, swimming, aerobics, strenuous sports) and the frequency as 'rarely or never', 'a few times a year', 'a few times a month', about once a week', 'two to four times per week' and 'more than four times per week' [109]. Researchers concluded that the study did not provide evidence that physical activity during postmenopausal years is associated with breast cancer incidence. Sesso et al. (1998) also completed one of the earlier studies the effect of activity on postmenopausal breast cancer risk as part of the College Alumni Health Study [110]. Compared to the sedentary referent group of females expending less than 500 kilocalories per week (kcal/wk), the RR of breast cancer was 0.95 (95% CI = 0.58-1.57) for females with an energy expenditure of 500-999 kcal/wk after age 55. The most active females (> 1000 kcal/wk) had a RR of 0.49 (95% CI = 0.28-0.86; *p* for trend = 0.015). No statistically significant association was reported between increased amounts of caloric expenditure and premenopausal breast cancer risk. Thus, it was concluded that a significant association existed between physical activity and postmenopausal (but not

premenopausal) breast cancer risk. Lee et al. (2001) reported a similar association between physical activity and breast cancer risk in over 39,000 participants from the Women's Health Study [111]. The researchers assessed the relative risks of breast cancer associated with energy expenditures of <840, 840-2519, 2520-6299, and ≥6300 kilojoules per week from a variety of recreational activities including walking or hiking, jogging, running, bicycling, aerobic dance, strength exercise machines, flexibility exercises, racket sports, and swimming. Results for postmenopausal females were RRs of 1.0, 0.97 (95% CI = 0.68-1.40), 0.78 (95% CI = 0.54-1.10), and 0.67 (95% CI = 0.44-1.0; *p* for trend = 0.03), for each of the aforementioned energy expenditure groups, respectively [111]. The researchers did not find an association between energy expenditure and physical activity for pre- and postmenopausal females combined, but did report that higher levels of activity may decrease postmenopausal breast cancer risk.

Steindorf et al. (2003) completed a case-control study that examined the effects of physical activity on premenopausal breast cancer risk [112]. Females were placed into quartiles of physical activity in total (as opposed to only leisure-time) MET hours-per-week. The researchers compared each of the three higher quartiles with the referent lowest quartile group, and reported an inconsistent pattern of results, as odds ratios of the three quartiles (in increasing order) were 0.97 (95% CI = 0.68-1.38), 0.68 (95% CI = 0.46-0.99), and 0.94 (95% CI = 0.65-1.35), respectively for females exercising between the ages of 12 and 30 (*p* for trend = 0.29). The researchers concluded that while physical activity may be associated with somewhat of a breast cancer risk reduction among premenopausal females, the study did not demonstrate a true inverse relationship.

The Effect of *Compendium*-Quantified Leisure-Time Physical Activity on Breast Cancer Risk

In 1999, researchers began assessing the effects of physical activity on both pre- and postmenopausal breast cancer risk using the *Compendium of Physical Activities*, which was published a few years earlier [80]. A complete description of the methods and attributes associated with the *Compendium* can be found in Chapter II. Using the *Compendium*, researchers were able to ask study participants about their types of activity and estimated the intensity (METs), duration (hours, or in the case of one study, minutes that could be converted to hours), and overall quantification of weekly energy expenditure (MET-hours per week).

Many *Compendium*-quantified studies of physical activity and breast cancer risk have focused on postmenopausal females. Carpenter et al. (1999) investigated the effects of lifetime physical activity on breast cancer risk among females of Los Angeles County, California [113]. Subjects were Caucasian or Hispanic and between the age of 55 and 64. A total of 1123 cases and 904 controls were included as part of this case-control study. Females who engaged in activity levels of 0.1 to 17.59 MET-hours per week had an OR of 0.88 (95% CI = 0.72-1.07). Females with a higher energy expenditure of at least 17.6 MET hours-per-week had an OR of 0.55 (95% CI = 0.37-0.83; p for trend = 0.01).

McTiernan et al. (2003) completed a prospective cohort study of 74,171 postmenopausal females between the ages of 50 and 79 years with a mean follow-up time of 4.7 years [114]. A majority of the cohort consisted of Caucasian females, but approximately 15% of females were of minority races including African-American, Hispanic, Asian, and Native American. A total of 1,768 cases were confirmed over the

five-year period. The referent group consisted of females who did not complete any leisure-time activity. Compared to the referent group, females completing between 0.1 and 5 MET hours-per-week had a RR of 0.90 (95% CI = 0.77-1.07), and females completing 5.1-10 MET hours-per-week had a RR of 0.82 (95% CI = 0.68-0.97). Females with a moderate amount of physical activity had similar RRs (0.89 (95% CI = 0.76-1.00); 10.1-20 MET hours-per-week and 0.83 (95% CI = 0.70-0.98); 20.1-40 MET hours-per-week). The most active postmenopausal females (> 40 MET hours-per-week) had a RR of 0.78 (95% CI = 0.62-1.00; *p* for trend = 0.03). The researchers concluded that increased amounts of physical activity are associated with postmenopausal breast cancer risk reduction. It was also concluded that the total amount of weekly energy expenditure is more associated with risk reduction than merely completing higher-intensity exercises of shorter duration [114].

Another study of postmenopausal females during the same year reported a similar association between physical activity and breast cancer risk reduction. Patel et al. (2003) collected information on the physical activity patterns over a five-year span (1992-1997) of over 72,000 postmenopausal females [115]. The referent group was females who completed only 0.1 to 7.0 MET hours-per-week of activity. Compared to the referent group, females with both an energy expenditure of 7.0 to 17.5 and 17.5 to 31.5 MET hours-per-week had an age-adjusted RR of 0.92 (95% CI = 0.81-1.04) and 0.94 (95% CI = 0.81-1.09) respectively, while those completing a total of 31.5 to 42.0 MET hours-per-week had a RR of 0.77 (95% CI = 0.56-1.06). The most active postmenopausal females had the greatest amount of risk reduction, with a RR of 0.71 (95% CI = 0.49-1.02; *p* for

trend = 0.08). Overall, results showed a similar association between physical activity and postmenopausal breast cancer risk as in other studies.

Friedenreich et al. (2001) were the authors of the first study assessing the effect of *Compendium*-quantified physical activity on the breast cancer risk of both premenopausal and postmenopausal females in separate analyses [116]. The researchers completed a population-based case-control study consisting of 1,233 cases and 1,237 controls. More specifically, 462 breast cancer cases and 475 controls among premenopausal females were included in an analysis of the effects of lifetime recreational activity on breast cancer risk. Females exercising between 0 and 6.7 MET hours-per-week were included in the referent group, and those expending energy of 6.7 to 11.79 MET hours-per-week had an OR of 0.81 (95% CI = 0.55-1.19). Additionally, more active females expending between 11.8 and 20.69 MET hours-per-week had an age-adjusted OR of 1.03 (95% CI = 0.70-1.52), while the most active premenopausal females also had an OR of 1.13 (95% CI = 0.77-1.66; *P* value for trend = 0.22). Thus, the researchers reported that there was no relationship between recreational activity and breast cancer risk among premenopausal females. A separate analysis was completed for postmenopausal females (771 breast cancer cases and 762 controls). For this group of females, the referent group was those completing activity of 0 to 5.09 MET hours-per-week. Females expending between 5.1 and 9.39 MET hours-per-week had an OR of 0.96 (95% CI = 0.71-1.28) compared to the referent group, while those with an energy expenditure of 9.4 to 16.89 MET hours-per-week had an OR of 0.88 (95% CI = 0.65-1.19), and the most active postmenopausal females had an OR of 1.10 (95% CI = 0.82-1.47; *P* value for trend = 0.33). Friedenreich et al. (2003) concluded that there was no association between recreational activity and

breast cancer risk reduction among postmenopausal females (a non-statistically significant trend existed) and that only total lifetime activity reduced the risk of breast cancer among postmenopausal females [116]. The researchers also concluded that total lifetime activity (recreational plus occupational and household) was associated with a breast cancer risk reduction in postmenopausal females only. Details on the association between occupational physical activity and breast cancer risk are discussed later in this chapter.

Matthews et al. (2003) also examined the effect of physical activity on both pre- and postmenopausal females (combined in one analysis), as part of the Shanghai Breast Cancer Study that included Chinese residents of urban Shanghai [117]. Recreational physical activity amounts over the last ten years were measured for 1,459 breast cancer cases and 1,553 age-matched controls. The study quantified physical activity using the *Compendium* in MET hours-per-day, and this was converted to MET hours-per-week for the purpose of the present meta-analysis. Females completing no exercise were part of the referent group, and those with an expenditure of 0.01-0.35 MET hours-per-day (equivalent to 0.1 to 2.45 MET hours-per-week) had an OR of 0.56 (95% CI = 0.39-0.80), while those expending between 0.36 and 0.88 MET hours-per-day per year (equivalent to 2.46 to 6.16 MET hours-per-week per year) had an OR of 0.80 (95% CI = 0.60-1.07). Females completing greater amounts of physical activity (0.89-1.91 MET hours-per-day, equivalent to 6.23 to 13.37 MET hours-per-week), had an OR of 0.66 (95% CI = 0.48-0.91), while the most active females expending more than 1.92 MET hours-per-day (equivalent to >13.37 MET hours-per-week) had the lowest OR of 0.40 (95% CI = 0.28-0.58; p for trend = <0.01). The researchers concluded that their findings

"demonstrate that consistently high activity levels throughout life reduce breast cancer risk" [117]. The researchers also examined the effect of lifetime occupational activity on breast cancer risk, and those results are discussed near the end of this chapter.

A few other studies have examined the effects of physical activity on pre- and postmenopausal females in a combined analysis. Yang et al. (2003) completed a population-based case-control study in Los Angeles County (the same area where Carpenter et al. conducted their study). This was one of the few U.S. based studies on a sample of females that was not primarily Caucasian [118]. The study included 501 Asian-American breast cancer cases and 594 Asian-American controls. After adjusting for menopausal status and establishing a referent group that included females who did not complete any physical activity, the researchers reported a statistically significant risk reduction of breast cancer risk with increasing amounts of lifetime recreational physical activity (p for trend <0.001). Females who logged activity amounts of 0.1 to 3 MET hours-per-week had an OR of 0.91 (95% CI = 0.55-1.49), while those expending between 3 and 6 MET hours-per-week had a significantly reduced OR of 0.65 (95% CI = 0.39-1.10). This inverse relationship between activity and risk was further identified among females expending between 6 and 12 MET hours-per-week, as their OR was 0.53 (95% CI = 0.31-0.90). The most active females with an energy expenditure of > 12 MET hours-per-week had the lowest odds of developing breast cancer, as their OR was 0.47 (95% CI = 0.28-0.80). The relationship between physical activity and breast cancer risk appears to be independent of race, as similar results among samples of different races have been reported [118]. Patel et al. (2003) completed another study of breast cancer risk among females from Los Angeles County, albeit one of White and Black females as

opposed to Asian females [119]. Pre- and postmenopausal females were combined in the analysis, and the referent group included females with no recreational energy expenditure. After adjusting for menopausal status, females expending between 0.01 and 3.0 MET hours-per-week had an OR of 0.70 (95% CI = 0.48-1.03) compared to the referent group. Females completing between 3.01 and 8.0, and 8.01 and 16.0 had a reported OR of 0.65 (95% CI = 0.44-0.96) and 0.61 (95% CI = 0.41-0.92), respectively. However, the two most active groups (16.01 to 32.0 and >32.0 MET hours-per-week) had slightly higher relative odds of breast cancer development (OR = 0.63, 95% CI = 0.40-0.98; OR = 0.65, 95% CI = 0.39-1.08, respectively). The *P* trend for the physically active was a non-statistically significant 0.81, and the researchers concluded that physical activity may provide a risk modification for breast cancer, but the relationship remains unclear.

More recently, the impact of lifetime recreational activity on breast cancer risk was assessed by Bernstein et al. (2005) [120]. This study included both black and White females in a pre- and postmenopausal combined analysis. Females who were completely sedentary (zero MET hours-per-week) were considered the referent group, and minimal risk reduction was reported among females exercising between 0.1 and 2.2 MET hours-per-week and 2.3 to 6.6 MET hours-per-week (OR = 0.95, 95% CI = 0.84-1.08 and OR = 0.92, 95% CI = 0.81-1.04, respectively). Females engaging in activity equivalent to 6.7 to 15.1 MET hours-per-week had a slightly lower risk of breast cancer development (OR = 0.87, 95% CI = 0.77-0.99), while females expending the most energy per week (at least 15.2 MET hours-per-week) had the lowest OR (0.85, 95% CI = 0.75-0.97; *p* for trend = 0.018). No significant differences in the effect of physical activity on breast cancer risk

reduction were reported between Black and White females, and the researchers reported a consistently inverse relationship between physical activity and breast cancer risk for females of both races.

While Bernstein studied the effects of physical activity on pre- and postmenopausal females combined, John et al. (2003) was one of two studies (the other was Friedenreich et al., 2001) that examined the effect of *Compendium*-quantified activity on breast cancer risk for pre- and postmenopausal females in separate analyses [121]. John et al. completed a population-based case-control study of White, black, and Latina females in the San Francisco Bay Area Breast Cancer Study. Breast cancer cases were confirmed between 1995 and 1998, and the study included 403 premenopausal breast cancer cases, 483 premenopausal controls, 847 postmenopausal cases, and 1065 postmenopausal controls. The established referent groups were different for pre- and postmenopausal females, and in general, differed from most other studies. All females expending 0 to 6.8 MET hours-per-week were considered part of the referent group, and females in the 6.9 to 16.6 MET hours-per-week category had an OR of 0.94 (95% CI = 0.69-1.29) compared to the referent group. The most active females whose energy expenditure was at least 16.7 MET hours-per-week were nearly half as likely to develop breast cancer (OR = 0.56, 95% CI = 0.46-0.96). A separate analysis not included in the present meta-analysis was completed for more vigorous physical activity, and the investigators reported similar risk reductions for moderate and vigorous activities. This supports earlier findings that one's total energy expenditure is more important than the intensity of completed activities [121]. Additionally, it is important to note that risk reductions associated with recreational physical activity were greater among

premenopausal females relative to their postmenopausal counterparts. Such a finding is inconsistent with much of the other literature that supports a greater effect of activity on postmenopausal breast cancer risk.

Colditz et al. (2003) completed the only study specifically assessing the relationship between *Compendium*-quantified physical activity and premenopausal breast cancer risk, analyzing data from the Nurses' Health Study II [122]. Over a 10-year follow-up period of 934,100 person-years (questionnaires sent out every two years), 849 premenopausal breast cancer cases were identified. This study is essentially an extension of the Rockhill et al. study discussed earlier in the chapter that also used the Nurses Health Study II dataset, but only analyzed recent physical activity amounts, as opposed to 10-years of follow-up, which allowed for an additional 477 cases and thousands of additional person-years [101]. Females exercising between 0 and 3 MET hours-per-week were included in the referent group. There was no statistically significant reduction in risk among females at any exercise level, as the adjusted RR for females was 1.05 (95% CI = 0.82-1.34), 0.96 (95% CI = 0.75-1.23), 1.05 (95% CI = 0.80-1.37), and 1.07 (95% CI = 0.84-1.36) for energy expenditures of 3-8.9, 9-17.9, 18-26.9 and >26.9 MET hours-per-week, respectively. The *p*-value for the trend was a non-statistically significant 0.69 and it was concluded "no overall association between physical activity and risk of breast cancer among premenopausal women", but suggested the effects of physical activity on adiposity in these females required further research [122].

One study that did not use multiple MET hours-per-week categorizations also examined the relationship between physical activity and breast cancer risk [123]. A study comparing pre- and postmenopausal White and Hispanic females between the ages of 35

and 74 in New Mexico examined the effects of physical activity on breast cancer risk. Analyses were conducted separately for each race and menopausal status. It should be noted that energy expenditure categories were not very specific, as the only quantities were 0, 1-25 and >25 MET hours-per-week. This may have been responsible for the large risk reduction differences seen between races in the pre- and postmenopausal risk analyses. Regardless of race or menopausal status, 0 was considered the referent group. Premenopausal Hispanic females expending 1-25 MET hours-per-week had an OR of 0.50 (95% CI = 0.26-0.97) compared to the referent group, while the most active females had an OR of 0.17 (95% CI = 0.08-0.36; *p* for trend < 0.001). Premenopausal White females expending 1-25 MET hours-per-week had an OR of 0.68 (95% CI = 0.32-1.42), while those expending >25 MET hours-per week had an OR of 0.85 (95% CI = 0.40-1.79; *p* for trend = 0.834). Postmenopausal Hispanic females expending between 1 and 25 MET hours-per-week had an OR of 0.65 (95% CI = 0.38-1.10), while those who were more active had an OR of 0.52 (95% CI = 0.29-0.93; *p* for trend = 0.028). Finally, postmenopausal White females expending 1-25 MET hours-per-week had an OR of 0.58 (95% CI = 0.35-0.97), while those expending > 25 MET hours-per-week had an OR of 0.50 (95% CI = 0.30-0.84; *p* for trend = 0.010). A statistically significant interaction with ethnicity was reported among premenopausal females [123]. However, there is no current explanation for such a disparity.

The Effects of Occupational Physical Activity on Breast Cancer Risk

Several research studies have assessed the effect of occupational physical activity on breast cancer risk. However, most of these studies do not quantify physical activity

using the *Compendium* and simply report a few occupational activities such as walking, lifting, and heavy manual labor. Thune et al. (1997) administered an occupational activity questionnaire to 25,624 females and examined their risk for breast cancer[62]. Postmenopausal females who were consistently active at work had a RR of 0.78 (95% CI = 0.52-1.18; *p* for trend = 0.24) compared to their moderately active counterparts (RR = 0.87, 95% CI = 0.61-1.24). Occupational physical activity provided a similar protective effect among highly active and moderately active postmenopausal females and comparable premenopausal females (RR = 0.82, 95% CI = 0.50-1.34; RR = 0.48, 95% CI = 0.24 to 0.95, respectively; *p* for trend = 0 .03). The researchers concluded occupational physical activity was associated with a reduction in breast cancer risk, especially among premenopausal females.

Levi et al. (1999) did not specifically utilize the *Compendium,* but analyzed a Swiss dataset of females and assigned grades of physical activity using activities that could be accessed in the *Compendium* [102]. Occupational activity was categorized as 1 to 3, with 3 being the highest amount of occupational activities including walking and manual labor. The most active females aged 50-59 years had an OR of 0.69 (95% CI = 0.38-1.24) compared to moderately active females (OR = 0.64, 95% CI = 0.36-1.14) and the referent sedentary group. Additionally, highly active females between the ages of 30 and 39 had an OR of 0.53 (95% CI = 0.29-0.96), while moderately active females had an OR of 0.50 (95% CI = 0.27-0.94) compared to sedentary females. Consistent with prior research, no additional protective effect of occupational physical activity was identified among postmenopausal females compared to premenopausal females [102]. Results from

this study were similar for leisure-time and occupational activity, however such a finding may be associated with an overestimation of physical activity while at work.

More recently, two studies examined the association between occupational activity and breast cancer using the *Compendium* [116, 117]. Friedenreich et al. (2003) reported an OR of 0.90 (95% CI = 0.61-1.34; *p* for trend = 0.94) for premenopausal females expending at least 61.2 MET hours-per-week per year, while less active groups (47.5-61.19 and 35.0-47.49 MET hours-per-week per year) had a respective OR of 0.67 (95% CI = 0.45-1.00) and 0.76 (95% CI = 0.51-1.11) compared to the referent group of 0-34.99 MET hours-per-week per year. Consistent with some other *Compendium*-quantified studies of leisure-time physical activity, no statistically significant relationship was noted between increasing amounts of physical activity and premenopausal breast cancer risk. However, a statistically significant association was reported between higher amounts of activity and postmenopausal breast cancer risk, as females expending greater than 61.8 MET-hours-per-week per year had an OR of 0.59 (95% CI = 0.44-0.81; *p* for trend = 0.003). While the OR was slightly higher (0.67; 95% CI = 0.49-0.92) for females expending 43.6-61.79 MET hours-per-week per year, the OR for those expending 26.2-43.59 was 0.77 (95% CI = 0.57-1.03). Each OR was compared to the referent group which consisted of an expenditure of 0-26.19 MET hours-per-week per year. The researchers concluded that higher amounts of occupational activity were associated with a notable breast cancer risk reduction among postmenopausal females. Matthews et al. (2001) also concluded that lifetime occupational activity was associated with a reduction in breast cancer risk [117]. Using job-code classifications that were divided into quintiles of physical activity exposure (Q1 = lowest amount of activity; Q5 = greatest amount of

activity), physical activity was quantified in MET hours-per-day per year using the *Compendium*. Females with the highest amount of activity (and least amount of sitting time) on the job had an age-adjusted OR of 0.81 (95% CI = 0.63 to 1.04; *p* for trend <0.01) compared to the referent group with the lowest amount of job-related activity (and greatest amount of sitting time). Notably, Q2 and Q3 had an OR of 0.82 (95% CI = 0.66-1.03) and 0.84 (95% CI = 0.67-1.06), respectively. While this study did not adjust for menopausal status, Q4 had an OR of 1.10 (95% CI = 0.88-1.38), indicating that a somewhat linear inverse relationship existed between lifetime occupational activity level and breast cancer risk.

Most recently, Kruk et al. (2003) completed an analysis of occupational activity and breast cancer risk by categorizing 257 breast cancer cases and 565 controls into sedentary (<2 METS), light (2-3 METS), and moderate (>3 METS) job activity classes [124]. The moderate group actually consisted of females with an activity amount of 3-6 METS, as no woman reported having a job with high physical demands (≥6 METS). There was no difference between the sedentary, light, and moderate activity groups in females younger than age 55. However, for females over the age of 55, compared to the sedentary reference group, the light activity group had an OR of 0.51 (95% CI = 0.28-0.95), while the moderate activity group had an OR of 0.49 (95% CI = 0.25-0.94). The authors concluded that increased amounts of occupational activity were only statistically significantly associated a lower breast cancer risk (*p* for trend = 0.03) among females over the age of 55. While the researchers did not adjust for menopausal status, the odds ratio trend associated with age suggests that occupational activity, much like leisure-time physical activity, may be more beneficial for postmenopausal females.

Summary of the Relationship between Physical Activity and Breast Cancer Risk

Studies examining the effect of physical activity on breast cancer risk are numerous and diverse. In addition to evaluating the key methodological differences that exist among the studies of physical activity and breast cancer risk, an approximate overall estimate from these studies would allow for the synthesis and summary of data from studies in this research area. This is important because there is not a consensus on the effect of activity on breast cancer risk, even among females of the same menopausal status. Additionally, many of the studies described above employ different methodology, and only studies quantifying and measuring physical activity according to the methodological criteria outlined in Chapter II were included in the present meta-analyses. While these meta-analyses will not contain all the studies in this research area, the summarized effect measures of studies employing the most specific quantifications of physical activity using the *Compendium* will provide an approximate quantitative summary that allows for further understanding of the association between physical activity and breast cancer risk.

Summary of Project Rationale

There is a large and rich body of research into the effects of physical activity on the risk of colon and breast cancer. However, there is much heterogeneity across studies, with differences in terms of the type of study, the ethnicity and geographic location of the populations included, the instrumentation used to assess physical activity, and the time periods and total amount of time for which physical activity was measured. Additionally, differences in the categorization of 'low', 'moderate', and 'high' activity and the types of confounding variables that were included in the analyses were present. Currently, there are no summary estimates that assess the effect of leisure-time physical activity on colon and breast cancer risk. A comprehensive analysis that provides a critique of study methodologies and a synthesis of results will help to assess the current state of the evidence and point to new directions for future research.

Chapter II

Methods

Overview of Methods

The first part of this dissertation critiques the methodology of the published studies of the relationship between leisure-time physical activity and the risk of colon and breast cancer, to put the current evidence in context. Summaries were provided of the types of studies (cohort vs. case-control), effect measures used, ethnicity and geographic location of study participants, and the potential confounding factors included in each study. Additionally, aspects of physical activity assessment were compared, including the time period for which physical activity was measured, the instrumentation used to assess the type and amount of activity, and the categorization of activity intensity.

The second part of this dissertation included a series of meta-analyses that provide a quantitative estimate across studies of the relationship between leisure-time physical activity and the risk of colon and breast cancer. The use of a meta-analysis allowed for the combination of results from studies to address the specific study hypotheses described on the next page.

Sutton et al. describe a meta-analysis as a quantitative summary of relevant studies, with a final selection based on clearly stated criteria [125]. The inclusion criteria for studies in each of the meta-analyses are discussed later in this chapter, when each of the meta-analyses is introduced.

Study Questions and Hypotheses

The present meta-analyses utilized *Compendium*-quantified or *Compendium*--estimated studies of physical activity and cancer of the colon or breast to develop a quantitative summary estimate of the effect of physical activity on risk for these cancers. Unadjusted effect measures and confidence intervals from these studies were calculated and were used in the analyses. Results from these analyses addressed the following research questions:

Question One: Is there an association between higher amounts of physical activity and a reduction in colon cancer risk in males?

H_0: There is no association between higher levels of physical activity and colon cancer risk in males

H_A: There is an association between higher levels of physical activity and colon cancer risk in males

Question Two: Is there an association between higher amounts of physical activity and a reduction in colon cancer risk in females?

H_0: There is no association between higher levels of physical activity and colon cancer risk in females

H_A: There is an association between higher levels of physical activity and colon cancer risk in females

Question Three: Is there an association between higher amounts of physical activity and a reduction in breast cancer risk among combined pre- and postmenopausal females?

H_0: There is no association between higher levels of physical activity and breast cancer risk among combined pre- and postmenopausal females

H_A: There is an association between higher levels of physical activity and breast cancer risk among combined pre- and postmenopausal females

Question Four: Is there an association between higher amounts of physical activity and a reduction in breast cancer risk among premenopausal females?

H_0: There is no association between higher levels of physical activity and breast cancer risk among premenopausal females

H_A: There is an association between higher levels of physical activity and breast cancer risk among premenopausal females

Question Five: Is there an association between higher amounts of physical activity and a reduction in breast cancer risk among postmenopausal females?

H_0: There is no association between higher levels of physical activity and breast cancer risk among postmenopausal females

H_A: There is an association between higher levels of physical activity and breast cancer risk among postmenopausal females

Q1 was addressed through meta-analyses of colon cancer risk for males, while Q2 was addressed through meta-analyses of colon cancer risk for females. Q3 was addressed through meta-analyses of breast cancer risk for pre- and postmenopausal females combined. Q4 was addressed through meta-analyses of breast cancer risk for premenopausal females, while Q5 was addressed through meta-analyses of breast cancer risk for postmenopausal females.

Methodological Differences between Studies

The overall methodological differences among studies included in the meta-analyses were assessed. Specifically, characteristics of study participants, selection criteria of study participants, and time frame for case diagnoses and selection of controls were included in Tables 3-5 for colon cancer studies and Tables 6-8 for breast cancer studies. Also, the measurement of physical activity (length of time physical activity was measured, categorizations of quantified physical activity) and instrumentation used to record modes of physical activity were compared for each study.

Confounding

The issues of confounding and the use of unadjusted effect measures in the meta-analyses were addressed by comparing the unadjusted measures to the age-adjusted and multivariate-adjusted effect measures to determine if any major differences existed. Unadjusted and adjusted effect measures for each level of physical activity quantification (i.e. each level of MET hours-per-week) were compared for the moderate vs. low activity and high vs. low activity analyses. These comparisons were completed

by calculating the percent difference between the unadjusted and adjusted effect measures for each activity level. A list of factors adjusted for in each study is included in a series of tables at the end of Chapter III.

The meta-analyses combine a number of different studies, each of which adjusts for a number of different possible confounding variables. In order to combine these studies without the availability of raw data, unadjusted measures were calculated. The possible effects of confounding variables that may cause a potential bias among the study results, either by over- or underestimating the effects of physical activity on colon cancer risk, were addressed by calculating the percent differences between the adjusted and unadjusted effect measures using the formula shown below:

% Difference in Unadjusted Effect measure vs. Adjusted Effect measure = 100[(Unadjusted Effect measure – Adjusted Effect measure) / Adjusted Effect measure]*

Because it is important to determine if a potential decrease in colon cancer risk is associated with higher amounts of physical activity, a higher odds ratio estimate actually means less of an effect. For example, an odds ratio of 0.90 shows less of an activity effect than an odds ratio of 0.80 because 0.90 is closer to the no-effect level of 1.0. An unadjusted measure that is consistently lower or higher than the adjusted measure is one potential indication of bias in the results. When comparisons are calculated for all studies, it can be determined whether the unadjusted effect measures were likely to over- or underestimate the multivariate-adjusted effect measure.

Definition of Meta-Analysis

A meta-analysis is a quantitative summary of a number of study results [125]. It is a compilation of relevant studies, following a comprehensive search for all potentially relevant studies, with a final selection of studies based on clearly stated criteria. The utilization of a meta-analysis allows for the combination of several studies in order to answer relevant hypotheses through the combination of smaller studies and sample sizes. The dependent variable in a meta-analysis is the effect size [125] (in this case, the effect measure reporting the relationship between physical activity and cancer risk). Because physical activity has previously been reported to be an independent predictor of female breast cancer risk and combined male and female colon cancer risk, a primary goal of this meta-analysis was to quantify the effect of leisure-time physical activity on risk of these two cancers [18, 57].

Cohort studies and case-control studies were included in the meta-analyses. Cohort studies typically include large subsets of a defined population followed over a long period of time for which individuals were identified as either exposed or not exposed to a risk factor (e.g. physical activity) hypothesized to influence occurrence of a given disease (e.g. breast or colon cancer) [126]. Case-control studies observe individuals having a given disease (e.g. breast or colon cancer) and a comparable group of persons without the disease (controls). The past history of exposure to a risk factor such as physical activity is then compared between the two study groups [126].

The meta-analyses were carried out separately for colon and breast cancer risk, with both groups of analyses using the following study criteria. Studies examining the effect of diet in combination with physical activity on cancer risk were excluded from the

meta-analysis in order to prevent any results due to a potential confounding relationship between physical activity and diet from being included in the analysis. Additionally, only studies that used the *Compendium of Physical Activities* to assign MET-scores to physical activities were included in the primary meta-analyses to ensure comparability in the quantification of physical activity assessment across all included studies [64]. Studies merely quantifying physical activity in terms of 'low', 'moderate', and 'high' without sufficient numerical quantification were excluded. Although most studies included in the meta-analyses reported physical activity in MET-hours-per-week, additional studies that reported either a MET value or number of activity hours per week along with examples of specific completed activities allowed for a translation into MET hours-per-week, and were also included in some meta-analyses. The method of estimating MET hours per week based on partial reports of physical activity is described in further detail later in this chapter.

Compendium of Physical Activities

The *Compendium of Physical Activities*, originally published by Ainsworth et al. in 1993, was most recently revised in 2000 [64, 80]. The purpose of the *Compendium* is to "facilitate the coding of physical activity intensities obtained from physical activity records, logs, and surveys and to promote comparison of coded physical activity levels across observational studies" [64]. It is a widely used method for quantifying physical activity for epidemiological studies, and groups activities by intensities expressed as metabolic equivalents (METs), which are the ratio of working metabolic rate to the standard resting metabolic rate (RMR) of 1.0. The *Compendium* provides a

comprehensive classification of energy costs for a multitude of leisure-time, occupational, household, and self-care human physical activities. Additionally, the coding of specific MET values allows for physical activity to be determined over a given time period (e.g. MET hours-per-week).

Activities are included in the *Compendium* as multiples of RMR and coded using a five digit coding sequence for the classification of physical activity. The first two digits display the purpose of the activity, while the last three numbers are representative of the specific activity. Additionally, a specific MET intensity value for each activity is reported. While the *Compendium* remains the most widely-used source of quantifying physical activity when completing occupational studies, research reports that the *Compendium* may underestimate the cost of energy cost of weight-bearing activities and overestimate the actual energy cost of non-weight-bearing activities among heavier individuals [127].

The inclusion of *Compendium*-quantified studies in an analysis allows for the consistent utilization of a physical activity instrument that is considered to be appropriate for quantifying physical activity in observational studies. Examples of common activities among colon and breast cancer studies that are listed in the *Compendium* include recreational walking (4.0 METs), brisk walking (8.0 METs), jogging (7.0 METs), fast jogging (8.0-18.0 METs, depending on speed), stationary bicycling (7.0 METs) and various occupational activities such as moving or pushing heavy objects (7.5 METs).

Inclusion Criteria for Meta-Analyses

A comprehensive review of international literature in the English language was completed using the Cochrane, Embase, and Medline (PubMed) library databases, as well as the Proquest periodical database. Studies in which MET hours-per-week could be directly calculated using the *Compendium* were included in the primary meta-analyses. No other physical activity quantification instrumentation was included.

However, some studies provided partial information allowing for approximate quantification using the *Compendium*. Specifically, some studies reported either the total METs or the total amount of weekly activity (typically in hours-per-week), along with a detailed description of the activity type. These studies allowed for the MET value or hours-per-week to be estimated, to quantify indirectly the amount of completed activity in MET hours-per-week using the *Compendium*. The estimated studies were combined with *Compendium*-quantified studies in larger, secondary analyses to provide additional assessment of the relationship between physical activity and cancer risk among a greater number of individuals. It should be noted that while these additional analyses provided a greater number of studies for which the relationship between leisure-time physical activity and cancer risk could be assessed, inclusion of these studies was associated with limitations. Specifically, the analyses that also included studies for which *Compendium*-quantified physical activity was estimated rather than directly quantified were subject to the conditions qualifying the studies for inclusion in the meta-analyses. For example, noting the specific activities mentioned in the original studies and assigning a MET value from the *Compendium* is likely to produce a different result compared to a study that directly quantified activity using the *Compendium.* Similarly, assigning an arbitrary

amount of activity completed during the week to accompany an activity of a given MET value reported in a study is likely to produce a different result than a study that directly quantified activity in MET hours-per-week from the beginning using the *Compendium*.

Overview of Meta-Analyses

Colon Cancer

Two meta-analyses were performed to examine the relationship between physical activity and colon cancer risk. Analyses I and II included only studies that used the *Compendium* to quantify leisure-time physical activity for males and females, respectively, while Analyses III and IV included studies from the first analysis as well as studies that provided either a MET value or number of hours of physical activity along with sample physical activities. Including studies providing partial activity information allowed for an estimation of leisure-time physical activity in MET hours-per-week using the *Compendium*. Information detailing the number of studies and study criteria for inclusion for each physical activity and colon cancer risk analysis can be found in Table 3.

Breast Cancer

The specific relationship between leisure-time physical activity (as quantified by the *Compendium of Physical Activities*), and breast cancer risk was assessed using a total of seven meta-analyses. Analysis I included only studies that used the *Compendium* to quantify leisure-time physical activity, while Analysis II included those studies from Analysis I that quantified the amount of physical activity for ten years or longer (up to

lifetime). Eight of the ten *Compendium*-quantified studies met this requirement. This analysis was completed to control for a possible measurement time effect. Analysis III included studies from Analysis I as well as studies that provided either a MET value or number of hours of physical activity along with sample physical activities, so that MET hours-per-week could be estimated.

Separate *Compendium*-quantified analyses were carried out for breast cancer risk for pre- and post-menopausal females. Analysis IV included only *Compendium*-quantified studies that examined the relationship between physical activity and breast cancer risk for premenopausal females. Analysis V had the same study criteria for inclusion for postmenopausal females. While there were insufficient studies to have a meta-analysis including both *Compendium* quantifications and MET hour-per-week estimations for premenopausal females, Analysis VI included studies from Analysis V as well as studies including either a MET value or number of hours of physical activity along with sample physical activities, allowing studies with estimated MET hours-per-week to be included in this analysis. Information detailing the number of studies and study criteria for inclusion for each physical activity and breast cancer meta-analysis can be found in Table 6.

Statistical Methods used for Meta-Analyses

Studies included in the meta-analyses differed in terms of the type of effect measures that they reported and the covariates that were controlled in the analysis. Prospective studies reported either relative risks (RR) or incidence density ratios (IDR) [11], and retrospective studies reported odds ratios (OR) [128]. For comparability across

studies, relative risks and incidence density ratios were converted to approximate odds ratios. The odds ratios were then converted to the log scale, and the variance, standard error (SE) of the log of OR, confidence intervals (CI) and *p*-values were calculated for each combined physical activity level for each study, based on the published, unadjusted data. All hand-calculations of effect measures, log of the effect measures, standard error of the log of the effect measures, and confidence intervals are presented in Appendices I and II for studies of colon and breast cancer risk, respectively. Pooled effect measures and variances were calculated using the Mantel-Haenszel method and statistical analyses were completed using the Metan meta-analysis procedure with Stata 9.2 software [129]. A significance level of alpha = 0.05 was used for all analyses.

Effect Measures

Because studies included in the present analyses controlled for different variables, unadjusted effect measures were calculated for each study to allow the studies to be combined. Adjustments for covariates, such as age, were not included in the meta-analyses, because studies controlled for a variety of different covariates and individual subject-level covariate values were not available for each study. Five studies examined postmenopausal breast cancer risk, and three studies examined premenopausal breast cancer risk, including two studies that completed separate analyses by menopausal status within the same study. This allowed for the analysis of the effect of physical activity on premenopausal and postmenopausal females in independent meta-analyses.

All effect measures were based on four possible exposure-disease categories, labeled *a, b, c,* and *d,* displayed below:

	Disease Status Present	**Disease Status Absent**	**Disease Status Total**
Protective Factor Present	*a*	*b*	*a+b*
Protective Factor Absent	*c*	*d*	*c+d*
Protective Factor Total	*a+c*	*b+d*	*a+b+c+d*

Where *a* = the number of cases in the higher amount of activity group; *b* = the number of controls in the higher amount of activity group; *c* = the number of cases in the lower amount of activity referent group; *d* = the number of controls in the lower amount of activity referent group) [126, 128].

All effect measures were calculated to show the possible protective effect of the exposure (e.g. physical activity) on disease risk (e.g. colon or breast cancer). For retrospective studies, the odds ratio is defined as the odds of the event (colon or breast cancer) among participants having a higher amount of physical activity divided by the odds of developing cancer among participants having a lower amount physical activity. The odds ratio may be calculated as:

$$\psi = \frac{a \times d}{b \times c}$$

Most cohort studies included in the meta-analysis reported the number of cases, based on the exposure time measured in person-years of risk. This allowed for the calculation of an incidence density ratio (IDR), which is described below:

$$IDR = \frac{r_2 \times t_1}{r_1 \times t_2}$$

where r_2 = the number of cases in the higher amount of activity group; t_1 = total number of person-years in low activity referent group; r_1 = number of cases in low activity referent group; t_2 = total number of person-years in higher activity group) [128]. The IDR is calculated as the number of incident cases occurring over a given time period and its units are defined as the number of cases per unit of person-time [130]. It is important to note that Mietennen (1976) reported the OR to be an unbiased estimator of the IDR, regardless of whether or not the condition is rare [131, 132].

For two cohort studies of breast cancer risk, relative risks were calculated because the only available information was the number of cases and non-cases for each activity level, which is insufficient for IDR calculations because person-years were not reported. The relative risk is the probability of an event (e.g. breast or colon cancer) in the higher physical activity group divided by the probability of an event in the lower physical activity group:

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

In this equation, the numerator represents the proportion of persons in the higher physical activity group who had an event (colon or breast cancer), and the denominator represents the proportion of persons in the lower physical activity group who had an event.

Prior research reports that while some measurement error may exist when the odds ratio is obtained as an estimate from another effect measure, such an estimate provides an acceptable approximation to the risk ratio and no assumption of rarity of disease is needed for the approximation calculation [132].

Log and Standard Error of the Effect Measure

When combining effect measures as part of a meta-analysis, it is recommended to log transform the data prior to combining, so each effect measure is transformed to the log scale. This allows for an easier method of calculating the variance of the log odds ratio can be calculated and confidence intervals for each study's log odds ratio can be developed. The variance for the log of the effect measure is calculated using the equation: 1/a + 1/b + 1/c + 1/d, for the OR and RR, while the variance of the log of the IDR is calculated as $(r1+r2) / (r1 \cdot r2)$ [128].

The standard error (SE) is defined as the sampling variability of a particular estimate, and is determined by calculating the square root of the variance of the log effect measure ($\sqrt{1/a + 1/b + 1/c + 1/d}$ for the OR and RR, and $\sqrt{(r1+r2)/(r1 \cdot r2)}$ for the IDR). Utilizing the log of the effect measure and the SE of the log effect measure allow for the calculation of the 95% CI for the unadjusted effect measures:
(Log Effect measure ± 1.96 · *SE* of Log Effect measure). After confidence intervals have been determined, they can be transformed from the log scale back to the odds ratio scale by exponentiating the two endpoints of a 95% CI for the log effect measure to derive the endpoints of a 95% CI for the effect measure.

Meta-Analytical Methodology

Types of Meta-Analytical Methods

A variety of analytical methods are available for the pooling of existing data, including the general fixed effects model (the inverse variance-weighted method), the Mantel-Haenszel method, and the Peto method [133-135]. The latter two methods are

fixed effects methods for pooling odds ratios and combining effect measures, and do not account for heterogeneity between studies [133]. Another method used for combining study measures is the random effects model, which is widely considered a more conservative statistical method for combining effect measures, as it accounts for heterogeneity between studies [136]. In the mid 1980's, DerSimonian and Laird developed the typical random effects model used in meta-analyses [137]. The primary difference between a fixed and random effects model is that the random effects model is based on an assumption that effect sizes are randomly distributed with a fixed mean and variance [137]. The fixed effects model is appropriate to use for analyses of smaller studies with more homogeneity in the effect measures from each study, while the random effects model is appropriate to use for analyses of a larger number of studies with greater heterogeneity, as often found in observational studies.

The general fixed effects model was developed over 70 years ago [138, 139] and is based on giving each study effect measure a weight that is directly proportional to its precision, which would also be inversely proportional to its variance [133]. The fixed effects model is based on the assumption that all population effect sizes are equal and does not account for the study heterogeneity typically associated with analyses of observational studies [133, 140].

The Mantel-Haenszel (M-H) method is a commonly used fixed effect method for combining odds ratios from case-control studies [134]. In 1963, Mantel indicated that the M-H method was appropriate for combining effect measures from both retrospective and prospective studies, which is particularly important for calculating the pooled measures in

the present project [141]. The pooled M-H effect measure was calculated using the equation:

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

where a_i, b_i, c_i, and d_i represent each of the four cells of the 2x2 tables for i =…k studies, and n_i is the total number of people in the ith study. The pooled variance for the Mantel-Haenszel method is calculated using the equation:

$$V_{MH(\ln(OR))} = \frac{\sum_{i=1}^{k} P_i R_i}{2(\sum_{i=1}^{k} R_i)^2} + \frac{\sum_{i=1}^{K} (P_i S_i + Q_i R_i)}{2(\sum_{i=1}^{k} R_i)(\sum_{i=1}^{k} S_i)} + \frac{\sum_{i=1}^{k} Q_i S_i}{2(\sum_{i=1}^{k} S_i)^2}$$

where $P_i = (a_i+d_i)/n_i$, $Q_i = (b_i+c_i)/n_i$, $R_i = a_i d_i/n_i$, $S = b_i c_i/n_i$[142].

The Mantel-Haenszel estimate of the combined effect was hand-calculated and also calculated using Stata 9.2 for all of the case-control studies for Analysis II of the colon cancer analyses and Analyses I, III, IV, V, and VI of the breast cancer analyses to compare results [129]. Additionally, the 95% confidence interval for the Mantel-Haenszel estimate was hand-calculated for Analysis III of the breast cancer analyses (the analysis with the largest number of studies and subjects) and calculated using Stata for Analysis II of the colon cancer analyses and Analysis I, III, IV, V, and VI of the breast cancer analyses. In all cases the hand-calculated Mantel-Haenszel estimate results

matched those from Stata within rounding error. All Mantel-Haenszel and 95% confidence interval hand-calculations are included in Appendix III.

Another specific fixed effects method for the pooling of odds ratios is the Peto method, which is a modified version of the Mantel-Haenszel method that allows for calculation when there are occurrences of cell frequencies within the 2x2 tables of individual studies that are zero [135]. However, prior research reports that utilization of the Peto method for observational studies (e.g. epidemiological studies as opposed to clinical trials) is not ideal, as this method is associated with underestimations of risk when there is a large amount of variation in the odds ratio due to large treatment or exposure effects [143, 144]. Therefore, the Peto method was not used for the present analyses.

