# Physical Activity and Breast Cancer Prevention

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**Abstract** Breast cancer is the most commonly diagnosed invasive malignancy and the second leading cause of cancer death in women. This chapter considers epidemiologic evidence regarding the association between physical activity and breast cancer risk from 73 studies conducted around the world. Across these studies there was a 25% average risk reduction amongst physically active women as compared to the least active women. The associations were strongest for recreational activity, for activity sustained over the lifetime or done after menopause, and for activity that is of moderate to vigorous intensity and performed regularly. There is also some evidence for a stronger effect of physical activity amongst postmenopausal women, women who are normal weight, have no family history of breast cancer, and are parous. It is likely that physical activity is associated with decreased breast cancer risk via multiple interrelated biologic pathways that may involve adiposity, sex hormones, insulin resistance, adipokines, and chronic inflammation. Future research should include prospective observational epidemiologic studies relating proposed biomarkers to breast cancer risk and also randomized controlled trials to examine how physical activity influences the proposed biomarkers. Exercise trials will provide more clarity regarding the appropriate type, dose, and timing of activity that relate to breast cancer risk reduction.

## 2.1 Introduction

Physical inactivity is one of the few established breast cancer risk factors amenable to intervention. Over 90 studies conducted worldwide have investigated some aspect of this association. In this chapter, we review the epidemiologic literature on physical activity and breast cancer risk, examining the effect of the different parameters of activity and effect modification within different population subgroups. We also review the biologic mechanisms whereby physical activity may influence the risk of breast cancer.

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## 2.2
## Epidemiologic Evidence

### 2.2.1
### Background

Breast cancer is the most common invasive malignancy diagnosed in women, with 1,151,298 new cases estimated worldwide in 2002 (Ferlay et al. 2004). Female breast cancer represents 27% of all new female cancers in developed countries: estimates project 192,370 new cases in the U.S. and 22,700 cases in Canada in 2009 (Canadian Cancer Society 2009; Jemal et al. 2009). The lifetime risk of a woman being diagnosed with breast cancer is approximately one in eight in the United States (Jemal et al. 2009), and slightly lower in other developed countries (Australian Institute of Health and Welfare and National Breast and Ovarian Cancer Centre 2009; Canadian Cancer Society 2009; Cancer Research UK 2009).

Worldwide, breast cancer is the most common cause of cancer death among women; the number of estimated deaths in 2002 was 410,712 (Ferlay et al. 2004). In developed countries breast cancer is often the second leading cause of cancer death in women, following lung cancer (Canadian Cancer Society 2009; Jemal et al. 2009; Office for National Statistics 2008). A total of 40,170 and 5,400 breast cancer deaths are projected to occur in the U.S. and Canada, respectively, in 2009 (Canadian Cancer Society 2009; Jemal et al. 2009). However, 5-year relative survival is high, approaching 90% in developed countries (Australian Institute of Health and Welfare and National Breast and Ovarian Cancer Centre 2009; Canadian Cancer Society 2009; Jemal et al. 2009; Office for National Statistics 2008).

Most of the established risk factors for breast cancer are not easily modifiable. These include: age, race, a family history of breast cancer, genetic susceptibility, benign breast disease, early age at menarche, late age at menopause, and nulliparity (Bernstein 2009; Monninkhof et al. 2007a). Physical inactivity is one of the few behavioral risk factors amenable to change, and as such represents an opportunity to reduce the burden of disease from breast cancer.

There have been a number of reviews and reports written on the topic of physical activity and breast cancer prevention. These have generally concluded that the evidence supporting this association is convincing (Friedenreich and Cust 2008; Friedenreich and Orenstein 2002; IARC Working Group 2002; Monninkhof et al. 2007a); however the World Cancer Research Fund was more cautious, labeling the association probable (World Cancer Research Fund and the American Institute for Cancer Research 2007).

This chapter updates the review of physical activity and breast cancer risk provided by Friedenreich and Cust (2008). Here, we have incorporated the epidemiologic literature published to December 2009: 33 cohort studies and 40 case-control studies. Where multiple publications from the same study were found, the most recent publication (cohort studies), or the original publication (case-control studies), was selected for inclusion in our main results. We defined study results as null if the odds or hazard ratios fell between 0.9 and 1.1, inclusive. If the upper limit of the 95% confidence intervals (95% CI) was less than 1.05, we considered the results to be of borderline statistical significance.

### 2.2.2
### Overall Associations Between Physical Activity and Breast Cancer Risk

Twenty-nine of the 73 studies reviewed (40%) found a statistically significant risk reduction for breast cancer when comparing the highest versus lowest level of physical activity (Bernstein et al. 2005; Breslow et al. 2001; Carpenter et al. 2003; Calle et al. 1998; Dallal et al. 2007; Dirx et al. 2001; Fraser and Shavlik 1997; Friedenreich et al. 2001; Kruk 2007a, b; Kruk and Aboul-

Enein 2003; Levi et al. 1999; Mathew et al. 2009; Matthews et al. 2001; Mezzetti et al. 1998; Moradi et al. 2000; Peplonska et al. 2008; Peters et al. 2009a; Rintala et al. 2002; Rockhill et al. 1999; Sesso et al. 1998; Shoff et al. 2000; Suzuki et al. 2008; Thune et al. 1997; Ueji et al. 1998; Verloop et al. 2000; Wyrwich and Wolinsky 2000; Wyshak and Frisch 2000; Yang et al. 2003). An additional eight studies (11%) had a borderline, statistically significant breast cancer risk reduction (Hirose et al. 2003; John et al. 2003; Lee et al. 2001b; Leitzmann et al. 2008; Maruti et al. 2008; McTiernan et al. 1996; McTiernan et al. 2003; Patel et al. 2003), and 14 (19%) observed a statistically nonsignificant reduction (Adams-Campbell et al. 2001; Chang et al. 2006; Dey et al. 2009; Dorn et al. 2003; Dosemeci et al. 1993; Friedenreich and Rohan 1995; Gilliland et al. 2001; Hu et al. 1997; Marcus et al. 1999; Moradi et al. 2002; Rintala et al. 2003; Shin et al. 2009; Slattery et al. 2007; Sprague et al. 2007). Nineteen (26%) studies produced null effects (Bardia et al. 2006; Calle et al. 1998; Chen et al. 1997; Colditz et al. 2003; Coogan and Aschengrau 1999; Gammon et al. 1998; Gao et al. 2009; Howard et al. 2009; Lahmann et al. 2007; Lee et al. 2001a; Luoto et al. 2000; Magnusson et al. 2005; Mertens et al. 2006; Nkondjock et al. 2006; Schmidt et al. 2008; Silvera et al. 2006; Steindorf et al. 2003; Taioli et al. 1995; Tehard et al. 2006), and three (4%) studies observed a statistically nonsignificant increased risk of breast cancer among the most physically active women (Dorgan et al. 1994; Margolis et al. 2005; Schnohr et al. 2005). Statistically significant risk reductions were reported as frequently in the case-control studies (16 studies from a total of 40; 40%) as in the cohort studies (13 from 33; 39%) (Figs. 2.1 and 2.2). Across all studies there was a 25% average risk reduction, with a stronger effect found in the case-control studies (an average risk reduction of 30%) than in the cohort studies (a 20% risk reduction). Of the 51 studies that found a decreased risk of breast cancer with increased

levels of physical activity, 41 examined the trend of this relationship (Adams-Campbell et al. 2001; Bernstein et al. 2005; Breslow et al. 2001; Carpenter et al. 2003; Cerhan et al. 1998; Chang et al. 2006; Dallal et al. 2007; Dey et al. 2009; Dirx et al. 2001; Dorn et al. 2003; Dosemeci et al. 1993; Friedenreich et al. 2001; Friedenreich and Rohan 1995; Gilliland et al. 2001; Hirose et al. 2003; Hu et al. 1997; Kruk 2007a; b; Lee et al. 2001b; Leitzmann et al. 2008; Levi et al. 1999; Marcus et al. 1999; Maruti et al. 2008; Mathew et al. 2009; Matthews et al. 2001; McTiernan et al. 1996, 2003; Mezzetti et al. 1998; Moradi et al. 2000, 2002; Patel et al. 2003; Peplonska et al. 2008; Rockhill et al. 1999; Sesso et al. 1998; Shin et al. 2009; Shoff et al. 2000; Slattery et al. 2007; Sprague et al. 2007; Thune et al. 1997; Ueji et al. 1998; Yang et al. 2003). Thirty-three of these studies found evidence for a dose–response relation between increasing levels of physical activity and decreasing breast cancer risks (Adams-Campbell et al. 2001; Bernstein et al. 2005; Breslow et al. 2001; Carpenter et al. 2003; Cerhan et al. 1998; Dallal et al. 2007; Dey et al. 2009; Dirx et al. 2001; Friedenreich et al. 2001; Gilliland et al. 2001; Kruk 2007a; b; Lee et al. 2001b; Levi et al. 1999; Maruti et al. 2008; Mathew et al. 2009; Matthews et al. 2001; McTiernan et al. 1996, 2003; Mezzetti et al. 1998; Moradi et al. 2000, 2002; Patel et al. 2003; Peplonska et al. 2008; Rockhill et al. 1999; Sesso et al. 1998; Shin et al. 2009; Shoff et al. 2000; Slattery et al. 2007; Sprague et al. 2007; Thune et al. 1997; Ueji et al. 1998; Yang et al. 2003).