The random effects method is a more conservative statistical tool than the fixed effects method, as it assumes that individual studies have different treatment effects and that "study specific effect sizes come from a random distribution of effect sizes with a fixed mean and variance" [136]. Accounting for this additional variation among study effect sizes is appropriate for analyses of epidemiologic studies. Typically, if results of fixed and random analyses are similar, it is unlikely that statistically significant heterogeneity exists. However, because a fixed effects model does not account for random variation between studies, the more conservative random effects model is often considered a more appropriate statistical method to use if heterogeneity exists between studies.

When a fixed or random effects analysis is completed within Stata, a DerSimonian and Laird Q-test for heterogeneity is also calculated, to determine if

heterogeneity exists among the studies [145]. While the test for heterogeneity does not indicate the reasons for such an occurrence, likely factors contributing to methodological heterogeneity include differences in the ways subjects were selected and outcomes were measured, while statistical heterogeneity is often associated with varying sample sizes among studies within the analysis [146]. Such variation is sometimes responsible for the differing treatment effects that often exist among observational studies.

For the analyses of physical activity and colon cancer risk, fixed and random effects models were compared using the 'Meta' and 'Metan' meta-analytical procedures in Stata 9.2. While the colon cancer analyses included a smaller number of studies that would typically warrant a fixed effects model, they also included one study (Tang et al., 1999) that had fewer subjects, which had an effect measure that differed greatly from the other studies. This heterogeneity in the study effect would indicate the use of a random effects model. Fixed and random effects models were also compared for the analyses of physical activity and breast cancer risk among premenopausal females, as the analysis included a smaller number of studies, yet was also subject to the heterogeneity often found among observational studies. Random effects models were completed for the larger analyses of physical activity and breast cancer risk among postmenopausal females and pre- and postmenopausal females combined because these analyses included a larger number of studies.

Study Weighting for Meta-Analyses

Meta-analytical weights were initially developed by Hedges to account for study variation [147]. The purpose of weighting the studies in a meta-analysis is to give more

weight to studies providing greater information about the effect from the study through a larger sample size. Each combined effect measure from a meta-analysis is based on a weighted average of the effect from each individual study. The weight for a study represents a degree of precision derived from the random variation in effect size due to sample size [146]. A few years following Hedges' development, Colditz et al. (1995) suggested that future research of random effects weighting is necessary, as it likely places too much emphasis on larger observational studies, but still weights them more favorably than the fixed effect model [81].

Forest Plots

The relative study weights are graphically displayed in forest plots for each meta-analysis throughout the results section. A greater study weight, which indicates a larger sample size, is associated with a larger box size as part of the forest plot. The vertical line that intersects the x-axis at 1.0 indicates no effect. The relative horizontal placement along the x-axis represents the effect measure for each study. Boxes farther to the left indicate more of a protective effect, while the horizontal line that intersects the box represents the 95% confidence interval for that particular effect measure. The dashed vertical line that intersects the diamond at the bottom of the plot represents the pooled effect measure, with the left and right endpoints of the diamond representing the pooled 95% confidence interval.

Regression Model for Meta-Analyses

Random effects regression models for the meta-analyses, which are also known as mixed effects models, were completed. These models attempted to assess whether the relationship between physical activity and colon and breast cancer risk differed by sex and menopausal status, respectively. This model can be used to investigate the heterogeneity of effects across studies and examines the relationship between one or more study-level characteristics and the sizes of effect observed in the studies [140, 146]. This regression model can be used when variation between studies included in the meta-analysis is due to sampling error and the covariates measured [147]. In the present analyses, it is important to determine whether statistically significant differences exist among menopausal status when examining the effect of physical activity on breast cancer risk.

Meta-Analytical Procedures

The study name and year, sex (colon cancer analyses), and menopausal status (breast cancer analyses) were entered into the Stata meta-analytical procedures. The effect measure (odds ratio, approximate incidence density ratio, or relative risk), log effect measure, standard error of the log effect measure, number of cases, and number of controls (or person-years) for each study were calculated across all physical activity groups from all studies included in any of the meta-analyses. Using this information, meta-analyses were calculated and the pooled estimate, upper and lower ends of the 95% summary confidence interval, p-value, and individual study weights were reported. A forest plot was generated for each meta-analysis, with the studies listed on the Y-axis and

summary effect measure listed on the X-axis. The summary effect measure, summary 95% confidence interval, effect measure for each study, and 95% confidence interval for each study were graphically displayed. All analyses separately compared the 'moderate' and 'high' activity groups to the reference 'low' activity group.

Organization of Data for All Meta-Analyses

Because studies included in the analyses reported different physical activity categories, it was decided to combine the amount of physical activity from all studies into three groups for each of the meta-analyses. Based on the amount of physical activity in total MET hours-per-week, information from all studies was combined, and the amount of physical activity was categorized as a 'low', 'moderate', or 'high'. The risks of the 'moderate' and 'high' activity groups were separately compared to the referent 'low' activity group for all analyses. Individual unadjusted effect measures, log of the effect measures, standard error of the log of the effect measures, and 95% confidence intervals were calculated for the moderate and high activity level groups and compared to the low physical activity group for all colon cancer (separately for males and females) and breast cancer (females only) analyses.

Physical Activity Categorizations for Colon and Breast Cancer Meta-Analyses

Because each study used different categories of MET hours-per-week to define amounts of physical activity, it was necessary to combine these categories for the meta-analyses. Table 1 illustrates the amounts of physical activity that were combined from each study to make the 'low', 'moderate', and 'high' physical activity categories for the

meta-analyses. Cut-points for each category were designed to be as inclusive as possible. Thus, for the *Compendium*-quantified colon cancer Analysis I, 'low' activity ranged from 0 to 7.30 MET hours-per-week, 'moderate' activity ranged from 0.1 to 20.0 MET hours-per-week, and 'high' activity ranged from > 11.3 MET hours-per-week (median) to > 20 MET hours-per-week. For females in Analysis II, 'low' activity ranged from 0 to 7.30 MET hours-per-week, 'moderate' activity ranged from 0.1 to 21.0 MET hours-per-week, and 'high' activity ranged from > 16.0 to > 20.0 MET hours-per-week. Categorizations for the *Compendium* combined and estimated colon cancer Analysis III ranged from 0 to 7.30 MET hours-per-week for the 'low' activity group, 0.1 to 20.0 MET hours-per-week for the 'moderate' activity group, and ranged from > 11.3 MET hours-per-week (median) to >20.0 MET hours-per-week for the 'high' activity group for males, while the categorizations for females in Analysis IV ranged from 0 to 8.0 MET hours-per-week for the 'low' activity group, 0.1 to 21.0 MET hours-per-week for the 'moderate' activity group, and ranged from >16.0 to >20.0 MET hours-per-week for the 'high' activity group. Specific physical activity categorizations in MET hours-per-week for the individual studies included in the colon cancer analyses are reported in Table 1 below.

Table 1. Physical activity categorizations (MET hours-per-week or estimated MET hours-per week) for colon cancer meta-analyses

Study	**Relevant Analyses**	**Sex**	**Low Activity**	**Moderate Activity**	**High Activity**
Giovannucci ('95)	I, III	M	0-4.8*	4.8-11.3*	>11.3*
Longnecker ('95)	III	M	≤4.0	4.1-16.0	>16.0
White ('96)	I, II, III, IV	M, F	<7.30	7.30-17.88	>17.88
Martinez ('97)	II, IV	F	<5.0	5.0-21.0	>21.0
Tang ('99)	I, II, III, IV	M, F	0	0.1-20.0	>20.0
Calton ('05)	IV	F	<8.0	8.0-16.0	>16.0

* Median MET hours-per-week reported

Categorizations for breast cancer Analyses I and II ranged from 0 to 8.9 MET hours-per-week for the 'low' activity group, 5.1 to 20.7 MET hours-per-week for the 'moderate' activity group, and ranged from >12.0 to >20.7 MET hours-per-week for the high activity group. Analysis III categorizations ranged from 0 to 10.0 MET hours-per-week for 'low' activity group, 0.1 to 20.7 MET hours-per week for the 'moderate' activity group, and ranged from >12.0 to >20.7 MET hours-per-week for the 'high' activity group. For Analysis III, one study (Thune et al., 1997) had a moderate activity categorization of 0.1 to 16.0 MET hours-per-week, while all of the others ranged from 5.1 to 20.7 MET-hours-per-week. The Analysis IV categorizations ranged from 0 to 8.9 MET hours-per-week for the 'low' activity group, 6.7 to 20.7 MET hours-per-week for the 'moderate' activity group, and ranged from >16.6 to >20.7 MET hours-per-week for the 'high' activity group. Physical activity categorizations for Analysis V ranged from 0 to 7.6 MET hours-per-week for the 'low' activity group, 5.1 to 20.0 for the 'moderate' activity group, and ranged from >16.6 to >20.0 MET hours-per-week for the 'high' activity group. Finally, physical activity categorizations for Analysis VI ranged from 0 to 8.74 MET hours-per-week for the 'low' activity group, 5.1 to 20.7 MET hours-per-week for the 'moderate' activity group, and ranged from >16.6 to >20.0 MET hours-per-week for the 'high' activity group. Specific physical activity categorizations in MET hours-per-week for the individual studies for the breast cancer analyses are reported in Table 2.

Table 2. Physical activity categorizations (MET hours-per-week or estimated MET hours-per week) for breast cancer meta-analyses

Study	Relevant Analyses	Low Activity	Moderate Activity	High Activity
Thune (’97)	III	0	0.1-16.0	>16.0
Carpenter (’99)	I, II, III, V, VI	0-8.74	8.75-17.59	>17.59
Levi (’99)	III	<8.0	8.0-16.0	>16.0
Rockhill (’99)	III	<9.75	9.75-17.5	>17.5
Moradi (’00)	III, VI	0-7.5	7.5-15.0	>15.0
Friedenreich (’01) – Pre	I, II, III, IV	0-6.7	6.7-20.7	>20.7
Friedenreich (’01) – Post	I, II, III, V, VI	0-5.1	5.1-16.9	>16.9
Matthews (’01)	I, II, III	0-6.16	6.16-13.37	>13.37
Dirx (’01)	III, VI	<10.0	10.0-15.0	>15.0
Colditz (’03)	I, II, III, IV	0-8.9	9.0-17.9	>17.9
John (’03) – Pre	I, II, III, IV	<6.8	6.9-16.6	>16.6
John (’03) – Post	I, II, III, V, VI	<7.6	7.6-17.7	>17.7
Patel (’03) – Cohort	I, III, V, VI	0-7.0	7.0-17.5	>17.5
Patel (’03) – Case-Control	I, II, III	0-8.0	8.0-16.0	>16.0
McTiernan (’03)	I, III, V, VI	<5.1	5.1-20.0	>20.0
Yang (’03)	I, II, III	<6.0	6.0-12.0	>12.0
Bernstein (’05)	I, II, III	<6.7	6.7-15.1	>15.1

Physical Activity and Colon Cancer Risk Meta-Analyses

Four studies (total = 874 cases, 221 controls, 564,722 person-years) measuring the effect of leisure-time physical activity on colon cancer risk using the *Compendium* to quantify the amount of physical activity (MET hours-per-week) were included in Analysis I for males and Analysis II for females. Additionally, six studies (total = 1279 cases, 758 controls, 835,047 person-years) were included in Analysis III for males and Analysis IV for females that allowed for both *Compendium* quantifications and MET hour-per-week estimations from studies providing either a weekly MET accumulation or weekly hours of physical activity. A mixed effects model was also completed to assess whether the relationship between physical activity and colon cancer risk differed by sex.

Physical Activity and Breast Cancer Risk Meta-Analyses

Ten studies analyzing the effect of leisure-time physical activity on breast cancer risk among pre- and postmenopausal females using the *Compendium* to quantify the amount of physical activity (MET hours-per-week) were included in the largest meta-analysis (Analysis I). A total of 14,339 cases, 11,097 controls, 43,635 non-cases from cohort studies, and 1,250,896 person-years were included in Analysis I. Additionally, after only including *Compendium*-quantified studies that measured the amount of physical activity for at least ten years, eight studies measuring breast cancer risk were included in Analysis II (total = 11,503 cases, 11,097 controls, and 934,100 person-years). Furthermore, Analysis III included fifteen studies examining the effect of leisure-time physical activity on breast cancer risk using both *Compendium* quantifications and MET hour-per-week estimations from studies providing either a weekly MET accumulation or weekly hours of physical activity (total = 27,208 cases, 14,098 controls, 68,894 non-cases from cohort studies, and 2,448,056 person years). Analysis IV measured the effect of leisure-time physical activity on breast cancer risk among premenopausal females using the *Compendium*, and included three studies (total = 1714 cases, 958 controls, and 934,100 person-years). A similar analysis using *Compendium*-quantified activity solely among postmenopausal females utilized five studies (total = 5577 cases, 2731 controls, 43,635 non-cases from cohort studies, and 316,796 person-years) as part of Analysis V. Analysis VI included seven studies of postmenopausal females that either quantified activity using the *Compendium* or contained a weekly MET accumulation or weekly hours of physical activity (total = 8,539 cases, 5,361 controls, 43,635 non-cases).

Finally, a mixed effects model was completed to assess whether the relationship between physical activity and breast cancer risk differed by menopausal status.

For each of the colon and breast cancer risk meta-analyses, specific information for each study is included (first author's last name, year of study, type of study, age and sex distribution (colon cancer), menopausal status (breast cancer), number of cases, number of controls, number of non-cases or person-years for cohort studies, and estimation status of the quantified physical activity (Table 9 for colon cancer studies and Table 12 for breast cancer studies). An additional table for each meta-analysis includes the length of time physical activity was measured for categorizing physical activity (reported in MET hours-per-week), effect measures, and confidence intervals for each category of physical activity for each study (Tables 10 and 11 for colon cancer analyses and Tables 13 through 18 for breast cancer analyses).

Special Conditions for Meta-Analyses

As reported earlier, a few studies in the meta-analyses included some, but not all, of the relevant information necessary to be properly quantified according to the *Compendium*. Some studies provided the total weekly physical activity in hours but did not provide a total weekly MET accumulation. These studies reported the types of activities performed (e.g. walking, cycling) that assisted in the estimation of MET hours-per-week, but did not assign a MET value and therefore did not directly quantify activity in MET hours-per-week. Similarly, other studies provided only a weekly MET accumulation, allowing for an estimation of physical activity in MET hours-per-week when an arbitrary weekly amount of physical activity in hours-per-week was used with

the MET accumulation. This hourly amount allowed for the amount of MET hours-per-week to be comparable to that of other studies in a similar activity group, as these additional studies did not directly report a total weekly amount of physical activity in MET hours-per-week.

For some of these *Compendium* 'estimated' studies, the MET level was determined according to the types of activity described in the study. Weekly activity accumulation (in hours) was determined by the amount of total weekly METs in order to produce appropriate MET hour-per-week categorizations that were comparable to *Compendium*-quantified studies examining a similar relationship between physical activity and cancer risk. Four meta-analyses (Analyses III and IV for colon cancer and Analyses III and VI for breast cancer) included studies that had these 'estimated' MET hours-per-week quantifications. The studies in each of these respective analyses are listed below and accompanied by their assumptions and relevant analyses for which they are included. For colon cancer analyses, a MET value of 8.0 for vigorous activity was assumed for Longnecker et al. (1995) and Calton et al. (2006). For breast cancer analyses, an assumption of two hours per week of activity at the mean MET value originally reported in the Dirx et al. (2001) study was included in the 'estimated' analyses. Additionally, MET values of 4.0, 4.0, and 6.0 were assumed to estimate MET hours-per-week for Levi et al. (1999), Rockhill et al. (1999) and Moradi et al. (2000), respectively. Finally, for Thune et al. (1997), physical activity grades of 1, 2, 3, and 4, were placed into 0, <16, and >16 MET-hours-per week categorizations. Such assumptions were based on a detailed description of the activity types and amount of weekly activity hours reported in the original study.

Comparability of Studies within Meta-Analyses

Methodological differences among studies included in the meta-analyses were inevitable. In the present study, study participant characteristics (Tables 3 and 6), time-span of physical activity exposure (Tables 4 and 7), type of activity (Tables 5 and 8) instrumentation used to record modes of physical activity (Tables 5 and 8), and variables included in multivariate analyses (Tables 42.1-42.8 and Tables 43.1-43.17) were described in detail for all studies included in each of the colon and breast cancer meta-analyses.

Tables 4 and 5 (colon cancer studies) and Tables 7 and 8 (breast cancer studies) were created to report the assessment methods of physical activity, type of physical activity quantification (e.g. *Compendium* or estimated using *Compendium)*, time-span of exposure (e.g. years physical activity was followed), physical activity assessment instrumentation (e.g. self-developed by researchers or use of an established physical activity questionnaire), and activity type of the study (e.g. leisure-time/recreational). For the breast cancer studies, three studies used a similar physical activity assessment tool developed by Bernstein et al. (1994), which was reportedly the most appropriate assessment instrumentation in a review of physical activity assessment methods for breast cancer studies [100, 148]. Additionally, two breast cancer studies and one colon cancer study used a physical activity assessment tool developed by Wolf et al. and used in the Nurses Health Study [149]. All analyses focused on the effect of leisure-time or recreational physical activity on colon and breast cancer risk, and specific activities mentioned in each of the original studies (e.g. running, walking, swimming, cycling, etc.)

were also included in the tables assessing physical activity (Table 5 for colon cancer studies and Table 8 for breast cancer studies).

Additionally, a thorough description of study participants was included in a series of tables for all studies included in the analyses of colon and breast cancer (Table 3 for colon cancer studies and Table 6 for breast cancer studies). The study type (e.g. case-control or cohort), participant characteristics (e.g. demographic information), selection criteria, and time period for participant selection and exposure measurement were included for all studies. Furthermore, for cohort studies, the number of participants, study location(s), and total follow-up time was included, while information for the case-control studies included the total number of cases, controls, a comprehensive description of selection criteria (e.g. community-based or hospital controls, geographic location, etc.) and the specific time period of case diagnoses and selection of controls.

Although the present colon and breast cancer effect measures were unadjusted and could not be controlled for confounding variables, the unadjusted effect measures were compared to the age-adjusted and multivariate-adjusted analyses in a table for each study (where applicable) to determine if any major differences existed. Tables 42.1-42.8 (colon cancer studies) and 43.1-43.17 (breast cancer studies) report the unadjusted effect measures for each level of physical activity quantification (e.g. each level of MET-hours-per-week) compared to the age-adjusted and multivariate-adjusted effect measures for the moderate vs. low activity and high vs. low activity groups as a way of assessing the possible effects of confounding.

Methodological Limitations

Several methodological limitations are present in this project. Currently, more studies have utilized the *Compendium* to analyze the effect of physical activity on breast cancer risk compared to colon cancer risk. As a result more data are available for the meta-analyses of breast cancer risk. Additionally, there were not enough total studies or subjects to complete a meta-analysis examining the effect of occupational physical activity on colon and breast cancer risk, or an additional secondary meta-analysis on breast cancer risk among premenopausal females. Each study utilized different classifications (e.g. MET hours-per-week) for 'low', 'moderate', and 'high' physical activity groups, which caused the activity category cut-points in the meta-analyses to overlap, as opposed to having an absolute cut-point between activity categories. This results in a less precise estimate of the overall quantification of the relationship between physical activity and cancer risk than would be possible if all studies used similar activity categorizations.

Finally, as described earlier in the section discussing confounding, original data could not be obtained from study authors, so all pooled effect measures from the meta-analyses were unadjusted for individual participant characteristics. The unadjusted analyses would not allow for the direct assessment of the effect of confounding variables or the assessment of effect modifying variables. Because it is not possible to compare the adjusted and unadjusted effect measures statistically, calculations of the percent difference between the adjusted versus unadjusted effect measures were completed to determine if using unadjusted effect measures resulted in generally under- or overestimating the effect of physical activity. Percent differences between the adjusted

and unadjusted rates were calculated using the formula described earlier in this chapter. Completion of percent difference calculations assisted in determining whether the unadjusted measures of risk would bias the study results, either by under- or overestimating the effects of physical activity on colon or breast cancer risk.

Tables of Methodological Differences among Studies

Summary of Colon Cancer Studies

Table 3 describes each study and year, the type of study, number and detailed description of study participants, and time-period of follow-up (cohort studies) or case and control selection (case-control studies). Table 6 reports the same information for the breast cancer studies.

Table 3. Description of study participants – studies in colon cancer analyses

Study	Type	Participants	Time Period
Giovannucci et al. (1995)	Prospective Cohort	47,723 male health professional questionnaire respondents in the United States between age 40 and 75; 200 cases were identified over 263,554 person-years of follow-up; No reporting of race distribution in this study	Followed from 1986 to 1992

Table 3. Description of study participants – studies in colon cancer analyses

Longnecker et al. (1995)	Case-Control	**Cases:** 163 male cases with colon cancer were interviewed in Massachusetts, Rhode Island, Vermont, New Hampshire, and Connecticut identified through hospital records or the Massachusetts Cancer Registry; 19 cases aged 31-60; 34 cases aged 60-69; 77 cases aged 70-79; 33 Cases over age 80; 97.6% of cases were White individuals **Controls:** 275 community controls matched approximately 1.5:1 to cases by age (±5 years) and matching zip code or next closest possible location by town; no history of colon cancer; over age 31, selected by random digit dialing; 275 controls: 46 aged 31-60; 68 aged 60-69; 116 aged 70-79; 45 over age 80; 96.7% of controls were White individuals	Cases occurred from 1986 to 1988; Controls selected from a list holding driver's licenses from the same states as the cases in 1986
White et al. (1996)	Case-Control	**Cases:** 251 White males (23 aged 30-44; 29 aged 45-49; 37 aged 50-54; 94 aged 55-59; 68 aged 60-62) and 193 White females (14 aged 30-44; 24 aged 45-49; 34 aged 50-54; 63 aged 55-59; 58 aged 60-62) in three counties in Seattle, Washington area identified by Seattle-Puget Sound Surveillance, Epidemiology and End Results Registry **Controls:** 233 White males (31 aged 30-44; 23 aged 45-49; 31 aged 50-54; 89 aged 55-59; 59 aged 60-62) and 194 White females (24 aged 30-44; 19 aged 45-49; 26 aged 50-54; 70 aged 55-59; 55 aged 60-62); Frequency matched approximately 1:1 by age, sex, and county distribution of cases; Selected by random digit dialing of individuals with	Cases occurred from July 1985 to September 1989; Controls selected during same time period

Table 3. Description of study participants – studies in colon cancer analyses

		no history of colon cancer or irritable bowel syndrome; No Discussion of race distribution in the study	
Martinez et al. (1997)	Cohort	121,701 female registered nurses in the U.S. aged 30 to 55 who were respondents to a questionnaire and cancer free in 1976; Cohort taken from this group for the present study included 67,802 females and included 212 colon cancer cases over 67,802 person-years of follow-up; No reporting of race distribution in the study	Followed from 1986 to 1992
Tang et al. (1999)	Case-Control	**Cases:** 163 Taiwanese individuals (92 males and 71 females) between age 33 and 80; All cases were diagnosed in 1992 by one of two attending surgeons in the Chang Gung Medical Center in Taiwan; Mean age for cases was 61.0 ± 17.5 years for males and 59.6 ± 11.8 for females; Specific age distribution not reported	Cases were identified and controls were selected in 1992
		Controls: 163 individuals (92 males and 71 females) between the ages of 34 and 81 selected in 1992; History of cancer admitted to same hospital for unrelated treatment; Frequency-matched to cases for sex at a 1:1 ratio on age ±5 years compared to case distribution; Mean age for controls was 60.1 ± 11.9 for males and 59.4 ± 11.7 for females	
Calton et al. (2006)	Cohort	31,783 U.S. females participating in the Breast Cancer Detection Demonstration Project Follow-up Study without any type of cancer or missing/outlying values of energy intake and/or BMI; originally part of a cohort of 64,182	Followed from 1987 to 1998

Table 3. Description of study participants – studies in colon cancer analyses

						from 1979-1998; 243 cases identified among 270,325 person-years of follow-up; 89% of females were White, 5% were African-American, 3% were Asian-American, 2% Hispanic, and 1% unreported

Table 4 provides the time frame for physical activity measurement and type of physical activity quantification utilized for each individual study. The study name, year, and type, as well as the length of time physical activity was measured and method of physical activity quantification was included in this table. Table 5 reports the same information for the breast cancer studies.

Table 4. Time frame of physical activity measured for studies in colon cancer analyses

Study	**Type**	**Time Frame Measured and Quantification of Activity**
Giovannucci et al. (1995)	Prospective Cohort	Previous 6 Years (MET-hr/week)
Longnecker et al. (1995)	Case-Control	Previous 5 Years (MET values only – Estimated using *Compendium*)
White et al. (1996)	Case-Control	Previous 10 Years (MET-hr/week)
Martinez et al. (1997)	Cohort	Previous 1 Year (MET-hr/week)
Tang et al. (1999)	Case-Control	Previous 1 Year (MET-hr/week)
Calton et al. (2006)	Cohort	Previous 1 Year – (MET values only – Estimated using *Compendium*)

Table 5 provides an overview of the assessment of physical activity for each study included in the colon cancer meta-analyses. Specifically, the study name and year, type of physical activity quantification, length of time physical activity (the exposure) was measured, description of physical activity assessment instrumentation, and type of activity were included in this table. It should be noted that analyses of occupational activity were not included in the colon cancer meta-analyses due to a lack of studies or lack of appropriate energy expenditure quantification. Table 8 reports the same information for the breast cancer studies.

Table 5. Assessment of physical activity – studies in colon cancer analyses

Study	Quantification	Exposure Time	PA Assessment Instrumentation	Activity Type
Giovannucci et al. (1995)	*Compendium*	Previous 6 Years	Self-Developed Questionnaire; 5 categories (median 0.9, 4.8, 11.3, 22.6, and 46.8 MET hrs-per-wk); Mentioned activities included walking, tennis, running	Leisure-Time
Longnecker et al. (1995)	Estimated using *Compendium;* MET values given	Previous 5 Years	Self-Developed Interview; 4 categories (0, ≤1/2, 1, or ≥2 hours per week of vigorous activity (>4 METs per week); activities included jogging, running, bicycling, swimming, tennis, calisthenics, rowing	Leisure-Time Occupational

Table 5. Assessment of physical activity – studies in colon cancer analyses

White et al. (1996)	*Compendium*	Previous 10 Years	Interview and Questionnaire developed by Taylor et al. (1978) for assessing activity; 4 categories (0, <7.30, 7.30-17.88, >17.88 MET hrs-per-wk); Mentioned activities included walking, dancing, running	Leisure-Time Occupational Total (Leisure Time plus Occupational)
Martinez et al. (1997)	*Compendium*	Previous 1 Year	PA Questionnaire from the Nurses' Health Study; 5 categories (<2, 2-4, 5-10, 11-21, and >21 MET hrs-per-wk; Mentioned activities included walking, hiking, golf, jogging, running, bicycling, swimming, tennis, calisthenics, aerobics, rowing)	Leisure-Time
Tang et al. (1999)	*Compendium*	Previous 1 Year	Self-Developed Interview and Questionnaire; 3 categories (Light, Moderate, and Heavy), Activities mentioned included walking, tennis, swimming, hiking, stair climbing, martial arts, jogging, additional aerobic activities	Leisure-Time Occupational
Calton et al. (2006)	Estimated using *Compendium*; MET values given	Previous 1 Year	Self-Developed Questionnaire; 4 categories (None; Light – Office work; Moderate – Hiking Golf, Light Housework; Heavy – Strenuous Sports and Aerobic Activity)	Leisure-Time

Summary of Breast Cancer Studies

Table 6. Description of study participants – studies in breast cancer analyses

Study	Type	Participants	Time Period
Thune et al. (1997)	Prospective Cohort	25,624 females aged 20 to 54 and free of cancer were invited by the National Health Screening Service in three counties in Norway; The cohort was initially followed between 1974 and 1978, but the second follow-up period of 1977 to 1983 was used as the baseline, as parity and nutritional factors were not initially assessed; Within this cohort, 351 cases were identified over a median follow-up time of 13.7 years; Distribution of race not reported	Followed between 1977 and 1983; Median follow-up time was 13.7 years
Carpenter et al. (1999)	Case-Control	**Cases:** 1,123 White and Hispanic female residents of Los Angeles County aged 55 to 64, born in the US, Canada, or Western Europe; Out of 2,373 cases Identified by the University of Southern California Cancer Surveillance Program (LA county cancer registry), 1,165 cases were initially eligible for the study and 1,123 cases were eventually included. **Controls:** Out of an original 1,169 controls, 904 healthy controls were able to be individually matched to cases on neighborhood, date of birth (within 36 months) and race (White or Hispanic); In-person interviews for each case-control pair were usually conducted by same female interviewer	Cases were diagnosed between March 1, 1987 and December 31, 1989; Controls were selected during same time period

Table 6. Description of study participants – studies in breast cancer analyses

Levi et al. (1999)	Case-Control	**Cases:** 246 females aged 29 to 74 (median age = 56) admitted to the University Hospital of Lausanne in Switzerland; Race distribution not reported **Controls:** 374 females aged 27-74 (median age = 58) admitted to the same hospital for non-cancer and non-gynecological related conditions (usually orthopedic problems); Controls were matched on age, education, age at menarche, parity, age at birth of first child, menopausal status, BMI, family history, and total caloric intake; Interviews and questionnaire were the same for both cases and controls	Cases were diagnosed between January 1993 and August 1998; Controls selected based on hospital admissions during same time period
Rockhill et al. (1999)	Cohort	Among 121,701 females aged 30-55 in 1976 in the Nurses' Health Study, 3,137 breast cancer cases (1,036 premenopausal and 2,101 postmenopausal) were identified; Participants were female registered nurses in the U.S.; Distribution of race not reported	Followed-up every other year from 1980 to 1996; most activity assessed from 1986 to 1996
Moradi et al. (2000)	Case-Control	**Cases:** From the entire native population of females aged 50-74 living in Sweden from October 1993 through March 1995, 2,838 postmenopausal cases without any previous cases were selected among 3,347 total cases that were identified from six Swedish regional cancer registers; Majority of cases were White (specific proportion not reported) **Controls**: Out of a potential 3,455 controls, 3,108 were	Cases were diagnosed between October 1993 and March 1995; Controls were identified from same population during same time period

Table 6. Description of study participants – studies in breast cancer analyses

		randomly selected from the same 5-year age groups as the cases in the consistently updated Swedish register in an attempt to frequency match the expected age distribution of cases on a 1:1 basis; All controls and cases were free of previous cancer and premenopausal controls were excluded; Majority of controls were also White	
Friedenreich et al. (2001)	Case-Control	**Cases:** 1,233 were identified by the Alberta Cancer Registry; Cases were residents of Alberta, Canada, under the age of 80; 92.4% of cases were White **Controls:** 1,237 female controls were identified through random digit dialing and frequency matched to cases on a 1:1 basis; Controls were frequency matched on age (±5 years) and place of residence, and were cancer-free; 94.8% of controls were White	Cases were diagnosed between August 1995 and August 1997; Controls were selected from same population during same time period
Matthews et al. (2001)	Case-Control	**Cases:** 1,459 females aged 25 to 64 who were residents of urban Shanghai, China between August 1996 and March 1998; No prior history of cancer and all completed interviews (out of the 1,602 originally identified by the population-based Shanghai Cancer Registry); All cases were Asian individuals **Controls:** 1,556 females were randomly selected among permanent female residents of urban Shanghai and frequency matched to cases on an approximate 1:1 ratio	Cases were diagnosed between August 1996 and March 1998; Controls were identified from same population during time period; however age-matching of controls was based on

Table 6. Description of study participants – studies in breast cancer analyses

		by age (±5 years) and place of residence; All controls were Asian individuals	age distribution of cases in Shanghai Registry from 1990-1993
Dirx et al. (2001)	Prospective Cohort	62,537 postmenopausal females aged 55-69 in 1986 as part of the Netherlands Cohort Study were included in the study; Among the cohort, 1,208 cases were identified over 7.3 years of follow-up from over 200 municipalities with population cancer registries throughout the country; Majority of females were White (specific proportion not reported)	Individuals were followed from September 1986 to December 1993
McTiernan et al. (2003)	Prospective Cohort	74,171 females (including 10,863 non-White females) aged 50-79 recruited by 40 clinical centers throughout the United States; Out of original cohort of 93,676, females were eligible if postmenopausal, planned to live in clinical center area for at least 3 years, and free of serious health conditions; 1780 breast cancer cases were identified during follow-up; 85% of all study participants were White, while the remaining 15% of females were African-American, Hispanic, Asian/Pacific Islander, and Native American	Followed from October 1993 to December 1998 with a mean follow-up time of 4.7 years
Yang et al. (2003)	Case-Control	**Cases:** 501 Asian-American females aged 25 to 74 living in Los Angeles County; Identified through the Los Angeles County Cancer Surveillance Program that is part	Cases were diagnosed between January 1, 1995 through the end

Table 6. Description of study participants – studies in breast cancer analyses

		of the Surveillance, Epidemiology, and End Results (SEER) program and the statewide California Cancer Registry; All cases were Asian-American **Controls:** 594 Asian-American females living in Los Angeles Country; Controls were frequency matched on an approximate 1:1 ratio for place of residence, Asian ethnicity and age (±5 years); All controls were Asian-American	of 1997; Controls were selected from same time period
Patel et al. (2003; Cohort)	Prospective Cohort	72,608 American postmenopausal females aged 50-74 who were cancer free at the age of enrollment in 1992; Females were drawn from the American Cancer Society Cancer Prevention Study II Nutrition Cohort; 1520 cases were identified over a five-year period; Approximately 97.4% of participants were White, 1.5% were Black, and 1.1% were of another or missing race	Individuals were followed from 1992 until August, 1998
Patel et al. (2003; C-C)	Case-Control	**Cases:** 567 White and Black females aged 35 to 64 living in Los Angeles County with no previous history of breast cancer identified by the University of Southern California Cancer Surveillance Program, the population-based cancer registry for Los Angeles County; Approximately 84% of cases were White and 16% were Black **Controls:** 616 White and Black females selected from the Females' Contraceptive and Reproductive	Cases were diagnosed between March 1, 1995 and May 31, 1998; Controls were selected during the identical time period

Table 6. Description of study participants – studies in breast cancer analyses

		Experiences (CARE) Study in Los Angeles County using random-digit dialing from the same counties as the case patients; Controls reported a mammogram within the previous two years and were frequency matched based on race (White or Black) and age (± 5 years); Approximately 59% of controls were White and 41% were Black	
Colditz et al. (2003)	Cohort	110,468 premenopausal participants of the Nurses Health Study II aged 25 to 42 living within 14 U.S. states without any previous history of cancer other than a nonmelanoma skin cancer; Within this cohort, 849 breast cancer cases over a 10-year follow-up period were included in the present study; Distribution of race not reported	Individuals were followed from 1989 through June 1, 1999
John et al. (2003)	Case-Control	**Cases:** 403 premenopausal cases and 847 postmenopausal cases; Females were Latina, African-American, and White aged 35 to 79, and resided in a five county area in the San Francisco Bay area; Cases were identified by a population-based cancer registry that is part of the Surveillance, Epidemiology, and End Results (SEER) program and the statewide California Cancer Registry; Approximately 41% of cases were Latina, 31% were African-American, and 28% were White **Controls:** 483 premenopausal females and 1065	Cases were diagnosed between April 1, 1995 and April 30, 1998; Controls were selected during the same time period

Table 6. Description of study participants – studies in breast cancer analyses

		postmenopausal females; Resided in the same San Francisco Bay area as cases and were frequency matched 1:1 for African Americans and Whites and 1:1.5 for Latinas; All controls were matched to the age distribution of cases (± 5 years) and were identified through random digit dialing; Approximately 47% were Latina, 26% were African-American, and 26% were White	
Bernstein et al. (2005)	Case-Control	**Cases:** 4538 females (1605 Black and 2933 White) diagnosed with breast cancer between July 1, 1994 and April 30, 1998 in Atlanta, Detroit, Los Angeles, Seattle, and Philadelphia and identified by the Surveillance, Epidemiology and End Results (SEER) cancer registries; Approximately 65% of cases were White and 35% were Black	Cases were identified between July 1, 1994 and April 30, 1998; Controls were selected during the same time span
		Controls: 4649 females (1646 Black and 3033 White) selected via random digit dialing from the same geographic regions as the corresponding case patients; Frequency matched approximately 1:1 to case patients based on geographic site, race, and age (±5 years); Approximately 65% of controls were White and 35% were Black	

Table 7. Time frame of physical activity measured for studies in breast cancer analyses

Study	Type	Time Frame Measured and Quantification of Activity
Thune et al. (1997)	Prospective Cohort	3 to 5 years prior to study (Graded 1 to 4: 1 = sedentary; 2 = ≥4 hours recreational activity; 3 = ≥4 hours Moderate Activity; 4 = ≥4 hours vigorous leisure-time physical activity
Carpenter et al. (1999)	Case-Control	Lifetime (MET-hr/week)
Levi et al. (1999)	Case-Control	Age 15-19; Age 30-39; Age 50-59 (Graded 1 to 3: 1 = < 2 hrs/wk; 2 = 2-4 hrs/wk; 3 = ≥ 5 hrs/wk of leisure-time physical activity)
Rockhill et al. (1999)	Cohort	Assessed 6 Times over a 14-Year Period (<1, 1-1.9, 2-2.9, 3-3.0, 4-6.9, ≥ 7 hrs/week of moderate or vigorous activity
Moradi et al. (2000)	Case-Control	Age 30 up to Study; Age 18-30; Before Age 18 (<1, 1-2, >2 hours/week)
Friedenreich et al. (2001)	Case-Control	Lifetime (MET-hr/week)
Matthews et al. (2001)	Case-Control	10 Years Prior to Study; Age 13-19 (MET-hr/day → MET-hr/week)
Dirx et al. (2001)	Prospective Cohort	Current year - recreational activity (MET scores and minutes/day); Lifetime - sports participation (MET scores and duration of sports in years)
McTiernan et al. (2003)	Prospective Cohort	Current (MET-hr/week); Age 18, 35, 50 (Activity reported dichotomously)
Yang et al. (2003)	Case-Control	Age 10 to reference age = 1 year before diagnosis/interview (MET-hr/week)
Patel et al. (2003; Cohort)	Cohort	Current; At age 40 (MET-hr/week); 10 Years Prior (Graded 'Slight', 'Moderate', and 'Heavy' – Dichotomous)
Patel et al. (2003; C-C)	Case-Control	Lifetime (MET-hr/week); 10 Years after menarche; Age 20-34; 10 Years Prior (<1, 1-4, >4 hours/wk)
Colditz et al. (2003)	Cohort	Assessed 3 Times over a 10-Year Period (MET-hr/week)
John et al. (2003)	Case-Control	Lifetime – from Menarche (MET-hr/week)
Bernstein et al. (2005)	Case-Control	Lifetime (MET-hr/week)

Table 8. Assessment of physical activity – studies in breast cancer analyses

Study	Menopausal Status	Quantification	Exposure Time	PA Assessment Instrumentation	Activity Type
Thune et al. (1997)	Pre and Post Combined	Estimated using *Compendium;* hour values given	Previous 3 to 5 Years	Self-developed questionnaire; Leisure-time activity graded 1 to 4 where 1= sedentary; 2= ≥4 hrs/wk walking, bicycling; 3= ≥4 hours recreational sports; 4= regular, vigorous activity or sports several times a week; Occupational activity coded as 1) sedentary; 2) job with walking; 3) job with lifting and walking; 4) heavy manual labor; For occupational analysis, METs can be estimated based on activity type	Leisure-Time Occupational
Carpenter et al. (1999)	Post	*Compendium*	Lifetime	Self-developed questionnaire; Type and duration (at least 2 hrs/wk of activity) was assessed over the lifetime (from menarche to reference date) and MET-hr/wk categorizations were 0, 0.1-17.59 and ≥17.6; Activity in the previous 10 years before reference	Leisure-Time

Table 8. Assessment of physical activity – studies in breast cancer analyses

				date were also categorized in MET-hrs/wk (0, 0.1-6.9, 7.0-13.9, 14.0-24.4, and ≥24.5); Activities included walking, jogging, field hockey, and aerobics	
Levi et al. (1999)	Pre and Post Combined	Estimated using *Compendium;* hour values given	Lifetime (age 15-19; 30-39 and 50-59)	Self-Developed Questionnaire; Activities throughout lifespan (age 15-19, 30-39, and 50-59) were elicited; Number of hours were reported for leisure-time; specific examples included walking, gardening, and cycling; Cut-offs were <2, 2-4, and ≥ 5 hours per week); Occupational was graded as 1, 2, or 3 ('very tiring' or 'tiring', 'standing' and 'mainly sitting', respectively	Leisure-Time Occupational
Rockhill et al. (1999)	Pre and Post Combined	Estimated using *Compendium;* hour values given	Previous 14 Years	PA Questionnaire from the Nurses Health Study was used; Number of hours of activity each week during for moderate and vigorous activity were reported; Specific mentioned activities included walking, hiking, jogging, running, bicycling, swimming, tennis,	Leisure-Time

Table 8. Assessment of physical activity – studies in breast cancer analyses

				calisthenics, aerobics, and rowing; Vigorous activity included those with a MET value over 6.0	
Moradi et al. (2000)	Post	Estimated using *Compendium;* hour values given	Age 30 to time of study (total of 20 to 44 years)	Self-Developed questionnaire on exercise during three periods: 1) before age 18, 2) age 18-30, and 3) age 30 to time of data collection; 4 Categories: Never, <1 hour per week, 1-2 hours per week, >2 hours per week; Aerobic exercise and sport were specifically mentioned; Occupations were classified as 'very high', 'high', 'moderate', 'light', or 'sedentary', but were not part of any analyses	Leisure-Time Occupational*
Friedenreich et al. (2001)	Pre, Post Stratified	*Compendium*	Lifetime	Self-developed questionnaire separately assessed recreational, occupational, and household activity throughout the lifetime; Frequency, duration were obtained and MET values were assigned to specific activities for leisure-time activities including walking, jogging, running, and	Leisure-Time Occupational Household Total (Leisure-Time plus Occupational plus Household)

Table 8. Assessment of physical activity – studies in breast cancer analyses

				bicycling; MET-hrs/wk categorizations were 0-<6.7, 6.7-<11.8, 11.8-<20.7, and ≥20.7 for leisure-time activity for premenopausal females and 0-<5.1, 5.1-<9.4, 0.4-<16.9, and ≥16.9 MET-hr/wk for postmenopausal females; for occupational activities, intensity was self-reported as 'light', moderate', or 'heavy' and estimated and also estimated as MET-hr/wk	
Matthews et al. (2001)	Pre and Post Combined	*Compendium*	Previous 10 Years	Self-developed questionnaire for leisure-time (walking, cycling, aerobic exercises, sports), occupational ('sitting', 'standing' or 'walking'), and household activities; Leisure-time activity was assessed 10-years prior to entering the study and between age 13 and 19, and was reported in MET-hrs/day (0.01-0.35, 0.36-0.88, 0.89-1.91, >1.91, which can easily be converted to MET-	Leisure-Time Occupational* Household*

Table 8. Assessment of physical activity – studies in breast cancer analyses

				hrs/wk; Occupational activity was reported in average time 'standing or walking' and classified into heavy, medium, light, or non-physical work (not part of analyses)	
Dirx et al. (2001)	Post	Estimated using *Compendium;* MET values given	Current	Self-developed questionnaire assessed baseline recreational activity (e.g. walking, bicycling, various sports); Mean MET scores for recreational activities were provided (<4.00, 4.01-6.00, >6.00 Mean MET score per year); A history of sports participation was also assessed and a MET score was provided; Lifetime occupational activity was categorized as low, moderate, or high activity according to amount of time sitting and estimated energy expenditure in kJ/minute (these were not part of the occupational analysis)	Leisure-Time Occupational*
McTiernan et al. (2003)	Post	*Compendium*	Current	Self-developed questionnaire assessed current moderate and	Leisure-Time

Table 8. Assessment of physical activity – studies in breast cancer analyses

				strenuous physical activity; Specific activities included walking, bicycling, calisthenics, aerobics, dancing, jogging, tennis, and swimming, and MET-hr/wk categorizations were 0, ≤5, 5.1-10, 10.1-20, 20.1-40, >40	
Yang et al. (2003)	Pre and Post Combined	*Compendium*	Lifetime	PA Questionnaire developed by Bernstein et al. (1994) that assessed frequency, duration, and type of activity; Recreational activity was reported in MET-hrs/wk over the lifetime (age 10 to reference age); MET-hr/wk categorizations were ≤3, >3-6, >6-12, >12) Recreational activities included walking and bicycling; Occupational activities were coded into four categories: sedentary, mixed sedentary and moderately active, moderately active, and highly active (not part of the occupational analysis)	Leisure-Time Occupational*
Patel et al. (2003; Cohort)	Post	*Compendium*	Current; At	Self-developed questionnaire assessed baseline physical activity	Leisure-Time

Table 8. Assessment of physical activity – studies in breast cancer analyses

			age 40	over the past year for the following activities: walking, jogging, running, swimming, racquet sports, bicycling, aerobics, calisthenics, and dancing; MET-hrs/wk categorizations were >0-7.0, >7.0-17.5, >17.5-31.5, >31.5-42.0, >42.0	
Patel et al. (2003; C-C)	Pre and Post Combined	*Compendium*	Lifetime	Self-developed questionnaire included the type and average duration per week of activity; Specific activities included walking, jogging, bicycling, aerobics, swimming, sports, and dance; MET-hrs/wk were calculated over the lifetime (>0-3.0, >3.0-8.0, >8.0-16.0, >16.0-32.0, >32.0), as well as for the first 10 years after menarche, ages 20-34, and previous 10 years before reference date	Leisure-Time
Colditz et al. (2003)	Pre	*Compendium*	Previous 10 Years	PA questionnaire from the Nurses Health Study was used and average amount of time spent per week during the previous year for	Leisure-Time

Table 8. Assessment of physical activity – studies in breast cancer analyses

					each of the following activities was recorded; Activities included walking, hiking, jogging, running, bicycling, racquet sports, swimming, calisthenics, and aerobics; Each activity was assigned a MET value and MET-hrs/wk categorizations were <3, 3-8.9, 9-17.9, 18-26.9, and ≥27	
	John et al. (2003)	Pre, Post Stratified	*Compendium*	Lifetime	PA Questionnaire developed by Bernstein et al. (1994) that assessed frequency, duration, and type of activity; Amount of recreational activity over the lifespan were recorded in MET-hrs/wk (≤6.8, 6.9-16.6, ≥16.7); Leisure-time activities included walking and bicycling; occupational activities were recorded as 'mostly sitting', 'mostly standing or walking', 'mostly moderate physical activities', or 'mostly strenuous activities', or 'hard labor'; Household activities included	Leisure-Time Occupational Household Total

Table 8. Assessment of physical activity – studies in breast cancer analyses

				‘scrubbing floors, weeping’, washing windows’ ‘mowing lawn’, other outdoor chores	
Bernstein et al. (2005)	Pre and Post Combined	*Compendium*	Lifetime	Self-developed questionnaire included type and duration of activity in hours; Specific activities included walking, jogging, running, hiking, bicycling, aerobics, swimming, and dancing; Average number of MET-hrs/wk over the lifespan were calculated (≤2.2, 2.3-6.6, 6.7-15.1, ≥15.2)	Leisure-Time

* Cannot be quantified or estimated using the *Compendium*

Summary of Meta-Analyses for Colon Cancer Studies

Table 9 summarizes the four meta-analyses examining the relationship between physical activity and colon cancer risk. Analysis I only includes studies using the *Compendium* to quantify physical activity for males, while Analysis II only includes studies using the *Compendium* for females. Analysis III uses all studies from Analysis I, as well as additional studies with estimated *Compendium* quantification for males, based on total MET value or number of weekly physical activity hours, while Analysis IV includes all studies from Analysis II as well as additional studies with estimated *Compendium* quantification for females.

Table 9. Studies in colon cancer meta-analyses

Analysis	Sex	# Studies	Exposure Time	Quantification
I	Males	3	Previous 1-10 Years	*Compendium*
II	Females	3	Previous 1-10 Years	*Compendium*
III	Males	4	Previous 1-10 Years	*Compendium* or estimated from *Compendium* using provided MET value or number of activity hours
IV	Females	4	Previous 1-10 Years	*Compendium* or estimated from *Compendium* using provided MET value or number of activity hours

Table 10 reports the specific information about the four studies included in Analysis I (males) and Analysis II (females) of colon cancer risk.

Table 10. Analyses I and II – Description of studies included in *Compendium*-quantified colon cancer risk meta-analyses

Study	Year	Study Type	Sex	Age	# M / F Cases	# M / F Controls	Person-Yrs
Giovannucci et al.	1995	Prospective Cohort	M	40-75	200 / -	-	263,554
White et al.	1996	Case-Control	M, F	30-62	251 / 193	233 / 194	-
Martinez et al.	1997	Cohort	F	30-55	- / 161	-	301,168
Tang et al.	1999	Case-Control	M, F	33-81	42 / 27	43 / 27	-

Table 11 reports the specific information about the six studies included in Analysis II of colon cancer risk.

Table 11. Analyses III and IV – Description of studies included in *Compendium*-quantified and estimated colon cancer risk meta-analyses

Study	Year	Study Type	Sex	Age	# M / F Cases	# M / F Controls	Person-Yrs	Estimated MET hrs/wk
Giovannucci et al.	1995	Cohort	M	40-75	200 / -	-	263,554	No
Longnecker et al.	1995	Case-Control	M	31-81	162 / -	261 / -	-	Yes
White et al.	1996	Case-Control	M, F	30-62	251 / 193	233 / 194	-	No
Martinez et al.	1997	Cohort	F	30-55	- / 161	-	301,168	No
Tang et al.	1999	Case-Control	M, F	33-81	42 / 27	43 / 27	-	No
Calton et al.	2006	Cohort	F	61-avg	- / 243	-	270,325	Yes

IV. Summary of Meta-Analyses for Breast Cancer Studies

Table 12 reports specific information for the six meta-analyses that will examine the effects of physical activity on breast cancer risk for pre- and postmenopausal females. The analysis title, number of studies included in each meta-analysis, minimum exposure time to physical activity for each meta-analysis, and physical activity quantification type are included in the table. Analyses I, II, IV and V included only studies utilizing the *Compendium* for physical activity quantification, while Analyses III and VI included additional studies that only provided total MET values or weekly physical activity hours allowing for estimation using the *Compendium*.

Table 12. Studies in breast cancer meta-analyses

Analysis	# Studies	Menopausal Status	Exposure Time	Quantification
I	10	Pre and Post	At least one year of leisure-time physical activity	*Compendium*
II	8	Pre and Post	At least seven years of leisure-time physical activity	*Compendium*
III	15	Pre and Post	At least one year of leisure-time physical activity	*Compendium* or estimated from *Compendium* using provided MET value or number of activity hours
IV	3	Premenopausal	At least 10 years of leisure-time physical activity (up to lifetime)	*Compendium*
V	5	Postmenopausal	Current (1 study) to lifetime (4 studies) leisure-time physical activity	*Compendium*
VI	7	Postmenopausal	Current (2 studies) to lifetime (5 studies) leisure-time physical activity	*Compendium* or estimated from *Compendium* using provided MET value or number of activity hours

Tables 13 through 18 report specific information for each of the breast cancer meta-analyses. The study name, year, and type, menopausal status of the subjects, number of cases, controls (for case-control studies), non-cases, and person-years (cohort studies) were included in the tables for each specific meta-analysis.

Table 13. Analysis I – Description of studies included in *Compendium*-quantified pre- and postmenopausal breast cancer risk Meta-analysis

Study	Year	Study Type	Menopausal Status	# Cases	# Controls or Non-Cases	Person-Yrs
Carpenter et al.	1999	Case-Control	Post	1123	904	-
Friedenreich et al.	2001	Case-Control	Pre, Post Stratified	1233	1237	-
Matthews et al.	2001	Case-Control	Pre and Post Combined	1459	1553	-
McTiernan et al.	2003	Cohort	Post	1316	43635 (NC)	-
Yang et al.	2003	Case-Control	Pre and Post Combined	484	590	-
Patel et al.	2003	Case-Control	Pre and Post Combined	567	616	-
Patel et al.	2003	Cohort	Post	1520	-	316,796
Colditz et al.	2003	Cohort	Pre	849	-	934,100
John et al.	2003	Case-Control	Pre, Post Stratified	1250	1548	-
Bernstein et al.	2005	Case-Control	Pre and Post Combined	4538	4649	-

Table 14. Analysis II – Description of studies included in *Compendium*-quantified pre- and postmenopausal breast cancer risk meta-analysis (quantity of physical activity measured for ≥ 10 years)

Study	Year	Study Type	Menopausal Status	# Cases	# Controls	Person-Yrs
Carpenter et al.	1999	Case-Control	Post	1123	904	-
Friedenreich et al.	2001	Case-Control	Pre, Post Stratified	1233	1237	-
Matthews et al.	2001	Case-Control	Pre and Post Combined	1459	1553	-
Yang et al.	2003	Case-Control	Pre and Post Combined	484	590	-
Patel et al.	2003	Case-Control	Pre and Post Combined	567	616	-
Colditz et al.	2003	Cohort	Pre	849	-	934,100
John et al.	2003	Case-Control	Pre, Post Stratified	1250	1548	-
Bernstein et al.	2005	Case-Control	Pre and Post Combined	4538	4649	-

Table 15. Analysis III – Description of studies included in *Compendium*-quantified and estimated pre- and postmenopausal breast cancer risk meta-analysis

Study	Year	Study Type	Menopausal Status	# Cases	# Controls or Non-Cases (NC)	Person-Yrs	Estimated MET hrs/wk
Thune et al.	1997	Cohort	Pre and Post Combined	351	25259 (NC)	-	Yes
Carpenter et al.	1999	Case-Control	Post	1123	904	-	No
Levi et al.	1999	Case-Control	Pre and Post Combined	246	371		Yes
Rockhill et al.	1999	Cohort	Pre and Post Combined	3137	-	1,193,235	Yes
Moradi et al.	2000	Case-Control	Post	2534	2630	-	Yes
Friedenreich et al.	2001	Case-Control	Pre, Post Stratified	1233	1237	-	No
Matthews et al.	2001	Case-Control	Pre and Post Combined	1459	1553	-	No
Dirx et al.	2001	Cohort	Post	428	-	3925	Yes
McTiernan et al.	2003	Cohort	Post	1316	43635 (NC)	-	
Yang et al.	2003	Case-Control	Pre and Post Combined	484	590	-	No
Patel et al.	2003	Case-Control	Pre and Post Combined	567	616	-	No
Patel et al.	2003	Cohort	Post	1520	-	316,796	No
Colditz et al.	2003	Cohort	Pre	849	-	934,100	No
John et al.	2003	Case-Control	Pre, Post Stratified	1250	1548	-	No
Bernstein et al.	2005	Case-Control	Pre and Post Combined	4538	4649	-	No

Table 16. Analysis IV – Description of studies included in *Compendium*-quantified premenopausal breast cancer risk meta-analysis

Study	Year	Study Type	# Cases	# Controls	Person-Yrs
Friedenreich et al.	2001	Case-Control	462	475	-
Colditz et al.	2003	Cohort	849	-	934,100
John et al.	2003	Case-Control	403	483	-

Table 17. Analysis V – Description of studies included in *Compendium*-quantified postmenopausal breast cancer risk meta-analysis

Study	Year	Study Type	# Cases	# Controls or Non-Cases (NC)	Person-Yrs
Carpenter et al.	1999	Case-Control	1123	904	-
Friedenreich et al.	2001	Case-Control	771	762	-
McTiernan et al.	2003	Cohort	1316	43635 (NC)	-
Patel et al.	2003	Cohort	1520	-	316,796
John et al.	2003	Case-Control	847	1065	-

Table 18. Analysis VI – Description of studies included in *Compendium*-quantified and estimated postmenopausal breast cancer risk meta-analysis

Study	Year	Study Type	# Cases	# Controls or Non-Cases	Person-Yrs	Estimated MET hrs/wk
Carpenter et al.	1999	Case-Control	1123	904	-	No
Moradi et al.	2000	Case-Control	2534	2630	-	Yes
Friedenreich et al.	2001	Case-Control	771	762	-	No
Dirx et al.	2001	Cohort	428	-	3925	Yes
McTiernan et al.	2003	Case-Control	1316	43635 (NC)	-	No
Patel et al.	2003	Cohort	1520	-	316,796	No
John et al.	2003	Case-Control	847	1065	-	No

Table 19 details the relationship between occupational activity and breast cancer risk, which were not able to be included in any meta-analyses due to a lack of utilization of the *Compendium*

Table 19. Description of studies of occupational physical activity and breast cancer risk*

Study	Year	Study Type	Menopausal Status	# Cases	# Controls or Non-Cases	Person-Yrs	Estimated MET hrs/wk
Thune et al.	1997	Cohort	Pre, Post Stratified	350	25192 (NC)	-	Yes
Levi et al.	1999	Case-Control	Pre and Post Combined	181	260	-	Yes
Friedenreich et al.	2001	Case-Control	Pre, Post Stratified	1233	1237	-	No
Matthews et al.	2001	Case-Control	Pre and Post Combined	1440	1534	-	No
Kruk et al.**	2003	Case-Control	Pre and Post Combined	257	565	-	Yes

* It was determined that too much heterogeneity in the quantification of physical activity existed among the five studies to complete an appropriate and meaningful meta-analysis using the studies included in Table 19
** The Kruk et al. study only appears in Table 19 and was not part of any analysis because the study only assessed the relationship between occupational activity and breast cancer risk

Chapter III

Results

Overview of Results

The first portion of this chapter discusses the results of the meta-analyses of the relationship between leisure-time physical activity and the risk of colon and breast cancer. There are four meta-analyses of the effect of leisure-time physical activity on colon cancer risk. Analyses I and II report the effect of physical activity on the colon cancer risk of males and females, respectively, using only studies that quantified physical activity using the *Compendium of Physical Activities.* Analyses III and IV report the effect of physical activity on the risk of colon cancer among males and females, respectively, using studies that quantified and estimated physical activity in MET hours-per-week using the *Compendium*.

There are six meta-analyses of the effect of leisure-time physical activity on breast cancer risk. Analysis I reports the effect of physical activity on the risk of breast cancer among pre- and postmenopausal females combined using only studies with *Compendium*-quantified physical activity. Analysis II reports the effect of physical activity on the risk of breast cancer for pre- and postmenopausal females combined, including only studies with *Compendium*-quantified activity that was assessed for a time

period of ten years or longer. Analysis III reports the effect of physical activity on breast cancer risk among pre- and postmenopausal females combined, using studies with both *Compendium*-quantified and estimated amounts of physical activity. Analysis IV reports the effect of physical activity on breast cancer risk among premenopausal females, using only studies with *Compendium*-quantified activity. Analysis V examines the effect of physical activity on breast cancer risk among postmenopausal females, using only studies with *Compendium*-quantified activity. Finally, Analysis VI reports the effect of physical activity on breast cancer risk among postmenopausal females, including studies with both *Compendium*-quantified and estimated activity amounts.

The potential impact of confounding factors on results was assessed by calculating the percentage difference between the multivariate-adjusted effect measures in the original studies and the unadjusted effect measures used in the present meta-analyses, to determine if there was a bias in the reported results, introduced by not using age-adjusted or multivariate-adjusted effect measures for the individual studies in the meta-analyses.

Results for Colon Cancer Analyses

The relationship between physical activity and colon cancer was assessed for males and females in four meta-analyses, titled Analysis I through Analysis IV. For both sexes, moderately and highly active individuals were compared to the more sedentary individuals in the low activity reference group. Each unadjusted effect measure, confidence interval, log of the effect measure, and standard error calculations for the individual studies included in the colon cancer meta-analyses are included in Appendix I.

Additionally, calculating the percent-difference between the adjusted effect measures in the original studies and the unadjusted effect measures in the present analyses assessed the effect of confounding on the relationship between physical activity and colon cancer.

Analyses of *Compendium*-Quantified Studies (Males and Females)

Analysis I assessed colon cancer risk among moderately and highly active males versus low activity males in studies quantifying physical activity using the *Compendium of Physical Activities*. Three studies (Giovannucci et al., 1995; White et al., 1996; Tang et al., 1999) were included in this meta-analysis. This analysis included 202 cases, 108 controls, and 51,660 person-years in the low activity group; 183 cases, 101 controls, and 104,939 person-years in the moderate activity group; and the high activity group included 111 cases, 67 controls, and 106,955 person-years. For moderately active males, the unadjusted effect measure for the Giovannucci et al. (1995) study was 0.788 (95% CI = 0.562-1.103), and the weight of the study for the meta-analysis was 47.37%. The White et al. (1996) study measure was 0.606 (95% CI = 0.405-0.906), with a weight of 43.70%, while the Tang et al. (1999) effect measure was 4.286 (95% CI = 0.854-21.506) with a study weight of 8.92%. There was no statistically significant difference between the moderate and low activity groups. Additionally, there was some evidence of heterogeneity among these studies (χ^2 test for heterogeneity = 5.63, df = 2, $p = 0.060$), although the p-value for the test of heterogeneity did not reach significance based on the prespecified alpha level of .05. The fixed effects pooled estimate was 0.740 (95% CI = 0.573-0.955), $p = 0.021$, while the DerSimonian and Laird (D+L) random effects pooled

estimate for this meta-analysis was 0.817 (95% CI = 0.484-1.379, $p = 0.449$). The random effects results are displayed in Figure 1 below.

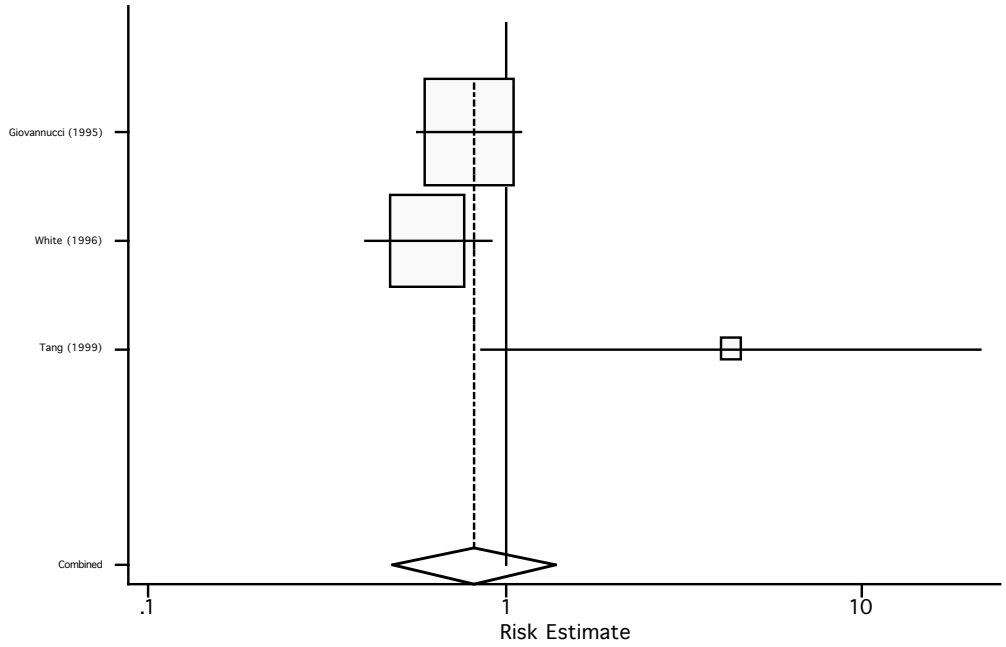


Figure 1. Meta-analysis of colon cancer risk among moderate versus low activity males in *Compendium* quantified studies in analysis I

A non-statistically significant difference ($p = 0.449$) between the moderate and low activity groups was present.

Table 20. Colon cancer risk among moderate versus low activity males in *Compendium* quantified studies in analysis I

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Giovannucci (1995)	0.788	0.562-1.103	47.37		
White (1996)	0.606	0.405-0.906	43.70		
Tang (1999)	4.286	0.854-21.506	8.92		
D+L Pooled Effect Size	**0.817**	**0.484-1.379**	**100.00**	**-0.757**	**0.449**

Heterogeneity $\chi^2 = 5.63$ (d.f. = 2) $p = 0.060$
Estimate of between-study variance $\tau^2 = 0.1208$

For the high activity group, the effect measure from Giovannucci et al. (1995) was 0.527 (95% CI = 0.365-0.760), with a study weight of 51.19%, while White et al. (1996) had a effect measure of 0.664 (95% CI = 0.408-1.079), with a weight of 38.89%. Tang et al. (1999) reported a effect measure of 0.202 (95% CI = 0.060-0.682), with a weight of 9.93%. The high activity group effect measure was statistically significantly lower than the estimate for the low activity group, and no statistically significant heterogeneity was reported for this analysis ($p = 0.200$). The fixed effects pooled estimate was 0.541 (95% CI = 0.407-0.719), $p < 0.001$ while the D+L random effects pooled estimate was 0.524 (95% CI = 0.348-0.788), $p = 0.002$. The results from the random effects method are displayed in Figure 2 below.

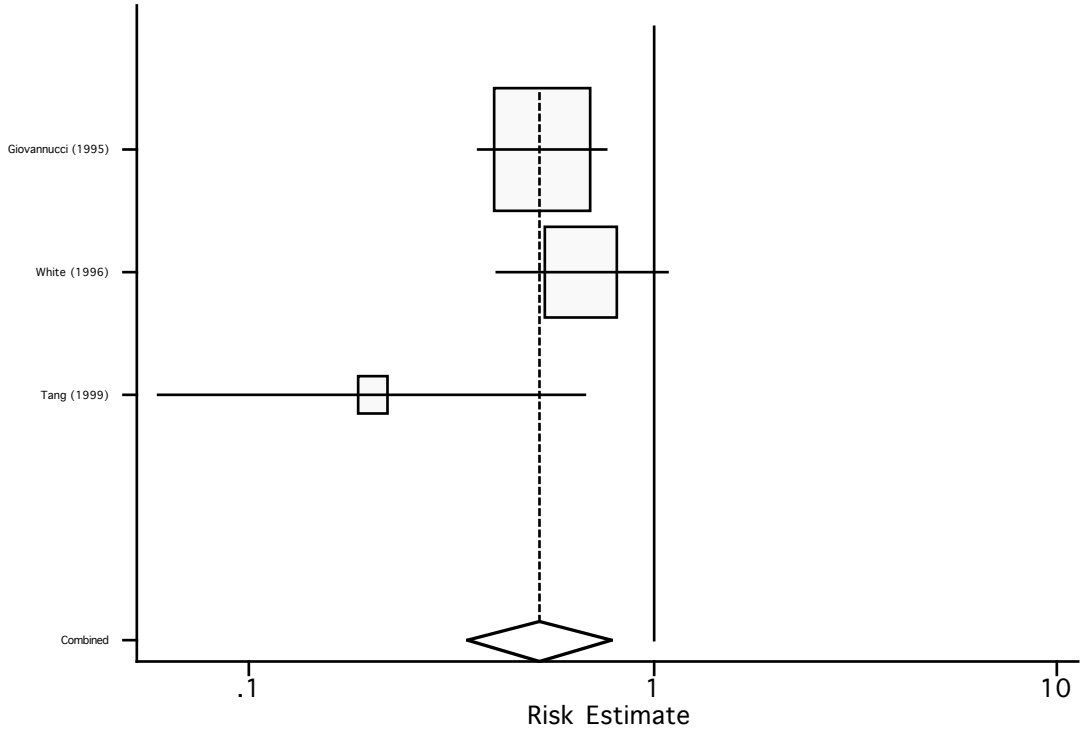


Figure 2. Meta-analysis of colon cancer risk among high versus low activity males in *Compendium* quantified studies in Analysis I

A statistically significant difference ($p = .002$) between the high and low activity groups was present.

Table 21. Colon cancer risk among high versus low activity males in *Compendium* quantified studies in Analysis I

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Giovannucci (1995)	0.527	0.365-0.760	51.19		
White (1996)	0.664	0.408-1.079	38.89		
Tang (1999)	0.202	0.060-0.682	9.93		
D+L Pooled Effect Size	**0.524**	**0.348-0.788**	**100.00**	**-3.107**	**0.002**

Heterogeneity $\chi^2 = 3.22$ (d.f. = 2) $p = 0.200$
Estimate of between-study variance $\tau^2 = 0.0497$

Colon cancer risk among moderately and highly active females in *Compendium* quantified studies was assessed in Analysis II. Three studies (White et al. (1996), Martinez et al. (1997), and Tang et al. (1999) were included in this analysis. This analysis included 175 cases, 97 controls, and 115,147 person-years in the low activity group; 149 cases, 81 controls, and 127,204 person-years in the moderate activity group; and 57 cases, 43 controls, and 58,817 person-years in the high activity group. For the moderately active group, the effect measure for the White et al. (1996) study was 0.990 (95% CI = 0.640-1.532), with a study weight of 35.90%. The effect measure for Martinez et al. (1997) was 0.806 (95% CI = 0.577-1.126), with a weight of 61.24%, while the estimate for Tang et al. (1999) was 0.941 (95% CI = 0.201-4.412), with a weight of 2.87%. Both the fixed effects and D+L random effects pooled estimate for this meta-analysis were 0.872 (95% CI = 0.671-1.132), $p = 0.760$). These results are displayed in Figure 3.

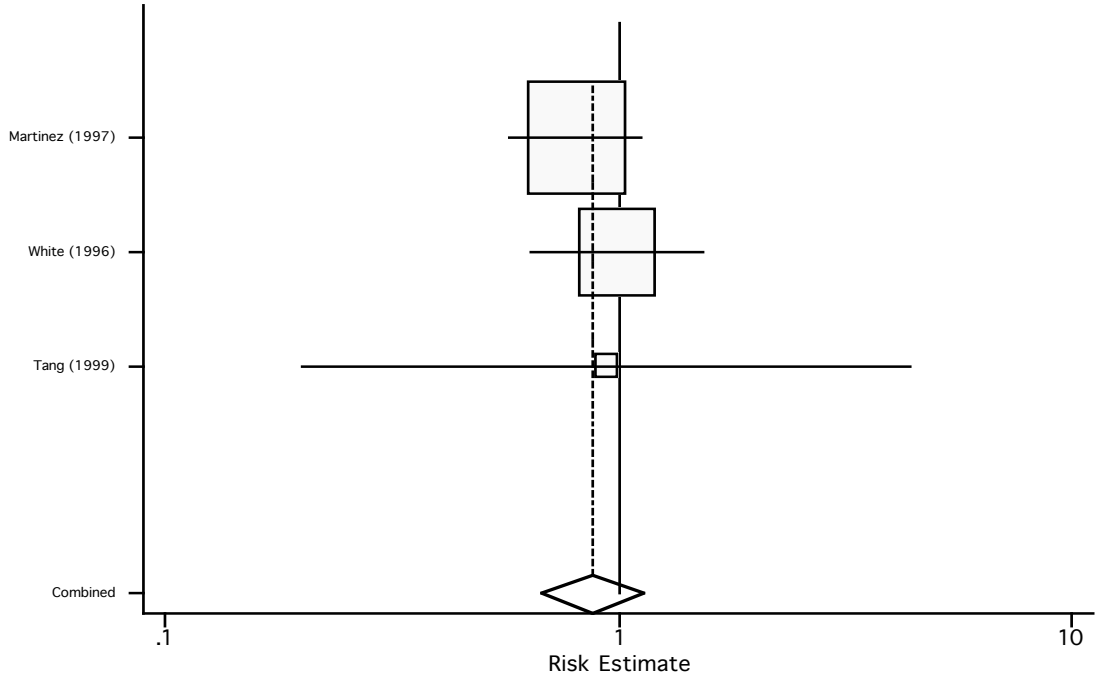


Figure 3. Meta-analysis of colon cancer risk among moderate versus low activity females in *Compendium* quantified studies in Analysis II

A non-statistically significant difference ($p = 0.760$) between the moderate and low activity groups was present.

Table 22. Colon cancer risk among moderate versus low activity females in *Compendium* quantified studies in Analysis II

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
White (1996)	0.990	0.640-1.532	35.90		
Martinez (1997)	0.806	0.577-1.126	61.24		
Tang (1999)	0.941	0.201-4.412	2.87		
D+L Pooled Effect Size	**0.872**	**0.671-1.132**	**100.00**	**-1.030**	**0.303**

Heterogeneity $\chi^2 = 0.55$ (d.f. = 2) $p = 0.760$
Estimate of between-study variance $\tau^2 = 0.0000$

There was no statistically significant difference between the effect measures of the moderate and low activity females, and no statistically significant heterogeneity existed among the studies ($p = 0.760$).

Among highly active females, the effect measure for White et al. (1996) was 0.741 (95% CI = 0.415-1.324), with a study weight of 36.55%, while Martinez et al. (1997) had a effect measure of 0.617 (95% CI = 0.386-0.986), with a weight of 56.02%. The effect measure for Tang et al. (1999) was 0.807 (95% CI = 0.223-2.920) with a weight of 7.43%. Both the fixed effects and D+L random effects pooled estimate for this meta-analysis were 0.673 (95% CI = 0.474-0.956; $p = 0.027$). These results are displayed in Figure 4 below. No statistically significant heterogeneity existed among the studies ($p = 0.854$).

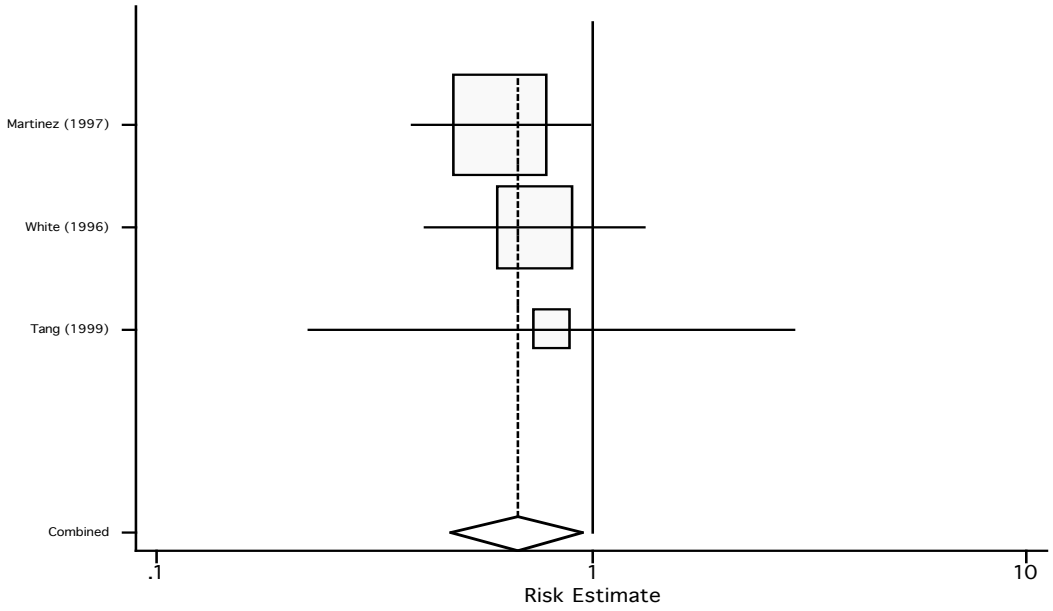


Figure 4. Meta-analysis of colon cancer risk among high versus low activity females in *Compendium* quantified studies in Analysis II

A statistically significant difference ($p = 0.027$) between the high and low activity groups was present.

Table 23. Colon cancer risk among high versus low activity females in *Compendium* quantified studies in Analysis II

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
White (1996)	0.741	0.415-1.324	36.55		
Martinez (1997)	0.617	0.386-0.986	56.02		
Tang (1999)	0.807	0.223-2.920	7.43		
D+L Pooled Effect Size	**0.673**	**0.474-0.956**	**100.00**	**-2.213**	**0.027**

Heterogeneity $\chi^2 = 0.32$ (d.f. = 2) $p = 0.854$
Estimate of between-study variance $\tau^2 = 0.0000$

Analyses of *Compendium*-Quantified and Estimated Studies (Males and Females)

Analysis III included studies of males in which physical activity could be quantified or estimated using the *Compendium.* Four studies (Giovannucci et al. (1995), Longnecker et al. (1995), White et al. (1996), Tang et al. (1999) were included in this analysis. A total of 306 cases, 249 controls, and 51,660 person-years were in the low activity group; 191 cases, 120 controls, and 104,939 person-years in the moderate activity group; and 161 cases, 168 controls, and 106,955 person-years in the high activity group. For moderately active males, the effect measures and confidence intervals for Giovannucci et al. (1995), White et al. (1996), and Tang et al. (1999) are reported above in the Analysis I section, while the study weights of the three studies for Analysis III were 41.01%, 36.75%, and 5.91%, respectively. The effect measure for Longnecker et al. (1995) was 0.571 (95% CI = 0.241=1.355), with a study weight of 16.33%. No statistically significant difference existed between the moderate and low activity group for males in Analysis III. Additionally, no statistically significant heterogeneity was reported within Analysis III ($p = 0.114$). The fixed effects pooled estimate was 0.724 (95% = 0.567-0.925), $p = 0.010$, while the D+L pooled estimate for this meta-analysis

was 0.750 (95% CI = 0.496-1.135), $p = 0.174$. These results are displayed in Figure 5 on the next page.

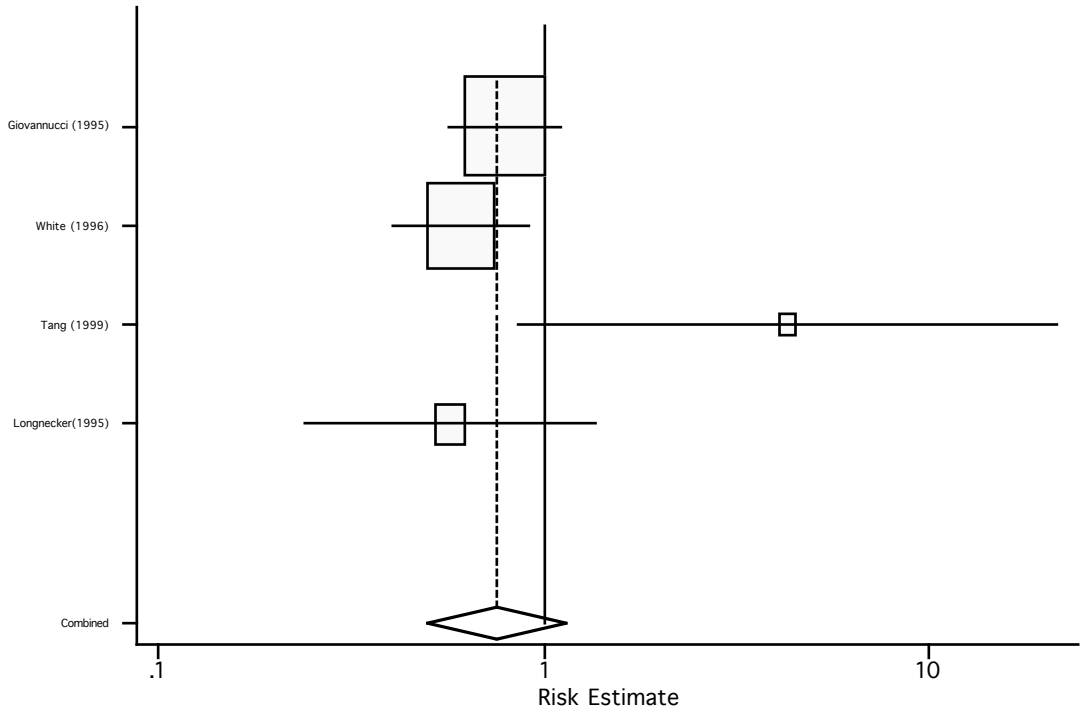


Figure 5. Meta-analysis of colon cancer risk among moderate versus low activity males in *Compendium* quantified and estimated studies in Analysis III

A non-statistically significant difference ($p = 0.174$) between the moderate and low activity groups was present.

Table 24. Colon cancer risk among moderate versus low activity males in *Compendium* quantified and estimated studies in Analysis III

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Giovannucci (1995)	0.788	0.562-1.103	41.01		
Longnecker (1995)	0.571	0.241-1.355	16.33		
White (1996)	0.606	0.405-0.906	36.75		
Tang (1999)	4.286	0.854-21.506	5.91		
D+L Pooled Effect Size	**0.750**	**0.496-1.135**	**100.00**	**-1.360**	**0.174**

Heterogeneity $\chi^2 = 5.95$ (d.f. = 3) $p = 0.114$
Estimate of between-study variance $\tau^2 = 0.0794$

For the male high activity group, the effect measures and confidence intervals for Giovannucci et al. (1995), White et al. (1996), and Tang et al. (1999) are reported above in the Analysis I section, while the study weights for the three aforementioned studies are 38.08%, 25.52%, and 5.10%, respectively. Longnecker et al. (1995) reported a effect measure of 0.671 (95% CI = 0.440-1.025) and a study weight of 31.31% for the meta-analysis. A statistically significant difference between the high and low activity groups existed among males, and no statistically significant heterogeneity was reported (p = 0.272). The fixed effects pooled estimate was 0.579 (95% CI = 0.457-0.733), $p < 0.001$, while the D+L random effects pooled estimate was 0.574 (95% CI = 0.433-0.761), $p < 0.001$). These results are displayed in Figure 6 below.

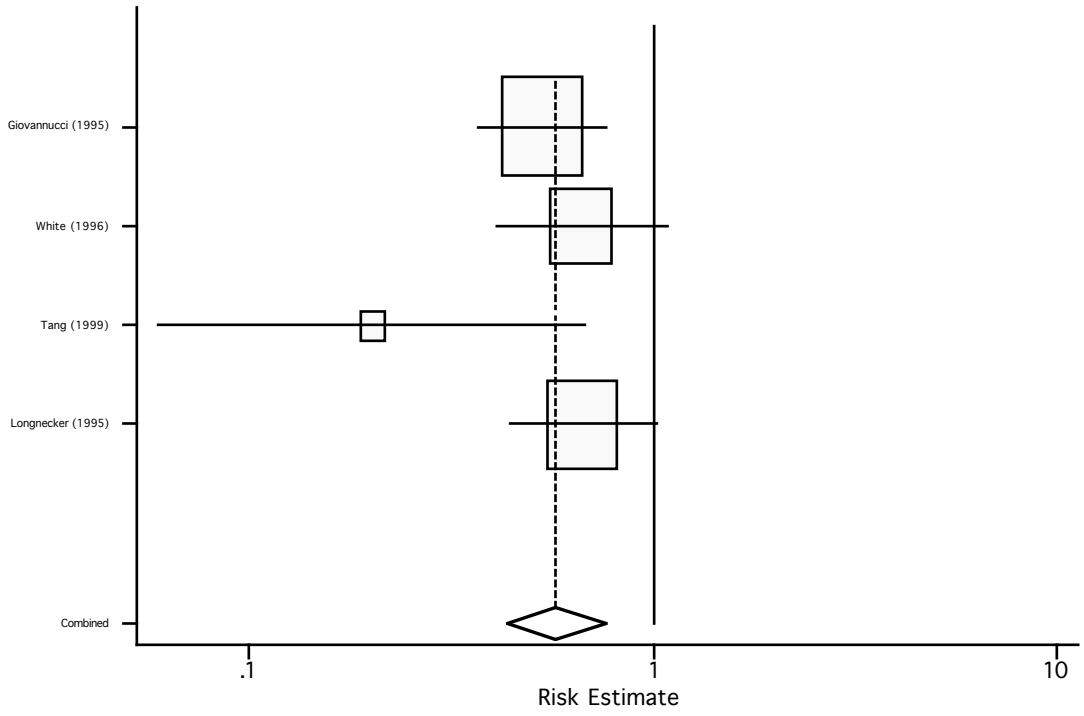


Figure 6. Meta-analysis of colon cancer risk among high versus low activity males in *Compendium* quantified and estimated studies in Analysis III

A statistically significant difference ($p < 0.001$) between the high and low activity groups was present.

Table 25. Colon cancer risk among high versus low activity males in *Compendium* quantified and estimated studies in Analysis III

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Giovannucci (1995)	0.527	0.365-0.760	38.08		
Longnecker (1995)	0.671	0.440-1.025	31.31		
White (1996)	0.664	0.408-1.079	25.52		
Tang (1999)	0.202	0.060-0.682	5.10		
D+L Pooled Effect Size	**0.574**	**0.433-0.761**	**100.00**	**-3.860**	**<0.001**

Heterogeneity $\chi^2 = 3.90$ (d.f. = 3) $p = 0.272$
Estimate of between-study variance $\tau^2 = 0.0195$

Colon cancer risk among moderately and highly active females in *Compendium* quantified and estimated studies were assessed in Analysis IV. A total of four studies (White et al. (1996), Martinez et al. (1997), Tang et al. (1999), and Calton (2006) were included in this meta-analysis. A total of 334 cases, 97 controls, and 280,216 person-years comprised the low activity group; 183 cases, 81 controls, and 177,935 person-years were included in the moderate activity group; and 107 cases, 43 controls, and 113,342 person-years were included in the high activity group. For moderately active females, the effect measures and confidence intervals for the White et al. (1996), Martinez et al. (1997), and Tang et al. (1999) studies are reported above in the Analysis II section. The weights for each of those three studies in Analysis IV are 40.86%, 23.95%, and 1.91%, respectively. The effect measure for Calton et al. (2006) was 0.696 (95% CI = 0.480-1.008), with a study weight of 33.28%. A slight, but non-statistically significant difference existed between the moderate and low activity groups and there was no evidence of statistically significant heterogeneity in this analysis ($p = 0.683$). Both the fixed effects and random effects D+L pooled estimate for this meta-analysis were 0.809

(0.653-1.001), $p = .051$, as the estimate of between-study variance was zero ($\tau^2 = 0$).

These results are reported in Figure 7 and Table 26 below.

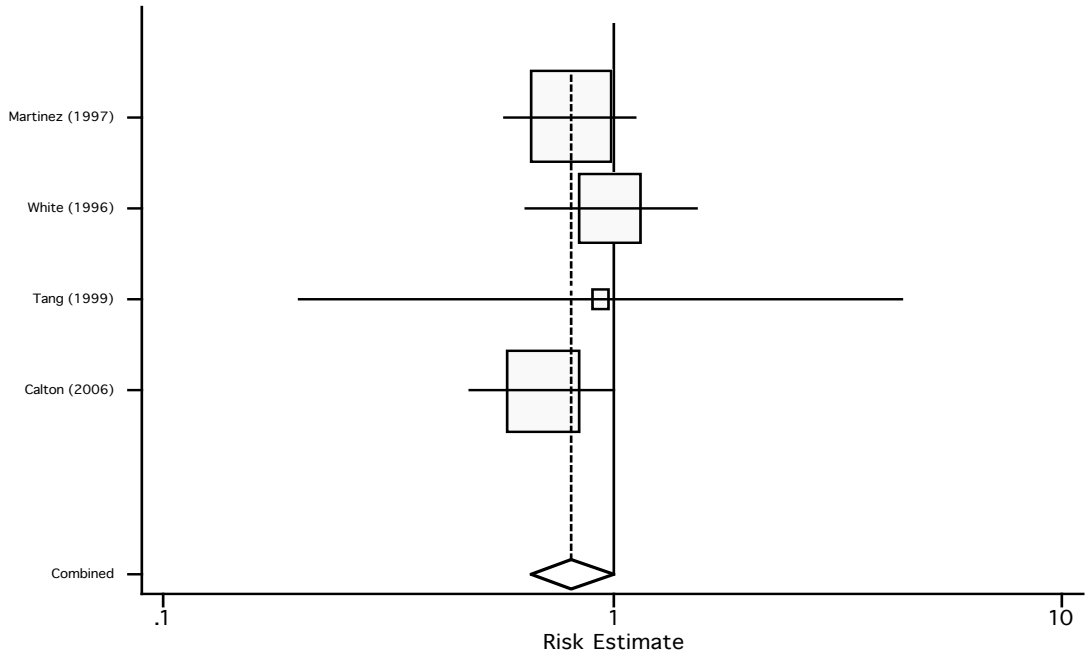


Figure 7. Meta-analysis of colon cancer risk among moderate versus low activity females in *Compendium* quantified and estimated studies in Analysis IV

A non-statistically significant difference ($p = 0.051$) between the moderate and low activity groups was present.