### 2.2.3
### Type, Dose, and Timing of Activity

One of the difficulties inherent in reviewing the physical activity and breast cancer literature is the heterogeneity of methods used to assess physical activity. Some studies have utilized comprehensive assessments of lifetime physical activity, whereas others have used single-item measures.
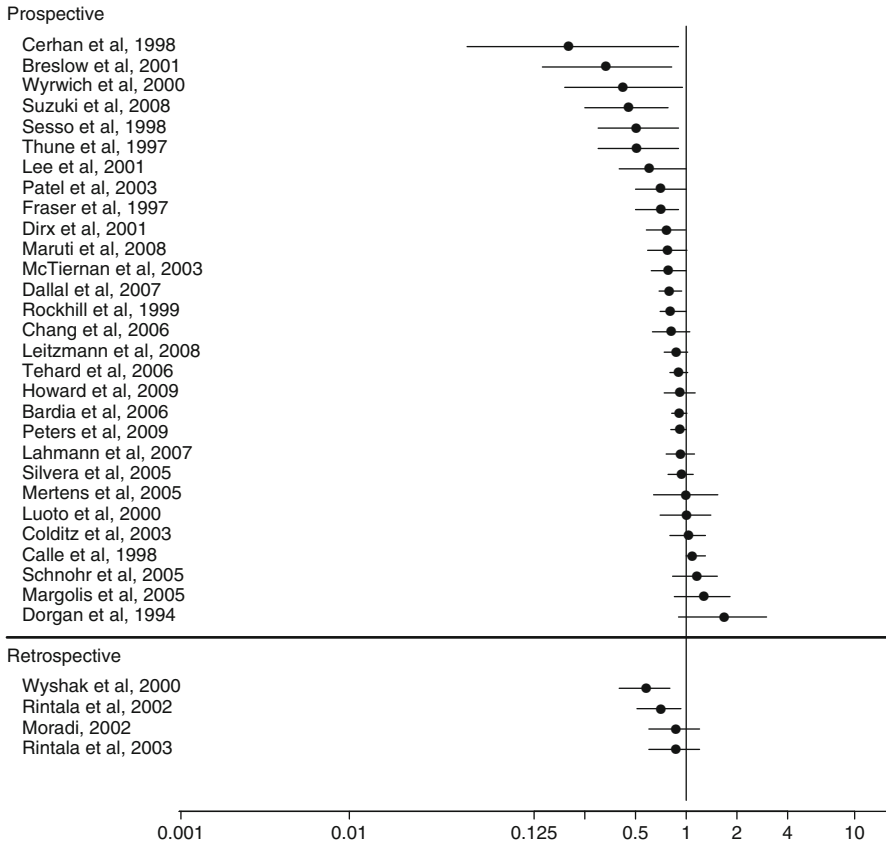
**2**

Prospective

Cerhan et al, 1998
Breslow et al, 2001
Wyrwich et al, 2000
Suzuki et al, 2008
Sesso et al, 1998
Thune et al, 1997
Lee et al, 2001
Patel et al, 2003
Fraser et al, 1997
Dirx et al, 2001
Maruti et al, 2008
McTiernan et al, 2003
Dallal et al, 2007
Rockhill et al, 1999
Chang et al, 2006
Leitzmann et al, 2008
Tehard et al, 2006
Howard et al, 2009
Bardia et al, 2006
Peters et al, 2009
Lahmann et al, 2007
Silvera et al, 2005
Mertens et al, 2005
Luoto et al, 2000
Colditz et al, 2003
Calle et al, 1998
Schnohr et al, 2005
Margolis et al, 2005
Dorgan et al, 1994

Retrospective

Wyshak et al, 2000
Rintala et al, 2002
Moradi, 2002
Rintala et al, 2003

0.001        0.01        0.125    0.5   1   2   4        10

**Fig. 2.1** Cohort studies of physical activity and breast cancer risk

Hence, we examined specific parameters of physical activity (i.e. type, dose, timing) and their association with breast cancer risk, separately.

Figures 2.3, 2.4, and 2.5 present study outcomes by type of physical activity: occupational, recreational, walking/cycling, and household activity. The greatest breast cancer risk reductions were found for recreational and household activity (average 21%), followed by walking/cycling (18%), and occupational activity (13%).

Dose refers to the combination of frequency, duration, and intensity of the activity performed. Frequency describes how many times a particular physical activity is undertaken, while duration describes the amount of time physical activity is undertaken for. Intensity

describes the level of exertion required to perform a particular physical activity, and is often categorized as light, moderate, or vigorous, according to energy expenditure.

Few studies reported frequency of physical activity, hence no figure is presented. Participation in moderate intensity physical activity was associated with an average decreased risk of 15%. A slightly greater risk reduction was found for vigorous intensity physical activity, 18% (Fig. 2.6). Similarly, greater decreases in breast cancer risk were observed with greater duration of activity (moderate-to-vigorous intensity or recreational activity) (Fig. 2.7). Hence, while participation in 2–3 h per week was associated with an
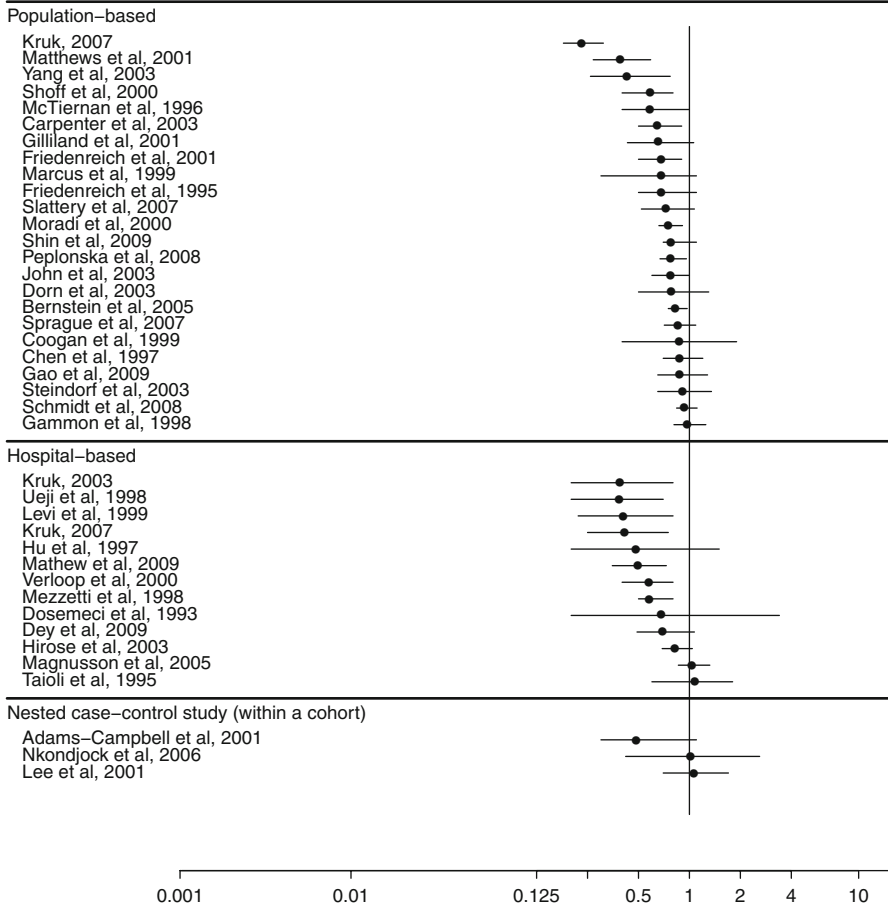
Population–based
    Kruk, 2007
    Matthews et al, 2001
    Yang et al, 2003
    Shoff et al, 2000
    McTiernan et al, 1996
    Carpenter et al, 2003
    Gilliland et al, 2001
    Friedenreich et al, 2001
    Marcus et al, 1999
    Friedenreich et al, 1995
    Slattery et al, 2007
    Moradi et al, 2000
    Shin et al, 2009
    Peplonska et al, 2008
    John et al, 2003
    Dorn et al, 2003
    Bernstein et al, 2005
    Sprague et al, 2007
    Coogan et al, 1999
    Chen et al, 1997
    Gao et al, 2009
    Steindorf et al, 2003
    Schmidt et al, 2008
    Gammon et al, 1998

Hospital–based
    Kruk, 2003
    Ueji et al, 1998
    Levi et al, 1999
    Kruk, 2007
    Hu et al, 1997
    Mathew et al, 2009
    Verloop et al, 2000
    Mezzetti et al, 1998
    Dosemeci et al, 1993
    Dey et al, 2009
    Hirose et al, 2003
    Magnusson et al, 2005
    Taioli et al, 1995

Nested case–control study (within a cohort)
    Adams–Campbell et al, 2001
    Nkondjock et al, 2006
    Lee et al, 2001

| 0.001 | 0.01 | 0.125 | 0.5 | 1 | 2 | 4 | 10 |

**Fig. 2.2**  Case–control studies of physical activity and breast cancer risk

average risk reduction of 9%, women who reported 6.5 h of activity per week or more had a decreased risk of 30%.

Studies also assessed physical activity performed during different periods of life: adolescence, early adulthood (20s), middle adulthood (30s/40s), and later adulthood (≥50 years) (Fig. 2.8). Although risk reductions were observed for physical activity performed at each age period, activity after age 50 seemed to have a slightly stronger effect than earlier periods of activity (an average risk reduction of 17%). The average decrease in breast cancer risk associated with physical activity performed during

adolescence was 16%; during early adulthood it was 8%, and during middle adulthood it was 15%. Sixteen studies assessed physical activity over the adult lifetime and the average risk reduction was even greater at 27% (data not shown).

## 2.2.4
## Population Subgroups

We also considered how the association between physical activity and breast cancer risk may vary between different population subgroups. There were sufficient data to examine effect modifica-
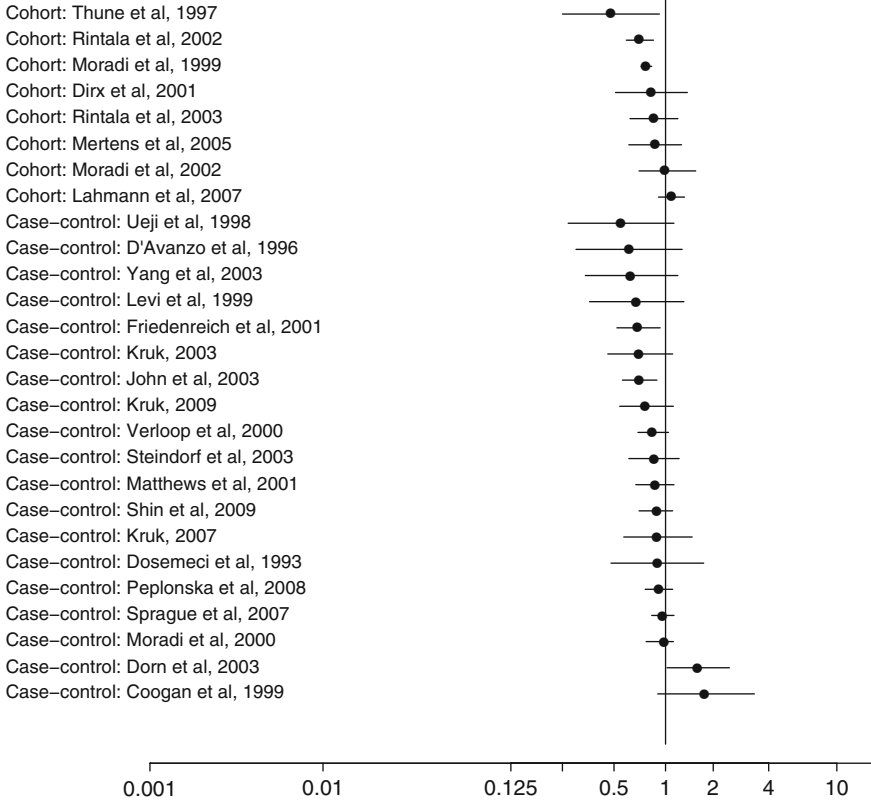
Occupational activity



**Fig. 2.3** Occupational physical activity and breast cancer risk

tion by menopausal status, body mass index (BMI; weight/height$^2$) race, family history of breast cancer, hormone receptor status, and parity.