Table 26. Colon cancer risk among moderate versus low activity females in *Compendium* quantified and estimated studies in Analysis IV

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
White (1996)	0.806	0.577-1.126	40.86		
Martinez (1997)	0.990	0.640-1.532	23.95		
Tang (1999)	0.941	0.201-4.412	1.91		
Calton (2006)	0.696	0.480-1.008	33.28		
D+L Pooled Effect Size	**0.809**	**0.653-1.001**	**100.00**	**-1.949**	**0.051**

Heterogeneity $\chi^2 = 1.50$ (d.f. = 3) $p = 0.683$
Estimate of between-study variance $\tau^2 = 0.0000$

Among highly active females, the effect measures and confidence intervals for White et al. (1996), Martinez et al. (1997), and Tang et al. (1999) were included above in the section reporting Analysis II results. The aforementioned three studies had study weights of 16.47%, 25.25%, and 3.35% for Analysis IV. The effect measure for Calton et al. (2006) was 0.952 (0.693-1.308) and the study weight of 54.93%. A non-statistically significant difference existed between the effect measures of the high and low activity groups among females in Analysis IV, and there was no statistically significant heterogeneity in this analysis ($p = 0.497$). Both the fixed effects and random effects D+L pooled estimate were the same for this meta-analysis (Pooled Effect Measure = 0.814 (95% CI = 0.643-1.030), $p = 0.087$) because the estimate of between-study variance was zero ($\tau^2 = 0$). These results are displayed in Figure 8 and Table 27 below.

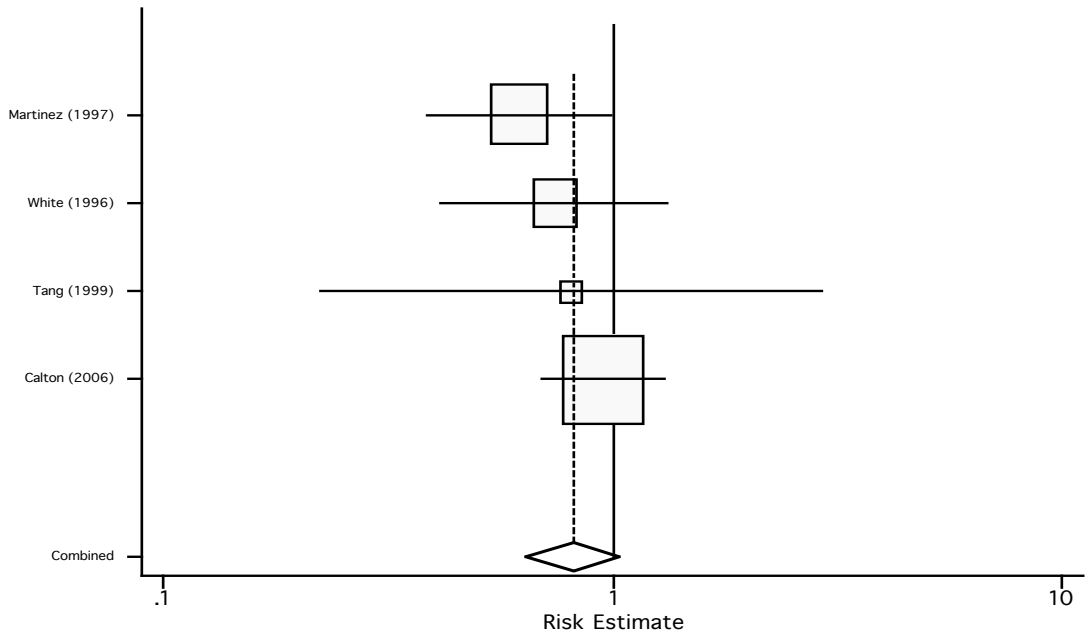


Figure 8. Meta-analysis of colon cancer risk among high versus low activity females in *Compendium* quantified and estimated studies in Analysis IV

A non-statistically significant difference ($p = 0.497$) between the high and low activity groups was present.

Table 27. Colon cancer risk among high versus low activity females in *Compendium* quantified and estimated studies in Analysis IV

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
White (1996)	0.741	0.415-1.324	25.25		
Martinez (1997)	0.617	0.386-0.986	16.47		
Tang (1999)	0.807	0.223-2.920	3.35		
Calton (2006)	0.952	0.693-1.308	54.93		
D+L Pooled Effect Size	**0.814**	**0.643-1.030**	**100.00**	**-1.711**	**0.087**

Heterogeneity $\chi^2 = 2.38$ (d.f. = 3) $p = 0.497$
Estimate of between-study variance $\tau^2 = 0.0000$

Results for Breast Cancer Analyses

The relationship between physical activity and breast cancer risk was assessed for pre- and postmenopausal females combined, premenopausal females, and postmenopausal females in six meta-analyses, titled Analysis I through Analysis VI. Unadjusted effect measures, confidence intervals, log of the effect measures, and standard errors for the original studies were calculated and included in Appendix II. For all females, moderately and highly active individuals were compared to the more sedentary low activity reference group. Additionally, calculating the percent-difference between the adjusted effect measures in the original studies and the unadjusted effect measures in the present analyses assessed the effect of confounding on the relationship between physical activity and breast cancer. The effects of confounding are reported later in this chapter.

Analysis I assessed breast cancer risk among moderately and highly active pre- and postmenopausal females combined in studies quantifying physical activity using the *Compendium of Physical Activities*. Ten studies (Carpenter et al., 1999; Friedenreich et

al., 2001; Matthews et al., 2001; McTiernan et al., 2003; Yang et al., 2003; Patel et al., 2003; Patel et al., 2003; Colditz et al., 2003; John et al., 2003; Bernstein et al., 2005) were included in this random effects meta-analysis. This analysis included 7889 cases, 5,972 controls, 23,826 non-cases, and 415,128 person-years in the low activity group; 3706 cases, 2,555 controls, 29,200 non-cases, and 328,211 person-years in the moderate group; and 2,947 cases, 2,192 controls, 18,576 non-cases, and 462,641 person-years in the high activity group.

For moderately active females in Analysis I, the unadjusted effect measure for the Carpenter et al. (1999) study was 1.043 (95% CI = 0.773-1.406), and the weight of the study for the meta-analysis was 4%. The Friedenreich et al. (2001) study estimate was 0.867 (95% CI = 0.634-1.185), with a weight of 3.70% for premenopausal females and 0.852 (95% CI = 0.669-1.086), with a weight of 5.81% for postmenopausal females. Matthews et al. (2001) had a pooled effect measure of 0.738 (95% CI = 0.538-1.014) and study weight of 3.61%, while McTiernan et al. (2003) had an estimate of 0.996 (95% CI = 0.894-1.109) and weight of 19.03%.

The pooled effect measure for Yang et al. (2003) was 0.640 (95% CI = 0.469-0.873) with a 3.73% weight, while Colditz et al. (2003) had a effect measure of 0.927 (95% CI = 0.775-1.109) and weight of 9.58%. Patel et al. (2003) published a cohort and a case-control study examining the relationship between *Compendium*-quantified physical activity and breast cancer risk. The cohort study had a effect measure of 0.924 (95% CI = 0.818-1.044) and study weight of 16.49%, while the case-control study had a effect measure of 0.987 (95% CI = 0.726-1.341) and study weight of 3.82%. Similar to the Friedenreich et al. (2001) study, John et al. (2003) examined pre- and postmenopausal

females separately. The effect measure and weight for the premenopausal females were 0.938 (95% CI = 0.687-1.281) and 3.71%, while the postmenopausal effect measure was 0.787 (95% CI = 0.634-0.977) and weight was 7.05%. Most recently, the effect measure for Bernstein et al. (2005) was 0.982 (95% CI = 0.884-1.092), with a study weight of 19.46%.

The overall D+L random effects pooled estimate for moderate versus low active females in Analysis I was 0.919 (95% CI = 0.863-0.978); $p = 0.008$, and a statistically significant difference existed between the effect measures of the two groups. No statistically significant heterogeneity existed among the studies in this analysis ($p = 0.240$). These results are reported in Figure 9 and the Stata output table below.

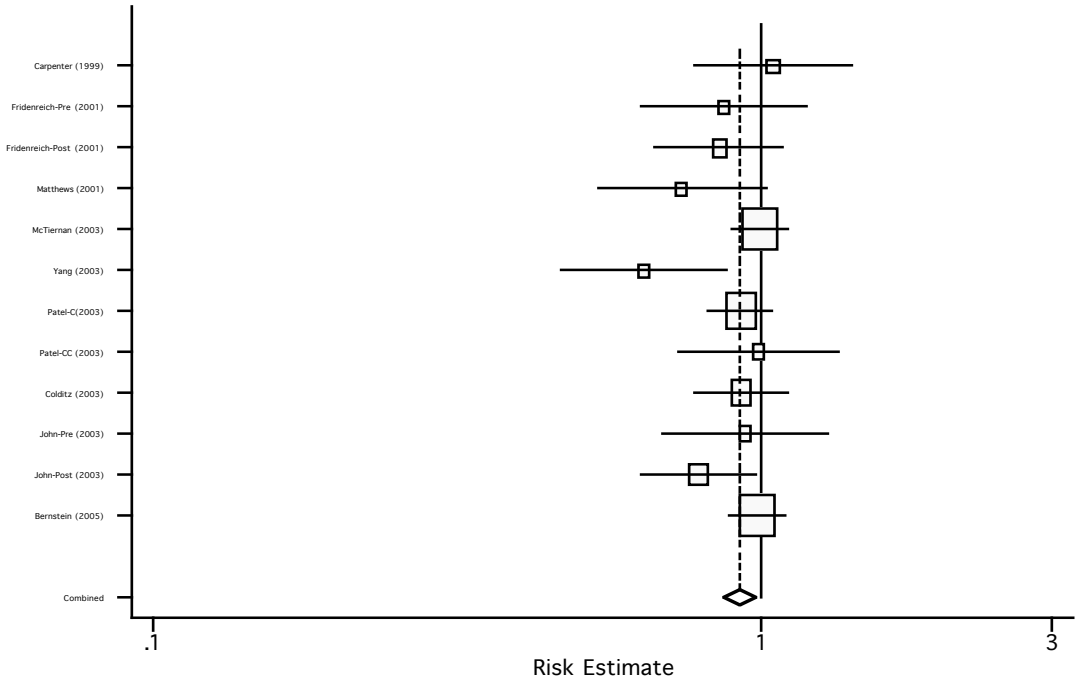


Figure 9. Meta-analysis of breast cancer risk among moderate versus low activity pre- and postmenopausal females combined in *Compendium* quantified studies in Analysis I

A statistically significant difference ($p = 0.008$) between the moderate and low activity groups was present.

Table 28. Breast cancer risk among moderate versus low activity pre- and postmenopausal females combined in *Compendium* quantified studies in Analysis I

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	1.043	0.773-1.406	4.00		
Friedenreich-Pre (2001)	0.867	0.634-1.185	3.70		
Friedenreich-Post (2001)	0.852	0.669-1.086	5.81		
Matthews (2001)	0.738	0.538-1.014	3.61		
McTiernan (2003)	0.996	0.894-1.109	19.03		
Yang (2003)	0.640	0.469-0.873	3.73		
Patel-C (2003)	0.924	0.818-1.044	16.49		
Patel-CC (2003)	0.987	0.726-1.341	3.82		
Colditz (2003)	0.927	0.775-1.109	9.58		
John-Pre (2003)	0.938	0.687-1.281	3.71		
John-Post (2003)	0.787	0.634-0.977	7.05		
Bernstein (2005)	0.982	0.884-0.977	19.46		
D+L Pooled Effect Size	**0.919**	**0.863-0.978**	**100.00**	**2.65**	**0.008**

Heterogeneity $\chi^2 = 13.88$ (d.f. = 11) $p = 0.240$
Estimate of between-study variance $\tau^2 = 0.0024$

For highly active females, the effect measure for Carpenter et al. (2001) was 0.702 (95% CI = 0.518-0.952), with a study weight of 7.09%. Friedenreich et al. (2001) examined pre- and postmenopausal separately and had an estimate of 1.000 (95% CI = 0.700-1.429) and weight of 6.11% for premenopausal females, and an estimate of 0.906 (95% CI = 0.685-1.199) and weight of 7.58% for postmenopausal females. The effect measure for Matthews et al. (2001) was 0.480 (95% CI = 0.336-0.687), with a study weight of 6.09%, while the estimate for McTiernan et al. (2003) was 1.017 (95% CI = 0.901-1.145) and larger study weight of 11.02%. The effect measure for Yang et al. (2003) was 0.544 (95% CI = 0.398-0.744) with a 6.92% study weight, while Colditz et al. (2003) had an estimate of 0.956 (95% CI = 0.820-1.115) and weight of 10.77%. The pooled effect measure from the cohort study of Patel et al. (2003) was 0.882 (95% CI = 0.771-1.008) with a study weight of 10.77%, while the effect measure for the case-

control study was higher (Pooled Effect Measure = 1.110, 95% CI = 0.826-1.464), with a smaller weight of 7.46%. John et al. (2003) reported separate estimates and weights for pre- and postmenopausal females (Pooled Effect Measure = 0.553, 95% CI = 0.394-0.775 and study weight of 6.46%; Pooled Effect Measure = 0.678, 95% CI = 0.544-0.847 and study weight of 8.85%, respectively). The pooled effect measure for Bernstein et al. (2005) was 0.982 (95% CI = 0.884-1.092) with a study weight of 11.29%.

The random effects pooled estimate for the highly active pre- and postmenopausal females combined compared to relatively sedentary group of females was 0.823 (95% CI = 0.725-0.933), $p = 0.001$. There was a statistically significant lower effect measure for the high versus low active females, and statistically significant heterogeneity within this analysis ($p < 0.001$). These results are reported below in Figure 10 and the Stata output table below.

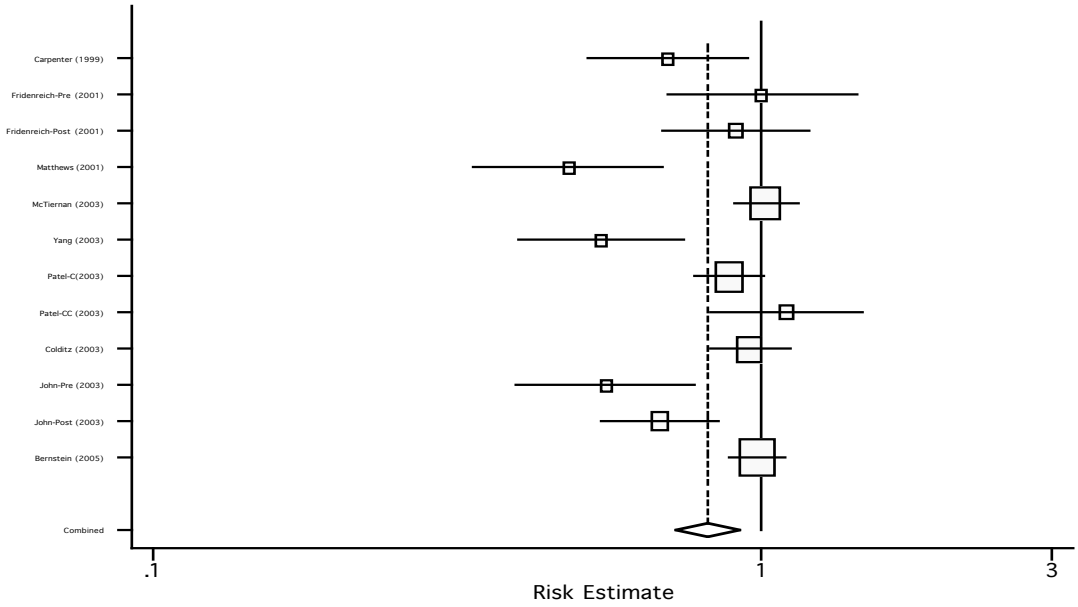


Figure 10. Meta-analysis of breast cancer risk among high versus low activity pre-and postmenopausal females combined in *Compendium* quantified studies in Analysis I

A statistically significant difference ($p = 0.001$) between the high and low activity groups was present.

Table 29. Breast cancer risk among high versus low activity pre- and postmenopausal females combined in *Compendium* quantified studies in Analysis I

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	0.702	0.518-0.952	7.09		
Friedenreich-Pre (2001)	1.000	0.700-1.429	6.11		
Friedenreich-Post (2001)	0.906	0.685-1.199	7.58		
Matthews (2001)	0.480	0.336-0.687	6.09		
McTiernan (2003)	1.017	0.901-1.148	11.02		
Yang (2003)	0.544	0.398-0.744	6.92		
Patel-C (2003)	0.882	0.771-1.008	10.77		
Patel-CC (2003)	1.100	0.826-1.464	7.46		
Colditz (2003)	0.956	0.820-1.115	10.35		
John-Pre (2003)	0.553	0.394-0.775	6.46		
John-Post (2003)	0.678	0.544-0.847	8.85		
Bernstein (2005)	0.982	0.884-1.092	11.29		
D+L Pooled Effect Size	**0.777**	**0.659-0.915**	**100.00**	**3.20**	**0.001**

Heterogeneity $\chi^2 = 47.96$ (d.f. = 11) $p < 0.001$
Estimate of between-study variance $\tau^2 = 0.0329$

Analysis II included *Compendium*-quantified studies from Analysis I that measured physical activity for at least ten years. Eight studies and their respective weights (Carpenter et al., 1999 (6.77%); Friedenreich et al., 2001 (6.29% for premenopausal females and 9.54% for postmenopausal females); Matthews et al., 2001 (6.14%); Yang et al., 2003 (6.34%); Patel et al., 2003 (6.49%); Colditz et al., 2003 (14.79%); John et al., 2003 (6.31% for premenopausal females and 11.32% for postmenopausal females); and Bernstein et al., 2005 (26.02%) were included in this random effects meta-analysis for moderate activity. The random effects D+L pooled estimate was 0.890 (95% CI = 0.818-0.969) with a significance level of $p = 0.007$. Both a statistically significant difference between moderate and low activity females and non-statistically significant amount of heterogeneity ($p = 0.221$) were present in this analysis, as shown in Figure 11 and Stata output below.

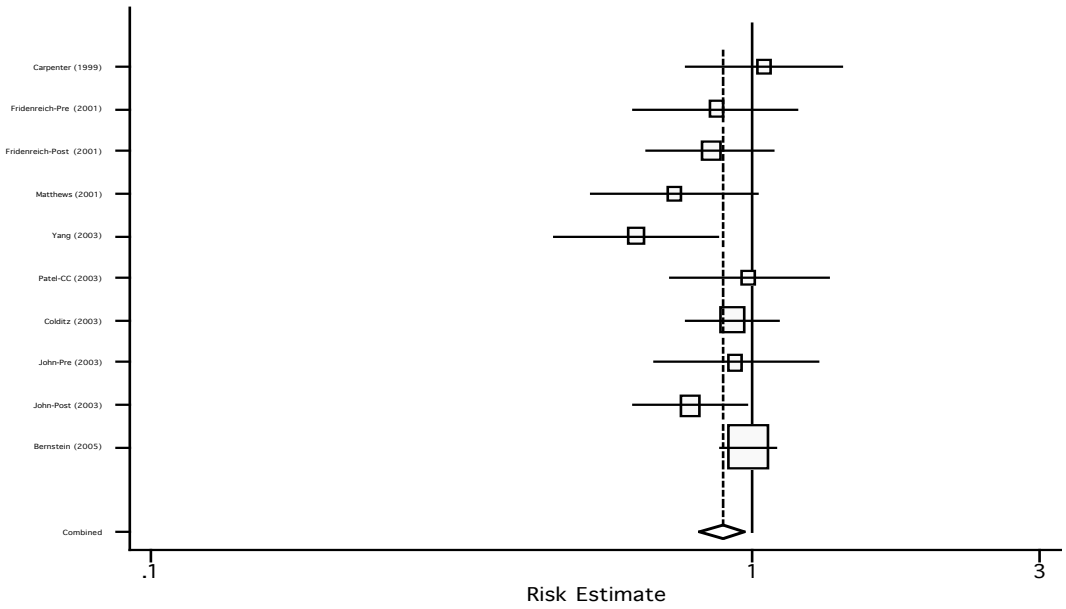


Figure 11. Meta-analysis of breast cancer risk among moderate versus low activity pre- and postmenopausal females combined in *Compendium* quantified (>10 years) studies in Analysis II

A statistically significant difference (p = 0.007) between the moderate and low activity groups was present.

Table 30. Breast Cancer Risk among Moderate Versus Low Activity Pre-and Postmenopausal Females Combined in *Compendium* Quantified (> 10 Years) Studies in Analysis II

Study	Effect measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	1.043	0.773-1.406	6.77		
Friedenreich-Pre (2001)	0.867	0.634-1.185	6.29		
Friedenreich-Post (2001)	0.852	0.669-1.086	9.54		
Matthews (2001)	0.738	0.538-1.014	6.14		
Yang (2003)	0.640	0.469-0.873	6.34		
Patel-CC (2003)	0.987	0.726-1.341	6.49		
Colditz (2003)	0.927	0.775-1.109	14.79		
John-Pre (2003)	0.938	0.687-1.281	6.31		
John-Post (2003)	0.787	0.634-0.977	11.32		
Bernstein (2005)	0.982	0.884-1.092	26.02		
D+L Pooled Effect Size	**0.890**	**0.818-0.969**	**100.00**	**2.69**	**0.007**

Heterogeneity χ^2 = 11.86 (d.f. = 9), p = 0.221
Estimate of between-study variance τ^2 = 0.0043

For the high activity analysis, the random effects D+L pooled estimate was 0.777 (95% CI = 0.659-0.915), $p = 0.002$, as reported below in Figure 12 and the Stata output. A statistically significant difference between the effect measures of the high and low activity females was reported. Additionally, statistically significant heterogeneity ($p < 0.001$) was reported for this analysis. Carpenter et al. (1999) had a weight of 9.37%, while Friedenreich et al. (2001) had a weight of 8.35% for premenopausal females and 9.86% for postmenopausal females, and the weight for Matthews et al. (2001) was 8.33%. In 2003, Yang et al., Patel et al., and Colditz et al. had weights of 9.19%, 9.73%, and 12.33%, respectively. Study weights for John et al. (2003) were 8.71% for premenopausal females and 11.04% for postmenopausal females. Finally, the Bernstein et al. (2005) study weight was 13.09%. The moderate and high activity effect measures and confidence intervals for the following studies are described above in the discussion of Analysis I results.

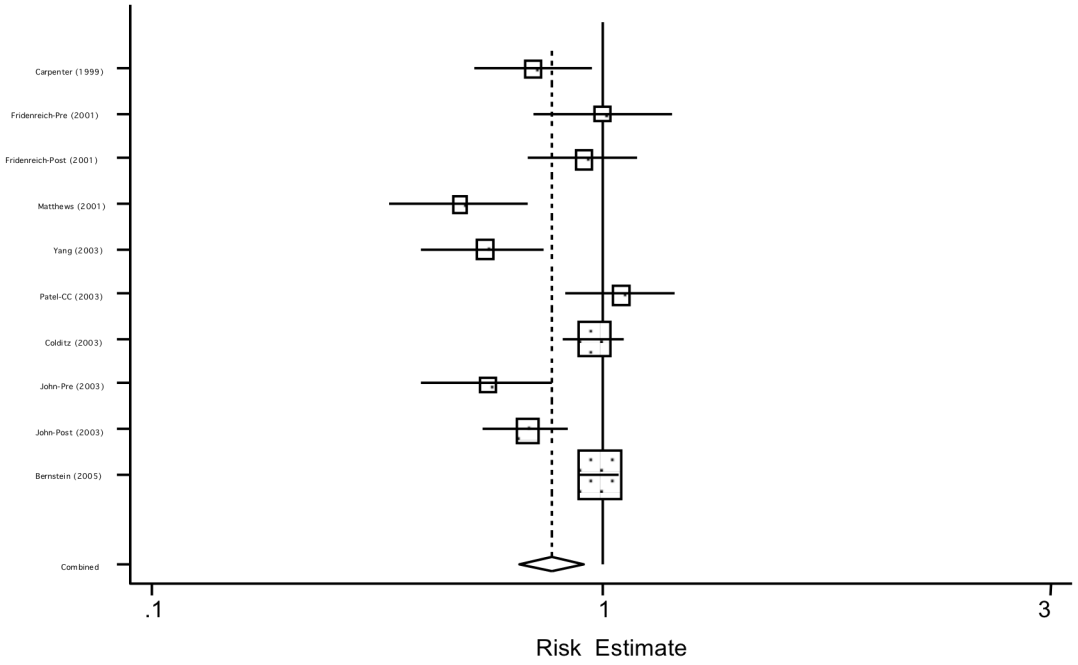


Figure 12. Meta-analysis of breast cancer risk among high versus low activity pre- and postmenopausal females combined in *Compendium* quantified (>10 Years) studies in analysis II

A statistically significant difference ($p = 0.002$) between the high and low activity groups was present.

Table 31. Breast cancer risk among high versus low activity pre- and postmenopausal females combined in *Compendium* quantified (> 10 years) studies in Analysis II

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	0.702	0.518-0.952	9.37		
Friedenreich-Pre (2001)	1.000	0.700-1.429	8.35		
Friedenreich-Post (2001)	0.906	0.685-1.199	9.86		
Matthews (2001)	0.480	0.336-0.687	8.33		
Yang (2003)	0.544	0.398-0.744	9.19		
Patel-CC (2003)	1.100	0.826-1.464	9.73		
Colditz (2003)	0.956	0.820-1.115	12.33		
John-Pre (2003)	0.553	0.394-0.775	8.71		
John-Post (2003)	0.678	0.544-0.847	11.04		
Bernstein (2005)	0.982	0.884-1.092	13.09		
D+L Pooled Effect Size	**0.777**	**0.659-0.915**	**100.00**	**3.03**	**0.002**

Heterogeneity $\chi^2 = 42.60$ (d.f. = 9) $p = <0.001$
Estimate of between-study variance $\tau^2 = 0.0505$

Fifteen studies were included in Analysis III. In addition to the ten studies included in Analysis I that directly quantified physical activity using the *Compendium*, five additional studies (Thune et al., 2007; Levi et al., 1999; Rockhill et al., 1999); Moradi et al., 2000; Dirx et al., 2001) for which the quantity of physical activity could be indirectly estimated using the *Compendium* were also included in this random effects meta-analysis. For moderately active pre- and postmenopausal females combined, the effect measures and confidence intervals for the five aforementioned studies were reported as 0.087 (95% CI = 0.676-1.163); 0.447 (95% CI = 0.334-0.598); 0.908 (95% CI = 0.844-0.976); 1.100 (95% CI = 0.960-1.260); and 1.164 (95% CI = 0.8731.551), respectively.

The effect measures and confidence intervals for moderately active females from the remaining ten studies included in Analysis III are described above with the Analysis I results.

The same study may have a different weight in each analysis dependent on this study's relative sample size compared to the other studies included in the analysis. For Analysis III, the following weights from the fifteen studies are included in parentheses next to the study author: Thune et al., 1997 (4.66%); Carpenter et al., 1999 (4.15%); Levi et al., 1999 (4.30%); Rockhill et al., 1999 (9.96%); Moradi et al., 2000 (8.17%); Friedenreich et al., 2001 (3.93% for pre- and 5.27% for postmenopausal females); Matthews et al., 2001 (3.86%); Dirx et al., 2001 (4.36%); McTiernan et al., 2003 (9.00%); Yang et al., 2003 (3.95%); Patel et al., 2003 (8.59% for the cohort study and 4.02% for the case-control study); Colditz et al., 2003 (6.89%); John et al., 2003 (3.94% for pre- and 5.88% for postmenopausal females); and Bernstein et al., 2005 (9.07%).

The random effects D+L pooled estimate for the moderate versus low active females for Analysis III was 0.897 (95% CI = 0.831-0.970), $p = 0.006$. A statistically significant difference existed between the moderate and low active females, and a statistically significant amount of heterogeneity between studies was reported ($p < 0.001$). These analyses are presented below in Figure 13 and the corresponding Stata output.

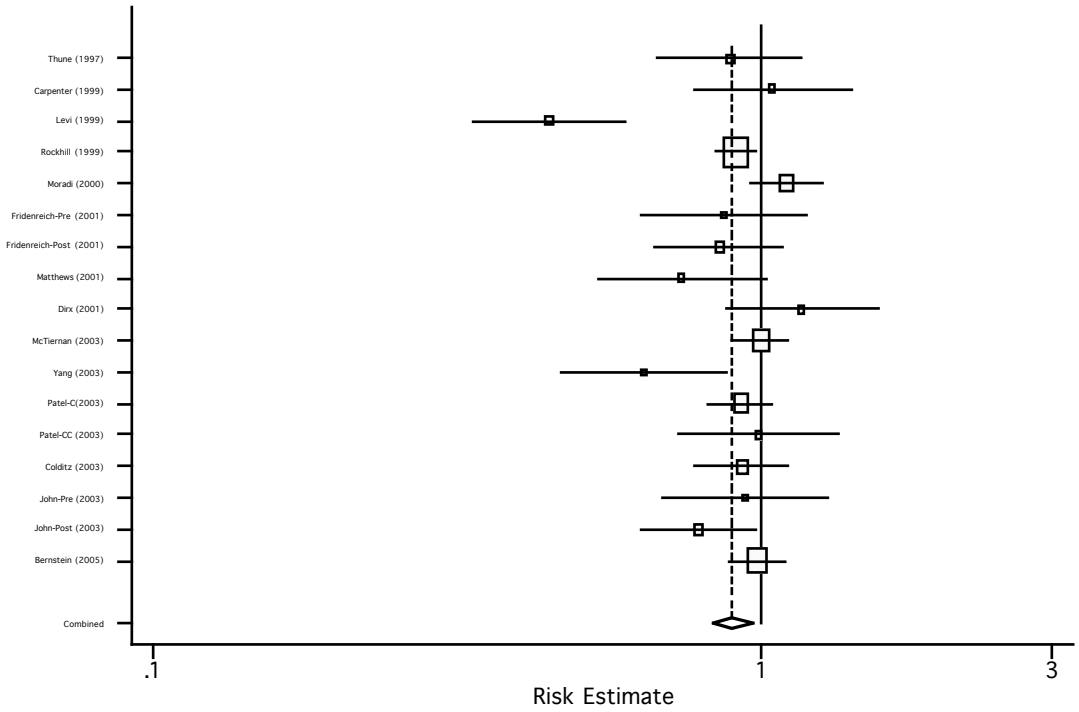


Figure 13. Meta-analysis of breast cancer risk among moderate versus low activity pre- and postmenopausal females combined in *Compendium* quantified and estimated studies in Analysis III

A statistically significant difference ($p = 0.006$) between the moderate and low activity groups was present.

Table 32. Breast cancer risk among moderate versus low activity pre- and postmenopausal females combined in *Compendium* quantified and estimated studies in Analysis III

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z -Value	P-Value
Thune (1997)	0.887	0.676-1.163	4.66		
Carpenter (1999)	1.043	0.773-1.406	4.15		
Levi (1999)	0.447	0.334-0.598	4.30		
Rockhill (1999)	0.908	0.844-0.976	9.96		
Moradi (2000)	1.100	0.960-1.260	8.17		
Friedenreich-Pre (2001)	0.867	0.634-1.185	3.93		
Friedenreich-Post (2001)	0.852	0.669-1.086	5.27		
Matthews (2001)	0.738	0.538-1.014	3.86		
Dirx (2001)	1.164	0.873-1.551	4.36		
McTiernan (2003)	0.996	0.894-1.109	9.00		
Yang (2003)	0.640	0.469-0.873	3.95		
Patel-C (2003)	0.924	0.818-1.044	8.59		
Patel-CC (2003)	0.987	0.726-1.341	4.02		
Colditz (2003)	0.927	0.775-1.109	6.89		
John-Pre (2003)	0.938	0.687-1.281	3.94		
John-Post (2003)	0.787	0.634-0.977	5.88		
Bernstein (2005)	0.982	0.884-1.092	9.07		
D+L Pooled Effect Size	**0.897**	**0.831-0.970**	**100.00**	**2.74**	**0.006**

Heterogeneity $\chi^2 = 46.98$ (d.f. = 16) $p = < 0.001$
Estimate of between-study variance $\tau^2 = 0.0143$

Highly active females had effect measures of 0.647 (95% CI = 0.431-0.971) for the Thune et al. (1997) study; 0.387 (95% CI = 0.222-0.674) for the Levi et al. (1999) study; 0.790 (95% CI = 0.718-0.868) for the Rockhill et al. (1999) study; 0.817 (95% CI = 0.715-0.933) for the Moradi et al. (2000) study, and 1.145 (95% CI = 0.861-1.524) for the Dirx et al. (2001) study. The effect measures and confidence intervals for the highly active females from the remaining ten studies included in Analysis III are discussed above with the Analysis I results.

The weights for the fifteen studies are included in parentheses next to the study author: Thune et al., 1997 (3.94%); Carpenter et al., 1999 (5.20%); Levi et al., 1999

(2.66%); Rockhill et al., 1999 (7.43%); Moradi et al., 2000 (7.77%); Friedenreich et al., 2001 (4.50% for pre- and 5.55% for postmenopausal females); Matthews et al., 2001 (4.49%); Dirx et al., 2001 (5.46%); McTiernan et al., 2003 (7.93%); Yang et al., 2003 (5.08%); Patel et al., 2003 (7.76% for the cohort study and 5.46% for the case-control study); Colditz et al., 2003 (7.48%); John et al., 2003 (4.75% for pre- and 6.43% for postmenopausal females); and Bernstein et al., 2005 (8.12%).

The random effects D+L pooled estimate for the moderate versus low activity females for Analysis III was 0.797 (95% CI = 0.715-0.889), and the difference was statistically significant ($p < 0.001$). A statistically significant amount of heterogeneity between studies was also present ($p < 0.001$). These analyses are presented below in Figure 14 and the corresponding Stata output.

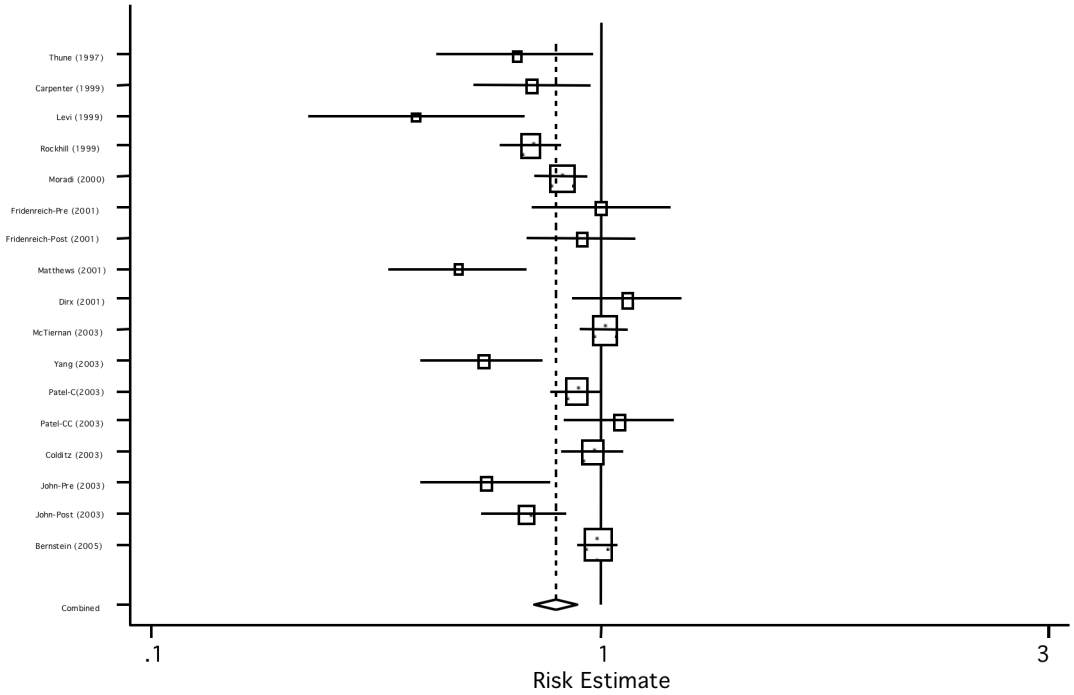


Figure 14. Meta-analysis of breast cancer risk among high versus low activity pre- and postmenopausal females combined in *Compendium* quantified and estimated studies in Analysis III

A statistically significant difference ($p < 0.001$) between the high and low activity groups was present.

Table 33. Breast cancer risk among high versus low activity pre- and postmenopausal females combined in *Compendium* quantified and estimated studies in Analysis III

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z- Value	P-Value
Thune (1997)	0.647	0.421-0.971	3.94		
Carpenter (1999)	0.702	0.518-0.952	5.20		
Levi (1999)	0.387	0.222-0.674	2.66		
Rockhill (1999)	0.696	0.595-0.815	7.43		
Moradi (2000)	0.817	0.715-0.933	7.77		
Friedenreich-Pre (2001)	1.000	0.700-1.429	4.50		
Friedenreich-Post (2001)	0.906	0.685-1.199	5.55		
Matthews (2001)	0.480	0.336-0.687	4.49		
Dirx (2001)	1.145	0.861-1.524	5.46		
McTiernan (2003)	1.017	0.901-1.148	7.93		
Yang (2003)	0.544	0.398-0.744	5.08		
Patel-C (2003)	0.882	0.771-1.008	7.76		
Patel-CC (2003)	1.100	0.826-1.464	5.46		
Colditz (2003)	0.956	0.820-1.115	7.48		
John-Pre (2003)	0.553	0.394-0.775	4.75		
John-Post (2003)	0.678	0.544-0.847	6.43		
Bernstein (2005)	0.982	0.884-1.092	8.12		
D+L Pooled Effect Size	**0.797**	**0.715-0.889**	**100.00**	**4.09**	**<0.001**

Heterogeneity $\chi^2 = 71.36$ (d.f. = 16) $p < 0.001$
Estimate of between-study variance $\tau^2 = 0.0348$
Test of Effect Size=1: $z = 4.09$, $p < 0.001$

Analyses of Premenopausal Females

Analysis IV consisted of three studies (Friedenreich et al., 2001; Colditz et al., 2003; John et al., 2003) included in an analysis of the relationship between *Compendium*-quantified physical activity and breast cancer risk among premenopausal females. The effect measures and confidence intervals for moderately and highly active females within these three studies are included above in the Analysis I results section. Both the fixed effects and random effects pooled estimate for the moderate activity group were the same

(Pooled Effect Measure = 0.917, 95% CI = 0.798-1.054, $p = 0.222$), as the estimate of between-study variance was zero ($\tau^2 = 0$). There was no statistically significant difference between the effect measures of the moderate versus low activity premenopausal females. The weights for the three studies included in the random effects analysis were 19.82% (Friedenreich et al., 2001), 60.28% (Colditz et al., 2003), and 19.90% (John et al., 2003). No statistically significant heterogeneity was reported for the random effects analysis ($p = 0.924$) and the fixed and random effects results are compared in the Stata output below. The random effects analysis results are displayed in Figure 15 below.

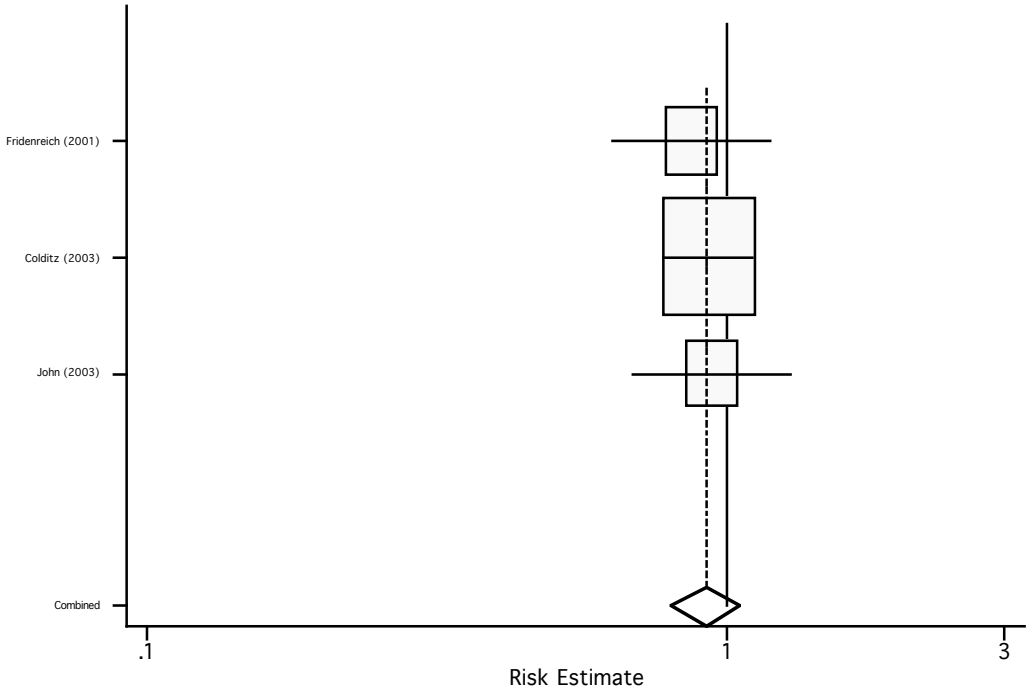


Figure 15. Meta-analysis of breast cancer risk among moderate versus low activity premenopausal females in *Compendium* quantified studies in Analysis IV

A non-statistically significant difference ($p = 0.222$) between the moderate and low activity groups was present.

Table 34. Breast cancer risk among moderate versus low activity premenopausal females in *Compendium* quantified studies in Analysis IV

Study	Effect measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Friedenreich (2001)	0.867	0.634-1.185	19.82		
Colditz (2003)	0.927	0.775-1.109	60.28		
John (2003)	0.938	0.687-1.281	19.90		
D+L Pooled Effect Size	**0.917**	**0.798-1.054**	**100.00**	**-1.222**	**0.222**

Heterogeneity $\chi^2 = 0.16$ (d.f. = 2) $p = 0.924$
Estimate of between-study variance $\tau^2 = 0.0000$

For the high activity group, the fixed effects pooled estimate was 0.887 (95% CI = 0.778-1.010), $p = 0.070$, while the D+L random effects pooled estimate was 0.820 (95% CI = 0.584-1.151), $p = 0.251$. The slight difference in pooled effect measures ($\tau^2 =$ 0.0684) indicated a slight of variance between the studies. A non-statistically significant difference existed between the effect measures of the high and low activity premenopausal females. These results are displayed in Figure 16 below. The weights for the Friedenreich et al. (2001), Colditz et al. (2003), and John et al. (2003) studies were 29.43%, 40.09%, and 30.48%, respectively, and a statistically significant amount of heterogeneity was present ($p = 0.012$), as reported in the Stata output below with the comparisons between the fixed and random effects analyses results.

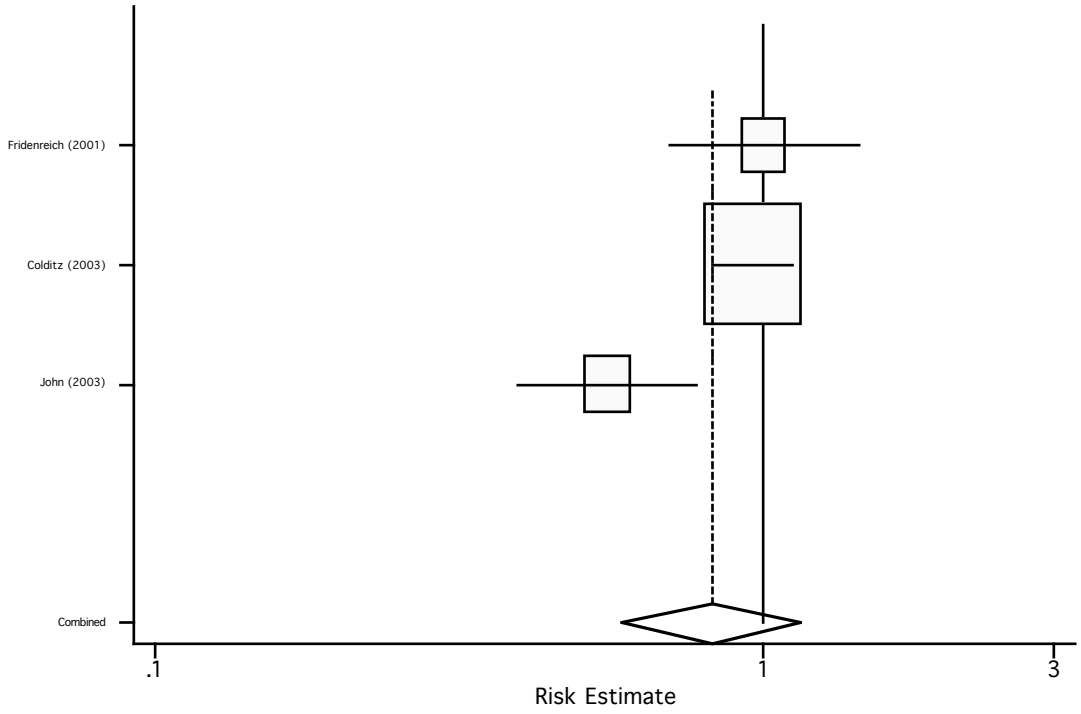


Figure 16. Meta-analysis of breast cancer risk among high versus low activity premenopausal females in *Compendium* quantified studies in Analysis IV

A non-statistically significant difference ($p = 0.012$) was present between the high and low activity groups.