A decrease in breast cancer risk was found for both pre- and postmenopausal women (Fig. 2.9); however, across all studies that reported on menopausal status, the average risk reduction was somewhat greater among postmenopausal women (31%) than among premenopausal women (27%). Twenty-five studies presented results stratified by menopausal status, i.e. both pre- and postmenopausal women in the same study population (Adams-Campbell et al. 2001; Dey et al. 2009; Dorn et al. 2003; Friedenreich et al. 2001; Friedenreich and Rohan 1995;

Gammon et al. 1998; Gilliland et al. 2001; Hirose et al. 2003; Howard et al. 2009; Hu et al. 1997; John et al. 2003; Kruk 2007a, b; Lahmann et al. 2007; Mathew et al. 2009; Matthews et al. 2001; Mezzetti et al. 1998; Moradi et al. 1999; Shin et al. 2009; Silvera et al. 2006; Slattery et al. 2007; Suzuki et al. 2008; Thune et al. 1997; Ueji et al. 1998; Yang et al. 2003). Only three observed statistically significant decreases in breast cancer risk for both pre- and postmenopausal women (Kruk 2007a; Suzuki et al. 2008; Yang et al. 2003). From the 25 studies that examined breast cancer risk reductions of pre- and postmenopausal women separately, 13 studies found greater risk reductions among postmenopausal
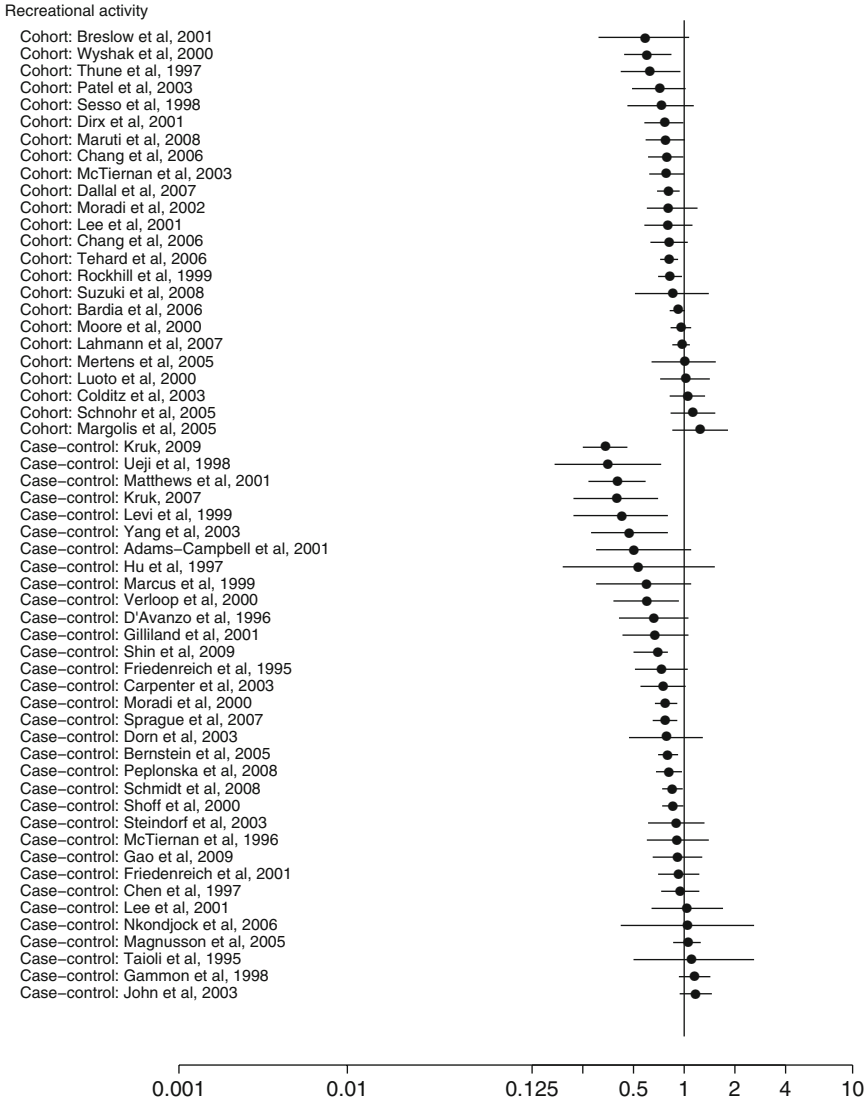
**Fig. 2.4** Recreational physical activity and breast cancer risk

women (Adams-Campbell et al. 2001; Dey et al. 2009; Dorn et al. 2003; Friedenreich et al. 2001; Friedenreich and Rohan 1995; Gammon et al. 1998; Gilliland et al. 2001; Hirose et al. 2003; Howard et al. 2009; Hu et al. 1997; John et al. 2003; Kruk 2007a, b; Lahmann et al. 2007; Mathew et al. 2009; Matthews et al. 2001; Mezzetti et al. 1998; Moradi et al. 1999; Shin et al. 2009; Silvera et al. 2006; Slattery et al. 2007; Suzuki et al. 2008; Thune et al. 1997; Ueji et al. 1998; Yang et al. 2003), 11 studies found a stronger effect among premenopausal women (Dorn et al. 2003; Friedenreich and Rohan 1995; Hirose et al. 2003; John et al. 2003; Lahmann
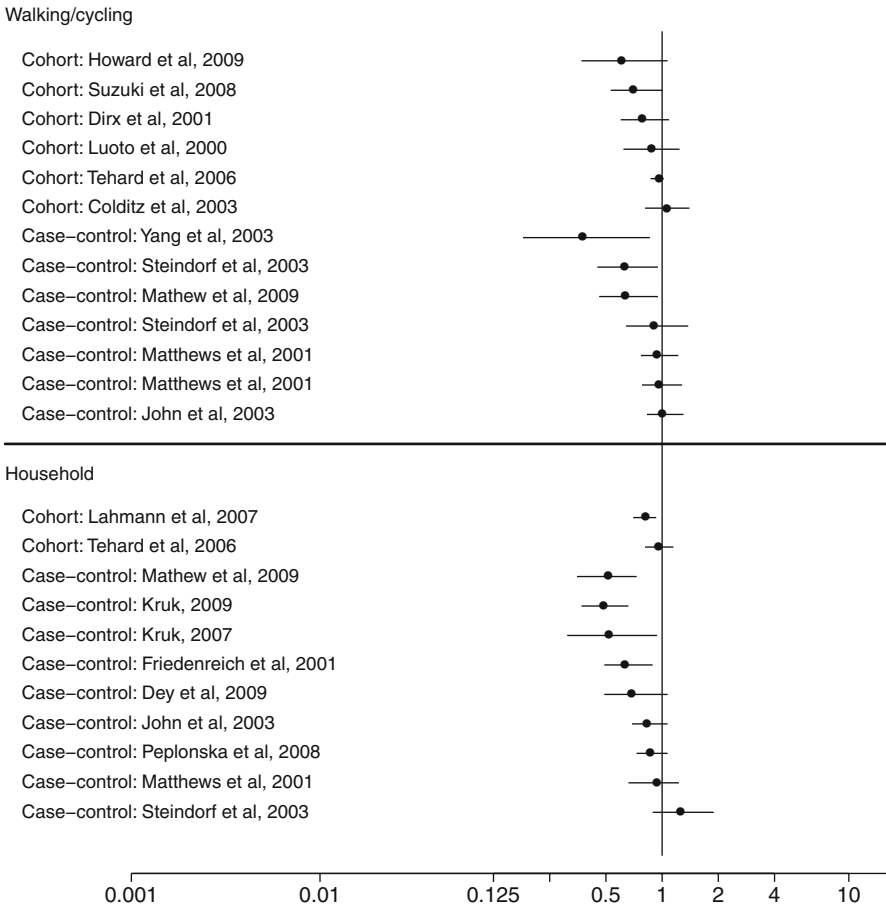
**Fig. 2.5** Household physical activity, walking, cycling, and breast cancer risk

et al. 2007; Silvera et al. 2006; Slattery et al. 2007; Suzuki et al. 2008; Thune et al. 1997; Ueji et al. 1998; Yang et al. 2003), and one study found no difference by menopausal status (Shin et al. 2009). It is noteworthy, however, that of these 25 studies that stratified by menopausal status, 12 yielded statistically significant risk reductions in postmenopausal women, whereas for premenopausal women only three studies showed statistically significant risk reductions.