Table 35. Breast cancer risk among high versus low activity premenopausal females in *Compendium* quantified studies in Analysis IV

Study	Effect measure	95% Confidence Interval	% Weight	Asymptotic P-Value	P-Value
Friedenreich (2001)	1.000	0.700-1.429	29.43		
Colditz (2003)	0.956	0.820-1.115	40.09		
John (2003)	0.553	0.394-0.775	30.48		
D+L Pooled Effect Size	**0.820**	**0.584-1.151**	**100.00**	**-1.148**	**0.251**

Heterogeneity $\chi^2 = 8.88$ (d.f. = 2) $p = 0.012$
Estimate of between-study variance $\tau^2 = 0.0684$

Analyses of Postmenopausal Females

Five studies and their respective weights for the moderate versus low activity and analysis (Carpenter et al., 1999 (7.03%); Friedenreich et al., 2001 (10.36%); McTiernan et al., 2003 (37.85%); Patel et al., 2003 (32.08%); and John et al., 2003 (12.67%) were included in Analysis V, a meta-analysis of the relationship between *Compendium*-quantified physical activity and postmenopausal breast cancer risk. The effect measures and confidence intervals for the aforementioned five studies are included above in the Analysis I results section. The random effects D+L pooled estimate for this meta-analysis was 0.932 (95% CI = 0.858-1.011), $p = 0.302$, and no statistically significant difference between the effect measures of moderate and low activity postmenopausal females was reported. The between-study heterogeneity was not statistically significant ($p = 0.302$). These results are reported below in Figure 17 and the Stata output.

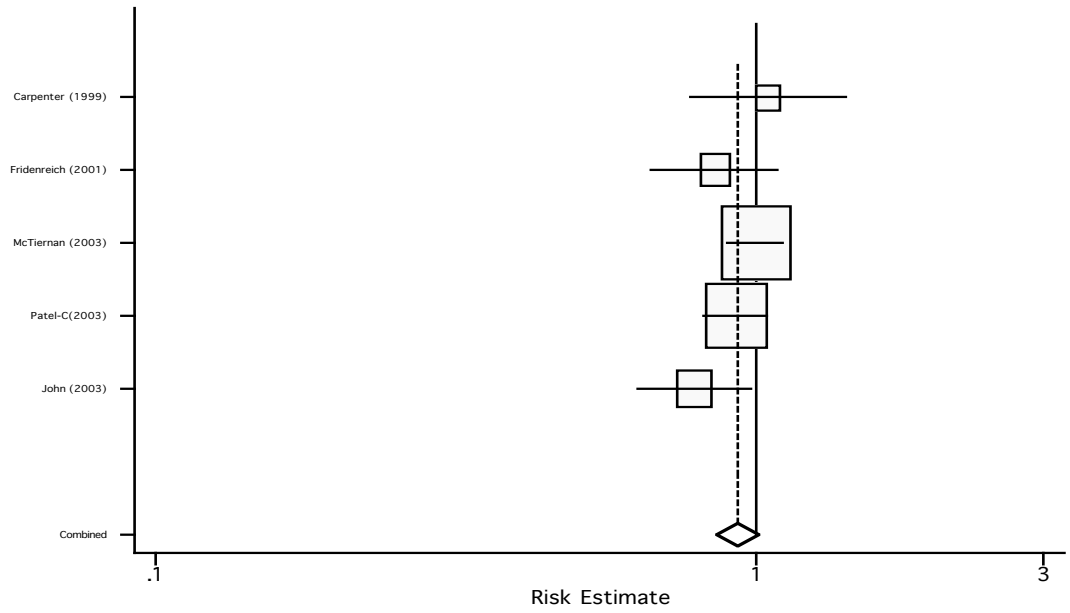


Figure 17. Meta-analysis of breast cancer risk among moderate versus low activity postmenopausal females in *Compendium* quantified studies in Analysis V

A non-statistically significant difference ($p = 0.090$) between the moderate and low activity groups was present.

Table 36. Breast cancer risk among moderate versus low activity postmenopausal females in *Compendium* quantified studies in Analysis V

Study	Effect measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	1.043	0.773-1.406	7.03		
Friedenreich (2001)	0.852	0.669-1.086	10.36		
McTiernan (2003)	0.996	0.894-1.109	37.85		
Patel - C (2003)	0.924	0.818-1.044	32.08		
John (2003)	0.787	0.634-0.977	18.96		
D+L Pooled Effect Size	**0.932**	**0.858-1.011**	**100.00**	**1.69**	**0.090**

Heterogeneity $\chi^2 = 4.86$ (d.f. = 4) $p = 0.302$
Estimate of between-study variance $\tau^2 = 0.0016$

Among highly active postmenopausal females, the study weights in the meta-analysis for the five studies were 14.03% (Carpenter et al., 1999); 15.34% (Friedenreich et al., 2001); 26.30% (McTiernan et al., 2003); 25.38% (Patel et al., 2003), and 18.96% (John et al., 2003), while the effect measures and confidence intervals for the five studies are included above in the Analysis I results section. The random effects D+L pooled estimate for this analysis was 0.847 (95% CI = 0.727-0.987), with a statistical significance of $p = 0.034$. A statistically significant difference between the effect measures of the high and low activity postmenopausal females was reported, as was a statistically significant amount of between-study heterogeneity ($p = 0.012$). These results are reported in Figure 18 and the Stata output below.

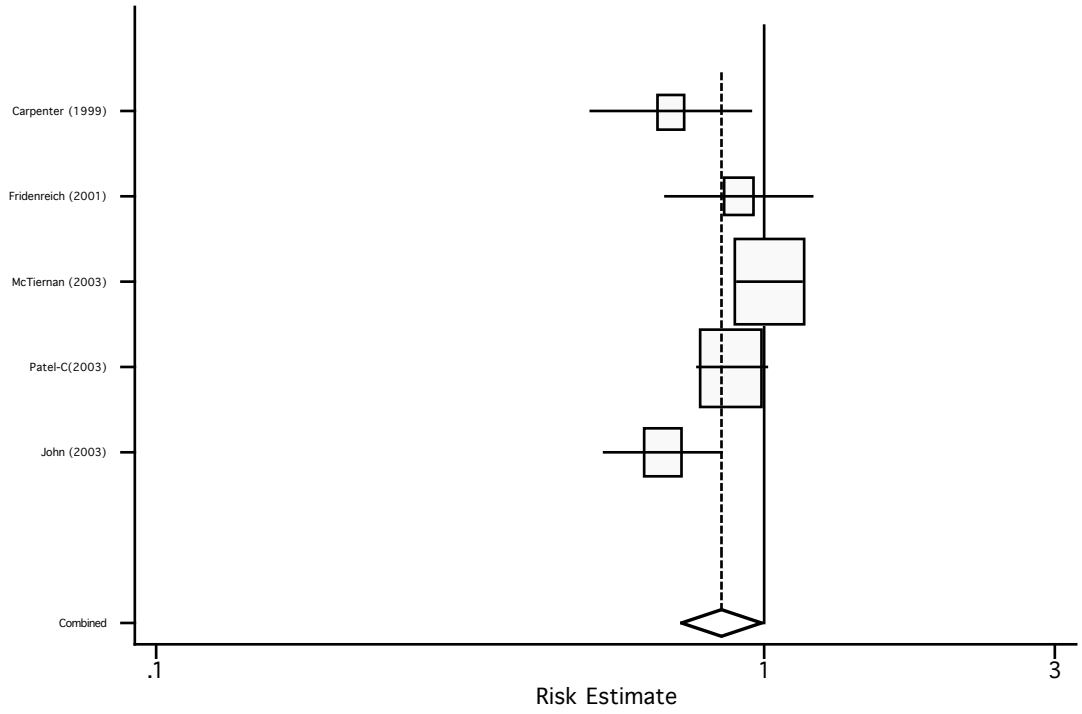


Figure 18. Meta-analysis of breast cancer risk among high versus low activity postmenopausal females in *Compendium* quantified studies in Analysis V

A Statistically significant difference ($p = 0.034$) between the high and low activity groups was present.

Table 37. Breast cancer risk among high versus low activity postmenopausal females in *Compendium* quantified studies in Analysis V

Study	Effect measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	0.702	0.518-0.952	24.03		
Friedenreich (2001)	0.906	0.685-1.199	15.34		
McTiernan (2003)	1.017	0.901-1.148	26.30		
Patel - C (2003)	0.882	0.771-1.008	25.38		
John (2003)	0.678	0.544-0.847	18.96		
D+L Pooled Effect Size	**0.847**	**0.727-0.987**	**100.00**	**2.12**	**0.034**

Heterogeneity $\chi^2 = 12.77$ (d.f. = 4), $p = 0.012$
Estimate of between-study variance $\tau^2 = 0.0194$

Analysis VI includes the five studies from Analysis V as well as two additional studies (Moradi et al., 2000; Dirx et al., 2001) for which MET hours-per-week could be estimated using the *Compendium*. The effect measures and confidence intervals for these two studies are included in the Analysis III results, while the estimates and intervals from the other five studies are included in the results discussion of Analysis I. The weights for the studies in this analysis of moderate versus low activity postmenopausal females were 7.01% (Carpenter et al., 1999); 19.49% (Moradi et al., 2000); 9.69% (Friedenreich et al., 2001); 7.48% (Dirx et al., 2001); 23.51% (McTiernan et al., 2003); 21.44% (Patel et al., 2003); and 11.38% (John et al., 2003). The random effects D+L pooled estimate was 0.973 (95% CI = 0.890-1.062), $p = 0.536$. Both a non-statistically significant difference between the two effect measures and non-statistically significant level of between-study heterogeneity were reported for this analysis ($p = 0.105$). These results are reported in Figure 19 and the Stata output on the next page.

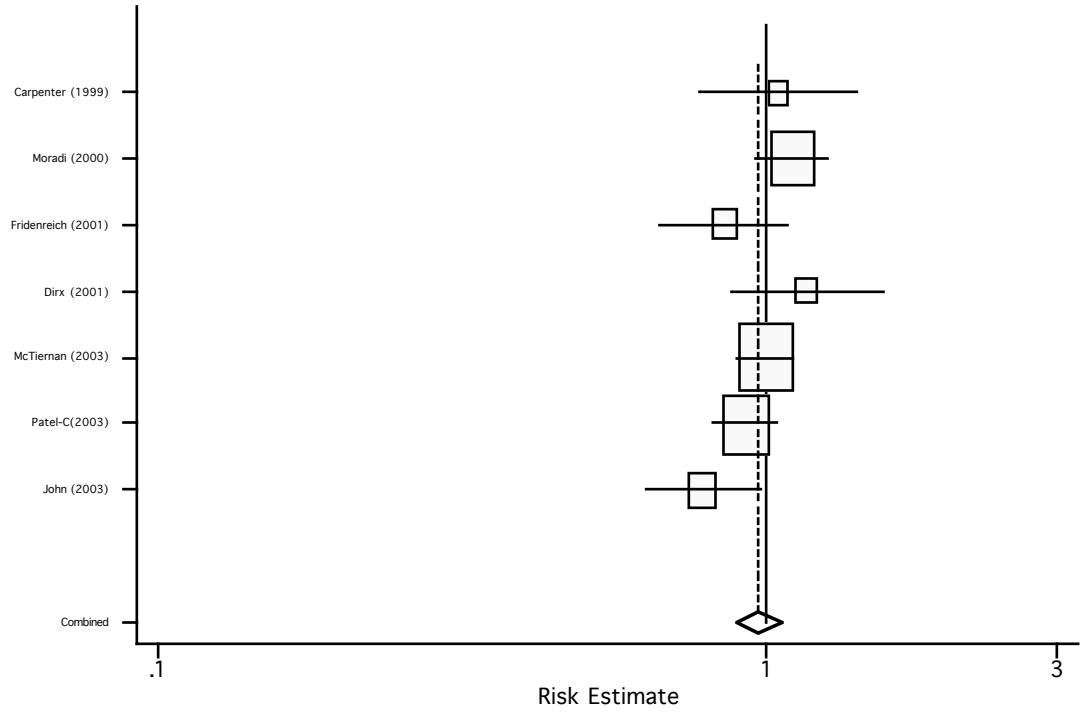


Figure 19. Meta-analysis of breast cancer risk among moderate versus low activity postmenopausal females in *Compendium* quantified and estimated studies in Analysis VI

A non-statistically significant difference ($p = 0.536$) between the moderate and low activity groups was reported.

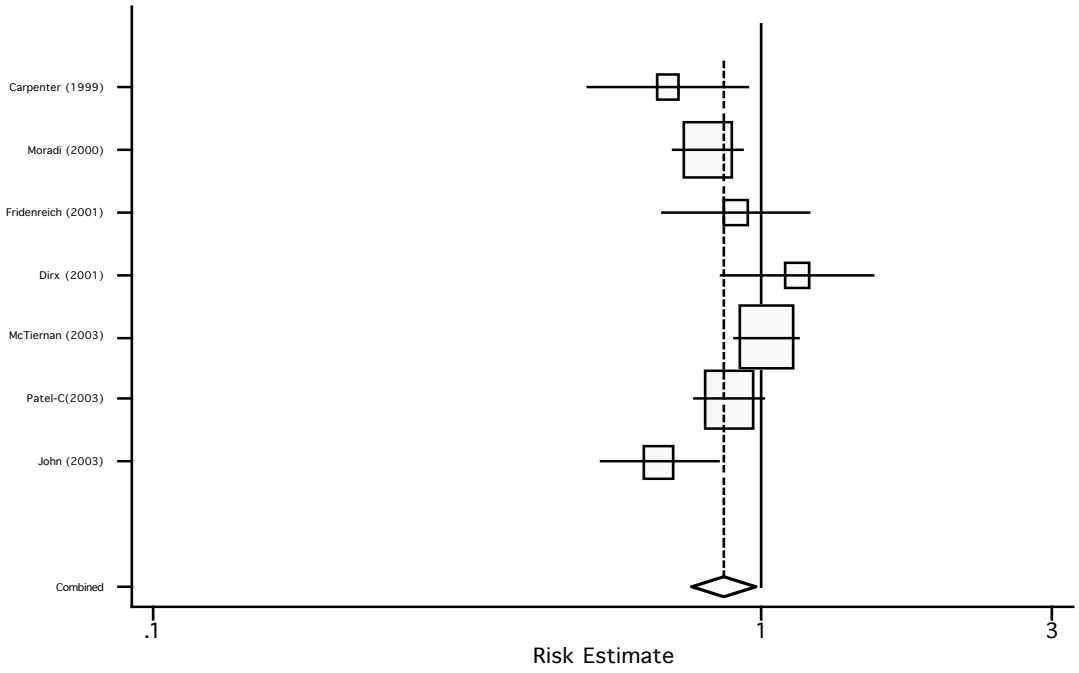
Table 38. The risk among moderate versus low Activity postmenopausal females in *Compendium* quantified and estimated studies in Analysis VI

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	1.043	0.773-1.406	7.01		
Moradi (2000)	1.100	0.960-1.260	19.49		
Friedenreich (2001)	0.852	0.669-1.086	9.69		
Dirx (2001)	1.164	0.873-1.551	7.48		
McTiernan (2003)	0.996	0.894-1.109	23.51		
Patel - C (2003)	0.924	0.818-1.044	21.44		
John (2003)	0.787	0.634-0.977	11.38		
D+L Pooled Effect Size	**0.973**	**0.890-1.062**	**100.00**	**0.62**	**0.536**

Heterogeneity $\chi^2 = 10.51$ (d.f. = 6), $p = 0.105$
Estimate of between-study variance $\tau^2 = 0.0056$

For highly active postmenopausal females, the effect measures and confidence intervals are reported in the Analysis I and III sections. The weights for the studies in this analysis of moderate versus low activity postmenopausal females were 9.51% (Carpenter et al., 1999); 18.60% (Moradi et al., 2000); 10.48% (Friedenreich et al., 2001); 10.25% (Dirx et al., 2001); 19.34% (McTiernan et al., 2003); 18.55% (Patel et al., 2003); and 13.27% (John et al., 2003). The random effects D+L pooled estimate was 0.870 (95% CI = 0.771-0.982), $p = 0.024$, and a statistically significant difference between the effect measures of the high and low activity postmenopausal females was reported. Additionally, a statistically significant amount of heterogeneity was reported for this analysis ($p = 0.008$). These results are reported in Figure 20 and the Stata output below.

Figure 20. Meta-analysis of breast cancer risk among high versus low activity postmenopausal females in *Compendium* quantified and estimated studies in Analysis VI



A statistically significant difference ($p = 0.024$) between the high and low activity groups was present.

Table 39. Breast cancer risk among high versus low activity postmenopausal females in *Compendium* quantified and estimated studies in Analysis VI

Study	Effect Measure	95% Confidence Interval	% Weight	Asymptotic Z-Value	P-Value
Carpenter (1999)	0.702	0.518-0.952	9.51		
Moradi (2000)	0.817	0.715-0.933	18.60		
Friedenreich (2001)	0.906	0.685-1.199	10.48		
Dirx (2001)	1.145	0.861-1.524	10.25		
McTiernan (2003)	1.017	0.901-1.148	19.34		
Patel - C (2003)	0.882	0.771-1.008	18.55		
John (2003)	0.678	0.544-0.847	13.27		
D+L Pooled Effect Size	**0.870**	**0.771-0.982**	**100.00**	**2.26**	**0.024**

Heterogeneity $\chi^2 = 17.37$ (d.f. = 6) $p = 0.008$
Estimate of between-study variance $\tau^2 = 0.0158$

Summary of Results from Meta-Analyses

Tables 40 and 41 provide a summary of the effect measures, confidence intervals, and *p*-values for the four meta-analyses of physical activity and colon cancer risk and the six meta-analyses of physical activity and breast cancer risk, respectively.

Colon Cancer Analyses

Table 40. Summary of results from colon cancer meta-analyses

Analysis	Moderate Versus Low Activity			High Versus Low Activity		
	Effect Measure	95% Confidence Interval	*p*-Value	Effect measure	95% Confidence Interval	*p*-Value
I	0.817	0.484-1.379	0.449	0.524	0.348-0.788	0.002
II	0.872	0.671-1.132	0.303	0.673	0.474-0.956	0.027
III	0.750	0.496-1.135	0.174	0.574	0.433-0.761	<0.001
IV	0.809	0.653-1.001	0.051	0.814	0.643-1.03	0.087

Breast Cancer Analyses

Table 41. Summary of results from breast cancer meta-analyses

Analysis	Moderate Versus Low Activity			High Versus Low Activity		
	Effect Measure	95% Confidence Interval	*p*-Value	Effect measure	95% Confidence Interval	*p*-Value
I	0.919	0.863-0.978	0.008	0.816	0.721-0.924	0.033
II	0.890	0.818-0.969	0.007	0.777	0.659-0.915	0.002
III	0.897	0.831-0.970	0.006	0.797	0.715-0.889	<0.001
IV	0.917	0.798-1.054	0.222	0.820	0.584-1.151	0.251
V	0.932	0.858-1.011	0.090	0.847	0.727-0.987	0.034
VI	0.973	0.890-1.062	0.536	0.870	0.771-0.982	0.024

Comparisons of Unadjusted and Adjusted Effect measures

Colon Cancer Analyses

To assess the possible impact of confounding, all unadjusted, age-adjusted (where applicable), and multivariate-adjusted (where applicable) effect measures, confidence intervals, and percent differences between the effect measures across all physical activity categories are included in Tables 42.1-42.8. Overall, the percent difference between the adjusted and unadjusted estimates ranged from 0-31% across all physical activity categories for 5 of 6 studies, with one study (Tang et al., 1999) reporting a difference ranging from 5% to 93% between the adjusted and unadjusted effect measures.

Giovannucci et al. (1995) percent-differences between the multivariate-adjusted and unadjusted effect measures were calculated to be -1.37%, 10.64%, 16.67%, and 24.53% across five physical activity categories, while differences for Longnecker et al. (1995) were -30.86%, -21.28%, and -17.54% across three activity categories. While these two studies examined colon cancer risk in males, White et al. (1996) examined activity's relationship with the risk in males and females, and percent differences of

1.56%, -25.42%, and 4.35% across three activity categories were calculated in males and 3.45%, 1.67%, and -23.33% were calculated in females. Martinez et al. (1997) produced differences of 2.82%, 6.41%, 2.99%, and -14.81% in females, while differences of -93.24% and -5.26% across two activity categories in males and -80.77% and -28.57% in females were calculated for Tang et al. (1999). More recently, estimate differences for Calton et al. (2006) were calculated as 31.09%, 19.54%, and 13.64%.

Breast Cancer Analyses

To assess the possible impact of confounding on breast cancer analyses, all unadjusted, age-adjusted (where applicable), and multivariate-adjusted (where applicable) effect measures, confidence intervals, and percent differences between the effect measures across all physical activity categories are included in Tables 43.1 through 43.17. Overall, the percent difference between the adjusted and unadjusted estimates ranged from 0-21% across all physical activity categories for 14 of 15 studies, with one study (Patel et al., 2003) reporting a difference ranging from 20% to 64%.

Specifically, differences between the multivariate-adjusted and unadjusted effect measures for Thune et al. (1997) were calculated as 4.30% and -3.17% across two physical activity categories for pre- and postmenopausal females combined, while differences for Carpenter et al. (1999) were 4.65%, -2.17%, 2.80%, and 13.58% across four activity categories for postmenopausal females. Levi et al. (1999) produced differences of -2.27% and 7.14% across two activity categories for pre- and postmenopausal females combined, and differences for Rockhill et al. (1999) were calculated as 2.27%, 2.25%, 2.35%, and 20.73% across four activity categories for pre-

and postmenopausal females combined. In 2000, Moradi et al. reported consistently larger differences of 18.00%, 15.38%, and 12.73% across three physical activity categories for postmenopausal females. A year later, Friedenreich et al. (2001) allowed for a separate analysis of pre- and postmenopausal females. Estimate differences for premenopausal females were 7.41%, 4.85%, and 11.50% across three activity categories while postmenopausal differences were 7.29%, 6.82%, and 17.27%. The Matthews et al. study (2001) produced effect measure differences of -7.41%, -12.82%, -7.58%, and -20.00% across four activity categories for pre- and postmenopausal females combined, while differences for Dirx et al. were -5.41% and -7.48% across two categories for postmenopausal females.

More recently, differences between adjusted and unadjusted estimates for McTiernan et al. (2003) were -.6.67%, -10.98%, -14.61%, -18.07%, and -14.10% across five activity categories for postmenopausal females, while differences for Yang et al. (2003) were -2.20%, -2.99%, -20.75%, and -14.89% across four categories for pre- and postmenopausal females combined. In 2003, Patel et al. completed both a cohort and case-control study of the relationship between physical activity and breast cancer risk. Estimate differences for the cohort study were 1.06%, 1.30%, and 1.41% across three activity categories for postmenopausal females, while much larger differences of -20.00%, -27.69%, -63.93%, -52.38%, and -53.85% were calculated for combined pre- and postmenopausal females in the case-control study. Premenopausal effect measure differences from Colditz et al. (2003) were calculated as -2.86%, 2.11%, -0.97%, and 4.81% across four physical activity categories. Similar to the Friedenreich et al. (2001) study, John et al. (2003) analyzed pre- and postmenopausal females separately. The

differences in effect measures for premenopausal females were 10.48% and 17.91% across two activity categories, while differences of 7.06% and 8.11% were calculated for postmenopausal females. Most recently, Bernstein et al. (2005) had estimate differences of -3.23%, -8.05%, -19.51%, and -12.50% across four activity categories for pre- and postmenopausal females combined.

Results from Meta-Regression Model for Breast Cancer Analyses

Two mixed effects meta-regression models were completed for moderate and high activity females to determine if the relationship between physical activity and breast cancer risk differed between females of differing menopausal status. Only studies that stratified females by menopausal status when assessing the effect of physical activity on breast cancer risk were included in the mixed effects models. For the moderate activity females, there was no statistically significant difference in breast cancer risk between females of differing menopausal status ($p = 0.476$). A similar non-statistically significant difference was found between high activity pre- and postmenopausal females ($p = 0.865$). Results from the meta-regression analyses are in Appendix IV and possible reasons for the non-statistically significant findings are discussed in Chapter IV.

Tables of Confounding Effects for All Meta-Analyses

Table 42. Overview of the Effects of Confounding Variables – Colon Cancer

Table 42 shows the physical activity quantification level (e.g. # of MET Hours-Per-Week), the unadjusted effect measure for each of the combined physical activity categories, the unadjusted effect measure, age-adjusted effect measure (where included in the original study), and multivariate-adjusted effect measure (where included in the original study) are included for each individual physical activity categorization level. Finally, the percent different between the unadjusted effect measure and multivariate-adjusted effect measure (except in cases where only age-adjusted was reported) for each individual physical activity categorization level were calculated and reported. For each of the studies included in the meta-analyses, weekly physical activity quantifications were analyzed across three categories – low, moderate, and high activity. For some studies this required combining some of the original physical activity categories.

Table 42.1. Giovannucci et al. (Cohort; Males)

MET-Hours Per Week (Median)	Combined Unadjusted Effect Measure Used In Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0.9	1.0	1.0	1.0	1.0	-
4.8		0.74 (0.49-1.10)	0.69 (0.46-1.02)	0.73 (0.48-1.10)	-1.37%
11.3	0.79 (0.56-1.10)	0.84 (0.57-1.24)	0.83 (0.56-1.23)	0.94 (0.63-1.39)	10.64%
22.6		0.65 (0.43-0.99)	0.67 (0.44-1.02)	0.78 (0.51-1.20)	16.67%
46.8	0.53 (0.36-0.76)	0.40 (0.25-0.66)	0.44 (0.27-0.71)	0.53 (0.32-0.88)	24.53%

***** 4.8 and 11.3 median MET-hr/wk groups combined for moderate vs. low activity comparison
* 22.6 and 46.8 median MET-hr/wk groups combined for high vs. low activity comparison
** Multivariate model adjusted for body mass index, age, and history of endoscopic screening or polyp diagnosis, family history of colorectal cancer, smoking, aspirin use, folate, alcohol, methione, dietary fiber and red meat intake

Table 42.2. Longnecker et al. (Case-Control; Males)

Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Multivariate-Adjusted Effect Measure 1**	Multivariate-Adjusted Effect Measure 2***	% Difference between Multivariate-adjusted2 and Unadjusted Effect Measures
0	1.0	1.0	1.0	1.0	-
≤1/2		1.06 (0.38-2.94)	0.73 (0.23-2.29)	0.81 (0.26-2.54)	-30.86%
1	0.57 (0.24-1.36)	0.57 (0.24-1.36)	0.47 (0.16-1.36)	0.36 (0.11-1.14)	-21.28%
2+	0.67 (0.44-1.02)	0.67(0.44-1.02)	0.60 (0.35-1.00)	0.57 (0.33-0.97)	-17.54%

* 0 and ≤1/2 hr/wk groups combined for low activity and compared to 1 hr/wk for moderate vs. low activity
* 0 and ≤1/2 hr/wk groups combined for low activity and compared to 2+ hrs/wk for high vs. low activity
** Multivariate model adjusted for smoking, income , race, family history of colorectal cancer, body mass index, and alcohol intake
*** Multivariate model adjusted for same variables as above, as well as total energy, fat, fiber, and calcium intake

Table 42.3. White et al. (Case-Control; Males)

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure*	% Difference between Age-Adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	-
≤ 7.30	0.61 (0.41-0.91)	0.63 (0.37-1.05)	0.64 (0.38-1.07)	1.56%
7.30-17.88		0.74 (0.45-1.22)	0.59 (0.37-0.96)	-25.42%
≥ 17.88	0.66 (0.41-1.08)	0.66 (0.41-1.08)	0.69 (0.42-1.13)	4.35%

* ≤ 7.30 and 7.30-17.88 MET-hr/wk groups combined for moderate vs. low activity comparison
** Model only adjusted for age and no other variables

Table 42.4. White et al. (Case-Control; Females)

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure**	% Difference between Age-Adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	-
≤ 7.30	0.99 (0.64-1.53)	0.84 (0.49-1.43)	0.87 (0.51-1.49)	3.45%
7.30-17.88		1.18 (0.68-2.03)	1.20 (0.69-2.08)	1.67%
≥ 17.88	0.74 (0.41-1.32)	0.74 (0.41-1.32)	0.60 (0.41-1.34)	-23.33%

* ≤ 7.30 and 7.30-17.88 MET-hr/wk groups combined for moderate vs. low activity comparison
** Model only adjusted for age and no other variables

Table 42.5. Martinez et al. (Cohort; Females)

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure**	Multivariate-Adjusted Effect Measure***	% Difference between Multivariate Adjusted and Unadjusted Effect Measures
<2	1.0	1.0	1.0	1.0	-
2-4		0.69 (0.49-0.95)	0.69	0.71 (0.44-1.15)	2.82%
5-10		0.73 (0.48-1.13)	0.74	0.78 (0.50-1.20)	6.41%
11-21	0.81 (0.58-1.13)	0.65 (0.41-1.03)	0.65	0.67 (0.42-1.07)	2.99%
>21	0.62 (0.39-0.99)	0.62(0.39-0.99)	0.52	0.54 (0.33-0.90)	-14.81%

* <2 and 2-4 MET-hr/wk groups combined in low group and 5-10 and 11-21 MET-hr/wk groups combined in moderate group for moderate vs. low activity analysis

** No confidence intervals reported for the age-adjusted effect measures

*** Multivariate model adjusted for age, cigarette smoking, family history of colorectal cancer, body mass index, postmenopausal hormone use, aspirin use, red meat intake, and alcohol consumption

Table 42.6. Tang et al. (Case-Control; Males)

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis	Age-Adjusted Effect Measure 1	Multivariate-Adjusted Effect Measure 2*	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	-
<20	4.29 (0.85-21.41)	4.65 (0.54-40.12)	2.22 (0.68-7.21)	-93.24%
>20	0.20 (0.06-0.68)	0.11 (0.01-0.87)	0.19 (0.05-0.77)	-5.26%

* Multivariate model adjusted for total energy intake, dietary fiber, total vegetable protein, smoking, alcohol use, and water intake

Table 42.7. Tang et al. (Case-Control; Females)

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis	Age-Adjusted Effect Measure*	Multivariate-Adjusted Effect Measure**	Percent Difference between Multivariate-adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	-
<20	0.94 (0.20-4.41)	0.88 (0.11-7.09)	0.52 (0.13-2.03)	-80.77%
>20	0.81 (0.23-2.92)	0.78 (0.19-3.14)	0.63 (0.18-2.18)	-28.57%

* Multivariate model adjusted for total energy intake, dietary fiber, total vegetable protein, and water intake

Table 42.8. Calton et al. (Prospective Cohort; Females)

Hours Per Day*	Combined Unadjusted Effect Measure Used in Meta-Analysis	Unadjusted Effect Measure	Age-Adjusted Effect Measure*	Multivariate-Adjusted Effect Measure***	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	1.0	-
0.1-1.0		0.82 (0.59-1.14)	1.02 (0.73-1.43)	1.19 (0.85-1.66)	31.09%
1.1-2.0	0.70 (0.48-1.01)	0.70 (0.48-1.01)	0.78 (0.53-1.14)	0.87 (0.59-1.29)	19.54%
2.1-14.0	0.95 (0.69-1.31)	0.95 (0.69-1.31)	0.99 (0.71-1.39)	1.10 (0.78-1.55)	13.64%

* Hours per Day converted to Hours per Week
* MET value assumed from activities listed in study to estimate MET-hours/week
** 0 and 0.1-1.0 Hr/day groups combined in low activity group for moderate and high vs. low activity analyses
*** Multivariate model adjusted for age, body mass index, education, family history of colorectal cancer, smoking status, menopausal hormone use, aspiring use, alcohol consumption, energy intake, calcium intake, and red meat intake

Table 43. Overview of the Effects of Confounding Variables – Breast Cancer

Table 43 shows the physical activity quantification level (e.g. # of MET Hours-Per-Week), the unadjusted effect measure for each of the combined physical activity categories, the unadjusted effect measure, age-adjusted effect measure (where included in the original study), and multivariate-adjusted effect measure (where included in the original study) are included for each individual physical activity categorization level. Finally, the percent different between the unadjusted effect measure and multivariate-adjusted effect measure (except in cases where only age-adjusted was reported) for each individual physical activity categorization level were calculated and reported. For each of the studies included in the meta-analyses, weekly physical activity quantifications were analyzed across three categories – low, moderate, and high activity. For some studies this required combining some of the original physical activity categories.

Table 43.1. Thune et al. (Case-Control) – Pre and Postmenopausal Females Combined

Hours Per Week*	Combined Unadjusted Effect measure Used In Meta-Analysis	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
<2	1.0	1.0	1.0	-
2-4	0.89 (0.68-1.16)	0.98 (0.75-1.28)	0.93 (0.71-1.22)	4.30%
≥5	0.65 (0.43-0.97)	0.67 (0.44-1.00)	0.63 (0.42-0.95)	-3.17%

* MET values developed based on reported activities in study to estimate MET-hours per week
** Multivariate model adjusted for age, body mass index, height, county of residence, and number of children

Table 43.2. Carpenter et al. (Case-Control) – Postmenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect measure Used in Meta-Analysis*	Unadjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0		1.0	1.0	-
0.1-3.74	1.0	0.82 (0.59-1.15)	0.86 (0.60-1.23)	4.65%
3.75-8.74		0.94 (0.67-1.31)	0.92 (64-1.31)	-2.17%
8.75-17.59	1.04 (0.77-1.41)	1.04 (0.77-1.41)	1.07 (0.77-1.49)	2.80%
≥ 17.6	.70 (0.52-0.95)	.70 (0.52-0.95)	0.81 (0.57-1.15)	13.58%

* 0, 0.1-3.74, and 3.75-8.74 MET-hr/wk groups combined into low activity group for moderate vs. low activity analysis
** Multivariate model adjusted for body mass index, age at first full-term pregnancy, family history of breast cancer, age at menarche, and age at menopause

Table 43.3. Levi et al. (Case-Control) – Pre and Postmenopausal Females Combined

Hours Per Week	Combined Unadjusted Effect measure Used in Meta-Analysis*	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
<2	1.0	1.0	1.0	-
2-4	0.45 (0.33-0.60)	0.43 (0.28-0.67)	0.44 (0.28-0.70)	-2.27%
≥5	0.39 (0.22-.0.67)	0.39 (0.21-0.72)	0.42 (0.22-0.80)	7.14%

* Multivariate model adjusted for age, education, age at menarche, age at first birth, number of births, menopausal status, age at menopause, caloric intake, previous benign breast disease, and breast cancer history in first-degree relatives

Table 43.4. Rockhill et al. (Prospective Cohort) – Pre and Postmenopausal Females Combined

Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
<1	1.0	1.0	1.0	1.0	-
1.0-1.9	0.86 (0.79-0.94)	0.86 (0.77-0.96)	0.90 (0.81-1.00)	0.88 (0.79-0.98)	2.27%
2.0-3.9		0.87 (0.78-0.96)	0.91 (0.82-1.00)	0.89 (0.81-0.99)	2.25%
4.0-6.9	0.79 (0.72-0.87)	0.83 (0.75-0.92)	0.88 (0.80-0.97)	0.85 (0.77-0.94)	2.35%
≥7		0.65 (0.55-0.76)	0.81 (0.69-0.95)	0.82 (0.70-0.97)	20.73%

*1.0-1.9 and 2.0-3.9 hr/wk groups combined in moderate activity group for moderate vs. low activity analysis
*4.0-6.9 and ≥7 hr/wk groups combined in high activity group for high vs. low activity analysis
** Multivariate model adjusted for age, age at menarche, history of benign breast disease, breast cancer history in first degree relative, height, parity, age at first birth, body mass index, menopausal status, and postmenopausal hormone use

Table 43.5. Moradi et al. (Case-Control) – Postmenopausal Females

Hours Per Week*	Combined Unadjusted Effect measure Used in Meta-Analysis**	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure***	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
>2	0.82 (0.71-0.93)	0.82 (0.71-0.93)	1.0	1.0	18.00%
1-2	1.10 (0.96-1.26)	1.10 (0.96-1.26)	1.3 (1.2-1.5)	1.3 (1.1-1.5)	15.38%
<1		0.96 (0.86-1.16)	1.2 (1.0-1.4)	1.1 (1.0-1.3)	12.73%
0	1.0	1.0	1.3 (1.1-1.5)	1.3 (1.1-1.5)	-

*Most active group instead of sedentary group used as the reference group
** 0 and <1 hr/wk groups combined in low activity group for moderate and high vs. low activity analyses
*** Multivariate model adjusted for age, age at menarche, parity, age at first birth, body mass index, height, use of hormone replacement therapy, age at menopause, and use of oral contraceptives

Table 43.6. Friedenreich et al. (Case-Control) – Premenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0 - <6.7	1.0	1.0	1.0	1.0	-
6.7 - <11.8		0.75 (0.52-1.09)	0.76 (0.53-1.11)	0.81 (0.55-1.19)	7.41%
11.8 - <20.7	0.86 (0.63-1.18)	0.98 (0.69-1.40)	1.00 (0.70-1.44)	1.03 (0.70-1.52)	4.85%
≥ 20.7	1.00 (0.70-1.43)	1.00 (0.70-1.43)	1.00 (0.70-1.45)	1.13 (0.77-1.66)	11.50%

* 6.7- <11.8 and 11.8- <20.7 MET-hr/wk groups combined in moderate activity group for moderate vs. low activity analysis

** Multivariate model adjusted for age, waist-hip ratio, education, hormone replacement therapy use, benign breast disease, breast cancer history in first-degree relatives, alcohol consumption, and cigarette smoking

Table 43.7. Friedenreich et al. (Case-Control) – Postmenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0 - <5.1	1.0	1.0	1.0	1.0	-
5.1 - <9.4	0.85 (0.67-1.09)	0.89 (0.67-1.17)	0.89 (0.67-1.19)	0.96 (0.71-1.28)	7.29%
9.4 - <16.9		0.82 (0.62-1.08)	0.82 (0.61-1.09)	0.88 (0.65-1.19)	6.82%
≥ 16.9	0.91 (0.68-1.20)	0.91 (0.68-1.20)	0.93 (0.70-1.23)	1.10 (0.82-1.47)	17.27%

* 5.1- <9.4 and 9.4- <16.9 MET-hr/wk groups combined in moderate activity group for moderate vs. low activity analysis

** Multivariate model adjusted for age, waist-hip ratio, education, hormone replacement therapy use, benign breast disease, breast cancer history in first-degree relatives, alcohol consumption, and cigarette smoking

Table 43.8. Matthews et al. (Case-Control) – Pre and Postmenopausal Females Combined

MET-Hours Per Day*	Combined Unadjusted Effect Measure Used in Meta-Analysis**	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure***	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	1.0	-
0.01-0.35		0.58 (0.40-0.83)	0.56 (0.39-0.80)	0.54 (0.37-0.79)	-7.41%
0.36-0.88	0.83 (0.67-1.03)	0.88 (0.67-1.17)	0.80 (0.60-1.07)	0.78 (0.58-1.05)	-12.82%
0.89-1.91		0.71 (0.58-0.89)	0.66 (0.48-0.91)	0.66 (0.47-0.92)	-7.58%
1.92 +	0.48 (0.33-0.68)	0.48 (0.33-0.68)	0.40 (0.28-0.58)	0.40 (0.27-0.59)	-20.00%

* MET-Hr/day converted to MET-Hr/wk

** 0 and 0.01-0.35 MET-hr/day groups were combined in low activity group for moderate and high vs. low activity analyses

** 0.36-0.88 and 0.89-1.91 MET-hr/day groups were combined in moderate activity group for moderate vs. low activity analysis

*** Multivariate model adjusted for age, education, household income, breast cancer history in first-degree relatives, history of benign breast disease, age at menarche, age at first birth, and age at menopause

Table 43.9. Dirx et al. (Cohort) – Postmenopausal Females

Average MET Scores*	Combined Unadjusted Effect Measure	Age-Adjusted Effect Measure**	Multivariate-Adjusted Effect Measure***	Percent Difference between Adjusted and Unadjusted Effect Measures
<4	1.0	1.0	1.0	-
4.01-6.00	1.17 (0.87-1.55)	1.09	1.11 (0.74-1.66)	-5.41%
>6.00	1.15 (0.86-1.52)	1.12	1.07 (0.71-1.60)	-7.48%

*METs combined with estimated hours-per-week of activity to estimate MET-hours per week of lifetime sports and exercise participation

** No confidence intervals reported with age-adjusted effect measures

** Multivariate model adjusted for age, age at menarche, age at menopause, history of benign breast disease, parity, age at first birth, breast cancer history in first-degree relatives, education, height, alcohol consumption, and energy intake

Table 43.10. McTiernan et al. (Prospective Cohort) – Postmenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect measure Used In Meta-Analysis*	Unadjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0	1.0	1.0	1.0	-
≤5.0		0.96 (0.81-1.13)	0.90 (0.77-1.07)	-6.67%
5.1-10.0		0.91 (0.76-1.08)	0.82 (0.68-0.97)	-10.98%
10.1-20.0	0.62	1.02 (0.88-1.20)	0.89 (0.76-1.00)	-14.61%
20.1-40.0		0.98 (0.83-1.15)	0.83 (0.70-0.98)	-18.07%
>40.0	0.61	0.89 (0.71-1.13)	0.78 (0.62-1.00)	-14.10%

* 0 and ≤5.0 MET-hr/wk groups combined in low activity group for moderate and high vs. low activity analyses
* 5.1-10.0 and 10.1-20.0 MET-hr/wk groups combined in moderate activity group for moderate vs. low activity analysis
* 20.1-4.0 and >40.0 MET-hr/wk groups combined in high activity group for high vs. low activity analysis
** Multivariate model adjusted for age, age at menarche, age at menopause, body mass index, hormone therapy status, race, geographic location, income, education, breastfed status, hysterectomy status, breast cancer history in first degree relative, smoking status, parity, age at first birth, number of mammograms in 5 years prior to study enrollment, and alcohol consumption

Table 43.11. Yang et al. (Case-Control) – Pre and Postmenopausal Females Combined

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Multivariate-Adjusted Effect Measure 1**	Multivariate-Adjusted Effect Measure 2***	% Difference between Multivariate2 Adjusted and Unadjusted Effect Measures
0		1.0	1.0	1.0	-
≤3	1.0	0.93 (0.60-1.43)	0.84	0.91 (0.55-1.49)	-2.20%
>3-6		0.69 (0.43-1.12)	0.64	0.67 (0.39-1.10)	-2.99%
>6-12	0.64 (0.47-0.87)	0.64 (0.47-0.87)	0.52	0.53 (0.31-0.90)	-20.75%
>12	0.54 (0.40-0.74)	0.54 (0.40-0.74)	0.45	0.47 (0.28-0.80)	-14.89%

* 0, ≤3, and >3-6 MET-hr/wk groups combined into low activity group for moderate and high vs. low activity analyses
** No confidence intervals reported with first multivariate-adjusted model
** Multivariate-adjusted model 1 adjusted for age, ethnicity, education, and migration history
** Multivariate-adjusted model 2 adjusted for age, ethnicity, education, migration history, parity, family history of breast cancer, menopausal status, job activity category, and soy intake

Table 43.12. Patel et al. (Cohort) – Postmenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
>0 – 7.0	1.0	1.0	1.0	1.0	-
> 7.0 – 17.5	0.95 (0.85-1.07)	0.95 (0.85-1.07)	0.92 (0.82-1.04)	0.92 (0.81-1.04)	0
> 17.5 – 31.5		0.93 (0.80-1.07)	0.92 (0.80-1.07)	0.94 (0.81-1.09)	1.06%
>31.5 – 42.0	0.91 (0.80-1.04)	0.76 (0.55-1.05)	0.76 (0.55-1.05)	0.77 (0.56-1.06)	1.30%
>42.0		0.70 (0.49-1.01)	0.70 (0.49-1.01)	0.71 (0.49-1.02)	1.41%

* >17-31.5, >31.5-42.0, and >42.0 MET-hr/wk groups combined in high activity group for high vs. low activity analysis

** Multivariate model adjusted for age, race, body mass index, lifetime weight change, family history of breast cancer, history of benign breast disease, duration of oral contraceptive use, hormone replacement therapy use, parity, age at menarche, age at menopause, smoking, alcohol consumption, caloric intake, education, and mammography history

Table 43.13. Patel et al. (Case-Control) – Pre and Postmenopausal Females Combined

MET-Hours Per Week	Combined Unadjusted Effect measure Used in Meta-Analysis*	Unadjusted Effect measure	Age-Adjusted Effect measure	Multivariate-Adjusted Effect measure**	% Difference between Multivariate-adjusted and Unadjusted Effect measures
0	1.0	1.0	1.0	1.0	-
>0-3.0		0.84 (0.59-1.20)	0.84 (0.59-1.20)	0.70 (0.48-1.03)	-20.00%
>3.0-8.0		0.83 (0.58-1.20)	0.84 (0.58-1.20)	0.65 (0.44-0.96)	-27.69%
>8.0-16.0	1.00 (0.73-1.34)	1.00 (0.73-1.34)	0.89 (0.61-1.29)	0.61 (0.41-0.92)	-63.93%
>16.0-32.0		0.96 (0.64-1.44)	0.96 (0.64-1.44)	0.63 (0.40-0.98)	-52.38%
>32.0	1.10 (0.83-1.46)	1.00 (0.63-1.60)	1.00 (0.63-1.60)	0.65 (0.39-1.08)	-53.85%

* 0, >0-3.0, >3.0-8.0 MET-hr/wk groups combined into low activity group for moderate and high vs. low activity analyses
* >16.0-32.0 and >32.0 MET-hr/wk groups combined into high activity group for high vs. low activity analyses
** Multivariate model adjusted for age, race, age at menarche, income, body mass index, family history of breast cancer, menopausal status, age at menopause, postmenopausal hormone use, smoking, and number of pregnancies

Table 43.14. Colditz et al. (Prospective Cohort) – Premenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect Measure Used in Meta-Analysis*	Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
<3.0	1.0	1.0	1.0	1.0	-
>3.0-8.9		1.08 (0.84-1.36)	1.07 (0.84-1.37)	1.05 (0.82-1.33)	-2.86%
9.0-17.9	0.93 (0.77-1.11)	0.93 (0.77-1.11)	0.99 (0.77-1.26)	0.95 (0.74-1.21)	2.11%
18.0-26.9		1.04 (0.80-1.36)	1.08 (0.83-1.41)	1.03 (0.79-1.35)	-0.97%
>27.0	0.96 (0.82-1.12)	0.99 (0.77-1.25)	1.07 (0.84-1.36)	1.04 (0.82-1.33)	4.81%

* <3.0 and >3.0-8.9 MET-hr/wk groups combined into low activity group for moderate and high vs. low activity analyses
* 18.0-26.9 and >27.0 MET-hr/wk groups combined into high activity group for high vs. low activity analysis
** Multivariate model adjusted for age, height, alcohol consumption, age at menarche, age at first birth, oral contraceptive use, history of benign breast disease, breast cancer history in first degree relative, and body mass index

Table 43.15. John et al. (Case-Control) – Premenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure*	Percent Difference between Adjusted and Unadjusted Effect Measures
<6.8	1.0	1.00	1.00	-
6.8-16.6	0.94 (0.69-1.28)	0.94 (0.69-1.29)	1.05 (0.75-1.47)	10.48%
≥16.7	0.55 (0.39-0.77)	0.56 (0.40-0.78)	0.67 (0.46-0.96)	17.91%

* Multivariate model adjusted for age, race/ethnicity, country of birth, education, breast cancer family history, prior biopsy for benign breast disease, age at menarche, parity, age at first full-term pregnancy, breast-feeding status, and body mass index

Table 43.16. John et al. (Case-Control) – Postmenopausal Females

MET-Hours Per Week	Combined Unadjusted Effect Measure	Age-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure*	Percent Difference between Adjusted and Unadjusted Effect Measures
<7.6	1.0	1.00	1.00	-
7.6-17.7	0.79 (0.64-0.98)	0.79 (0.64-0.98)	0.85 (0.68-1.06)	7.06%
≥17.8	0.68 (0.54-0.85)	0.70 (0.56-0.88)	0.74 (0.59-0.94)	8.11%

* Multivariate model adjusted for age, race/ethnicity, country of birth, education, breast cancer family history, age at menarche, parity, breast-feeding status, and age at menopause

Table 43.17. Bernstein et al. (Case-Control) – Pre and Postmenopausal Females Combined

MET-Hours Per Week	Combined Unadjusted Effect Measure Used In Meta-Analysis*	Unadjusted Effect Measure	Age and Race-Adjusted Effect Measure	Multivariate-Adjusted Effect Measure**	% Difference between Multivariate-adjusted and Unadjusted Effect Measures
0		1.0	1.0	1.0	-
<2.2	1.0	0.96 (0.85-1.09)	0.95 (0.84-1.08)	0.93 (0.82-1.06)	-3.23%
2.3-6.6		0.94 (0.83-1.06)	0.92 (0.81-1.04)	0.87 (0.77-0.99)	-8.05%
6.7-15.1	0.98 (0.88-1.09)	0.98 (0.88-1.09)	0.87 (0.77-0.99)	0.82 (0.71-0.93)	-19.51%
≥15.2	0.90 (0.81-1.00)	0.90 (0.81-1.00)	0.85 (0.75-0.97)	0.80 (0.70-0.92)	-12.50%

* 0, <2.2, and 2.3-6.6 MET-hr/wk groups combined into low activity group for moderate and high vs. low activity analyses

** Multivariate model adjusted for age, race, study site, exercise activity questionnaire type, breast cancer history in a first degree relative, age at menarche, menopausal status, age at menopause, age at first term pregnancy, total number of term pregnancies, body mass index, and number of months of breastfeeding

Chapter IV

Discussion

The relationship between physical activity and cancer of the colon and breast is complex. The quantity of activity is likely an important factor in the reduction of risk of developing these two cancers, as combined effect measures of studies using the *Compendium* indicate that higher amounts of leisure-time physical activity appear to reduce the risk for colon cancer among males and females, and reduce the risk of breast cancer for postmenopausal females. However, the association between activity and premenopausal breast cancer risk remains unclear. While the physical activity quantification instrumentation was consistent among studies included in the meta-analyses (i.e. all studies used the *Compendium*), physical activity quantification categories differed widely across studies. Additionally, methodological differences such as the number and demographic characteristics of individuals studied, length of time that physical activity was measured, and potential confounding variables inevitably differed among studies. Future studies examining the relationship between physical activity and cancer risk should stratify pre- and postmenopausal females in their analyses, and should also adhere to both a standardized questionnaire for assessing modes of physical activity and standard time-frame for physical activity measurement.

Colon Cancer Meta-Analyses

Methodological Differences between Studies of Colon Cancer Risk among Males

Three case-control studies (Longnecker et al., 1995; White et al., 1996; Tang et al., 1999) and one cohort study (Giovannucci et al., 1995) examined the effects of activity on colon cancer risk among males between 1985 and 1992. The race of participants was one source of differences among studies. One study (Giovannucci et al.) did not report the race distribution while two studies (Longnecker et al.; White et al.) consisted of Caucasian individuals residing in the United States. A fourth study (Tang et al.) examined colon cancer risk among Taiwanese males.

The measurement of physical activity also differed among studies, as the time physical activity was measured ranged from the year prior to follow-up (Tang et al.) to ten years prior to follow-up (White et al., 1996). The quantification of physical activity also differed among studies. Three studies (Giovannucci et al.; White et al.; Tang et al.) quantified physical activity using the *Compendium of Physical Activities*, however, Giovannucci et al. reported median MET hours-per-week, while the remaining studies reported mean MET hours-per-week [80]. Although the mean and median are different, the categories of amounts of physical activity were large enough to allow for the use of both measures. One additional study (Longnecker et al., 1995) quantified physical activity in hours per week and reported specific types of physical activity, which allowed for an estimation of MET hours-per-week using the *Compendium*. Common physical activities reported for most studies of male colon cancer risk included walking, running, tennis, and bicycling. Three studies (Giovannucci et al.; Longnecker et al.; Tang et al.) assessed physical activity using a self-developed questionnaire, while White et al. used a

questionnaire previously developed by Taylor et al. [150]. While some studies included analyses of both leisure-time and occupational activity, only analyses examining the effect of leisure-time physical activity on colon cancer risk were included in the meta-analyses to allow comparability among studies included in the analyses.

Methodological Differences between Studies of Colon Cancer Risk among Females

Two case-control studies (White et al., 1996; Tang et al., 1999) and two cohort studies (Martinez et al., 1997; Calton et al., 2006) were included in the analyses of colon cancer risk among females, and risk was assessed between 1985 and 1998. Again, the race of participants differed among studies. While Martinez et al. did not specifically report a race distribution, the majority of females were likely Caucasian American females, as the dataset was taken from the U.S. Nurses' Health Study. Two other studies (White et al.; Calton et al.) primarily included White females, while Tang et al. examined Taiwanese females.

The time span of physical activity measurement ranged from the previous year (Calton et al.) to ten years prior to follow-up (White et al.). Three studies (White et al.; Martinez et al.; Tang et al.) directly quantified physical activity using the *Compendium*, while Calton et al. report activity in hours per week along with the typically completed physical activities, allowing for an estimation of the quantity of physical activity using the *Compendium*. Typical activities reported by all studies of female colon cancer risk included walking, running, bicycling, and swimming.

Two studies (Tang et al.; Calton et al.) used self-developed instrumentation for physical activity assessment, while White et al. used a questionnaire developed by Taylor et al., and Martinez et al. used the physical activity questionnaire from the Nurses Health Study developed by Wolf et al. [149]. Only leisure-time physical activities were included in the analyses of female colon cancer risk.

Discussion of Results of Colon Cancer Meta-Analyses

Analysis I

A non-statistically significant difference in the risk of developing colon cancer between moderate and low exercising males was found in Analysis I (Pooled Effect Measure = 0.817 (95% CI = 0.484-1.379), $p = 0.449$). This lack of statistical significance was probably due to one of the studies (Tang et al.) that included an increased unadjusted effect measure of colon cancer for those with moderate compared to low activity (OR = 4.286). It is highly improbable that a greater amount of activity would be associated with such a large increase in colon cancer risk. However, the Tang study included only twelve males in the moderate activity group and fifty-two males in the low activity group. Each study was given a weight based on sample size relative to other studies included in a given analysis. While Analysis I gave the Tang et al. study a weight of only 8.92%, the resulting effect measure of this analysis after excluding the Tang et al. study was 0.707 (95% CI = 0.546-0.915), indicating that the unusual effect measure for this small study did indeed affect the overall results. The other studies included in this analysis had lower effect measures that were in the direction expected for a protective effect (Giovannucci et al. = 0.788; White et al. = 0.606).

Such a disparity did not exist in the analysis of the high versus low activity males in Analysis I. In this group, Tang et al. found a effect measure of 0.202 (95% CI = 0.060-0.682), while Giovannucci et al. and White et al. had effect measures of 0.527 (95% CI = 0.364-0.760) and 0.664 (95% CI = 0.408-1.080), respectively. The pooled effect measure for this meta-analysis was 0.525, and was statistically significant (p = .002). While this effect measure indicated more of a protective effect for the high versus low activity group compared to the moderate versus low activity group, it is difficult to compare these results due to the presence of the unusual Tang results for the moderate versus low activity groups.

Analysis II

Among females, a non-statistically significant difference for the risk of colon cancer was found between moderate and low activity groups (Pooled Effect Measure = 0.872; p = 0.303). Again, as in Analysis I for males, a statistically significant difference in colon cancer risk was found for high versus low activity females (Pooled Effect Measure = 0.673, p = 0.027). Overall, females had a slightly smaller effect, although comparable, for both moderate and high amounts of activity compared to males (0.872 to 0.817 and 0.673 to 0.524, respectively).

Analysis III

When an additional study with *Compendium*-estimated activity (Longnecker et al.) was added to the analysis of male colon cancer risk, the difference between the moderate and low active groups remained non-statistically significant (Pooled Effect

Measure = 0.750, p = 0.174). However, the overall risk level and level of significance were lower with the additional study, possibly providing further evidence that the unusual findings of Tang et al. study may have caused a misinterpretation of an otherwise potentially statistically significant reduction in colon cancer risk among moderately active males. For the high versus low analysis, a statistically significant difference between the two groups remained (Pooled Effect Measure = 0.574, p = <0.001), similar to Analysis I.

Analysis IV

When the *Compendium*-estimated Calton et al. study was added to the analysis of female colon cancer risk), a nearly significant difference was seen between the moderate and low activity groups (Pooled Effect Measure = 0.809, p = 0.051). The lower effect measure and level of significance could be due to additional subjects in the meta-analysis provided by the Calton et al. study. The difference in effect measures between high and low activity females was no longer statistically significant in this Analysis (Pooled Effect Measure = 0.814, p = 0.087). However, the weight for the Calton et al. study was 54.93% due to a much greater number of subjects in this study compared to the others included in this analysis. Because this study did not find a significant relationship between physical activity and colon cancer risk, results from this particular meta-analysis were likely influenced by this study.

Mixed Effects Meta-Regression Model

No significant differences in colon cancer risk were found between moderate activity males and females or between high activity males and females. However, the non-significant findings must be considered with the fact that a smaller number of studies examined the effect of physical activity on colon cancer risk by sex. Because only three studies reported results of *Compendium*-quantified activity on colon cancer risk by sex, the sample size was small, resulting in an imprecise estimate. Results from the colon cancer mixed effects models are presented in Appendix IV.

Application of Results from Colon Cancer Analyses

Results from the present meta-analyses indicate that weekly leisure-time physical activity amounting to approximately 16 MET hours-per-week or more is associated with a 48% and 33% decrease in the odds of developing colon cancer among high versus low activity males and females, respectively, although the magnitude of this reduction varies between the two sexes (Effect measure = 0.524, males; Effect measure = 0.673, females) and is subject to the variability among individual study effect measures, as only three studies were included in the analyses. These results are relevant for exercise programmers and specialists planning to prescribe physical activity for high-risk individuals. Walking at a brisk pace of 4.0 miles-per-hour on a level firm surface for at least four hours weekly, bicycling at a general pace for more than two hours per week, running a 12 minute mile twice per week, swimming freestyle laps at a slow effort for approximately two-and-a-half hours weekly, and even golfing for five hours weekly

while using a power cart, are examples of meeting the recommended requirement of at least 16 MET hours-per-week.

Potential Confounding for Colon Cancer Meta-Analyses

Many individual studies adjusted their effect measures for potentially confounding factors. Most studies adjusted for age, while typical variables in the multivariate-adjusted models of the original studies included age, body mass index, total caloric intake, smoking, total fiber intake, and alcohol consumption. Comparisons between the unadjusted effect measures from the present analyses and the multivariate (where applicable) or age-adjusted (where applicable) effect measures from the original studies were reasonably similar for five of the six studies, as the percent difference between the estimates for these studies ranged from 0 to 31%. However, one study (Tang et al.) consistently had greater percent differences between the adjusted and unadjusted effect measures (5% to 93% across various physical activity categorizations) [83]. Such differences may be due to the smaller number of subjects in this study. Specifically, in a study with a small sample size, even a few individuals that are associated with confounding variables that could potentially influence the relationship between physical activity and colon cancer risk could result in a substantial difference between the unadjusted and adjusted effect measures.

Breast Cancer Meta-Analyses

Methodological Differences between Studies in Breast Cancer Analyses

Five case-control studies (Levi et al., 1999; Matthews et al., 2001; Yang et al., 2003; Patel et al., 2003; Bernstein et al., 2005) and two cohort studies (Thune et al., 1997; Rockhill et al., 1999) examined the effects of physical activity on breast cancer risk among combined pre- and postmenopausal females, while two additional case-control studies (Friedenreich et al., 2001; John et al., 2001) assessed the effect of activity on pre- and postmenopausal females separately. The relationship between physical activity and postmenopausal breast cancer risk was assessed in two case-control studies (Carpenter et al., 1999; Moradi et al., 2000) and three cohort studies (Dirx et al., 2001; McTiernan et al., 2003; Patel et al. 2003). Finally, Colditz et al. (2003) assessed the relationship between activity and premenopausal breast cancer risk.

Females of different races and geographic locations were included in the breast cancer analyses. Specifically, two studies (McTiernan et al.; Patel et al.) primarily included White females from throughout the United States, and while Colditz et al. and Rockhill et al. did not specifically report a race distribution, the females were participants in the U.S. Nurses' Health Study and most participants were likely White. Two additional studies (Patel et al.; Bernstein et al.) had a majority of White females, but also included a substantial proportion of Black females (16% and 35%, respectively). Patel et al. studied females from Los Angeles County, while Bernstein et al. studied females from five Surveillance, Epidemiology, and End Results (SEER) cancer registries: Los Angeles, Atlanta, Detroit, Seattle and Philadelphia. Carpenter et al. included residents of Los Angeles County that were mostly White, but also Hispanic, while John et al. included

residents of the San Francisco Bay Area that were primarily Latina, but also White and Black. Yang et al. studied the relationship between physical activity and breast cancer risk among Asian American residents of Los Angeles County.

Some studies examined females from other countries. Friedenreich et al. studied White females from Alberta, Canada, while Thune et al. studied Norwegian females, Moradi et al. studied Swedish females, Levi et al. studied Swiss females, and Dirx et al. included females from the Netherlands. Matthews et al. examined the relationship between physical activity and breast cancer risk among Chinese females.

Ten of the fifteen studies included in the meta-analyses for breast cancer risk directly quantified physical activity using the *Compendium*, whereas the five remaining studies provided a weekly amount of activity and description of physical activities (Thune et al.; Rockhill et al.; Levi et al.; Moradi et al.) or MET value (Dirx et al.) allowing MET hours-per-week to be estimated using the *Compendium*. All of the studies listed above were included in *Compendium*-quantified and/or *Compendium* quantified and estimated meta-analyses of pre- and postmenopausal females combined. Activities reported for a majority of studies included walking, jogging, bicycling, swimming aerobics, and calisthenics.

For the *Compendium* quantified and *Compendium* quantified and estimated analyses of pre- and postmenopausal females combined (Analyses I and III, respectively), the time span of physical activity measurement ranged from current (McTiernan et al.; Patel et al.) to lifetime (Carpenter et al.; Friedenreich et al.; Patel et al., John et al., Bernstein et al.). Analysis II only included studies measuring physical activity for at least ten years. The range of physical activity measurement for the analysis of premenopausal

females (Analysis IV) was ten years (Colditz et al.) to lifetime (Friedenreich et al., John et al.), while the range for the analyses of postmenopausal females (Analysis V – *Compendium* quantified; Analysis VI – *Compendium* quantified and estimated) was current (Dirx et al., McTiernan et al., Patel et al.) to lifetime (Carpenter et al., Friedenreich et al., John et al.). A majority of the studies in the breast cancer analyses used self-developed or unreported questionnaires for the assessment of physical activity (Thune et al.; Carpenter et al.; Levi et al.; Moradi et al.; Friedenreich et al., Matthews et al.; Dirx et al., McTiernan et al.; Patel et al. (cohort); Patel et al. (case-control). Three studies (Yang et al.; John et al.; Bernstein et al.) used a physical activity assessment instrument developed by Bernstein et al (1994), while two studies (Rockhill et al., Colditz et al.) used the physical activity assessment questionnaire from the Nurses' Health Study developed by Wolf et al [147, 148].

Results of Breast Cancer Meta-Analyses

Analysis I

A statistically significant difference was reported in the risk of developing breast cancer between moderate and low activity females (pre- and postmenopausal combined) in Analysis I (Pooled Effect Measure = 0.919; $p = 0.008$). This indicates that females completing a moderate amount of activity had approximately 8% lower odds of developing breast cancer than women with a low amount of activity. While a difference of 8% does not indicate a substantial risk reduction compared to the low activity reference group, the difference was nonetheless statistically significant. Not surprisingly,

a statistically significant difference for the high activity versus low activity group was also present (Pooled Effect Measure = 0.816, $p = 0.001$).

Analysis II

Analysis II excluded two studies that assessed physical activity for less than ten years, but still reported similar results among combined pre- and postmenopausal females for the moderate versus low activity group (Pooled Effect Measure = 0.890, $p = 0.007$). A result that was similar to the one found in Analysis I was reported for the high versus low activity group for Analysis II (0.777, $p = 0.002$).

Analysis III

While Analyses I and II only included *Compendium* quantified studies, Analysis III included studies of pre- and postmenopausal females combined that both quantified and estimated physical activity using the *Compendium.* MET hours-per-week were estimated for five additional studies, allowing for a total of fifteen studies to be included in this meta-analysis. The pooled effect measure for the moderate versus low activity groups was 0.897 and the difference was statistically significant compared to the low exercising group ($p = 0.006$). The similarity of results for Analyses I and III suggests that including studies with estimated weekly MET hours-per-week did not change the effect size substantially for these particular breast cancer analyses. Given the statistically significant difference between the moderate and low groups, it was expected that the high activity females would also have a statistically significant difference in the pooled effect measure compared to the low activity group (Pooled Effect Measure = 0.797, $p < 0.001$),

and this was indeed the case. Once again, these results were similar to the findings of Analysis I, suggesting that the MET hours-per-week estimations were comparable to the direct *Compendium* quantifications and did not alter the analysis.

Analysis IV

Analysis IV was the first analysis that examined the relationship of physical activity on either premenopausal or postmenopausal breast cancer risk. In this analysis, a meta-analysis of *Compendium* quantified studies of premenopausal females, the pooled effect measure was 0.917 ($p = 0.222$), indicating that a non-statistically significant difference existed between the moderate and low activity groups, which is consistent with prior research reporting no relationship between physical activity and premenopausal breast cancer risk. For the high versus low premenopausal activity groups, the pooled effect measure was 0.820, but was not statistically significant ($p = 0.251$), suggesting little association between higher amounts of physical activity and premenopausal breast cancer risk.

Analysis V

Given the findings in Analyses I through IV, one might assume that the statistically significant findings reported in the analyses of combined pre- and postmenopausal females was likely attributable to the postmenopausal females included in those analyses. However, a non-statistically significant difference between the pooled effect measures of moderately active females and the low activity reference group was reported among postmenopausal females in this analysis (Pooled Effect Measure = 0.932,

$p = 0.090$). The result from this analysis is quite different than the result from the moderately active combined pre- and postmenopausal females combined in Analysis I. A statistically significant difference existed between the postmenopausal high and low activity groups (Pooled Effect Measure = 0.847, $p = 0.034$). This result was similar to that of pre-and postmenopausal females combined in Analysis I.

Analysis VI

When studies that could be estimated using the *Compendium* were included in addition to the directly quantified studies, the relationship between moderate physical activity and postmenopausal breast cancer risk remained non-statistically significant in this analysis (Pooled Effect Measure = 0.973, $p = 0.536$). Adding more studies to this analysis actually made Analysis VI less significant than Analysis V. Therefore, it may not be the number of females, but perhaps more heterogeneity in the measurement of physical activity that contributed to the differences in effect size between the two breast cancer meta-analyses.

Mixed Effects Meta-Regression Model

No statistically significant differences in breast cancer risk were found between moderate activity pre- and postmenopausal females or between high activity pre- and postmenopausal females. This finding was surprising as higher amounts of physical activity were associated with reduced breast cancer risk in the analyses of postmenopausal females only, but studies of premenopausal females only did not show the same effect. The non-statistically significant findings can most likely be attributed to

a lack of precision due to a much smaller number of studies that examined the effect of physical activity on breast cancer risk by menopausal status. Because few studies reported results by menopausal status, the sample size was small, resulting in an imprecise estimate. Results from the breast cancer mixed effects model are presented in Appendix IV.

Application of Results from Breast Cancer Analyses

Results from the breast cancer meta-analyses indicated that weekly leisure-time physical activity amounting to approximately 17 MET hours-per-week or more is likely associated with a 15% decrease in the odds of developing breast cancer among high versus low activity postmenopausal females (Effect measure = 0.847), although the relationship between physical activity and premenopausal breast cancer risk remains unclear. For health professionals prescribing physical activity to females at a higher risk for developing breast cancer, walking at a brisk pace of 3.5 miles-per-hour on a level firm surface for approximately five hours weekly, bicycling at a general pace for just over two hours per week, running an 11.5 minute mile twice per week, completing four hours of water aerobics classes weekly, swimming freestyle laps at a slower effort for two-and-a-half hours weekly, and completing two hours of step aerobics classes with a six to eight inch step each week are examples of meeting the recommended requirement of at least 17 MET hours-per-week.

Potential of Confounding for Breast Cancer Meta-Analyses

Comparisons between the unadjusted effect measures from the present analyses and the multivariate (where applicable) or age-adjusted (where applicable) effect measures from the original studies were reasonably similar for fourteen of the fifteen studies, as the percent difference between the estimates for these studies ranged from 0 to 21%. However, one case-control study (Patel et al.) consistently had greater percent differences between the multivariate-adjusted effect measure and age- and unadjusted effect measures, ranging from 20% to 64% [119]. This resulted in the calculated unadjusted effect measure being much higher than published multi-variate effect measure, and was one of only two effect measures that was greater than 1.0 among studies directly quantifying activity using the *Compendium*. It cannot be determined why such consistent differences existed across all physical activity MET hours-per-week categorizations for the Patel et al. study. The multivariate model for this study adjusted for many variables, including age, race, age at menarche, income, body mass index, family history of breast cancer, menopausal status, age at menopause, postmenopausal hormone use, smoking, and number of pregnancies. These variables, along with alcohol use, parity, and age at first birth represented the typical variables adjusted for in studies included in the breast cancer analyses. The type and number of adjusted variables were consistent with other studies that had substantially lower percent differences between unadjusted and adjusted effect measures. Additionally, the activity categorizations in the Patel et al. study (0, ≤3, 3-6, >6-12, and >12 MET hours-per-week) were comparable with other studies.

Limitations

Methodological Differences

Some of the studies included in the meta-analyses were cohort studies, while others were case-control studies. The cohort studies produced incidence density ratios or relative risks, while the case-control studies produced odds ratios. The different effect measures had to be combined in the meta-analyses. While the incidence density ratios and relative risks could be approximated to the odds ratios for a uniform effect measure for each of the meta-analyses, a degree of error in those mathematical approximations was inevitably present.

Demographic Differences

Individuals included in the meta-analyses (especially females in the breast cancer meta-analyses) represented a wide range of demographic groups (White, Black, Hispanic, and Asian Americans, White Canadians, Scandinavians, and Chinese). Despite the variety of demographic groups represented, effect measures were typically, but not always, similar across groups. For example, the effect measures of John et al. (White, Black, and Hispanic Americans), Friedenreich et al. (White Canadians), Yang et al. (Asian Americans), and Matthews et al. (Chinese), were all similar, while Bernstein et al. (White and Black Americans), and some of the studies of Scandinavian females had effect measures that were higher.

Assessment of Physical Activity

The physical activity assessment instrumentation, time span of activity measurement, and categorization of activity differed among studies. Most of the studies used their own instrumentation to assess the various types of activities being completed by the subjects. While the *Compendium* assists by providing a MET value for a given activity, regardless of how that activity was assessed, it would still be very helpful if studies of physical activity and cancer risk utilized a similar activity assessment questionnaire.

Additionally, the present analyses only examined the effect of leisure-time physical activity on the risk of colon and breast cancer risk. The effect of total physical activity, which is typically defined as the sum of leisure-time, occupational, and household activities, on cancer risk could not be assessed as most studies have not quantified total physical activity using the *Compendium*.

Measurement of Physical Activity

The length of time that physical activity was measured also varied among studies of colon and breast cancer risk, as the time span of measured activity ranged from current to lifetime activity. While an individual's current level of activity may be indicative of what that individual has completed in the past, more consistent and cumulative measurement of completed activity throughout the lifespan is important for assessing the relationship between physical activity and cancer risk. Although the effect measures in breast cancer analyses I and II were similar, it would probably be most helpful if activity were measured for at least ten years.

Some studies utilizing *Compendium*-quantified amounts of physical activity used MET hour-per-week ranges that likely were too large to determine the effects of specifically quantified physical activity on breast cancer risk. For example, if a study had an odds ratio of 0.88 for the 0.1-17.59 MET hour-per-week group, that odds ratio may have been lower if more individuals in the group exercised closer to the 17.59 cut-off point, while the OR may have been higher if more individuals in the group exercised closer to the 0.1 cut-off point for this group, which includes individuals who are nearly, but not quite, completely sedentary. Given the fact that each study utilized these different physical activity classifications (e.g. MET hours-per-week) of 'low', 'moderate', and 'high', exact cut-points for physical activity categorizations could not be used for all meta-analyses. This caused the activity cut-points between activity categories to include some degree of overlap. However, when all subjects and studies were included in the analyses, three groups ('low', 'moderate', and 'high') could be compared when assessing the relationship between physical activity and cancer risk.

Additionally, the analyses that also included studies for which *Compendium*-quantified physical activity were estimated rather than directly quantified were subject to the conditions qualifying the studies for inclusion in the meta-analyses. Specifically, noting the activities mentioned in the original studies and assigning a MET value from the *Compendium* was likely to be less accurate compared to a study that directly quantified activity using the *Compendium.* Similarly, assigning an arbitrary amount of activity completed during the week to accompany an activity of a given MET value reported in a study is likely to be less accurate than a study that directly quantified activity in MET hours-per-week from the beginning using the *Compendium*.

Potential for Confounding

It would be desirable to have original data from each study to make a more complete assessment of possible confounding factors. However, despite personalized requests mailed out from the University of Michigan to the original study authors, original data was unable to be obtained. The unadjusted analyses that were used did not allow for the direct adjustment for confounding variables or the assessment of effect modifying variables. Percent differences between unadjusted and age-adjusted or multivariate-adjusted effect measures were calculated to determine whether unadjusted results generally over- or overestimated differences between the high and moderate activity groups versus the low activity group. As discussed earlier in this chapter, five of six colon cancer studies and fourteen of fifteen breast cancer studies used in their respective reported percent differences of 0-31% and 0-21%. It is important to note that the use of the unadjusted effect measures did not bias the study results by consistently over- or underestimating the association of physical activity with cancer risk. There was no consistent pattern of variability between the unadjusted and adjusted effect measures, suggesting that no consistent bias in the results either toward over- or underestimating the risk reduction associated with activity categories existed.

While all of the aforementioned methodological factors could not be directly controlled, the most appropriate instrument for physical activity quantification was used (the *Compendium)*, and the most appropriate meta-analytical procedures were used, given the total number of subjects and types of study in each analysis. For the smaller colon cancer and premenopausal breast cancer analyses, both a fixed and random effects model were used and results were compared. For the larger postmenopausal breast cancer

analyses that likely had a greater amount of methodological differences, only the more appropriate random effects model was used.

It is notable that despite these methodological differences, and the apparent heterogeneity between studies, a rather strong and consistent relationship was found between high levels of activity and risk reduction for both colon cancer and breast cancer among postmenopausal females.

Summary of *Compendium*-Quantified Colon and Breast Cancer Analyses

The analyses including studies that directly quantified leisure-time physical activity using the *Compendium* provide the most accurate estimate of the relationship between physical activity and the risk colon and breast cancer. The effect measures from these analyses (Analyses I and II for colon cancer risk and Analyses IV and V for pre- and postmenopausal breast cancer risk) are summarized in Table 44.

Table 44. Summary of *Compendium*-Quantified Analyses

	Risk Estimate	95% Confidence Interval	P-Value
Colon Cancer Analysis I: Males			
Moderate[1] Vs. Low Activity[2]	0.817	0.484-1.379	0.449
High[3] Vs. Low Activity[2]	0.524	0.348-0.788	**0.002**
Colon Cancer Analysis II: Females			
Moderate[4] Vs. Low Activity[5]	0.872	0.671-1.132	0.303
High[6] Vs. Low Activity[5]	0.673	0.474-0.956	**0.027**
Breast Cancer Analysis IV: Premenopausal			
Moderate[7] Vs. Low Activity[8]	0.917	0.798-1.054	0.222
High[9] Vs. Low Activity[8]	0.820	0.584-1.151	0.251
Breast Cancer Analysis V: Postmenopausal			
Moderate[10] Vs. Low Activity[11]	0.932	0.858-1.011	0.090
High[12] Vs. Low Activity[11]	0.847	0.727-0.987	**0.034**

[1] 0.1 to 20.0 MET hours-per-week
[2] 0 to 7.30 MET hours-per-week
[3] > 11.3 (median) to >20 MET hours-per-week
[4] 0.1 to 21.0 MET hours-per-week
[5] 0 to 7.30 MET hours-per-week
[6] >16.0 to >20.0 MET hours-per-week
[7] 6.7-20.7 MET hours-per-week
[8] 0 to 8.9 MET hours-per-week
[9] >16.6 to >20.7 MET hours-per-week
[10] 5.1-20.0 MET hours-per-week
[11] 0 to 7.6 MET hours-per-week
[12] >16.6 to >20.0 MET hours-per-week

Substantial variability among individual studies for the categorization of 'low', 'moderate', and 'high' activity in MET hours-per-week was present, and this variability likely impacted the effect measures of the meta-analyses. Specifically, when lower amounts of activity in MET hours-per-week are included in the 'moderate' and 'high' activity groups, the protective effect of physical activity may be underestimated for those two groups in the meta-analyses.

In Analysis I of colon cancer risk, the effect measure for high versus low activity males was 0.524 (95% CI = 0.348-0.788). This effect measure represented a 48% risk reduction, which was substantial and statistically significant ($p = 0.002$). The effect

measures from the individual studies were all less than one, but were not consistent among the three studies, although the test for heterogeneity was not statistically significant (effect measures = 0.202, 0.527, and 0.664; *p*-value for DerSimonian and Laird (D+L) Q-test of heterogeneity = 0.200). The Tang et al. study had an unusually low effect measure of 0.202, but only had a study weight of 10% due to the small sample size in this study. In Analysis II of colon cancer risk, the colon cancer effect measure for high versus low activity females was 0.673 (95% CI = 0.474-0.956). There was a substantial risk reduction of 33%, which was statistically significant ($p = 0.027$). The effect measures across studies in this meta-analysis were quite consistent (0.617, 0.741, 0.807; *p*-value for D+L Q-test of heterogeneity = 0.854) despite the different sample sizes and only a 7% weight for the Tang et al. study.

For moderate versus low activity males in Analysis I, the colon cancer effect measure was 0.817 (95% CI = 0.484-1.379). This risk reduction of 18% was found to be not statistically significant ($p = 0.449$). Effect measures from the individual studies were not consistent (0.60, 0.79, and 4.29), although the test for heterogeneity was not statistically significant ($p = 0.06$). The unusually high effect measure of 4.29 reported by Tang et al. was the only individual effect measure from this analysis that exceeded 1.0. Although this study had a weight of only 9%, its exclusion resulted in a combined estimate of 0.707 (95% CI = 0.546-0.915, $p = 0.009$) from the two remaining studies, indicating that Tang et al. did substantially influence the results of this meta-analysis. Moderate versus low activity females in Analysis II had a effect measure of 0.872 (95% CI = 0.671-1.132). This colon cancer risk reduction of 13% was found to be non-statistically significant ($p = 0.303$). Individual study effect measures were reasonably

consistent in this meta-analysis (0.806, 0.941, 0.990; *p*-value for D+L Q-test of heterogeneity = 0.760) despite study weights ranging from 2.87% for the Tang et al. study up to 61.24% for the Martinez et al. study.

In Analysis IV of breast cancer risk, the effect measure for high versus low activity females for premenopausal breast cancer was 0.820 (95% CI = 0.584-1.151). This effect measure represented an 18% risk reduction, although the result was found to be non-statistically significant ($p = 0.251$). Only three studies met the inclusion criteria for this analysis, and effect measures from the individual studies showed a statistically significant amount of heterogeneity (0.55, 0.96, 1.00; *p*-value for test of heterogeneity = 0.012). Results from the premenopausal analyses were largely influenced by the Colditz et al. study, which had a study weight of approximately 60%. The combined effect measure for high versus low activity females for postmenopausal cancer in Analysis V was 0.847 (95% CI – 0.727-0.987). This effect measure represented a 15% breast cancer risk reduction, which was statistically significant ($p = 0.034$). In contrast to the findings for premenopausal females, the effect measures for the five individual studies were more consistent (0.68, 070, 0.88, 0.91, 1.02), with four of the five studies having a effect measure of less than 1.0. Although the effect measures for the individual studies appeared to be somewhat similar, statistically significant heterogeneity was present ($p = 0.012$).

The effect measure for moderate versus low activity premenopausal females in Analysis IV was 0.917 (95% CI = 0.798-1.054). This represented a breast cancer risk reduction of 8%. The effect measures from the three individual studies were relatively consistent (0.87, 0.93, 0.94; *p*-value for test of heterogeneity = 0.924), and the estimate

was found to be non-statistically significant ($p = 0.222$). The effect measure for moderate versus low activity postmenopausal females in Analysis V was 0.932 (95% CI = 0.858-1.011). This effect measure represented a 7% risk reduction, but was found to be non-statistically significant ($p = 0.090$). Results from this analysis were heavily influenced by the McTiernan et al. and Patel et al. studies, which had a total combined weight of 70%. Despite the difference in sample sizes among the five studies, the effect measures were relatively consistent across the five individual studies (0.79, 0.85, 0.92, 1.00, 1.04), and the test for heterogeneity was not statistically significant ($p = 0.302$).

With the exception of the moderate activity colon cancer analyses for males and females, it is encouraging that effect measures for both colon and breast cancer analyses were highly consistent, despite the heterogeneity in sample size and methodology. In the future, more studies researching the effect of *Compendium*-quantified leisure-time physical activity on the risk of colon, premenopausal breast, and postmenopausal breast cancer are needed to assess more accurately the effect of physical activity on the risk of colon and breast cancer. Additional methodological recommendations are detailed in the 'Future Recommendations' section below.

Sensitivity Analysis

Sensitivity analyses can be completed to address the potential biases associated with unmeasured confounders. Although all individual studies included in the meta-analyses controlled for confounders in their analyses, it is possible that their adjusted estimates failed to control for important unmeasured confounders. Typically, studies of the relationship between physical activity and breast cancer controlled for the effects of such confounders as age at menarche, age at first birth, body mass index, smoking status,

oral contraceptive use, and in some cases, postmenopausal hormone replacement therapy use. Studies of the relationship between physical activity and colon cancer controlled for the effects of confounders such as fiber intake, body mass index, alcohol intake, and smoking status. Any unmeasured confounders would have had to produce sufficient effects to mitigate the potentially beneficial effects of physical activity, thereby influencing the majority of the studies in the same direction, to greatly affect the results that were reported in these meta-analyses. It is unlikely that such a consistent confounder was missed by all these studies.

Another way to gauge the sensitivity of these meta-analyses is to assess the impact of certain studies that had potentially large effects on the overall effect measure. Because most studies of postmenopausal females in Analysis V had an effect size of less than 1.0 with the exception of McTiernan et al., it is possible that unmeasured confounders could have caused this unexpectedly high, unadjusted effect measure. To address this, Analysis V was reanalyzed without the McTiernan study, yielding a effect measure of 0.815 (95% CI = 0.672-0.989). Thus, despite the larger effect measure (1.02) and weight (26.30%) of the McTiernan et al. study, the protective effect of physical activity on postmenopausal breast cancer risk was only slightly masked by including this study.

Although individual studies measured the effects of confounders on their adjusted effect measures, the estimates included in the meta-analyses could only be based on the unadjusted effect measures because original data could not be obtained. A comparison of the unadjusted to the adjusted effect measures provided another method of assessing the

potential influence of confounders, and is reported in the 'Results' chapter and discussed earlier in this chapter.

Population Attributable Fraction

The population attributable fraction (PAF) is defined as the "proportion of disease cases in a population that would be prevented if an exposure were to eliminated, assuming the exposure to be causal" [151]. In this case, the 'exposure' is physical inactivity. Determining the amount of risk reduction potentially associated with physical activity is important because activity is something that is amenable to behavior change and consistent completion for most people. For postmenopausal females, a 13% reduction in breast cancer could be achieved, assuming that the 26% of highly active females from the McTiernan et al. cohort study (the only cohort study that included cases and non-cases, rather than person-years) is representative of the proportion of highly active females in the population as a whole. The PAF was derived by estimating the proportion of high activity postmenopausal females in the population from the proportion of high activity females in the McTiernan et al. cohort study. The calculation of the PAF is detailed in Appendix V.

Because cohort studies of male and female colon cancer risk did not provide the number of cases and non-cases but rather person-years, the proportions of high activity and low plus moderate activity males were estimated based on person-years reported in the Giovannucci et al. study for males and the Martinez et al. study for females to represent the proportion of high activity males and females in the population as a whole. For males, a reduction in colon cancer risk of approximately 39% could be achieved,

assuming the 41% of high activity males from the Giovannucci et al. cohort study is representative of the proportion of highly active males in the population as a whole. For females, a reduction in colon cancer of approximately 33% reduction could be achieved, assuming the 24% of high activity females from the Martinez et al. cohort study is representative of the proportion of highly active females in the population.

Conclusions

Future studies assessing the relationship between physical activity and cancer risk can address many of the methodological issues that currently exist. While individual research studies typically report that greater amounts of physical activity are likely effective for reducing the risk of colon and breast cancer, the present meta-analyses demonstrate that some aspects of the relationship between activity and cancer risk remain unclear. Specifically, high, but not moderate amounts of leisure-time physical activity likely reduce male and female colon cancer risk, as well as postmenopausal breast cancer risk. The relationship between moderate amounts of activity and risk of postmenopausal breast cancer remain unclear, as does the relationship between any amount of physical activity and premenopausal breast cancer risk. Finally, results from the colon and postmenopausal breast cancer analyses provide an initial guideline (> 16 MET hours-per-week and > 17 MET hours-per-week, respectively) for exercise professionals prescribing activity to higher risk individuals.

The issue of confounding did not appear to be a major factor affecting the results from the meta-analyses. However, it would still be helpful if future studies of physical

activity and cancer risk adjusted for the same variables to better understand the isolated impact of activity on the risk of colon and breast cancer.

Based on the results from Analyses V and VI of the breast cancer meta-analyses, it cannot be assumed that menopausal status is the only factor responsible for the differences between the analyses of combined and stratified menopausal statuses. The total number of individuals included in the analyses could also be important, as the statistically significant findings in the combined pre- and postmenopausal analyses had a greater number of studies and subjects compared to the stratified pre- and postmenopausal analyses.

One notable problem among studies of physical activity and breast cancer is that many of the studies examined the effect of activity on both pre- and postmenopausal females combined, rather than looking at the specific relationships between activity and breast cancer risk separately for pre- and postmenopausal females. Friedenreich et al. (2001) and John et al. (2003) were the only two studies to stratify menopausal status when assessing the relationship between activity and breast cancer. While some of the other studies statistically adjusted for menopausal status, it would be best if all studies followed the method of Friedenreich and John when assessing the relationship between physical activity and breast cancer risk in the future.

There are other methodological considerations that should be addressed in future studies. While many studies appropriately use the *Compendium* to quantify an individual's amount of physical activity, the instrumentation used to record the various activities vary among the studies. Two physical activity assessment tools (Wolf et al., 1994; Bernstein et al., 1994) were used across multiple studies, but most methods of

assessment were self-developed for individual studies. A uniform questionnaire for recording physical activity for studies of activity and cancer risk would be helpful in the future.

Additionally, indirectly quantifying physical activity using the *Compendium* may not be as accurate as directly quantifying activity due to a greater amount of heterogeneity in the measurement of physical activity. Therefore, it is highly recommended that future studies assessing the relationship between physical activity and breast cancer risk examine pre- and postmenopausal females separately and continue to quantify activity using the *Compendium*, while measuring physical activity in a more consistent manner.