The second effect modifier, BMI, was examined in 22 studies (Breslow et al. 2001; Colditz et al. 2003; Dallal et al. 2007; Friedenreich et al. 2001; Gammon et al. 1998; Hirose et al. 2003; Kruk and Aboul-Enein 2003; Leitzmann et al. 2008; Luoto et al. 2000; Maruti et al. 2008; McTiernan et al. 2003; Moradi et al. 2002; Patel et al. 2003; Peplonska et al. 2008; Peters et al. 2009b; Schmidt et al. 2008; Sesso et al. 1998; Suzuki et al. 2008; Tehard et al. 2006; Thune et al. 1997; Verloop et al. 2000; Yang et al. 2003). Figure 2.10 presents the results of these studies categorized as low BMI (<22 kg/m$^2$), medium BMI (22–25 kg/m$^2$), high BMI (≥25 kg/m$^2$), and very high BMI (≥30 kg/m$^2$). Greater decreases in breast cancer risk for highest
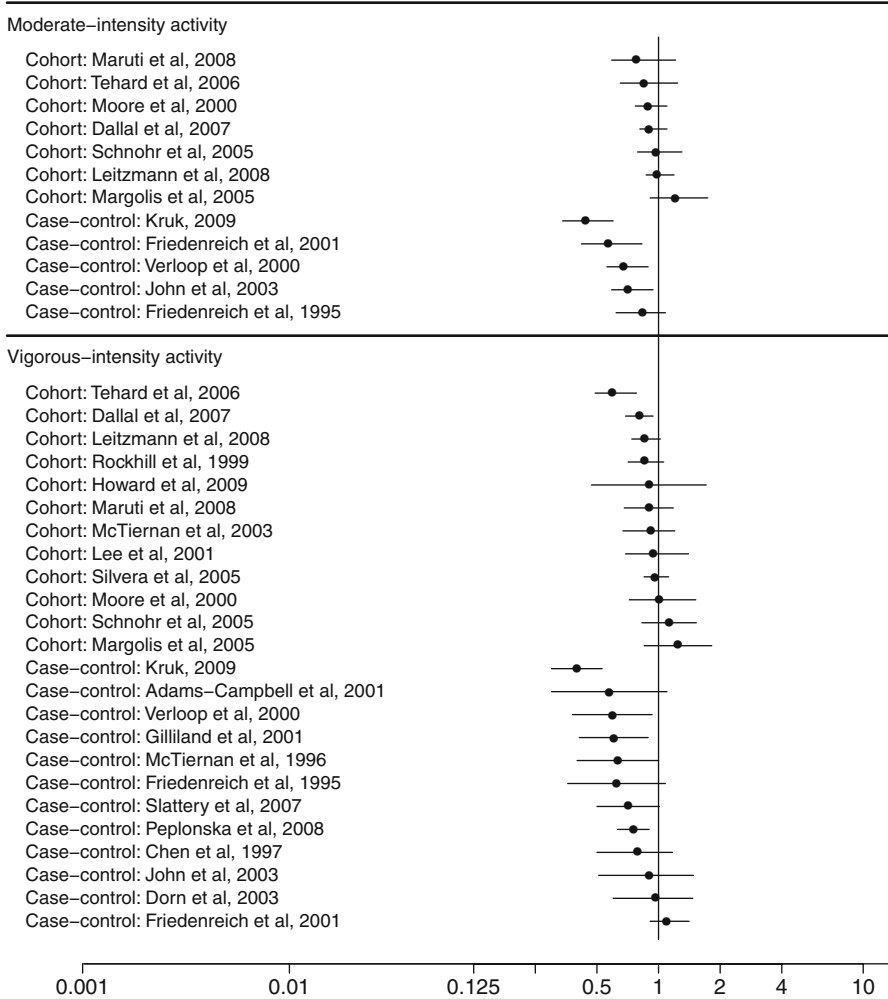
**Fig. 2.6** Intensity of physical activity and breast cancer risk

versus lowest categories of physical activity were observed among women with lower BMI. The average risk reduction for low BMI was 27%; for medium BMI breast cancer risk was decreased by 24%; for high BMI it decreased by 18%; and, among women with very high BMI, the average risk reduction was less than 1%.

Only four studies calculated risk estimates separately for different racial/ethnic groups within their samples (Bernstein et al. 2005;

Gilliland et al. 2001; John et al. 2003; Slattery et al. 2007) (Fig. 2.11). However, most of the studies included in this review could be classified according to the main racial group of their sample. An effect of physical activity on breast cancer risk was observed across all racial groups. Each of the three studies that included black women found a reduced risk (on average a relative decrease of 41%) (Adams-Campbell et al. 2001; Bernstein et al. 2005; John et al.
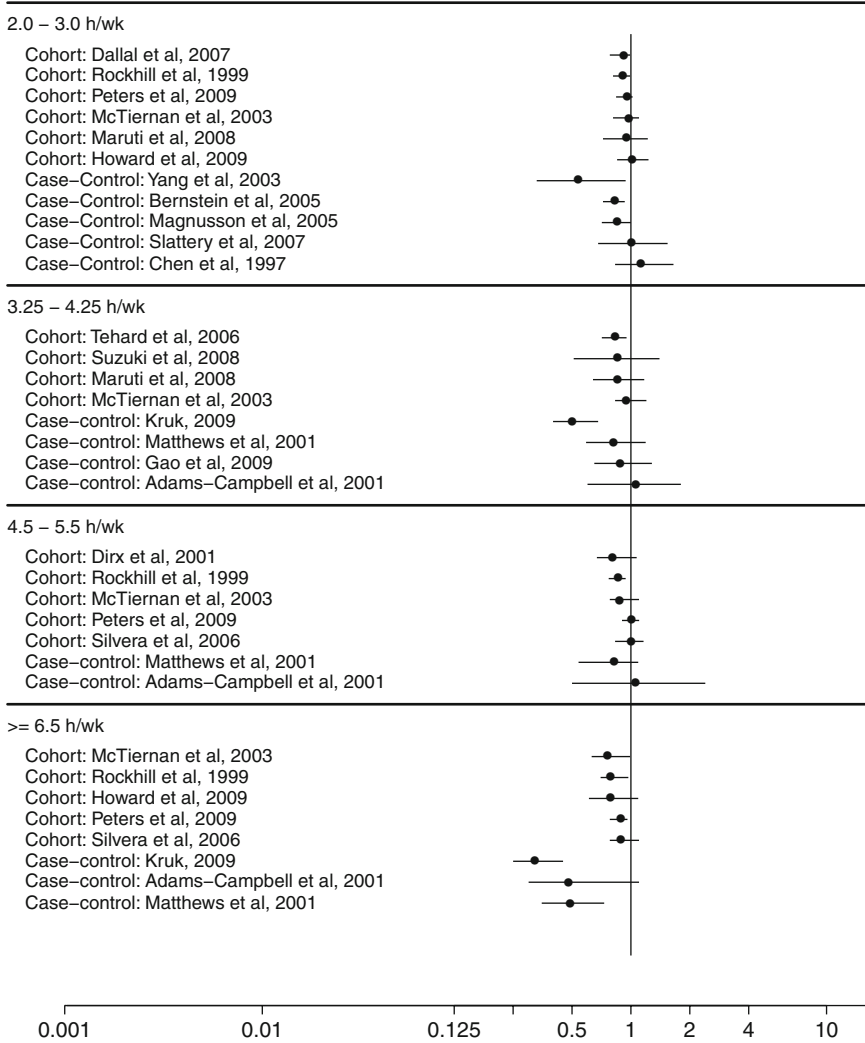
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**2.0 – 3.0 h/wk**

    Cohort: Dallal et al, 2007
    Cohort: Rockhill et al, 1999
    Cohort: Peters et al, 2009
    Cohort: McTiernan et al, 2003
    Cohort: Maruti et al, 2008
    Cohort: Howard et al, 2009
    Case–Control: Yang et al, 2003
    Case–Control: Bernstein et al, 2005
    Case–Control: Magnusson et al, 2005
    Case–Control: Slattery et al, 2007
    Case–Control: Chen et al, 1997

**3.25 – 4.25 h/wk**

    Cohort: Tehard et al, 2006
    Cohort: Suzuki et al, 2008
    Cohort: Maruti et al, 2008
    Cohort: McTiernan et al, 2003
    Case–control: Kruk, 2009
    Case–control: Matthews et al, 2001
    Case–control: Gao et al, 2009
    Case–control: Adams–Campbell et al, 2001

**4.5 – 5.5 h/wk**

    Cohort: Dirx et al, 2001
    Cohort: Rockhill et al, 1999
    Cohort: McTiernan et al, 2003
    Cohort: Peters et al, 2009
    Cohort: Silvera et al, 2006
    Case–control: Matthews et al, 2001
    Case–control: Adams–Campbell et al, 2001

**>= 6.5 h/wk**

    Cohort: McTiernan et al, 2003
    Cohort: Rockhill et al, 1999
    Cohort: Howard et al, 2009
    Cohort: Peters et al, 2009
    Cohort: Silvera et al, 2006
    Case–control: Kruk, 2009
    Case–control: Adams–Campbell et al, 2001
    Case–control: Matthews et al, 2001