The time span for which physical activity was measured had a great amount of variability, ranging from current activity to lifetime activity, for both the colon and breast cancer analyses. For the breast cancer analyses, it was possible to complete an additional analysis including only studies that measured activity for at least ten years, which produced results similar to the analysis that also included studies of shorter activity measurement time spans. While measuring current levels of activity may be indicative of the amount of activity that an individual has completed in the past, future studies should measure activity for longer periods of time to gain a better understanding of the association between consistent physical activity throughout the lifespan and cancer risk, future studies should measure activity for longer periods of time.

The present series of meta-analyses examining the relationship between physical activity and cancer of the colon and breast provided a quantitative synthesis of results from studies employing a similar physical activity quantification instrument, the

Compendium of Physical Activities [64, 80]. Pooling numerous studies to assess the association of physical activity and colon cancer risk among males and females, as well as breast cancer risk among pre- and postmenopausal females allowed for a more complete understanding of the role of physical activity in reducing one's risk of developing these two cancers. While a variety of methodological issues remain unaddressed, results from the present analyses indicate that greater amounts of physical activity are likely beneficial in the reduction of colon and breast cancer risk.

Future Recommendations

The results from the present analyses provide a general framework for estimating the approximate amount of physical activity that may be associated with a reduction in colon and breast cancer risk. Further study of the relationship between physical activity and the risk of colon and breast cancer is recommended, but a variety of specific methodological issues should be addressed in future research. The types and amounts of physical activity should be assessed using a common instrument, similar to the one developed by Bernstein et al. (1994). All future studies should utilize the *Compendium of Physical Activities* to quantify the MET hours-per-week of activity. This would allow for a more uniform and comprehensive quantification of the amount of leisure-time physical activity associated with a reduction in colon and postmenopausal breast cancer risk. A better understanding of the relationship between physical activity and breast cancer risk among premenopausal females may be established by including additional studies.

While the specific amount of time that physical activity should be measured during one's lifespan cannot be determined at this time, future studies should assess the

amount of activity completed over at least a ten-year period. This would provide a more reasonable indication of the typical amount of activity completed throughout the lifespan than merely measuring 'current' amounts of activity. For studies of physical activity and breast cancer risk, it is especially important to note the specific time-period during the lifespan when physical activity was measured, as activity likely has varying effects on the hormonal profiles of females at different time periods throughout the lifespan. Further study of the specific hormonal effects of physical activity at various points throughout the lifespan needs to be further studied. Also, future studies of physical activity and breast cancer risk should report results separately for pre- and postmenopausal females, to allow a better synthesis and understanding of the relationship between activity and breast cancer risk by menopausal status. The potential confounding factors that are included should be standardized in future studies, to allow for a better understanding of the effects of physical activity on the risk of colon and breast cancer, after adjusting for confounding.

A major limitation impacting the results of the present analyses was that each individual study had a different MET hour-per-week range for 'low', 'moderate', and 'high' activity, causing an overlap of quantified physical activity in the combined analyses. Future studies should use consistent categories of 'low', 'moderate', and 'high' activity in MET hours-per-week. For example, if three distinct categories of 'low', 'moderate', and 'high' were < 4, 4-16, and >16 MET hours-per-week across studies, the specific effects of 'moderate' and 'high' amounts of activity versus 'low' activity on the risk of colon and breast cancer could be better understood. While the results of the present analyses indicate > 16 MET hours-per-week of leisure-time physical activity for

colon cancer risk reduction and > 17 MET hours-per-week for postmenopausal breast cancer risk reduction, these levels cannot be considered to be definitive in reducing the risk of these two cancers. However, these results can provide guidelines so that future studies can ascertain the specific amount of quantified leisure-time physical activity associated with a reduction in colon and postmenopausal breast cancer risk with greater certainty.

Appendices

Appendix I

Calculations for Colon Cancer Analyses

Calculation of Effect measures, Natural Logs of the Effect measures, and Standard Errors of the Log of Effect measures for Colon Cancer Effect measures

For all Odds Ratios:

a = Higher Amount of Exercise; Case
b = Higher Amount of Exercise; Control
c = Lower Amount of Exercise; Case
d = Lower Amount of Exercise; Control

For all Relative Risks:

$\mathbf{r_1}$ = Cases in Lower Amount of Exercise
$\mathbf{r_2}$ = Cases in Higher Amount of Exercise
$\mathbf{T_1}$ = Total Person-Years of Lower Exercise Group
$\mathbf{T_2}$ = Total Person-Years of Higher Exercise Group

Calton et al. (2006)

Assumption = MET value of 8.0 for vigorous activity

Moderate Vs. Low Activity (Females)

$r_1 = 159$, $r_2 = 34$, $t_1 = 165069$ py, $t_2 = 50731$ py

OR ~ $\Psi = (r_2 * t_1 / r_1 * t_2)$
$\Psi = 34 * 165069$ py / $159 * .024450731$ py
$\Psi = 5612346 / 8066229 = .6958$
$(\ln \Psi) = \ln (.6958) = -.3627$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{159+34 / 159*34}$
SE $(\ln \Psi) = \sqrt{193 / 5406}$
SE $(\ln \Psi) = \sqrt{.0357}$
SE $(\ln \Psi) = .1889$
95% CI $(\ln \Psi) = -.3627 \pm 1.96(.1889)$
95% CI $(\Psi) = \exp (-.7329, .0075)$
95% CI $(\Psi) = (.4805, 1.01)$

High Vs. Low Activity (Females)

$r_1 = 159$, $r_2 = 50$, $t_1 = 165069$ py, $t_2 = 54525$ py

OR ~ $\Psi = (r_2 * t_1 / r_1 * t_2)$
$\Psi = 50 * 165069$ py / $159 * 54525$ py
$\Psi = 8253450 / 8669475 = .9520$
$(\ln \Psi) = \ln (.9520) = -.0492$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{159+50 / 159*50}$
SE $(\ln \Psi) = \sqrt{209 / 7950}$
SE $(\ln \Psi) = \sqrt{.0263}$
SE $(\ln \Psi) = .1621$
95% CI $(\ln \Psi) = -.0492 \pm 1.96(.1621)$
95% CI $(\Psi) = \exp (-.3669, .2685)$
95% CI $(\Psi) = (.6929, 1.3080)$

Giovannucci et al. (1995)

Moderate Vs. Low Activity (Males)

$r_1 = 55$, $r_2 = 88$, $t_1 = 51660$ py, $t_2 = 104939$ py

OR ~ $\Psi = (r_2 * t_1 / r_1 * t_2)$
$\Psi = 88 * 51660$ py / $55 * 104939$ py
$\Psi = 4546080 / 5771645 = .7877$
$(\ln \Psi) = \ln (.7877) = -.2387$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{55+88 / 55*88}$
SE $(\ln \Psi) = \sqrt{143 / 4840}$
SE $(\ln \Psi) = \sqrt{.0296}$
SE $(\ln \Psi) = .1719$
95% CI $(\ln \Psi) = -.2387 \pm 1.96(.1719)$
95% CI $(\Psi) = \exp (-.5756, .0982)$
95% CI $(\Psi) = (.5624, 1.1032)$

High Vs. Low Activity (Males)

$r_1 = 55$, $r_2 = 60$, $t_1 = 51660$ py, $t_2 = 106955$ py

OR ~ $\Psi = (r_2 * t_1 / r_1 * t_2)$
$\Psi = 60 * 51660$ py / $55 * 106955$ py
$\Psi = 3099600 / 5882525 = .5269$
$(\ln \Psi) = \ln (.5269) = -.6407$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{55+60 / 55*60}$
SE $(\ln \Psi) = \sqrt{115 / 3300}$
SE $(\ln \Psi) = \sqrt{.0348}$
SE $(\ln \Psi) = .1867$
95% CI $(\ln \Psi) = -.6407 \pm 1.96(.1867)$
95% CI $(\Psi) = \exp (-1.01, -.2748)$
95% CI $(\Psi) = (.3642, .7597)$

Longnecker et al. (1995)

(Assumption = MET value of 8 for vigorous activity)

Moderate Vs. Low Activity

a = 8, b = 19, c = 104, d = 141

$\Psi = (a/b) / (c/d)$
$\Psi = (8/19) / (104/141)$
$\Psi = .4211 / .7376$
$\Psi = .5709$
$\ln(\Psi) = \ln(.5709) = -.5605$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/8 + 1/19 + 1/104 + 1/141}$
$SE(\ln \Psi) = \sqrt{.1250 + .0526 + .0096 + .0071}$
$SE(\ln \Psi) = \sqrt{.1943}$
$SE(\ln \Psi) = .4408$
95% CI $(\ln \Psi) = -.5605 \pm 1.96(.4408)$
95% CI $(\Psi) = \exp(-1.4244, .3035)$
95% CI $(\Psi) = (.2406, 1.3546)$

High Vs. Low Activity

a = 50, b = 101, c = 104, d = 141

$\Psi = (a/b) / (c/d)$
$\Psi = (50/101) / (104/141)$
$\Psi = .4950 / .7376$
$\Psi = .6711$
$\ln(\Psi) = \ln(.6711) = -.3988$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/50 + 1/101 + 1/104 + 1/141}$
$SE(\ln \Psi) = \sqrt{.0200 + .0099 + .0096 + .0071}$
$SE(\ln \Psi) = \sqrt{.0466}$
$SE(\ln \Psi) = .2159$
95% CI $(\ln \Psi) = -.3988 \pm 1.96(.2159)$
95% CI $(\Psi) = \exp(-.8220, .0244)$
95% CI $(\Psi) = (.4396, 1.0247)$

Martinez et al. (1997)

Moderate Vs. Low Activity (Females)

$r_1 = 73$, $r_2 = 65$, $t_1 = 115{,}147$ py, $t_2 = 127{,}204$ py

OR ~ $\Psi = (r_2 * t_1 / r_1 * t_2)$
$\Psi = 65 * 115{,}147 / 73 * 127{,}204$
$\Psi = 7{,}484{,}555 / 9{,}285{,}892 = .8060$
$(\ln \Psi) = \ln (.8060) = -.2157$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{73+65 / 73*65}$
SE $(\ln \Psi) = \sqrt{138 / 4745}$
SE $(\ln \Psi) = \sqrt{.0291}$
SE $(\ln \Psi) = .1705$
95% CI $(\ln \Psi) = -.2157 \pm 1.96(.1705)$
95% CI $(\Psi) = \exp (-.5499, .1185)$
95% CI $(\Psi) = (.5770, 1.1258)$

High Vs. Low Activity (Females)

$r_1 = 73$, $r_2 = 23$, $t_1 = 115{,}147$ py, $t_2 = 58{,}817$ py

OR ~ $\Psi = (r_2 * t_1 / r_1 * t_2)$
$\Psi = 23 * 115{,}147$ py $/ 73 * 58{,}817$ py
$\Psi = 2{,}648{,}381 / 4{,}293{,}641 = .6168$
$(\ln \Psi) = \ln (.6168) = -.4832$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{73+23 / 73*23}$
SE $(\ln \Psi) = \sqrt{96 / 1679}$
SE $(\ln \Psi) = \sqrt{0572}$
SE $(\ln \Psi) = .2391$
95% CI $(\ln \Psi) = -.4832 \pm 1.96(.2391)$
95% CI $(\Psi) = \exp (-.9518, -.0146)$
95% CI $(\Psi) = (.3860, .9855)$

Tang et al. (1999)

Moderate Vs. Low Activity (Males)

a = 10, b = 2, c = 28, d = 24

Ψ = (a/b) / (c/d)
Ψ = (10/2) / (28/24)
Ψ = 5.0000 / 1.1667
Ψ = 4.2856
ln (Ψ) = ln (4.2856) = 1.4553
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/10 + 1/2 + 1/28 + 1/24}$
SE (ln Ψ) = $\sqrt{.1000 + .5000 + .0357 + .0417}$
SE (ln Ψ) = $\sqrt{.6774}$
SE (ln Ψ) = .8230
95% CI (ln Ψ) = 1.4553 ± 1.96(.8230)
95% CI (Ψ) = exp (-.1578, 3.0638)
95% CI (Ψ) = (.8540, 21.41)

High Vs. Low Activity (Males)

a = 4, b = 17, c = 28, d = 24

Ψ = (a/b) / (c/d)
Ψ = (4/17) / (28/24)
Ψ = (.2353 / 1.1667)
Ψ = .2017
ln (Ψ) = ln (.2017) = -1.6011
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/4 + 1/17 + 1/28 + 1/24}$
SE (ln Ψ) = $\sqrt{.2500 + .0588 + .0357 + .0417}$
SE (ln Ψ) = $\sqrt{.3862}$
SE (ln Ψ) = .6215
95% CI (ln Ψ) = -.1.6011 ± 1.96(.6215)
95% CI (Ψ) = exp (-2.8192, -.3830)
95% CI (Ψ) = (0.0597, 0.6818)

Moderate Vs. Low Activity (Females)

a = 4, b = 4, c = 17, d = 16

Ψ = (a/b) / (c/d)
Ψ = (4/4) / (17/16)
Ψ = 1.0000 / 1.0625
Ψ = .9412
ln (Ψ) = ln (1.0625) = -.0606
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/4 + 1/4 + 1/17 + 1/16}$
SE (ln Ψ) = $\sqrt{.2500 + .2500 + .0588 + .0625}$
SE (ln Ψ) = $\sqrt{.6213}$
SE (ln Ψ) = .7882
95% CI (ln Ψ) = -.0606 ± 1.96(.7882)
95% CI (Ψ) = exp (-1.6055, 1.4843)
95% CI (Ψ) = (.2008, 4.4119)

High Vs. Low Activity (Females)

a = 6, b = 7, c = 17, d = 16

Ψ = (a/b) / (c/d)
Ψ = (6/7) / (17/16)
Ψ = .8571 / 1.0625
Ψ = .8067
ln (Ψ) = ln (.8067) = -.2148
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/6 + 1/7 + 1/17 + 1/16}$
SE (ln Ψ) = $\sqrt{.1667 + .1429 + .0588 + .0625}$
SE (ln Ψ) = $\sqrt{.4309}$
SE (ln Ψ) = .6564
95% CI (ln Ψ) = -.2148 ± 1.96(.6564)
95% CI (Ψ) = exp (-1.5013, 1.0717)
95% CI (Ψ) = (.2228, 2.9203)

White et al. (1996)

Moderate Vs. Low Activity (Males)

a = 85, b = 99, c = 119, d = 84

$\Psi = (a/b) / (c/d)$
$\Psi = (85/99) / (119/84)$
$\Psi = .8586 / 1.4167$
$\Psi = .6061$
$\ln(\Psi) = \ln(.6061) = -.5008$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/85 + 1/99 + 1/119 + 1/84}$
$SE(\ln \Psi) = \sqrt{.0118 + .0101 + .0084 + .0119}$
$SE(\ln \Psi) = \sqrt{.0422}$
$SE(\ln \Psi) = .2054$
95% CI $(\ln \Psi) = -.5008 \pm 1.96(.2054)$
95% CI $(\Psi) = \exp(-.9034, -.0982)$
95% CI $(\Psi) = (.4052, .9065)$

High Vs. Low Activity (Males)

a = 47, b = 50, c = 119, d = 84

$\Psi = (a/b) / (c/d)$
$\Psi = (47/50) / (119/84)$
$\Psi = .9400 / 1.4167$
$\Psi = .6635$
$\ln(\Psi) = \ln(.6635) = -.4102$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/47 + 1/50 + 1/119 + 1/84}$
$SE(\ln \Psi) = \sqrt{.0213 + .0200 + .0084 + .0119}$
$SE(\ln \Psi) = \sqrt{.0616}$
$SE(\ln \Psi) = .2482$
95% CI $(\ln \Psi) = -.4102 \pm 1.96(.2482)$
95% CI $(\Psi) = \exp(-.8967, .0763)$
95% CI $(\Psi) = (.4079, 1.0793)$

Moderate Vs. Low Activity (Females)

a = 80, b = 77, c = 85, d = 81

Ψ = (a/b) / (c/d)
Ψ = (80/77) / (85/81)
Ψ = 1.0390 / 1.0494
Ψ = .9901
ln (Ψ) = ln (.9901) = -.0100
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/80 + 1/77 + 1/85 + 1/81}$
SE (ln Ψ) = $\sqrt{.0125 + .0130 + .0118 + .0123}$
SE (ln Ψ) = $\sqrt{.0496}$
SE (ln Ψ) = .2227
95% CI (ln Ψ) = -.0100 ± 1.96(.2227)
95% CI (Ψ) = exp (-.4463, .4265)
95% CI (Ψ) = (.6400, 1.5319)

High Vs. Low Activity (Females)

a = 28, b = 36, c = 85, d = 81

Ψ = (a/b) / (c/d)
Ψ = (28/36) / (85/81)
Ψ = .7778 / 1.0494
Ψ = .7412
ln (Ψ) = ln (.7412) = -.2995
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/28 + 1/36 + 1/85 + 1/81}$
SE (ln Ψ) = $\sqrt{.0357 + .0278 + .0118 + .0123}$
SE (ln Ψ) = $\sqrt{.0876}$
SE (ln Ψ) = .2960
95% CI (ln Ψ) = -.2995 ± 1.96(.2960)
95% CI (Ψ) = exp (-.8797, .2807)
95% CI (Ψ) = (.4149, 1.3241)

Appendix II

Calculations for Breast Cancer Analyses

Calculation of Effect measures, Natural Logs of the Effect measures, and Standard Errors of the Log of the Effect measures

For all Odds Ratios:

a = Higher Amount of Exercise; Case
b = Higher Amount of Exercise; Control
c = Lower Amount of Exercise; Case
d = Lower Amount of Exercise; Control

For all Relative Risks:

$\mathbf{r_1}$ = Cases in Lower Amount of Exercise
$\mathbf{r_2}$ = Cases in Higher Amount of Exercise
$\mathbf{T_1}$ = Total Person-Years of Lower Exercise Group
$\mathbf{T_2}$ = Total Person-Years of Higher Exercise Group

Bernstein et al. (2005)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

a = 822, b = 881, c = 2901, d = 2870

Ψ = (a/b) / (c/d)

Ψ = (822/881) / (2901/2870)

Ψ = .9930 / 1.0108

Ψ = .9824

ln (Ψ) = ln (.9824) = -.0178

SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$

SE (ln Ψ) = $\sqrt{1/822 + 1/881 + 1/2901 + 1/2870}$

SE (ln Ψ) = $\sqrt{.0012 + .0011 + .0003 + .0003}$

SE (ln Ψ) = $\sqrt{.0029}$

SE ln (Ψ) = .0539

95% CI (ln Ψ) = -.0178 ± 1.96(.0539)

95% CI (Ψ) = exp (-.1234, .0878)

95% CI (Ψ) = (.8839, 1.0918)

Premenopausal and Postmenopausal Females – High Vs. Low Activity

a = 815, b = 898, c = 2901, d = 2870

Ψ = (a/b) / (c/d)

Ψ = (815/898) / (2901/2870)

Ψ = .9076 / 1.0108

Ψ = .8979

ln (Ψ) = ln (.8979) = -.1077

SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$

SE (ln Ψ) = $\sqrt{1/815 + 1/898 + 1/2901 + 1/2870}$

SE (ln Ψ) = $\sqrt{.0012 + .0011 + .0003 + .0003}$

SE (ln Ψ) = $\sqrt{.0029}$

SE ln (Ψ) = .0539

95% CI (ln (Ψ)) = -.1077 ± 1.96(.0539)

95% CI (Ψ) = exp (-.2133, -.0021)

95% CI (Ψ) = (.8079, .9979)

Carpenter et al. (1999)

Postmenopausal Females – Moderate Vs. Low Activity

a = 112, b = 84, c = 923, d = 722

$\Psi = (a/b) / (c/d)$
$\Psi = (112/84) / (923/722)$
$\Psi = 1.3333 / 1.2784$
$\Psi = 1.0429$
$\ln(\Psi) = \ln(1.0429) = .0420$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/112 + 1/84 + 1/923 + 1/722}$
$SE(\ln \Psi) = \sqrt{.0089 + .0119 + .0011 + .0014}$
$SE(\ln \Psi) = \sqrt{.0233}$
$SE \ln(\Psi) = .1526$
95% CI $(\ln(\Psi)) = .0420 \pm 1.96(.1526)$
95% CI $(\Psi) = \exp(-.2571, .3411)$
95% CI $(\Psi) = (.7733, 1.4065)$

Postmenopausal Females – High Vs. Low Activity

a = 88, b = 98, c = 923, d = 722

$\Psi = (a/b) / (c/d)$
$\Psi = (88/98) / (923/722)$
$\Psi = .8980 / 1.2784$
$\Psi = .7024$
$\ln(\Psi) = \ln(.7024) = -.3532$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/88 + 1/98 + 1/923 + 1/722}$
$SE(\ln \Psi) = \sqrt{.0114 + .0102 + .0011 + .0014}$
$SE(\ln \Psi) = \sqrt{.0241}$
$SE \ln(\Psi) = .1552$
95% CI $(\ln \Psi) = -.3532 \pm 1.96(.1552)$
95% CI $(\Psi) = \exp(-.6574, -.0490)$
95% CI $(\Psi) = (.5182, .9522)$

Colditz et al. (2003)

Premenopausal Females – Moderate Vs. Low Activity

$r_1 = 305$, $r_2 = 197$, $T_1 = 323{,}600$ py, $T_2 = 225{,}500$ py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = 197 * 323{,}600$ py $/ 305 * 225{,}500$ py
$\Psi = 63{,}749{,}200 / 68{,}777{,}500 = .9269$
$(\ln \Psi) = \ln (.9269) = -.0759$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{305+197 / 305*197}$
SE $(\ln \Psi) = \sqrt{502 / 60{,}085}$
SE $(\ln \Psi) = \sqrt{.0084}$
SE $(\ln \Psi) = .0914$
95% CI $(\ln \Psi) = -.0759 \pm 1.96(.0914)$
95% CI $(\Psi) = \exp (-.2550, .1032)$
95% CI $(\Psi) = (.7749, 1.1087)$

Premenopausal Females – High Vs. Low Activity

r1 = 305, r2 = 347, T1 = 323,600 py, T2 = 385,000 py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = 347 * 323{,}600$ py $/ 305 * 385{,}000$ py
$\Psi = 112{,}289{,}200 / 117{,}425{,}000 = .9563$
$(\ln \Psi) = \ln (.9563) = -.0447$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{305+347 / 305*347}$
SE $(\ln \Psi) = \sqrt{652 / 105{,}835}$
SE $(\ln \Psi) = \sqrt{.0616}$
SE $(\ln \Psi) = .0785$
95% CI $(\ln \Psi) = -.0447 \pm 1.96(.0785)$
95% CI $(\Psi) = \exp (-.1986, .1092)$
95% CI $(\Psi) = (.8199, 1.1154)$

Dirx et al. (2001)

(Assumption = 2 Hours of Activity Per Week at Mean MET Value)

Postmenopausal Females – Moderate Vs. Low Activity

$r_1 = 63$, $r_2 = 178$, $T_1 = 652$ py, $T_2 = 1583$ py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = 178 * 652$ py $/ 63 * 1583$ py
$\Psi = 116{,}056 / 99{,}729 = 1.1637$
$(\ln \Psi) = \ln (1.1637) = .1516$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{63+178 / 63*178}$
SE $(\ln \Psi) = \sqrt{241 / 11{,}214}$
SE $(\ln \Psi) = \sqrt{.0215}$
SE $(\ln \Psi) = .1466$
95% CI $(\ln \Psi) = .1516 \pm 1.96(.1466)$
95% CI $(\Psi) = \exp (-.1357, .4389)$
95% CI $(\Psi) = (.8731, 1.5510)$

Postmenopausal Females – High Vs. Low Activity

r1 = 63, r2 = 187, T1 = 652 py, T2 = 1690 py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = 187 * 652$ py $/ 63 * 1690$ py
$\Psi = 121{,}924 / 106{,}470 = 1.1451$
$(\ln \Psi) = \ln (1.1451) = .1355$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{63+187 / 63*187}$
SE $(\ln \Psi) = \sqrt{250 / 11{,}781}$
SE $(\ln \Psi) = \sqrt{.0212}$
SE $(\ln \Psi) = .1457$
95% CI $(\ln \Psi) = .1355 \pm 1.96(.1457)$
95% CI $(\Psi) = \exp (-.1501, .4211)$
95% CI $(\Psi) = (.8606, 1.5236)$

Friedenreich et al. (2001)

Premenopausal Females – Moderate Vs. Low Activity

a = 216, b = 239, c = 123, d = 118

Ψ = (a/b) / (c/d)
Ψ = (216/239) / (123/118)
Ψ = .9038 / 1.0424
Ψ = .8670
ln (Ψ) = ln (.8670) = -.1427
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/216 + 1/239 + 1/123 + 1/118}$
SE (ln Ψ) = $\sqrt{.0046 + .0042 + .0081 + .0085}$
SE (ln Ψ) = $\sqrt{.0254}$
SE (ln Ψ) = .1594
95% CI (ln Ψ) = -.1427 ± 1.96(.1594)
95% CI (Ψ) = exp (-.4551, .1697)
95% CI (Ψ) = (.6344, 1.1849)

Premenopausal Females – High Vs. Low Activity

a = 123, b = 118, c = 123, d = 118

Ψ = (a/b) / (c/d)
Ψ = (123/118) / (123/118)
Ψ = 1.0424 / 1.0424
Ψ = 1.0000
ln (Ψ) = ln (1.0000) = 0
SE (ln Ψ) = $\sqrt{1/a + 1/b + 1/c + 1/d}$
SE (ln Ψ) = $\sqrt{1/123 + 1/118 + 1/123 + 1/118}$
SE (ln Ψ) = $\sqrt{.0081 + .0085 + .0081 + .0085}$
SE (ln Ψ) = $\sqrt{.0332}$
SE (ln Ψ) = .1822
95% CI (ln Ψ) = 0 ± 1.96(.1822)
95% CI (Ψ) = exp (-.3571, .3571)
95% CI (Ψ) = (.6997, 1.4292)

Postmenopausal Females – Moderate Vs. Low Activity

a = 364, b = 381, c = 213, d = 190

$\Psi = (a/b) / (c/d)$

$\Psi = (364/381) / (213/190)$

$\Psi = .9554 / 1.1211$

$\Psi = .8522$

$\ln(\Psi) = \ln(.8522) = -.1599$

$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$

$SE(\ln \Psi) = \sqrt{1/364 + 1/381 + 1/213 + 1/190}$

$SE(\ln \Psi) = \sqrt{.0027 + .0026 + .0047 + .0053}$

$SE(\ln \Psi) = \sqrt{.0153}$

$SE(\ln \Psi) = .1237$

95% CI $(\ln \Psi) = -.1599 \pm 1.96(.1237)$

95% CI $(\Psi) = \exp(-.4024, .0826)$

95% CI $(\Psi) = (.6687, 1.0861)$

Postmenopausal Females – High Vs. Low Activity

a = 194, b = 191, c = 213, d = 190

$\Psi = (a/b) / (c/d)$

$\Psi = (194/191) / (213/190)$

$\Psi = 1.0157 / 1.1211$

$\Psi = .9060$

$\ln(\Psi) = \ln(.9060) = -.0987$

$SE(\ln \Psi) = \sqrt{1/194 + 1/191 + 1/213 + 1/190}$

$SE(\ln \Psi) = \sqrt{.0052 + .0052 + .0047 + .0053}$

$SE(\ln \Psi) = \sqrt{.0204}$

$SE(\ln \Psi) = .1428$

95% CI $(\ln \Psi) = -.0987 \pm 1.96(.1428)$ .279888

95% CI $(\Psi) = \exp(-.3786, .1812)$

95% CI $(\Psi) = (.6848, 1.1987)$

John et al. (2003)

Premenopausal Females - Moderate Vs. Low Activity

a = 151, b = 160, c = 162, d = 161

$\Psi = (a/b) / (c/d)$
$\Psi = (151/160) / (162/161)$
$\Psi = .944 / 1.006$
$\Psi = .938$
$\ln(\Psi) = \ln(.938) = -.0639$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/151+1/160+1/162+1/161}$
$SE(\ln \Psi) = \sqrt{.0066+.0063+.0062+.0062}$
$SE(\ln \Psi) = \sqrt{.0253}$
$SE(\ln \Psi) = .1591$
95% CI $(\ln \Psi) = -.0639 \pm 1.96(.1591)$
95% CI $(\Psi) = \exp(-.3757, .2479)$
95% CI $(\Psi) = (.6868, 1.2813)$

Premenopausal Females – High Vs. Low Activity

a = 90, b = 162, c = 162, d = 161

$\Psi = (a/b) / (c/d)$
$\Psi = (90/162) / (163/161)$
$\Psi = (.556 / 1.006)$
$\Psi = .5527$
$\ln(\Psi) = \ln(.5527) = -.5928$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/90+1/162+1/162+1/161}$
$SE(\ln \Psi) = \sqrt{.0111+.0062+.0062+.0062}$
$SE(\ln \Psi) = \sqrt{.0297}$
$SE(\ln \Psi) = .1723$
95% CI $(\ln \Psi) = -.5928 \pm 1.96(.1723)$
95% CI $(\Psi) = \exp(-.9305, -.2551)$
95% CI $(\Psi) = (.3944, .7748)$

Postmenopausal Females – Moderate Vs. Low Activity

a = 271, b = 356, c = 343, d = 354

$\Psi = (a/b) / (c/d)$
$\Psi = (271/356) / (343/354)$
$\Psi = .761 / .967$
$\Psi = .787$
$\ln(\Psi) = \ln(.787) = -.2398$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/271 + 1/356 + 1/343 + 1/354}$
$SE(\ln \Psi) = \sqrt{.0037 + .0028 + .0029 + .0028}$
$SE(\ln \Psi) = \sqrt{.0122}$
$SE(\ln \Psi) = .1105$
95% CI $(\ln \Psi) = -.2398 \pm 1.96(.1105)$
95% CI $(\Psi) = \exp(-.4564, -.0232)$
95% CI $(\Psi) = (.6336, .9771)$

Postmenopausal Females – High Vs. Low Activity

a = 233, b = 355, c = 343, d = 354

$\Psi = (a/b) / (c/d)$
$\Psi = (233/355) / (343/354)$
$\Psi = .656 / .967$
$\Psi = .678$
$\ln(\Psi) = \ln(1.474) = -.3880$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/233 + 1/355 + 1/343 + 1/354}$
$SE(\ln \Psi) = \sqrt{.0043 + .0028 + .0029 + .0028}$
$SE(\ln \Psi) = \sqrt{.0128}$
$SE(\ln \Psi) = .1131$
95% CI $(\ln \Psi) = -.3880 \pm 1.96(.1131)$
95% CI $(\Psi) = \exp(-.6097, -.1663)$
95% CI $(\Psi) = (.5435, .8468)$

Levi et al. (1999)

Assumption = 4 METs per week

Postmenopausal Females – Moderate Vs. Low Activity

a = 52, b = 110, c = 111, d = 105

$\Psi = (a/b) / (c/d)$
$\Psi = (52/110) / (111/105)$
$\Psi = 0.4727 / 1.057$
$\Psi = 0.4472$
$\ln(\Psi) = \ln(0.4472) = -.8047$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/52 + 1/110 + 1/111 + 1/105}$
$SE(\ln \Psi) = \sqrt{.0192 + .0009 + .0009 + .0010}$
$SE(\ln \Psi) = \sqrt{.0220}$
$SE \ln(\Psi) = .1483$
95% CI $(\ln \Psi) = -.8047 \pm 1.96(.1483)$
95% CI $(\Psi) = \exp(-1.0954, -.5140)$
95% CI $(\Psi) = (.3344, .5981)$

Postmenopausal Females – High Vs. Low Activity

a = 18, b = 44, c = 111, d = 105

$\Psi = (a/b) / (c/d)$
$\Psi = (18/44) / (111/105)$
$\Psi = 0.4091 / 1.057$
$\Psi = 0.3870$
$\ln(\Psi) = \ln(0.3870) = -.9493$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/18 + 1/44 + 1/111 + 1/105}$
$SE(\ln \Psi) = \sqrt{.0555 + .0227 + .0009 + .0010}$
$SE(\ln \Psi) = \sqrt{.0801}$
$SE \ln(\Psi) = .2830$
95% CI $(\ln \Psi) = -.9493 \pm 1.96(.2830)$
95% CI $(\Psi) = \exp(-1.5040, -.3946)$
95% CI $(\Psi) = (.2222, .6739)$

Matthews et al. (2001)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

a = 70, b = 96, c = 1343, d = 1360

$\Psi = (a/b) / (c/d)$

$\Psi = (70/96) / (1343/1360)$

$\Psi = .7292 / .9875$

$\Psi = .7384$

$\ln(\Psi) = \ln(.7384) = -.3032$

$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$

$SE(\ln \Psi) = \sqrt{1/70 + 1/96 + 1/1343 + 1/1360}$

$SE(\ln \Psi) = \sqrt{.0143 + .0104 + .0007 + .0007}$

$SE(\ln \Psi) = \sqrt{.0261}$

$SE \ln(\Psi) = .1616$

95% CI $(\ln \Psi) = -.3032 \pm 1.96(.1616)$

95% CI $(\Psi) = \exp(-.6199, .0135)$

95% CI $(\Psi) = (0.5379, 1.0136)$

Premenopausal and Postmenopausal Females – High Vs. Low Activity

a = 46, b = 97, c = 1343, d = 1360

$\Psi = (a/b) / (c/d)$

$\Psi = (46/97) / (1343/1360)$

$\Psi = .4742 / .9875$

$\Psi = .4802$

$\ln(\Psi) = \ln(.4802) = -.7335$

$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$

$SE(\ln \Psi) = \sqrt{1/46 + 1/97 + 1/1343 + 1/1360}$

$SE(\ln \Psi) = \sqrt{.0217 + .0103 + .0007 + .0007}$

$SE(\ln \Psi) = \sqrt{.0334}$

$SE \ln(\Psi) = .1828$

95% CI $(\ln \Psi) = -.7335 \pm 1.96(.1828)$

95% CI $(\Psi) = \exp(-1.0918, -.3752)$

95% CI $(\Psi) = (.3356, .6872)$

McTiernan et al. (2003)

Postmenopausal Females – Moderate Vs. Low Activity

a = 590, b = 23826, c = 726, d = 29200

RR = (a / (a + b)) / (c / (c + d))

RR = [590 / (590 + 23826)] / [726 / (726 + 29200)]
RR = .0242 / .0243
RR = 0.9959
(ln RR) = -.0041
SE (ln Ψ) = $\sqrt{1/a - 1/(a+b) + 1/c - 1/(c+d)}$
SE (ln RR) = $\sqrt{1/590 - 1/(590+23826) + 1/726 - 1/(726+29200)}$
SE (ln RR) = $\sqrt{.0017 - .00004 + .0014 - .00003}$
SE (ln RR) = $\sqrt{.0030}$
SE (ln RR) = .0550
95% CI (ln RR) = -.0041 ± 1.96(.0550)
95% CI (RR) = exp (-.1119, .1037)
95% CI (RR) = (.8941, 1.1093)

Postmenopausal Females – High Vs. Low Activity

a = 590, b = 23826, c = 452, d = 18576

RR = (a / (a + b)) / (c / (c + d))

RR = [590 / (590 + 23826)] / [452 / (452 + 18576)]
RR = .0242 / .0238
RR = 1.0168
(ln RR) = .0167
SE (ln RR) = $\sqrt{1/a - 1/(a+b) + 1/c - 1/(c+d)}$
SE (ln RR) = $\sqrt{1/590 - 1/(590+23826) + 1/452 - 1/(452+18576)}$
SE (ln RR) = $\sqrt{.0017 - .00004 + .0022 - .00005}$
SE (ln RR) = $\sqrt{.00381}$
SE (ln RR) = .0617
95% CI (ln RR) = .0167 ± 1.96(.0617) .120932
95% CI (RR) = exp (-.1042, .1376)
95% CI (RR) = (.9010, 1.1476)

Moradi et al. (2000)

(Assumption = MET value of 6.0)

Postmenopausal Females – Moderate Vs. Low Activity

a = 882, b = 800, c = 840, d = 838

$\Psi = (a/b) / (c/d)$
$\Psi = (882/800) / (840/838)$
$\Psi = 1.1025 / 1.0024$
$\Psi = 1.1000$
$\ln(\Psi) = \ln(1.1000) = .0952$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/882 + 1/800 + 1/840 + 1/838}$
$SE(\ln \Psi) = \sqrt{.0011 + .0013 + .0012 + .0012}$
$SE(\ln \Psi) = \sqrt{.0048}$
$SE \ln(\Psi) = .0693$
95% CI $(\ln \Psi) = .0952 \pm 1.96(.0693)$
95% CI $(\Psi) = \exp(-.0406, .2310)$ .135828
95% CI $(\Psi) = (9602, 1.2699)$

Postmenopausal Females – High Vs. Low Activity

a = 812, b = 992, c = 840, d = 838

$\Psi = (a/b) / (c/d)$
$\Psi = (812/992) / (840/838)$
$\Psi = .8185 / 1.0024$
$\Psi = .8165$
$\ln(\Psi) = \ln(.8165) = -.2027$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/812 + 1/992 + 1/840 + 1/838}$
$SE(\ln \Psi) = \sqrt{.0012 + .0010 + .0012 + .0012}$
$SE(\ln \Psi) = \sqrt{.0046}$
$SE \ln(\Psi) = .0678$
95% CI $(\ln \Psi) = -.2027 \pm 1.96(.0678)$ .132888
95% CI $(\Psi) = \exp(-.3356, -.0698)$
95% CI $(\Psi) = (.7149, .9326)$

Patel et al. (2003; Case-Control)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

a = 100, b = 111, c = 341, d = 378

$\Psi = (a/b) / (c/d)$
$\Psi = (100/111) / (341/378)$
$\Psi = .9009 / .9021$
$\Psi = .9987$
$\ln(\Psi) = \ln(.9987) = -.0133$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/100 + 1/111 + 1/341 + 1/378}$
$SE(\ln \Psi) = \sqrt{.0100 + .0090 + .0029 + .0026}$
$SE(\ln \Psi) = \sqrt{.0245}$
$SE(\ln \Psi) = .1565$
95% CI $(\ln \Psi) = -.0133 \pm 1.96(.1565)$
95% CI $(\Psi) = \exp(-.3200, .2934)$
95% CI $(\Psi) = (.7261, 1.3410)$

Premenopausal and Postmenopausal Females – High Vs. Low Activity

a = 126, b = 127, c = 341, d = 378

$\Psi = (a/b) / (c/d)$
$\Psi = (126/127) / (341/378)$
$\Psi = .9921 / .9021$
$\Psi = 1.100$
$\ln(\Psi) = \ln(1.100) = .0951$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/126 + 1/127 + 1/341 + 1/378}$
$SE(\ln \Psi) = \sqrt{.0079 + .0079 + .0029 + .0026}$
$SE(\ln \Psi) = \sqrt{.0213}$
$SE(\ln \Psi) = .1459$
95% CI $(\ln \Psi) = .0951 \pm 1.96(.1459)$
95% CI $(\Psi) = \exp(-.1909, .3811)$
95% CI $(\Psi) = (.8262, 1.4639)$

Patel et al. (2003; Cohort)

Postmenopausal Females – Moderate Vs. Low Activity

$r_1 = 554$, $r_2 = 488$, $T_1 = 107{,}746$ py, $T_2 = 102{,}711$ py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = (488 * 107{,}746 \text{ py}) / (554 * 102{,}711 \text{ py})$
$\Psi = 52{,}580{,}048 / 56{,}901{,}894 = 0.9240$
$(\ln \Psi) = \ln (0.9240) = -.0790$
SE $(\ln \Psi) = \sqrt{(r1+r2) / (r1*r2)}$
SE $(\ln \Psi) = \sqrt{(554+488) / (554*488)}$
SE $(\ln \Psi) = \sqrt{1042 / 270{,}352}$
SE $(\ln \Psi) = \sqrt{.0039}$
SE $(\ln \Psi) = .0621$
95% CI $(\ln \Psi) = -.0790 \pm 1.96(.0621)$
95% CI $(\Psi) = \exp (-.2007, .0426)$
95% CI $(\Psi) = (.8181, 1.0436)$

Postmenopausal Females – High Vs. Low Activity

$r_1 = 554$, $r_2 = 352$, $T_1 = 107{,}746$ py, $T_2 = 77{,}641$ py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = (352 * 107{,}746 \text{ py}) / (554 * 77{,}641 \text{ py})$
$\Psi = 37{,}926{,}592 / 43{,}013{,}114 = .8817$
$(\ln \Psi) = \ln (.8817) = -.1259$
SE $(\ln \Psi) = \sqrt{(r_1 + r_2) / (r_1 \cdot r_2)}$
SE $(\ln \Psi) = \sqrt{554+352 / 554*352}$
SE $(\ln \Psi) = \sqrt{906 / 195008}$
SE $(\ln \Psi) = \sqrt{.0046}$
SE $(\ln \Psi) = .0682$
95% CI $(\ln \Psi) = -.1259 \pm 1.96(.0682)$
95% CI $(\Psi) = \exp (-.2596, .0077)$
95% CI $(\Psi) = (0.7714, 1.0078)$

Rockhill et al. (1999)

(Assumption = MET value of 4.0)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

$r_1 = 1341$, $r_2 = 1619$, $T_1 = 473{,}595$ py, $T_2 = 629{,}888$ py

OR ~ $\Psi = (r_2 * T_1) / (r_1 * T_2)$
$\Psi = (1619 * 473{,}595 \text{ py}) / (1341 * 629{,}888 \text{ py})$
$\Psi = 766{,}750{,}305 / 844{,}679{,}808 = .9077$
$(\ln \Psi) = \ln (.9077) = -.0968$
SE $(\ln \Psi) = \sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE $(\ln \Psi) = \sqrt{1341+1619 / 1341*1619}$
SE $(\ln \Psi) = \sqrt{2960 / 2{,}171{,}079}$
SE $(\ln \Psi) = \sqrt{.0014}$
SE $(\ln \Psi) = .0369$
95% CI $(\ln \Psi) = -.0968 \pm 1.96(.0369)$
95% CI $(\Psi) = \exp (-.1692, -.0244)$
95% CI $(\Psi) = (.8444, .9759)$

Premenopausal and Postmenopausal Females – High Vs. Low Activity

$r_1 = 1341$, $r_2 = 177$ $T_1 = 473{,}595$ py, $T_2 = 89{,}752$ py

OR ~ $\Psi = (r_2 * T_1 / r_1 * T_2)$
$\Psi = (177 * 473{,}595 \text{ py}) / (1341 * 89{,}752) \text{ py}$
$\Psi = 83{,}826{,}315 / 120{,}357{,}432 = .6965$
$(\ln \Psi) = \ln (.6965) = -.3617$
SE $(\ln \Psi) = \sqrt{(r_1 + r_2) / (r_1 \cdot r_2)}$
SE $(\ln \Psi) = \sqrt{(1341+177) / (1341*177)}$
SE $(\ln \Psi) = \sqrt{1518 / 237{,}357}$
SE $(\ln \Psi) = \sqrt{.0064}$
SE $(\ln \Psi) = .0800$
95% CI $(\ln \Psi) = -.3617 \pm 1.96(.0800)$
95% CI $(\Psi) = \exp (-.5184, -.2050)$
95% CI $(\Psi) = (.5954, .8147)$

Thune et al. (1997)

(Assumptions = Study Activity Grades from 1, 2, 3, and 4 converted to 0, <16, >16 MET Hours/Week, respectively)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

r1 = 66, r2 = 249, t1 = 4,344, t2 = 17,232

RR = (Number of Cases $_{High}$ / Number of Cases $_{High}$ + Number of Non-Cases $_{High}$) / (Number of Cases $_{Low}$ / Number of Cases $_{Low}$ + Number of Non-Cases $_{Low}$)

RR = [249 / (249 + 17,232] / [66 / (66 + 4,344)]
RR = .0133 / .0150
RR = .8867
(ln RR) = -.1203
SE (ln Ψ) = $\sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE (ln RR) = $\sqrt{66+249 / 66*249}$
SE (ln RR) = $\sqrt{315 / 16,434}$
SE (ln RR) = .1384
95% CI (ln RR) = -.1203 ± 1.96(.1384)
95% CI (RR) = exp (-.3916, .1510)
95% CI (RR) = (.6760, 1.1630)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

r1 = 66, r2 = 36, t1 = 4,344, t2 = 3,683

RR = (Number of Cases $_{High}$ / Number of Cases $_{High}$ + Number of Non-Cases $_{High}$) / (Number of Cases $_{Low}$ / Number of Cases $_{Low}$ + Number of Non-Cases $_{Low}$)

RR = [36 / (36 + 3,683] / [66 / (66 + 4,344)]
RR = .0097 / .0150
RR = .6467
(ln RR) = -.4359
SE (ln Ψ) = $\sqrt{r_1 + r_2 / r_1 \cdot r_2}$
SE (ln RR) = $\sqrt{66+36 / 66*36}$
SE (ln RR) = $\sqrt{102 / 2,376}$
SE (ln RR) = .2072
95% CI (ln RR) = -.4359 ± 1.96(.2072)
95% CI (RR) = exp (-.8420, -.0298)
95% CI (RR) = (.4308, .9706)

Yang et al. (2003)

Premenopausal and Postmenopausal Females – Moderate Vs. Low Activity

a = 88, b = 135, c = 315, d = 309

$\Psi = (a/b) / (c/d)$
$\Psi = (88/135) / (315/309)$
$\Psi = .6519 / 1.0194$
$\Psi = .6397$
$\ln(\Psi) = \ln(.6397) = -.4467$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/88 + 1/135 + 1/315 + 1/309}$
$SE(\ln \Psi) = \sqrt{.0114 + .0074 + .0032 + .0032}$
$SE(\ln \Psi) = \sqrt{.0252}$
$SE(\ln \Psi) = .1587$
95% CI $(\ln \Psi) = -.4467 \pm 1.96(.1587)$
95% CI $(\Psi) = \exp(-.7577, -.1356)$
95% CI $(\Psi) = (.4687, .8732)$

Premenopausal and Postmenopausal Females – High Vs. Low Activity

a = 81, b = 146, c = 315, d = 309

$\Psi = (a/b) / (c/d)$
$\Psi = (81/146) / (315/309)$
$\Psi = .5548 / 1.0194$
$\Psi = .5442$
$\ln(\Psi) = \ln(.5442) = .-6084$
$SE(\ln \Psi) = \sqrt{1/a + 1/b + 1/c + 1/d}$
$SE(\ln \Psi) = \sqrt{1/81 + 1/146 + 1/315 + 1/309}$
$SE(\ln \Psi) = \sqrt{.0123 + .0068 + .0032 + .0032}$
$SE(\ln \Psi) = \sqrt{.0255}$
$SE(\ln \Psi) = .1597$
95% CI $(\ln \Psi) = -.6084 \pm 1.96(.1597)$
95% CI $(\Psi) = \exp(-.9214, -.2954)$
95% CI $(\Psi) = (.3980, .7442)$

Appendix III

Mantel-Haenszel Odds Ratio Comparisons for Colon and Breast Cancer Analyses

Colon Cancer Analyses

The results from the Mantel-Haenszel (M-H) hand calculations and calculations using Stata 9.2 were similar for colon cancer analyses III and IV, as an insufficient number of case-control studies were present for M-H comparisons of Analyses I and II. The M-H results for Analysis III for males included three case-control studies (Longnecker et al., 1995; White et al., 1996; Tang et al., 1999) and the effect measure was 0.683 for moderately exercising males and . Two studies (White et al., 1996; Tang et al., 1999) were also included in Analysis IV for females. The effect measures for moderately and exercising females were 0.986 (hand-calculation) and 0.986 (Stata calculation), and 0.828 (hand-calculation) and 0.809 (Stata calculation) for highly exercising females. The purpose of completing the M-H calculations was to verify that the pooled results using Stata matched the pooled results from the hand calculations.