0.001         0.01         0.125    0.5    1    2    4       10

**Fig. 2.7** Duration of physical activity and breast cancer risk

2003), two of the three studies of Hispanic women observed a reduced risk (average 28%) (Gilliland et al. 2001; John et al. 2003), and a decreased risk was found in both studies of Indian women (average 38%) (Dey et al. 2009; Mathew et al. 2009) and in the eight studies that included Asian women (average 41%) (Gao et al. 2009; Hirose et al. 2003; Hu et al. 1997; Matthews et al. 2001; Shin et al. 2009; Suzuki et al. 2008; Ueji et al. 1998; Yang et al. 2003). The average risk reduction for white women was somewhat lower (20%) (Bardia et al. 2006; Bernstein et al. 2005; Chang et al. 2006; Chen et al. 1997; Coogan and Aschengrau 1999; Dallal et al. 2007; Dirx et al. 2001; Fraser and Shavlik 1997; Friedenreich et al. 2001; Gilliland et al. 2001; Hofvind and Thoresen 2001; Howard et al. 2009; John et al. 2003; Kruk
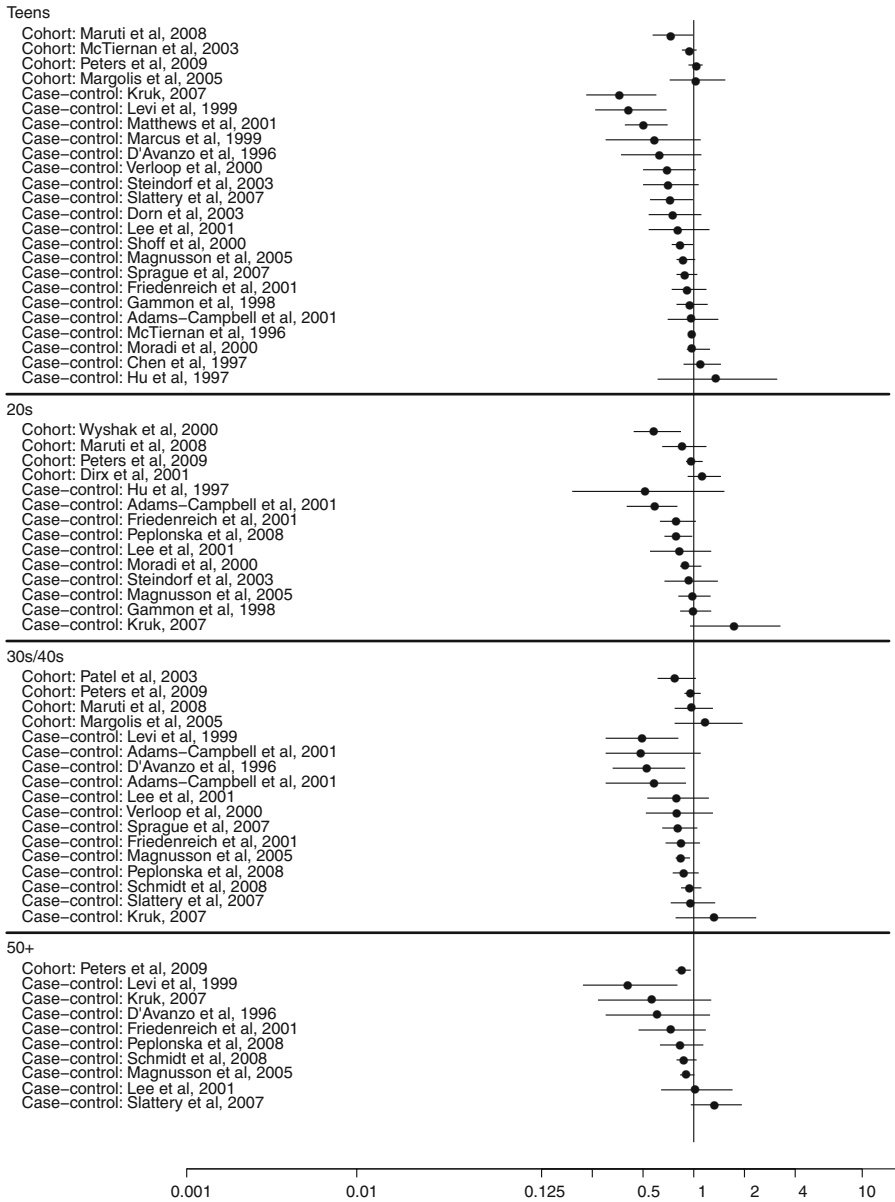
**Fig. 2.8** Physical activity and breast cancer risk by decade of life

2007a; Kruk and Aboul-Enein 2003; Lahmann et al. 2007; Leitzmann et al. 2008; Levi et al. 1999; Luoto et al. 2000; Magnusson et al. 2005; Margolis et al. 2005; Maruti et al. 2008; Mezzetti et al. 1998; Moradi et al. 1999, 2000, 2002; Peplonska et al. 2008; Peters et al. 2009a; Rintala et al. 2002, 2003; Schmidt et al. 2008; Schnohr et al. 2005; Slattery et al. 2007;
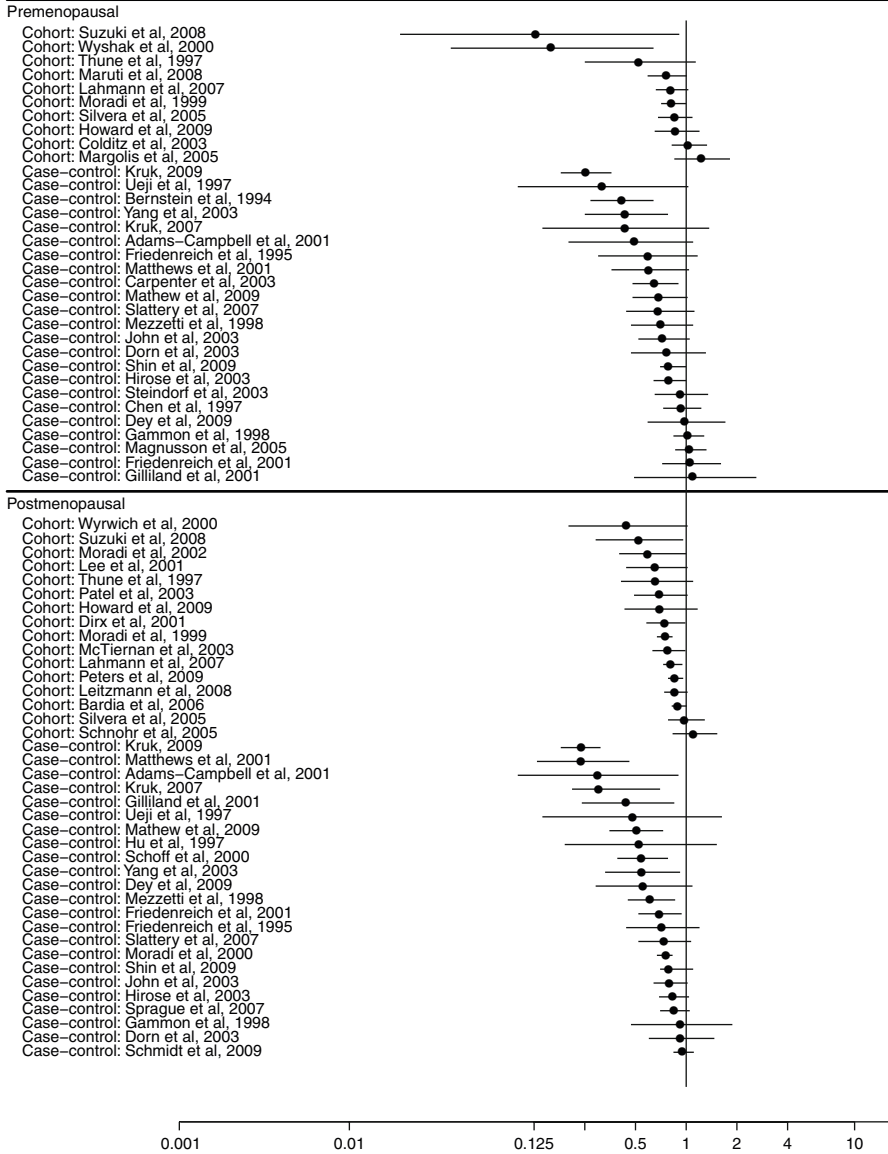
**2**



**Fig. 2.9** Physical activity and breast cancer risk by menopausal status

Steindorf et al. 2003; Tehard et al. 2006; Thune et al. 1997; Verloop et al. 2000).

Nine studies included separate risk estimates for women with and without a family history of breast cancer (Bernstein et al. 2005; Carpenter et al. 2003; Dallal et al. 2007; Hirose et al. 2003; Magnusson et al. 2005; Peplonska et al. 2008; Peters et al. 2009b; Schmidt et al. 2008; Sprague et al. 2007). A strong risk reduction, on average 21%, was observed among women without a

Low BMI (generally <22)

Cohort: Morad et al, 2002
Cohort: Sesso et al, 1998
Cohort: Luoto et al, 2000
Case–control: Thune et al, 1997
Case–control: Verloop et al, 2000
Case–control: Yang et al, 2003
Case–control: Schmidt et al, 2009
Case–control: Gammon et al, 1998
Case–control: Hirose et al, 2003

Medium BMI (approximately 22 – 25)

Cohort: Moradi et al, 2002
Cohort: McTiernan et al, 2003
Cohort: Dallal et al, 2007
Cohort: Patel et al, 2003
Cohort: Colditz et al, 2003
Cohort: Luoto et al, 2000
Case–control: Yang et al, 2003
Case–control: Friedenreich et al, 2001
Case–control: Verloop et al, 2000
Case–control: Schmidt et al, 2009
Case–control: Hirose et al, 2003
Case–control: Gammon et al, 1998
Case–control: Thune et al, 1997

High BMI (approximately >= 25)

Cohort: Breslow et al, 2001
Cohort: Suzuki et al, 2008
Cohort: McTiernan et al, 2003
Cohort: Dallal et al, 2007
Cohort: Maruti et al, 2008
Cohort: Peters et al, 2009
Cohort: Tehard et al, 2006
Cohort: Luoto et al, 2000
Cohort: Patel et al, 2003
Cohort: Colditz et al, 2003
Cohort: Leitzmann et al, 2008
Cohort: Moradi et al, 2002
Case–control: Yang et al, 2003
Case–control: Peplonska et al, 2008
Case–control: Friedenreich et al, 2001
Case–control: Kruk, 2003
Case–control: Schmidt et al, 2009
Case–control: Hirose et al, 2003
Case–control: Thune et al, 1997
Case–control: Verloop et al, 2000
Case–control: Gammon et al, 1998

Very high BMI (generally >= 30)

Cohort: McTiernan et al, 2003
Cohort: Patel et al, 2003
Cohort: Colditz et al, 2003
Case–control: Friedenreich et al, 2001
Case–control: Schmidt et al, 2009