Mantel-Haenszel Hand- and Stata Calculations for Colon Cancer Analyses

Moderate Physical Activity and Colon Cancer Risk in Males (Longnecker et al. (1995); White et al. (1996); Tang et al. (1999))

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(8x141)}{(112+160)} + \frac{(10x24)}{(38+26)} + \frac{(85x84)}{(204+183)}\right]}{\left[\frac{(19x104)}{(112+160)} + \frac{(2x28)}{(38+26)} + \frac{(99x119)}{(204+183)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{(1128)}{(272)} + \frac{(240)}{(64)} + \frac{(7140)}{(387)}\right]}{\left[\frac{(1976)}{(272)} + \frac{(56)}{(64)} + \frac{(11781)}{(387)}\right]}$$

$$T_{MH(OR)} = \frac{[4.147 + 3.750 + 18.450]}{[7.265 + .875 + 30.442]}$$

$$T_{MH(OR)} = \frac{[26.347]}{[38.582]}$$

$$T_{MH(OR)} = 0.683$$

Study	OR	[95% Conf.	Interval]	% Weight
White (1996)	0.606	0.405	0.906	78.90
Tang (1999)	4.286	0.854	21.507	2.27
Longnecker (1995)	0.571	0.241	1.354	18.83
M-H pooled OR	0.683	0.482	0.967	100.00

Heterogeneity chi-squared = 5.48 (d.f. = 2) p = 0.064
I-squared (variation in OR attributable to heterogeneity) = 63.5%

Test of OR=1: z = 2.15; p = 0.032

High Physical Activity and Colon Cancer Risk in Males (Longnecker et al. (1995); White et al. (1996); Tang et al. (1999))

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(50x141)}{(154+242)} + \frac{(4x24)}{(32+41)} + \frac{(47x84)}{(205+178)}\right]}{\left[\frac{(101x104)}{(154+242)} + \frac{(17x28)}{(32+41)} + \frac{(50x119)}{(205+178)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{(7050)}{(396)} + \frac{(96)}{(73)} + \frac{(3948)}{(383)}\right]}{\left[\frac{(10504)}{(396)} + \frac{(476)}{(73)} + \frac{(5950)}{(383)}\right]}$$

$$T_{MH(OR)} = \frac{\left[17.803 + 1.315 + 10.308\right]}{\left[26.525 + 6.521 + 15.535\right]}$$

$$T_{MH(OR)} = \frac{29.426}{48.581}$$

$$T_{MH(OR)} = 0.606$$

Study	OR	[95% Conf.	Interval]	% Weight
White (1996)	0.664	0.408	1.079	37.51
Tang (1999)	0.202	0.060	0.682	12.33
Longnecker (1995)	0.671	0.440	1.025	50.16
M-H pooled OR	0.610	0.449	0.829	100.00

Heterogeneity chi-squared = 3.48 (d.f. = 2) p = 0.175
I-squared (variation in OR attributable to heterogeneity) = 42.6%

Test of OR=1: z = 3.16; p = 0.002

Moderate Physical Activity and Colon Cancer Risk in Females (White et al. (1996); Tang et al. (1999))

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(4x16)}{(21+20)} + \frac{(80x81)}{(165+158)}\right]}{\left[\frac{(4x17)}{(21+20)} + \frac{(77x85)}{(165+158)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{(64)}{(41)} + \frac{(6480)}{(323)}\right]}{\left[\frac{(68)}{(41)} + \frac{(6545)}{(323)}\right]}$$

$$T_{MH(OR)} = \frac{[1.561 + 20.062]}{[1.659 + 20.263]}$$

$$T_{MH(OR)} = \frac{21.623}{21.922}$$

$$T_{MH(OR)} = 0.986$$

Study	OR	[95% Conf.	Interval]	% Weight
White (1996)	0.990	0.640	1.532	92.43
Tang (1999)	0.941	0.201	4.412	7.57
M-H pooled OR	0.986	0.648	1.501	100.00

Heterogeneity chi-squared = 0.00 (d.f. = 1) p = 0.951
I-squared (variation in OR attributable to heterogeneity) = 0.0%

Test of OR=1: z = 0.06; p = 0.949

High Physical Activity and Colon Cancer Risk in Females (White et al. (1996); Tang et al. (1999))

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(17x7)}{(23+23)} + \frac{(28x81)}{(151+160)}\right]}{\left[\frac{(16x6)}{(23+23)} + \frac{(36x85)}{(151+160)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{119}{46} + \frac{2268}{311}\right]}{\left[\frac{96}{46} + \frac{3060}{311}\right]}$$

$$T_{MH(OR)} = \frac{\left[2.587 + 7.293\right]}{\left[2.087 + 9.839\right]}$$

$$T_{MH(OR)} = \frac{\left[9.880\right]}{\left[11.926\right]}$$

$$T_{MH(OR)} = 0.828$$

Study	OR	[95% Conf.	Interval]	% Weight
White (1996)	0.741	0.415	1.324	86.44
Tang (1999)	1.240	0.342	4.487	13.56
M-H pooled OR	0.809	0.477	1.370	100.00

Heterogeneity chi-squared = 0.51 (d.f. = 1) p = 0.475
I-squared (variation in OR attributable to heterogeneity) = 0.0%

Test of OR=1: z = 0.79; p = 0.430

Mantel-Haenszel Odds Ratio Comparisons for Breast Cancer Analyses

The results from the M-H hand calculations and calculations using Stata 9.2 were similar for breast cancer analyses I, III, IV, V, and VI. The identical case-control studies were included in Analyses I and II, so it was not necessary to compare M-H results for Analysis II. The M-H results for Analysis I for pre- and postmenopausal females combined included eight case-control studies (Carpenter et al., 1999; Friedenreich et al., 2001; Matthews et al., 2001; Yang et al., 2003; Patel et al., 2003; John et al., 2003; Bernstein et al., 2005). The M-H pooled estimate was 0.880 (hand-calculation) and 0.886 (Stata calculation) for moderately exercising females and 0.805 (hand-calculation) and 0.803 (Stata calculation) for highly exercising females. Small differences in the two M-H estimates for these analyses are likely due to rounding during the hand-calculations.

Nine case-control studies (Carpenter et al., 1999; Levi et al., 1999; Moradi et al., 2000; Friedenreich et al., 2001; Matthews et al., 2001; Yang et al., 2003; Patel et al., 2003; John et al., 2003; Bernstein et al., 2005) were included in the M-H comparisons for Analysis III. For moderately exercising pre- and postmenopausal females combined, the M-H estimates were 0.908 (hand-calculated) and 0.914 (Stata calculated), while the estimates for highly exercising females were 0.801 (hand-calculated) and 0.799 (Stata calculated), respectively. Two *Compendium*-quantified case-control studies of premenopausal breast cancer risk were included in the M-H estimate of Analysis IV. Moderately exercising females had an estimate of 0.902 (hand-calculated and Stata calculated), while the estimate for highly exercising females was 0.730. Case control studies of postmenopausal females were included in the M-H estimates for Analysis V and VI. Three studies (Carpenter et al., 1999; Friedenreich et al., 2001; John et al., 2003)

were included in the Analysis V estimate, and moderately exercising females had an estimate of 0.856 (hand-calculated) and 0.861 (Stata calculated). Highly exercising females had a lower estimate of 0.742 (hand-calculated) and 0.744 (Stata calculated). Analysis VI's M-H estimate included four studies (Carpenter et al., 1999; Moradi et al., 2000; Friedenreich et al., 2001; John et al., 2003), and the pooled estimates for moderately exercising females were 0.977 (hand-calculated) and 0.955 (Stata calculated), while the highly exercising females' estimates were 0.782 (hand-calculated) and 0.769 (Stata calculated). The purpose of completing the M-H calculations was to verify that the pooled results using Stata matched the pooled results from the hand calculations.

Mantel-Haenszel Hand- and Stata Calculations for Breast Cancer Analyses:

Moderate Physical Activity and Breast Cancer Risk - *Compendium* quantified physical activity among pre- and postmenopausal females combined; Carpenter et al. (1999); Friedenreich et al. (2001); Matthews et al. (2001); Yang et al. (2003); Patel et al. (2003); John et al. (2003); Bernstein et al. (2005)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH\,(OR)} = \left[\frac{(112x722)}{(1035+806)} + \frac{(216x118)}{(339+357)} + \frac{(364x190)}{(577+571)} + \frac{(171x1248)}{(1413+1456)} + \frac{(88x309)}{(403+444)} + \frac{(100x378)}{(441+489)} + \frac{(151x161)}{(313+321)} \; \frac{(271x354)}{(614+710)} + \frac{(822x2870)}{(3723+3751)} \right]$$

$$\overline{\left[\frac{(84x923)}{(1035+806)} + \frac{(239x123)}{(339+357)} + \frac{(381x213)}{(577+571)} + \frac{(208x1242)}{(1413+1456)} + \frac{(135x315}{(403+444)} + \frac{(111x341)}{(441+489)} + \frac{(160x162)}{(313+321)} + \frac{(356x343)}{(614+710)} + \frac{(881x2901)}{(3723+3751)} \right]}$$

$$T_{MH\,(OR)} = \left[\frac{80864}{1841} + \frac{25488}{696} + \frac{69160}{1148} + \frac{213408}{2869} + \frac{27192}{847} + \frac{37800}{930} + \frac{24311}{634} + \frac{95934}{1324} + \frac{2359140}{7474} \right]$$

$$\overline{\left[\frac{77532}{1841} + \frac{29397}{696} + \frac{81153}{1148} + \frac{258336}{2869} + \frac{42525}{847} + \frac{37851}{930} + \frac{25920}{634} + \frac{122108}{1324} + \frac{2555781}{7474} \right]}$$

$$T_{MH\,(OR)} = [42.924 + 36.621 + 60.209 + 74.384 + 32.104 + 40.645 + 38.345 + 72.458 + 315.646]$$

$$\overline{[42.114 + 42.237 + 70.691 + 90.044 + 50.207 + 40.700 + 40.883 + 92.227 + 341.956]}$$

$$T_{MH\,(OR)} = 713.336$$

$$\overline{811.059}$$

$$T_{MH\,(OR)} = 0.880$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	1.043	0.773	1.407	5.39
Friedenreich-Pre (2001)	0.867	0.634	1.185	5.41
Friedenreich-Post(2001)	0.938	0.687	1.281	5.23
Matthews (2001)	0.826	0.665	1.026	11.53
Yang (2003)	0.639	0.469	0.873	6.43
Patel (2003)	0.999	0.734	1.358	5.21
John-Pre (2003)	0.938	0.687	1.281	5.23
John-Post(2003)	0.786	0.632	0.976	11.80
Bernstein (2005)	0.923	0.828	1.028	43.77
M-H pooled OR	0.886	0.825	0.953	100.00

Heterogeneity chi-squared = 8.36 (d.f. = 8) p = 0.400
I-squared (variation in OR attributable to heterogeneity) = 4.3%

Test of OR=1: z = 3.27; p = 0.001

High Physical Activity and Breast Cancer Risk - *Compendium* quantified physical activity among pre- and postmenopausal females combined; Carpenter et al. (1999); Friedenreich et al. (2001); Matthews et al. (2001); Yang et al. (2003); Patel et al. (2003); John et al. (2003); Bernstein et al. (2005)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(88x722)}{(844+675)} + \frac{(123x118)}{(246+236)} + \frac{(194x190)}{(407+381)} + \frac{(46x1248)}{(1288+1345)} + \frac{(81x309)}{(396+455)} + \frac{(126x378)}{(467+505)} + \frac{(90x161)}{(252+323)} + \frac{(233x354)}{(576+709)} + \frac{(822x2870)}{(3716+3768)}\right]}{\left[\frac{(98x923)}{(844+675)} + \frac{(118x123)}{(246+236)} + \frac{(191x213)}{(407+381)} + \frac{(97x1242)}{(1288+1345)} + \frac{(146x315)}{(396+455)} + \frac{(127x341)}{(467+505)} + \frac{(162x162)}{(252+323)} + \frac{(355x343)}{(576+709)} + \frac{(898x2901)}{(3716+3768)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{63536}{1519} + \frac{14514}{482} + \frac{36860}{788} + \frac{57408}{2633} + \frac{25029}{851} + \frac{47628}{972} + \frac{14490}{575} + \frac{82482}{1285} + \frac{2359140}{7484}\right]}{\left[\frac{90454}{1519} + \frac{14514}{482} + \frac{40683}{788} + \frac{120474}{2633} + \frac{45990}{851} + \frac{43307}{972} + \frac{26244}{575} + \frac{121765}{1285} + \frac{2605098}{7484}\right]}$$

$$T_{MH\,(OR)} = \frac{[41.828 + 30.112 + 46.777 + 21.803 + 29.411 + 49.000 + 25.200 + 64.188 + 315.224]}{[59.548 + 30.112 + 51.628 + 45.755 + 54.042 + 44.555 + 45.642 + 94.759 + 348.089]}$$

$$T_{MH\,(OR)} = \frac{623.543}{774.130}$$

$$T_{MH\,(OR)} = 0.805$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	0.702	0.518	0.952	6.47
Friedenreich-Pre (2001	1.000	0.700	1.429	3.94
Friedenreich-Post(2001)	0.906	0.685	1.198	6.76
Matthews (2001)	0.477	0.333	0.683	5.99
Yang (2003)	0.544	0.398	0.745	7.07
Patel (2003)	1.100	0.826	1.465	5.83
John-Pre (2003)	0.552	0.394	0.774	5.97
John-Post(2003)	0.677	0.542	0.846	12.40
Bernstein (2005)	0.898	0.806	1.000	45.56
M-H pooled OR	0.803	0.745	0.866	100.00

Heterogeneity chi-squared = 32.63 (d.f. = 8) p < 0.001
I-squared (variation in OR attributable to heterogeneity) = 75.5%

Test of OR=1: z = 5.72; p < 0.001

Moderate Physical Activity and Breast Cancer Risk - *Compendium* quantified and estimated physical activity among pre- and postmenopausal females combined; Carpenter et al. (1999); Levi et al. (1999); Moradi et al. (2000); Friedenreich et al. (2001); Matthews et al. (2001); Yang et al. (2003); Patel et al. (2003); John et al. (2003); Bernstein et al. (2005)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \left[\frac{(112x722)}{(1035+806)} + \frac{(52x105)}{(163+215)} + \frac{(882x838)}{(1722+1638)} + \frac{(216x118)}{(339+357)} + \frac{(364x190)}{(577+571)} + \frac{(171x1248)}{(1413+1456)} + \frac{(88x309)}{(403+444)} + \frac{(100x378)}{(441+489)} + \frac{(151x161)}{(313+321)} + \frac{(271x354)}{(614+710)} + \frac{(822x2870)}{(3723+3751)} \right]$$

$$\frac{}{\left[\frac{(84x923)}{(1035+806)} + \frac{(110x111)}{(163+215)} + \frac{(800x840)}{(1722+1638)} + \frac{(239x123)}{(339+357)} + \frac{(381x213)}{(577+571)} + \frac{(208x1242)}{(1413+1456)} + \frac{(135x315}{(403+444)} + \frac{(111x341)}{(441+489)} + \frac{(160x162)}{(313+321)} + \frac{(356x343)}{(614+710)} + \frac{(881x2901)}{(3723+3751)} \right]}$$

$$T_{MH(OR)} = \left[\frac{80864}{1841} + \frac{5460}{378} + \frac{739116}{3360} + \frac{25488}{696} + \frac{69160}{1148} + \frac{213408}{2869} + \frac{27192}{847} + \frac{37800}{930} + \frac{24311}{634} + \frac{95934}{1324} + \frac{2359140}{7474} \right]$$

$$\frac{}{\left[\frac{77532}{1841} + \frac{12210}{378} + \frac{672000}{3360} + \frac{29397}{696} + \frac{81153}{1148} + \frac{258336}{2869} + \frac{42525}{847} + \frac{37851}{930} + \frac{25920}{634} + \frac{122108}{1324} + \frac{2555781}{7474} \right]}$$

$$T_{MH\,(OR)} = \frac{[42.924 + 14.444 + 219.975 + 36.621 + 60.209 + 74.384 + 32.104 + 40.645 + 38.345 + 72.458 + 315.646]}{[42.114 + 32.302 + 200.000 + 42.237 + 70.691 + 90.044 + 50.207 + 40.700 + 40.883 + 92.227 + 341.956]}$$

$$T_{MH\,(OR)} = \frac{947.755}{1043.361}$$

$$T_{MH\,(OR)} = 0.908$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	1.043	0.773	1.407	4.16
Levi (1999)	0.447	0.293	0.683	3.19
Moradi (2000)	1.100	0.961	1.259	19.73
Friedenreich-Pre (2001)	0.867	0.634	1.185	4.17
Friedenreich-Post(2001)	0.938	0.687	1.281	4.03
Matthews (2001)	0.826	0.665	1.026	8.88
Yang (2003)	0.639	0.469	0.873	4.95
Patel (2003)	0.999	0.734	1.358	4.02
John-Pre (2003)	0.938	0.687	1.281	4.03
John-Post(2003)	0.786	0.632	0.976	9.10
Bernstein (2005)	0.923	0.828	1.028	33.74
M-H pooled OR	0.914	0.859	0.974	100.00

Heterogeneity chi-squared = 27.13 (d.f. = 10) p = 0.002
I-squared (variation in OR attributable to heterogeneity) = 63.1%

Test of OR=1: z = 2.78; p = 0.005

High Physical Activity and Breast Cancer Risk - *Compendium* quantified and estimated physical activity among pre- and postmenopausal females combined; Carpenter et al. (1999); Levi et al. (1999); Moradi et al. (2000); Friedenreich et al. (2001); Matthews et al. (2001); Yang et al. (2003); Patel et al. (2003); John et al. (2003); Bernstein et al. (2005)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \left[\frac{(88x722)}{(844+675)} + \frac{(18x105)}{(129+149)} + \frac{(812x838)}{(1652+1830)} + \frac{(123x118)}{(246+236)} + \frac{(194x190)}{(407+381)} + \frac{(46x1248)}{(1288+1345)} + \frac{(81x309)}{(396+455)} + \frac{(126x378)}{(467+505)} + \frac{(90x161)}{(252+323)} + \frac{(233x354)}{(576+709)} + \frac{(822x2870)}{(3716+3768)} \right]$$

$$\frac{}{\left[\frac{(98x923)}{(844+675)} + \frac{(44x111)}{(129+149)} + \frac{(992x840)}{(1652+1830)} + \frac{(118x123)}{(246+236)} + \frac{(191x213)}{(407+381)} + \frac{(97x1242)}{(1288+1345)} + \frac{(146x315)}{(396+455)} + \frac{(127x341)}{(467+505)} + \frac{(162x162)}{(252+323)} + \frac{(355x343)}{(576+709)} + \frac{(898x2901)}{(3716+3768)} \right]}$$

$$T_{MH(OR)} = \left[\frac{63536}{1519} + \frac{1890}{278} + \frac{680456}{3482} + \frac{14514}{482} + \frac{36860}{788} + \frac{57408}{2633} + \frac{25029}{851} + \frac{47628}{972} + \frac{14490}{575} + \frac{82482}{1285} + \frac{2359140}{7484} \right]$$

$$\frac{}{\left[\frac{90454}{1519} + \frac{4884}{278} + \frac{833280}{3482} + \frac{14514}{482} + \frac{40683}{788} + \frac{120474}{2633} + \frac{45990}{851} + \frac{43307}{972} + \frac{26244}{575} + \frac{121765}{1285} + \frac{2605098}{7484} \right]}$$

$$T_{MH\,(OR)} = \frac{[41.828 + 6.799 + 195.421 + 30.112 + 46.777 + 21.803 + 29.411 + 49.000 + 25.200 + 64.188 + 315.224]}{[59.548 + 17.568 + 239.311 + 30.112 + 51.628 + 45.755 + 54.042 + 44.555 + 45.642 + 94.759 + 348.089]}$$

$$T_{MH\,(OR)} = \frac{825.763}{1031.009}$$

$$T_{MH\,(OR)} = 0.801$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	0.702	0.518	0.952	4.84
Levi (1999)	0.387	0.210	0.712	1.72
Moradi (2000)	0.817	0.715	0.933	23.44
Friedenreich-Pre (2001)	1.000	0.700	1.429	2.95
Friedenreich-Post(2001)	0.906	0.685	1.198	5.06
Matthews (2001)	0.477	0.333	0.683	4.48
Yang (2003)	0.544	0.398	0.745	5.29
Patel (2003)	1.100	0.826	1.465	4.36
John-Pre (2003)	0.552	0.394	0.774	4.47
John-Post(2003)	0.677	0.542	0.846	9.28
Bernstein (2005)	0.898	0.806	1.000	34.10
M-H pooled OR	0.799	0.749	0.853	100.00

Heterogeneity chi-squared = 38.20 (d.f. = 10) p < 0.001
I-squared (variation in OR attributable to heterogeneity) = 73.8%

Test of OR=1: z = 6.76; p = 0.000

Moderate Physical Activity and Breast Cancer Risk - *Compendium* quantified physical activity among premenopausal females; Friedenreich et al. (2001); John et al. (2003)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(216x118)}{(339+357)} + \frac{(151x161)}{(313+321)}\right]}{\left[\frac{(239x123)}{(339+357)} + \frac{(160x162)}{(313+321)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{25488}{696} + \frac{24311}{634}\right]}{\left[\frac{29397}{696} + \frac{25920}{634}\right]}$$

$$T_{MH(OR)} = \frac{[36.621 + 38.345]}{[42.237 + 40.883]}$$

$$T_{MH(OR)} = \frac{74.966}{83.120}$$

$$T_{MH(OR)} = 0.902$$

Study	OR	[95% Conf.	Interval]	% Weight
Friedenreich-Pre (2001)	0.867	0.634	1.185	50.81
John-Pre (2003)	0.938	0.687	1.281	49.19
M-H pooled OR	0.902	0.723	1.124	100.00

Heterogeneity chi-squared = 0.12 (d.f. = 1) p = 0.727
I-squared (variation in OR attributable to heterogeneity) = 0.0%

Test of OR=1: z = 0.92; p = 0.359

High Physical Activity and Breast Cancer Risk - *Compendium* quantified physical activity among premenopausal females; Friedenreich et al. (2001); John et al. (2003)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(123x118)}{(246+236)} + \frac{(90x161)}{(252+323)}\right]}{\left[\frac{(118x123)}{(246+236)} + \frac{(162x162)}{(252+323)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{14514}{482} + \frac{14490}{575}\right]}{\left[\frac{14514}{482} + \frac{26244}{575}\right]}$$

$$T_{MH(OR)} = \frac{[30.112 + 25.200]}{[30.112 + 45.642]}$$

$$T_{MH(OR)} = \frac{55.312}{75.754}$$

$$T_{MH(OR)} = 0.730$$

Study	OR	[95% Conf.	Interval]	% Weight
Friedenreich-Pre (2001)	1.000	0.700	1.429	39.75
John-Pre (2003)	0.552	0.394	0.774	60.25
M-H pooled OR	0.730	0.572	0.932	100.00

Heterogeneity chi-squared = 5.61 (d.f. = 1) p = 0.018
I-squared (variation in OR attributable to heterogeneity) = 82.2%

Test of OR=1: z = 2.53; p = 0.011

Moderate Physical Activity and Breast Cancer Risk - *Compendium* quantified physical activity among postmenopausal females; Carpenter et al. (1999); Friedenreich et al. (2001); John et al. (2003)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(112x722)}{(1035+806)} + \frac{(364x190)}{(577+571)} + \frac{(271x354)}{(614+710)}\right]}{\left[\frac{(84x923)}{(1035+806)} + \frac{(381x213)}{(577+571)} + \frac{(356x343)}{(614+710)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{80864}{1841} + \frac{69160}{1148} + \frac{95934}{1324}\right]}{\left[\frac{77532}{1841} + \frac{81153}{1148} + \frac{122108}{1324}\right]}$$

$$T_{MH(OR)} = \frac{[42.924 + 60.209 + 72.458]}{[42.114 + 70.691 + 92.227]}$$

$$T_{MH(OR)} = \frac{175.591}{205.032}$$

$$T_{MH(OR)} = 0.856$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	1.043	0.773	1.407	20.54
Friedenreich (2001)	0.852	0.669	1.086	34.48
John (2003)	0.786	0.632	0.976	44.98
M-H pooled OR	0.861	0.747	0.993	100.00

Heterogeneity chi-squared = 2.27 (d.f. = 2) p = 0.321
I-squared (variation in OR attributable to heterogeneity) = 11.9%

Test of OR=1: z = 2.06; p = 0.040

High Physical Activity and Breast Cancer Risk - *Compendium* quantified physical activity among postmenopausal females; Carpenter et al. (1999); Friedenreich et al. (2001); John et al. (2003)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(88x722)}{(844+675)} + \frac{(194x190)}{(407+381)} + \frac{(233x354)}{(576+709)}\right]}{\left[\frac{(98x923)}{(844+675)} + \frac{(191x213)}{(407+381)} + \frac{(355x343)}{(576+709)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{63536}{1519} + \frac{36860}{788} + \frac{82482}{1285}\right]}{\left[\frac{90454}{1519} + \frac{40683}{788} + \frac{121765}{1285}\right]}$$

$$T_{MH(OR)} = \frac{41.828 + 46.777 + 64.188}{59.548 + 51.628 + 94.759}$$

$$T_{MH(OR)} = \frac{152.793}{205.935}$$

$$T_{MH(OR)} = 0.742$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	0.702	0.518	0.952	25.23
Friedenreich-Post(2001)	0.906	0.685	1.198	26.37
John-Post(2003)	0.677	0.542	0.846	48.40
M-H pooled OR	0.744	0.640	0.865	100.00

Heterogeneity chi-squared = 2.73 (d.f. = 2) p = 0.255
I-squared (variation in OR attributable to heterogeneity) = 26.7%

Test of OR=1: z = 3.84; p < 0.001

Moderate Physical Activity and Breast Cancer Risk - *Compendium* quantified and estimated physical activity among postmenopausal females; Carpenter et al. (1999); Moradi et al. (2000): Friedenreich et al. (2001); John et al. (2003)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(112x722)}{(1035+806)} + \frac{(882x838)}{(1722+1638)} + \frac{(364x190)}{(577+571)} + \frac{(271x354)}{(614+710)}\right]}{\left[\frac{(84x923)}{(1035+806)} + \frac{(800x840)}{(1722+1638)} + \frac{(381x213)}{(577+571)} + \frac{(356x343)}{(614+710)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{80864}{1841} + \frac{739116}{3360} + \frac{69160}{1148} + \frac{95934}{1324}\right]}{\left[\frac{77532}{1841} + \frac{672000}{3360} + \frac{81153}{1148} + \frac{122108}{1324}\right]}$$

$$T_{MH(OR)} = \frac{[42.924 + 219.975 + 60.209 + 72.458]}{[42.114 + 200.000 + 70.691 + 92.227]}$$

$$T_{MH(OR)} = \frac{395.566}{405.032}$$

$$T_{MH(OR)} = 0.977$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	1.043	0.773	1.407	10.33
Levi (1999)	0.447	0.293	0.683	7.93
Moradi (2000)	1.100	0.961	1.259	49.08
Friedenreich-Post(2001)	0.938	0.687	1.281	10.03
John-Post(2003)	0.786	0.632	0.976	22.63
M-H pooled OR	0.955	0.866	1.053	100.00

Heterogeneity chi-squared = 19.93 (d.f. = 4) p = 0.001
I-squared (variation in OR attributable to heterogeneity) = 79.9%

Test of OR=1: z = 0.92; p = 0.357

High Physical Activity and Breast Cancer Risk - *Compendium* quantified and estimated physical activity among postmenopausal females; Carpenter et al. (1999); Moradi et al. (2000): Friedenreich et al. (2001); John et al. (2003)

$$T_{MH(OR)} = \frac{\sum_{i=1}^{k} a_i d_i / n_i}{\sum_{i=1}^{k} b_i c_i / n_i}$$

$$T_{MH(OR)} = \frac{\left[\frac{(88x722)}{(844+675)} + \frac{(812x838)}{(1652+1830)} + \frac{(194x190)}{(407+381)} + \frac{(233x354)}{(576+709)}\right]}{\left[\frac{(98x923)}{(844+675)} + \frac{(992x840)}{(1652+1830)} + \frac{(191x213)}{(407+381)} + \frac{(355x343)}{(576+709)}\right]}$$

$$T_{MH(OR)} = \frac{\left[\frac{63536}{1519} + \frac{680456}{3482} + \frac{36860}{788} + \frac{82482}{1285}\right]}{\left[\frac{90454}{1519} + \frac{833280}{3482} + \frac{40683}{788} + \frac{121765}{1285}\right]}$$

$$T_{MH(OR)} = \frac{[41.828 + 195.421 + 46.777 + 64.188]}{[59.548 + 239.311 + 51.628 + 94.759]}$$

$$T_{MH(OR)} = \frac{348.214}{445.246}$$

$$T_{MH(OR)} = 0.782$$

Study	OR	[95% Conf.	Interval]	% Weight
Carpenter (1999)	0.702	0.518	0.952	10.91
Levi (1999)	0.387	0.210	0.712	3.88
Moradi (2000)	0.817	0.715	0.933	52.87
Friedenreich-Post (2001)	0.906	0.685	1.198	11.41
John-Post (2003)	0.677	0.542	0.846	20.93
M-H pooled OR	0.769	0.697	0.848	100.00

Heterogeneity chi-squared = 8.57 (d.f. = 4) p = 0.073
I-squared (variation in OR attributable to heterogeneity) = 53.3%

Test of OR=1: z = 5.24; p < 0.001

Variance Calculation: High Physical Activity and Breast Cancer Risk - *Compendium* quantified and estimated physical activity among pre- and postmenopausal females combined; Carpenter et al. (1999); Levi et al. (1999); Moradi et al. (2000); Friedenreich et al. (2001); Matthews et al. (2001); Yang et al. (2003); Patel et al. (2003); John et al. (2003); Bernstein et al. (2005)

$$V_{MH(\ln(OR))} = \frac{\sum_{i=1}^{k} P_i R_i}{2\left(\sum_{i=1}^{k} R_i\right)^2} + \frac{\sum_{i=1}^{K} (P_i S_i + Q_i R_i)}{2\left(\sum_{i=1}^{k} R_i\right)\left(\sum_{i=1}^{k} S_i\right)} + \frac{\sum_{i=1}^{k} Q_i S_i}{2\left(\sum_{i=1}^{k} S_i\right)^2}$$

$$\left[\left(\frac{(88x722)}{(844+675)} x \frac{(88+722)}{(844+675)}\right) + \left(\frac{(18x105)}{(129+149)} x \frac{(18+105)}{(129+149)}\right) + \left(\frac{(812x838)}{(1652+1830)} x \frac{(812+838)}{(1652+1830)}\right) + \left(\frac{(123x118)}{(246+236)} x \frac{(123+118)}{(246+236)}\right) + \left(\frac{(194x190)}{(407+381)} x \frac{(194+190)}{(407+381)}\right) + \left(\frac{(46x1248)}{(1288+1345)} x \frac{(46+1248)}{(1288+1345)}\right) + \left(\frac{(81x309)}{(396+455)} x \frac{(81+309)}{(396+455)}\right) + \left(\frac{(126x378)}{(467+505)} x \frac{(126+378)}{(467+505)}\right) + \left(\frac{(90x161)}{(252+323)} x \frac{(90+161)}{(252+323)}\right) + \left(\frac{(233x354)}{(576+709)} x \frac{(233+354)}{(576+709)}\right) + \left(\frac{(822x2870)}{(3716+3768)} x \frac{(822+2870)}{(3716+3768)}\right) \right]$$

$$+$$

$$\left[\left[\left(\frac{(88+722)}{(844+675)}x\frac{(98x923)}{(844+675)}\right)+\left(\frac{(18+105)}{(129+149)}x\frac{(44x111)}{(129+149)}\right)+\left(\frac{(812+838)}{(1652+1830)}x\frac{(992x840)}{(1652+1830)}\right)+\left(\frac{(123+118)}{(246+236)}x\frac{(118x123)}{(246+236)}\right)+\left(\frac{(194+190)}{(407+381)}x\frac{(191x213)}{(407+381)}\right)+\left(\frac{(46+1248)}{(1288+1345)}x\frac{(97x1242)}{(1288+1345)}\right)+\left(\frac{(81+309)}{(396+455)}x\frac{(146x315)}{(396+455)}\right)+\left(\frac{(126+378)}{(467+505)}x\frac{(127x341)}{(467+505)}\right)+\left(\frac{(90+161)}{(252+323)}x\frac{(162x162)}{(252+323)}\right)+\left(\frac{(233+354)}{(576+709)}x\frac{(355x343)}{(576+709)}\right)+\left(\frac{(822+2870)}{(3716+3768)}x\frac{(898x2901)}{(3716+3768)}\right)\right]$$

$$+$$

$$\left[\left(\frac{(98+923)}{(844+675)}x\frac{(88x722)}{(844+675)}\right)+\left(\frac{(44+111)}{(129+149)}x\frac{(18x105)}{(129+149)}\right)+\left(\frac{(992+840)}{(1652+1830)}x\frac{(812x838)}{(1652+1830)}\right)+\left(\frac{(118+123)}{(246+236)}x\frac{(123x118)}{(246+236)}\right)+\left(\frac{(191+213)}{(407+381)}x\frac{(194x190)}{(407+381)}\right)+\left(\frac{(97+1242)}{(1288+1345)}x\frac{(46x1248)}{(1288+1345)}\right)+\left(\frac{(146+315)}{(396+455)}x\frac{(81x309)}{(396+455)}\right)+\left(\frac{(127+341)}{(467+505)}x\frac{(126x378)}{(467+505)}\right)+\left(\frac{(162+162)}{(252+323)}x\frac{(90x161)}{(252+323)}\right)+\left(\frac{(355+343)}{(576+709)}x\frac{(233x354)}{(576+709)}\right)+\left(\frac{(898+2901)}{(3716+3768)}x\frac{(822x2870)}{(3716+3768)}\right)\right]$$

$$+$$

$$\left[\left(\frac{(98+923)}{(844+675)}x\frac{(98x923)}{(844+675)}\right)+\left(\frac{(44+111)}{(129+149)}x\frac{(44x111)}{(129+149)}\right)+\left(\frac{(992+840)}{(1652+1830)}x\frac{(992x840)}{(1652+1830)}\right)+\left(\frac{(118+123)}{(246+236)}x\frac{(118x123)}{(246+236)}\right)+\left(\frac{(191+213)}{(407+381)}x\frac{(191x213)}{(407+381)}\right)+\left(\frac{(97+1242)}{(1288+1345)}x\frac{(97x1242)}{(1288+1345)}\right)+\left(\frac{(146+315)}{(396+455)}x\frac{(146x315)}{(396+455)}\right)+\left(\frac{(127+341)}{(467+505)}x\frac{(127x341)}{(467+505)}\right)+\left(\frac{(162+162)}{(252+323)}x\frac{(162x162)}{(252+323)}\right)+\left(\frac{(355+343)}{(576+709)}x\frac{(355x343)}{(576+709)}\right)+\left(\frac{(898+2901)}{(3716+3768)}x\frac{(898x2901)}{(3716+3768)}\right)\right]\right]$$

$$2(825.763)^2 + 2(825.763)\,(\,1031.009) + 2\,(1031.009)^2$$

=

22.3043 + 3.0080 + 92.6047 + 15.0560 + 22.7947 + 10.7153 +
13.4787 + 25.4074 + 11.0003 + 29.3218 + 155.5063
+
[31.7539 + 7.7730 + 113.4011 + 15.0560 + 15.1589 + 22.4867 +
24.7667 + 23.1023 + 19.9236 + 43.2869 + 171.7189]
+
[28.1145 + 3.7906 + 102.8177 + 15.0560 + 23.9819 + 11.0880 +
15.9326 + 23.5926 + 14.1997 + 34.8665 + 160.0131]
+
[40.0256 + 9.7953 + 125.9096 + 15.0560 + 26.4693 + 23.2687 + 29.2756 + 21.4520 +
25.7181 + 51.4721 + 176.6956]

=

$$\frac{401.1975 + [488.4280 + 433.4532] + 545.1379}{2(825.763)^2 + 2(825.763)\,(\,1031.0090) + 2\,(1031.0090)^2}$$

=

$$\frac{401.1975 + [488.4280 + 433.4532] + 545.1379}{1363769.064 + 1702738.1700 + 2125959.1160}$$

=

$$\frac{1868.2166}{5192466.35}$$

Estimated $V_{\text{MH (LN OR)}}$ = 0.00035980

Comparison of Mantel-Haenszel and STATA 95% Confidence Intervals:

$T_{\text{MH (OR)}} = 0.801$
$\ln (T_{\text{MH (OR)}}) = -.2219$
$\text{SE} = \sqrt{(V_{\text{MH (LN OR)}}} = \sqrt{0.00035980}$
SE = .0189 (hand-calculated)
95% CI ($\ln T_{\text{MH (OR)}}$) = -.2219 ± 1.96(.0189)
95% CI ($\ln T_{\text{MH (OR)}}$) = exp (-.258944, -.182356)
95% CI ($\ln T_{\text{MH (OR)}}$) = (.771866, .831200)

This hand-calculated 95% CI range of 0.772-0.831 compares to that of 0.749-0.853 in the M-H Stata output. The difference between these 95% confidence intervals is within rounding error.

Appendix IV

Mixed Effects Meta-Regression Models

Colon cancer risk among moderate versus low activity stratified males and females in *Compendium* quantified studies included in the mixed effects meta-regression model

```
Meta-regression                                   Number of studies = 6

tau2 = 0.0000
------------------------------------------------------------------------------
logor |     exp(b)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
sex |   .8486012   .1966037    -0.71   0.518     .4460109    1.614588
------------------------------------------------------------------------------
```

Colon cancer risk among high versus low activity stratified males and females in *Compendium* quantified studies included in the mixed effects meta-regression model

```
Meta-regression                                   Number of studies = 6

tau2   =   0.0000
------------------------------------------------------------------------------
logor |     exp(b)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
sex |   .8039878   .1852178    -0.95   0.397     .4240977    1.524169
------------------------------------------------------------------------------
```

Breast cancer risk among moderate versus low activity stratified pre- and postmenopausal females in *Compendium* quantified studies included in the mixed effects meta-regression model

```
Meta-regression                                    Number of studies = 8

tau2 = 0.0012
------------------------------------------------------------------------------
logor |     exp(b)     Std. Err.    t     P>|t|   [95% Conf. Interval]
-------------+----------------------------------------------------------------
menostat |  1.062866   .085198     0.76   0.476   .8735652 - 1.293188
```

Breast cancer risk among high versus low activity stratified pre- and postmenopausal females in *Compendium* quantified studies included in the mixed effects meta-regression model

```
Meta-regression                                   Number of studies = 8

tau2 = 0.0339
------------------------------------------------------------------------------
logor |       exp(b)    Std. Err.     t     P>|t|  [95% Conf. Interval]
------------------------------------------------------------------------------
menostat |   1.030597   .1749801     0.18   0.865   .6802393-1.561408
------------------------------------------------------------------------------
```

Appendix V

Population Attributable Fraction (PAF) Calculation for Postmenopausal Breast Cancer Risk

Proportion of High Activity in Population estimated from McTiernan et al. cohort study:

High Activity:
355+14299+97+4277

Low and Moderate Activity:
355+14299+97+4277+456+17483+270+11717+351+14435+239+9391

Proportion of High Activity
19028 / 73370

= .2593

Exposure = Non-High Activity
= 1 - .2593 = .7407

PAF Calculation:

PAF = [Px (RR-1)] / [Px (RR-1) + 1]

PAF = [.74 (.847-1)] / [.74 (.847-1) + 1]

PAF = .74 (-0.153) / .74 (-0.153) + 1

PAF = -.11322 / .88678

PAF = -.12768

PAF ~ -13%

Population Attributable Fraction (PAF) Calculation for Male Colon Cancer Risk

Proportion of High Activity in Population estimated from Giovannucci et al. cohort study:

Low and Moderate Activity (person-years):
156,599

High Activity (person-years):
106,955

Proportion of High Activity
= .4058

Exposure = Non-High Activity
= 1 - .4058 = .5942

PAF Calculation:

PAF = [Px (RR-1)] / [Px (RR-1) + 1]

PAF = [.5942 (.524-1)] / [.5942 (.524-1) + 1]

PAF = .5942 (-0.476) / .5942 (-0.476) + 1

PAF = -0.2828 / 0.7172

PAF = -.3944

PAF ~ -39.4%

Population Attributable Fraction (PAF) Calculation for Female Colon Cancer Risk

Proportion of High Activity in Population estimated from Martinez et al. cohort study:

Low and Moderate Activity (person-years):
242,351

High Activity (person-years):
58,817

= .2427

Exposure = Non-High Activity
= 1 - .2427 = .7573

PAF Calculation:

PAF = [Px (RR-1)] / [Px (RR-1) + 1]

PAF = [.7573 (.673-1)] / [.7573 (.673-1) + 1]

PAF = .7573 (-0.327) / .7573 (-0.327) + 1

PAF = -0.2476 / 0.7524

PAF = -.3291

PAF ~ -32.9%

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