0.001        0.01        0.125        0.5    1    2    4    10



**Fig. 2.10**  Physical activity and breast cancer risk by body mass index
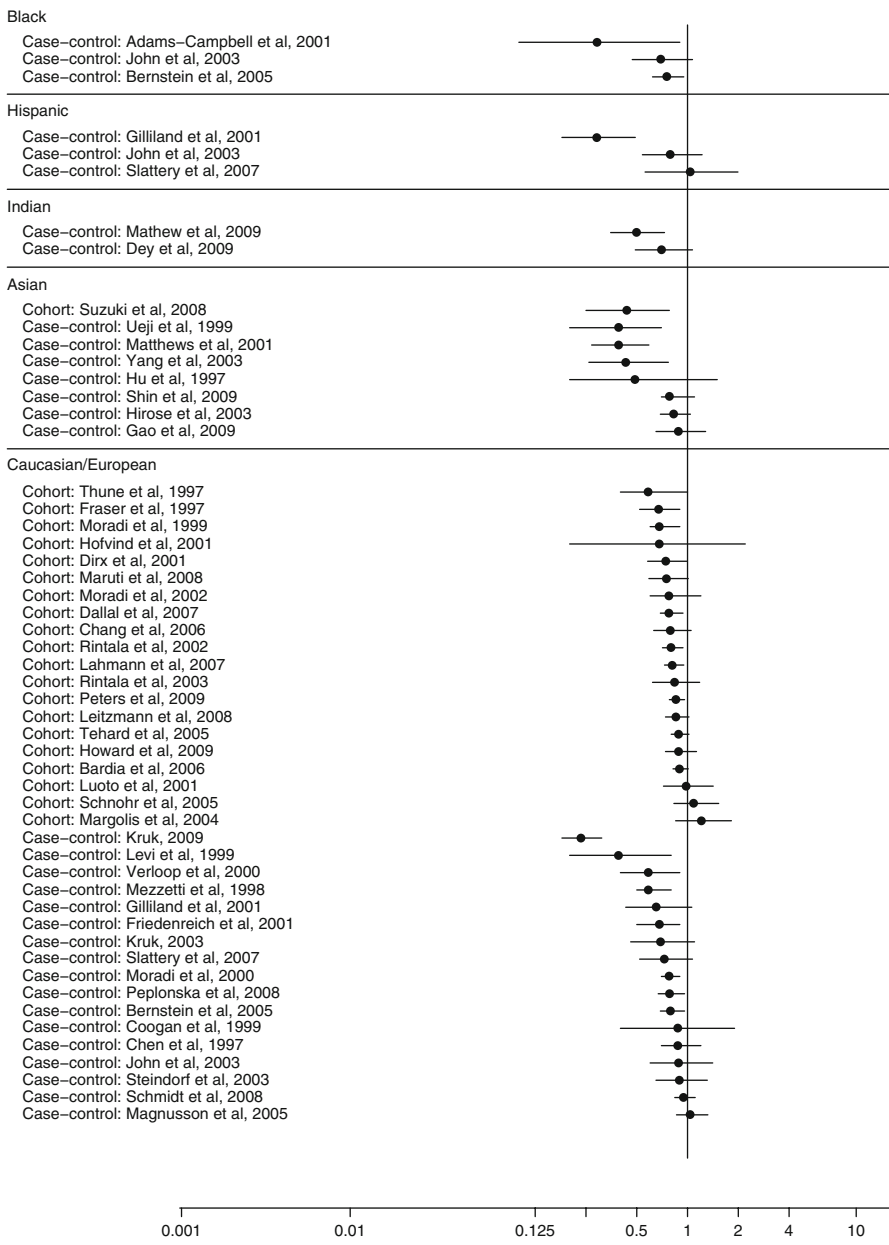
**Fig. 2.11** Physical activity and breast cancer risk by race

family history of breast cancer while women with a family history experienced no breast cancer risk reduction with higher levels of physical activity (less than 1% on average). These risk decreases were statistically significant in all studies except for one that found no effect modification by family history of breast cancer (Magnusson et al. 2005).

Hormone receptor status was examined in 11 studies as a potential effect modifier (Bardia et al. 2006; Bernstein et al. 2005; Dallal et al. 2007; Dey et al. 2009; Enger et al. 2000; Lee et al. 2001b; Leitzmann et al. 2008; Maruti et al. 2008; Peplonska et al. 2008; Peters et al. 2009a; Schmidt et al. 2008). Seven studies examined the association between physical activity and breast cancer for estrogen positive (ER+) and negative (ER-) tumors (Bardia et al. 2006; Bernstein et al. 2005; Dallal et al. 2007; Dey et al. 2009; Peplonska et al. 2008; Peters et al. 2009a; Schmidt et al. 2008). Five studies observed statistically significant breast cancer risk reductions for higher levels of physical activity among women with ER+ tumors (Bardia et al. 2006; Bernstein et al. 2005; Peplonska et al. 2008; Peters et al. 2009a; Schmidt et al. 2008); two studies found significant reductions for ER- tumors (Dallal et al. 2007; Dey et al. 2009). The average risk reduction across all studies that examined the association for ER+ and ER- was the same for both groups (20%). Three studies compared the breast cancer risk reductions for highest versus lowest physical activity categories among women with progesterone positive (PR+) and negative (PR-) tumors (Bardia et al. 2006; Peplonska et al. 2008; Schmidt et al. 2008). Peplonska et al. (2008) and Schmidt et al. (2008) found statistically significant breast cancer risk reductions for higher physical activity among women with PR+ tumors, and no effect for PR- tumors. Bardia et al. (2006) observed the reciprocal – significant risk reductions for PR- and no effect for PR+. Eight studies compared women with estrogen- and progesterone- positive (ER+/PR+) tumors with women that had estrogen and progesterone negative (ER-/PR-) tumors (Bardia et al. 2006; Bernstein et al. 2005; Dallal et al. 2007; Enger et al. 2000; Lee et al. 2001b; Leitzmann et al. 2008; Maruti et al. 2008; Peters et al. 2009a; Schmidt et al. 2008), and an additional study considered women with ER-/PR- alone (Bernstein et al. 2005). Statistically significant risk reductions were found in only one ER+/PR+ study (Schmidt et al. 2008) and one ER-/PR- study (Dallal et al. 2007). Average risk reductions were greater for women with ER-/PR- tumors (27%) than for women with ER+/PR+ tumors (14%).

Parity was considered by seven studies (Bernstein et al. 2005; Dallal et al. 2007; Friedenreich et al. 2001; Magnusson et al. 2005; Maruti et al. 2008; Moradi et al. 2000; Tehard et al. 2006). A greater risk reduction was found for parous women (average decrease in breast cancer risk 38%) than for nulliparous women (average decrease 18%).

### 2.2.5
### Summary of Epidemiologic Findings

In this review of 73 observational epidemiologic studies of physical activity and breast cancer risk, we found an average decrease in breast cancer risk of 25% when comparing the most physically active to the least active women. The risk reductions observed in studies assessing recreational and household activities were greater than for walking/cycling or occupational activity. Greater risk reductions were also observed for physical activity of longer than shorter duration. In terms of physical activity intensity, slightly stronger risk reductions were observed for women reporting participation in vigorous-intensity activities, in comparison with participation in moderate-intensity activities. We did not consider the associations of light-intensity activities or sedentary behavior separately in this review. Activity done after menopause appeared to have the greatest impact on the risk of breast cancer. However, risk reductions were apparent for physical activity performed across the lifespan. Within those studies that stratified by menopausal status, statistically significant risk reductions occurred more commonly amongst postmenopausal women than among premenopausal women. Physical activity reduced the risk of breast cancer within each BMI category except in obese women ($\geq 30$ kg/$m^2$) with a clear dose–response in the breast cancer risk reduction across BMI categories with the

greatest decrease risk among lean women (<22 kg/m$^2$). Effect modification was also observed between race, family history of breast cancer, and parity subgroups with a stronger effect of physical activity observed amongst women of non-Caucasian backgrounds, without a family history of breast cancer and who were parous. Clear effect modification of the association between physical activity and breast cancer risk by hormone receptor status was not elucidated.

This review of the epidemiologic findings is limited, first and foremost, by the heterogeneity of methods used to assess physical activity. The vast majority of studies in our review used physical activity questionnaires, with some assessing lifetime physical activity and others using a single-item measure. Study quality also varied because of differences across these studies in sampling procedures and in reporting the results regarding the association between physical activity and breast cancer. Hence, direct comparisons across studies regarding these associations are difficult to interpret. We have presented average risk reductions, calculated as the mean of the point estimates, to allow comparisons between subgroups. However, average risk reduction is a crude measure that does not account for differences in study methods or the precision of the risk estimates. All risk reductions presented in this review represent the highest versus lowest category of physical activity assessed within a particular study. Physical activity categories may differ significantly between studies, and hence the strength of associations may be dependent somewhat on cutoffs used to define the most and least active participants.

Another factor for consideration is the validity of the physical activity questionnaires that were used. It is well recognized that physical activity questionnaires are prone to recall error and social desirability and other biases. In addition, many questionnaires focus on moderate- to vigorous-intensity activity, as it is difficult to capture light-intensity activities accurately by questionnaire. Hence, only a small fraction of an individual's total physical activity may be measured in a given study. Physical activity questionnaires are frequently validated against other criterion measures, but these validation studies are limited by the lack of a true gold standard criterion method for measuring habitual activity over the long term.

Finally observational studies, whilst providing etiological insights, are not able to establish a direct, causal link between physical activity and breast cancer risk (Friedenreich 2001). Three randomized, controlled trials (RCTs) that were specifically designed to examine the etiologic pathways between physical activity and post-menopausal breast cancer risk have been conducted (Friedenreich et al. 2010a; McTiernan et al. 1999; Monninkhof et al. 2007b). These studies have involved supervised, controlled exercise interventions in which several proposed breast cancer biomarkers were measured and compared between the exercise and control groups to assess the impact of exercise on these biomarkers. The Physical Activity for Total Health (PATH) study (n = 173) and the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) trial (n = 320) administered a moderate- to vigorous-intensity physical activity intervention of approximately 225 min per week over 12 months (Friedenreich et al. 2010a; McTiernan et al. 1999); the Sex Hormones and Physical Exercise (SHAPE) study prescribed a combined strength and aerobic training program of approximately 150 min per week to 189 sedentary postmenopausal women over 12 months (Monninkhof et al. 2007b). The effects of exercise on a variety of proposed biomarkers of risk have been reported, with more published results anticipated in the future. Current findings are described in the sections below.

## 2.3
## Biologic Mechanisms

Various biologic pathways relating physical activity to breast cancer risk have been proposed (McTiernan 2008; Neilson et al. 2009; Rogers et al. 2008; Thompson et al. 2009;

Wetmore and Ulrich 2006), but these pathways are still not well understood. It is likely that multiple interrelated pathways act cooperatively to decrease breast cancer risk. It is also possible that certain mechanisms predominate with specific doses or types of physical activity or perhaps in select subgroups of women, as implied earlier in this chapter.

One common theme of many hypotheses explaining the relation between physical activity and breast cancer risk is a mediation of the effect through body weight. Adiposity, frequently measured in terms of BMI, is now convincingly associated with increased breast cancer risk in postmenopausal women, and weight gain and abdominal fatness are probably also causally related (Renehan et al. 2008; World Cancer Research Fund and the American Institute for Cancer Research 2007). In premenopausal women there is no such association; in fact an inverse relation with BMI is probable (World Cancer Research Fund and the American Institute for Cancer Research 2007). Physical activity is recommended as a means for achieving modest weight loss in overweight and obese adults and also for weight maintenance (Donnelly et al. 2009; Lau et al. 2007). However, there is only limited evidence supporting the effectiveness of physical activity for abdominal fat loss (Lau et al. 2007; Ross and Janssen 1999). It remains plausible, however, that postmenopausal women could be amenable to significant abdominal fat loss given the right exercise prescription (e.g., Cuff et al. 2003; Giannopoulou et al. 2005; Irwin et al. 2003). The PATH and ALPHA trials demonstrated a clear exercise effect in a range of body composition measures (Friedenreich et al. 2010b; Irwin et al. 2003) including abdominal fat, whereas the SHAPE trial found that exercisers decreased body fat and waist circumference, but not weight, in comparison with controls (Velthuis et al. 2009). Therefore, fat loss is a logical explanation for the association between exercise and postmenopausal breast cancer risk.

One currently hypothesized biologic model for breast cancer risk, focusing mainly on the promotion and progression of initiated cells, implicates sex hormones, insulin resistance, adipokines, and chronic inflammation as possible mediators of physical activity (Neilson et al. 2009) (Fig. 2.12). While all of the proposed biomarkers in this model are associated with adiposity, and specifically abdominal fat, many of them are also influenced by exercise irrespective of body fat changes. Hence, the extent to which fat loss is necessary to derive a significant risk benefit from exercise remains a matter of controversy. Below we discuss these hypothesized mechanisms in more detail.

## 2.3.1 Sex Hormones

Endogenous estrogen status has been the predominant hypothesized mechanism relating physical activity to breast cancer risk for both pre- and postmenopausal women. Estrogens can inhibit apoptosis and act as mitogens in the breast, stimulating mammary cell proliferation through estrogen receptor-mediated transcriptional activity and by activation of intracellular signaling pathways (Lorincz and Sukumar 2006; Yager and Davidson 2006). In addition, oxidative estrogen metabolites with genotoxic and mutagenic potential could contribute to breast cancer initiation (Coyle 2008; Yager and Davidson 2006). The successful use of antiestrogenic drugs for reducing breast cancer risk serves as very strong evidence of the causal role for estrogens in women with ER+ breast tumors (Uray and Brown 2006).

Compelling evidence from observational studies supports a positive association between breast cancer risk and estrogens in postmenopausal women. In a pooled analysis of nine prospective studies in postmenopausal women (Key et al. 2002), the odds ratio for breast cancer was 2.00 (95% CI: 1.47–2.71) for the highest versus the lowest quintiles of total estradiol while for estrone the odds ratio was 2.19 (95% CI: 1.48–3.22). Given these findings and others
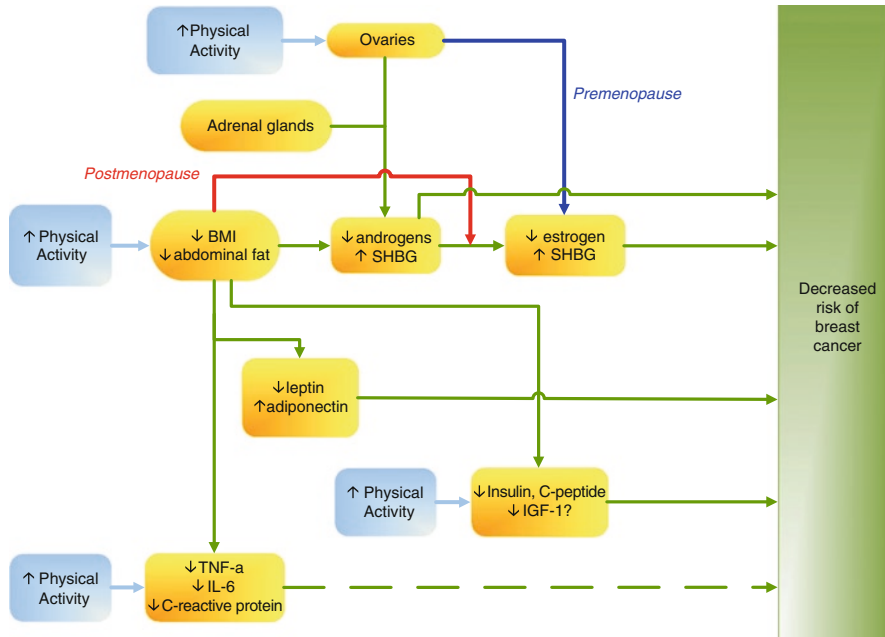
**Fig. 2.12** Hypothesized biologic model relating proposed biomarkers of risk to long-term exercise in pre- and postmenopausal women (Adapted from Neilson et al. 2009)

(Cleary and Grossmann 2009), it is now widely accepted that estrogen status is associated with postmenopausal breast cancer. Fewer studies have examined this association in premenopausal women given the complexities of studying circulating hormone levels amidst menstrual cycles, and findings in general have been less consistent than for postmenopausal women (Eliassen and Hankinson 2008). Interestingly, one large cohort study conducted within the Nurses' Health Study II showed that estradiol levels collected in the follicular phase of the menstrual cycle (but not the luteal phase) were significantly associated with an increased risk of premenopausal breast cancer, both overall and for ER+/PR+ tumors (Eliassen et al. 2006).

Multiple mechanisms could explain associations between postmenopausal breast cancer, estrogen levels, and physical activity. The first relates to BMI, which increases breast cancer risk specifically in postmenopausal women

(World Cancer Research Fund and the American Institute for Cancer Research 2007). This relation might exist in part because after menopause, ovarian estrogen production ceases and adipose tissue becomes a key endogenous source of circulating estrogens (Kendall et al. 2007; Lorincz and Sukumar 2006). Hence, by reducing body fat through exercise, estrogen levels may decrease resulting in a lower risk of breast cancer. Levels of adipokines that influence estrogen biosynthesis can also be altered with weight loss (Cleary and Grossmann 2009). Furthermore, physical activity can lower blood insulin levels thereby increasing circulating sex hormone binding globulin (SHBG) (Kaaks 1996; Pugeat et al. 1991) which binds reversibly to estrogens to affect their bioavailability.

In premenopausal women these biologic mechanisms are less well understood. Exercise has been linked to delayed menarche and menstrual dysfunction implying lower cumulative

exposure to sex hormones and presumably lower risk of breast cancer; however, the level of activity needed to achieve these effects is probably high (reviewed in Bernstein 2009; Campbell and McTiernan 2007) and an energy deficit, rather than exercise per se, may be the predominant mechanism (Loucks 2003). In observational studies of highly active premenopausal women, blood estrogen levels have generally been inversely related to activity but in cross-sectional studies of nonathletes, the relation is more equivocal (Coyle 2008).

Breast cancer risk may also be affected by androgen levels. Androgens can act directly on breast cells by binding to the androgen receptor to influence cell growth (Nicolas Diaz-Chico et al. 2007) and/or they may act indirectly via estrogen production: the aromatase enzyme converts testosterone to estradiol, and androstenedione to estrone, within adipose and other tissues in postmenopausal women and principally in the ovaries of premenopausal women (Kendall et al. 2007). Testosterone, which is one of the most powerful natural forms of androgen, is derived from androstenedione in the ovaries and also in peripheral tissues such as adipose and breast (Nicolas Diaz-Chico et al. 2007). In a pooled analysis of prospective studies in postmenopausal women (Key et al. 2002) and in at least one other cohort study (Kaaks et al. 2005), adjustment for estradiol levels only slightly attenuated the relative risk associated with testosterone, thus supporting an independent mechanism for androgens. Physical activity might lower testosterone levels by decreasing adiposity, or possibly by increasing SHBG levels (and decreasing the bioavailability of testosterone) on account of lowered blood insulin levels (Kaaks 1996; Pugeat et al. 1991).

Epidemiologic evidence supports a positive association between serum androgen levels and postmenopausal (Key et al. 2002; Neilson et al. 2009) and, to a lesser extent, premenopausal breast cancer risk (Eliassen and Hankinson 2008). In a pooled analysis of prospective studies, postmenopausal women in the highest quintiles of serum testosterone and androstenedione concentrations, respectively, had more than double the risk of developing breast cancer compared to women in the lowest quintiles (RR = 2.22, 95% CI: 1.59–3.10 for testosterone; RR = 2.15, 95% CI: 1.44–3.21 for androstenedione) (Key et al. 2002). In premenopausal women, fewer studies have been conducted but findings have been fairly consistent, showing nonsignificantly and significantly increased risks for those with higher blood levels of testosterone (Eliassen and Hankinson 2008).

The effect of physical activity on sex hormones may vary according to hormone receptor status (Sieri et al. 2009), across the menopausal transition (Schmitz et al. 2007), and also with body fat (McTiernan et al. 2004a; McTiernan et al. 2004b). Three RCTs have examined the effect of exercise on sex hormone levels and weight change in postmenopausal women. In the PATH trial, women assigned to the exercise group who lost more than 2% body fat experienced significantly lower blood estrogen and androgen levels relative to controls after 12 months of exercise (McTiernan et al. 2004a; McTiernan et al. 2004b). Likewise, the SHAPE trial showed that relative to controls, androgen (but not estrogen) levels decreased significantly in exercisers who lost >2% body fat after 4 months of exercise (Monninkhof et al. 2009). In the ALPHA trial, estrogen levels decreased significantly more in exercisers than in controls after 12 months, even after adjusting for weight change, whereas androgen levels did not change significantly (Friedenreich et al. 2010a). Unlike the first two trials, the ALPHA trial findings for estrogen suggest an independent role for physical activity. Similarly, some cross-sectional studies (but not all, Bertone-Johnson et al. 2009; Van Gils et al. 2009) in postmenopausal women have found significant inverse associations between physical activity

and sex hormone levels even after controlling for BMI or adiposity (Cauley et al. 1989; Chan et al. 2007; Madigan et al. 1998; Verkasalo et al. 2001). Therefore, it remains unclear whether or not fat loss is needed to induce changes in sex hormones.

### 2.3.2
### Insulin-Related Factors

A causal link between insulin resistance and breast cancer risk is biologically plausible. Insulin exerts mitotic, anti-apoptotic effects in breast cancer cells (Lann and LeRoith 2008; Osborne et al. 1976) and hyperinsulinemia increases the bioavailability of sex hormones by decreasing SHBG levels (Kaaks 1996; Pugeat et al. 1991). Insulin resistance and hyperinsulinemia are also strongly related to obesity (Haslam and James 2005) and particularly intraabdominal fat (Kaaks 1996), as well as various adipokines and inflammatory factors (Rose et al. 2004; Vona-Davis et al. 2007) that individually have been linked to breast cancer. Therefore, insulin may alter breast cancer risk independently or indirectly through other biomarkers of risk.

The epidemiologic evidence surrounding the role of insulin in breast cancer risk is growing but remains inconclusive. A modest causal association with breast cancer risk appears to exist with type 2 diabetes, specifically in postmenopausal women (Larsson et al. 2007; Xue and Michels 2007). Yet, while findings from retrospective studies have generally also shown positive associations between breast cancer risk and insulin and C-peptide (a marker of pancreatic insulin secretion (Bonser and Garcia-Webb 1984)) levels, cohort studies have typically produced null results (Pisani 2008). The effect may vary according to menopausal status. Yet within pre- and postmenopausal women, relations between breast cancer risk and insulin or C-peptide have been inconsistent (Neilson et al. 2009; Xue and Michels 2007). Recently, however,

one cohort study of 5,450 postmenopausal women that employed serial measurements of glucose and insulin found a statistically significant positive association between breast cancer risk and insulin levels (Kabat et al. 2009) and a case-cohort study found the same association but only amongst non-users of hormone therapy (Gunter et al. 2009). Another recent prospective study (Cust et al. 2009) found no association with C-peptide in postmenopausal women but did observe decreased risk with increasing $Hb_{A1C}$ levels, a measure of long-term blood glucose (Gabbay 1982).

Exercise combined with weight loss is generally accepted as an effective means for improving insulin sensitivity and preventing diabetes (Ivy 1997; Klein et al. 2004; Ryan 2000; Warburton et al. 2007). The effect of exercise may be strongest for those with impaired (versus normal) glucose tolerance (Ivy 1997), when as combined aerobic/resistance exercise versus aerobic exercise alone (Cuff et al. 2003), or at higher intensity (Gill 2007). In terms of abdominal fat loss (which correlates with insulin sensitivity), however, one 20-week exercise RCT in postmenopausal women on a calorie-restricted diet showed no difference whether moderate or vigorous aerobic exercise was undertaken (Nicklas et al. 2009). In the PATH trial, insulin levels decreased with moderate exercise and this change was significantly different from that of controls (Frank et al. 2005). Moreover, insulin change was modified by change in total fat mass: exercisers who lost >2 kg body fat over the year had a significantly larger decrease in insulin levels than those who gained fat mass. In addition, among those women who gained fat over the year, exercise prevented an increase in insulin levels. Hence, exercise appears to alter insulin levels through weight change but also independently of fat loss.

Higher levels of circulating insulin-like growth factor-1 (IGF) have also been hypothesized to increase breast cancer risk. IGF-1 may impact breast tissue directly by acting as

a potent mitogen which increases cell proliferation and decreases apoptosis within the breast (Yu and Rohan 2000). The epidemiologic evidence for a positive association with breast cancer is stronger in pre- than in postmenopausal women (Fletcher et al. 2005), but is generally inconsistent (Eliassen and Hankinson 2008; Lann and LeRoith 2008). Furthermore, the evidence relating IGF-1 and IGF binding protein-3 (IGFBP-3) levels to physical activity in women has been inconsistent and generally unconvincing (McTiernan et al. 2005; Orenstein and Friedenreich 2004; Tworoger et al. 2007b). Thus, IGF-1 may not be an important intermediate factor in the proposed physical activity–breast cancer pathway.

### 2.3.3
### Adipokines and Inflammation

Adipokines (adipocytokines) are a group of biologically active polypeptides produced by adipocytes or adipose tissue; they include leptin (Cirillo et al. 2008; Surmacz 2007), adiponectin (Barb et al. 2007; Wang et al. 2007), tumor necrosis factor-α (TNF-α) (Balkwill 2006; Szlosarek et al. 2006), and interleukin-6 (IL-6) (Knupfer and Preiss 2007). C-reactive protein (CRP) is not an adipokine, but an acute phase protein produced in the liver in response to TNF-α and IL-6 levels (Heikkila et al. 2007; Lee and Pratley 2005); all three are considered inflammatory markers. Obesity represents a chronic low-grade, systemic inflammatory state with elevated levels of inflammatory markers (Lee and Pratley 2005). Perpetual cell proliferation, microenvironmental changes and oxidative stress resulting from chronic inflammation could deregulate normal cell growth to promote initiated cells toward malignancy (Coussens and Werb 2002). Adipokines may also increase risk on account of their strong positive correlations with hyperinsulinemia, insulin resistance, and type 2 diabetes, by affecting estrogen bio-

synthesis and estrogen activity, or by directly altering cell growth and promoting metastases (reviewed in, Neilson et al. 2009).

While biologic plausibility exists, relatively little epidemiologic evidence has related elevated adipokines and inflammatory markers to a significantly increased risk of breast cancer in postmenopausal women (Neilson et al. 2009), for whom risk is most clearly associated with body fat. Among those studies that have examined these markers, most focused on leptin and adiponectin. Evidence was generally conflicting in the case of leptin and somewhat stronger for adiponectin (Barb et al. 2007), but for both of these proposed biomarkers only a few studies were of prospective design (Cust et al. 2009; Stattin et al. 2004; Tworoger et al. 2007a). The etiologic relevance of the adiponectin:leptin ratio also is now being considered (Cleary et al. 2009).

Exercise trials across various study populations have generally supported the absence of an effect of exercise on inflammatory markers, but differing study designs and study populations makes this overall finding difficult to interpret (Wetmore and Ulrich 2006). In fact recent RCT evidence from older type 2 diabetics implied that greater decreases in leptin, IL-6, TNF-α, and CRP and enhanced increases in adiponectin might be achieved with exercise of high intensity (versus low) and preferably using a combination of aerobic and resistance training (versus aerobic) (Balducci et al. 2009). In addition, the PATH trial in postmenopausal women demonstrated lowered leptin (Frank et al. 2005) and CRP (Campbell et al. 2009) levels after 12 months of exercise, but CRP was decreased only among women who were obese or had abdominal obesity.

Sustained physical activity probably lowers adipokine and CRP levels through several mechanisms. In one prospective cohort study, adipokine and inflammatory marker changes correlated significantly with changes in intraabdominal fat in women transitioning to menopause

(Lee et al. 2009), implying that biomarker decreases can be achieved through weight loss. Similarly, the PATH trial demonstrated significant decreases in CRP specifically in those who lost body fat (Campbell et al. 2009). Yet exercise RCTs have also shown decreases in adipokine and CRP levels that occurred independently of fat loss (Balducci et al. 2009; You et al. 2004). Such fat-independent mechanisms are generally not well understood, but hypotheses have been suggested (e.g., Mathur and Pedersen 2008).

### 2.3.4
### Other Mechanisms

Other pathways relating physical activity to breast cancer almost certainly exist. Biologic pathways causing DNA damage, cancer initiation, or cancer promotion and progression (Rundle 2005) may interact with the mechanisms already discussed to increase breast cancer risk even further. With improved understanding regarding these interrelated mechanisms and their role in the causal pathways between physical activity and breast cancer risk, the biologic model depicted in Fig. 2.12 could be modified or expanded. Mammographic density was not included in this model since exercise has not been proven to lower the dense area or dense volume of the breast, which are positively associated with breast cancer risk (Woolcott et al. 2010). Likewise, the ratio of estrogen metabolites 2-hydroxyestrone:16α-hydroxyestrone has been hypothesized to increase breast cancer risk, but relatively strong epidemiologic evidence suggests no effect of physical activity on this ratio (Atkinson et al. 2004; Campbell et al. 2007; Schmitz et al. 2008). Other proposed mechanisms that might relate physical activity to breast cancer risk include the ability of exercise to decrease oxidative stress (e.g., as measured by F2-isoprostanes (Dai et al. 2009; Schmitz et al. 2008)) and enhance resting immune function (Campbell et al. 2008; Wetmore and Ulrich

2006). Moreover, by altering estrogen levels, exercise may reduce promoter hypermethylation of tumor suppressor genes (i.e., gene silencing by estrogens) and also genotoxicity from estrogen metabolite–DNA adducts formed in breast tissue (Coyle 2008). Other hypotheses suggest that certain intracellular signaling pathways are affected favorably by exercise, whereby procarcinogenic pathways are suppressed and anticarcinogenic pathways are promoted within the breast (Thompson et al. 2009). Across many proposed mechanisms, effect modification by genetic subtype might better our understanding of the etiologic importance of proposed biomarkers (Han et al. 2008; Kendall et al. 2007) and their responses to exercise (Gill 2007).

### 2.4
### Conclusion

The criteria for causality for the association between physical activity and breast cancer risk are largely met with the evidence that has accumulated thus far from observational epidemiologic studies. There is consistent evidence from studies conducted around the world for a 25% risk reduction amongst physically active women as compared to the least active women. There is also evidence of a dose–response effect of decreasing risk with increasing levels of activity as well as mechanistic data from randomized exercise intervention trials that have examined intermediate biomarkers hypothesized to be part of the pathway between physical activity and breast cancer risk. The associations are strongest for recreational activity that is sustained over lifetime or at least after menopause, that is of moderate to vigorous intensity, and performed regularly. There is also emerging evidence that physical activity may have a differential effect amongst population subgroups with stronger effects found in postmenopausal women, normal weight women, non-Caucasians,

parous women, and women without a family history of breast cancer.

Several areas for future research can be considered. These would include examining how sedentary behavior and light-intensity activity additionally contribute to breast cancer risk or risk reduction. More precision is needed in the assessment of physical activity including the type, dose, and timing of activity over the lifetime for these studies. Research that focuses on effect modification by factors such as menopausal status, tumor subtype, and other components of type, timing, and dose of activity would improve our understanding of the nature of the association between physical activity and breast cancer risk. Investigations of the related biologic mechanisms would also inform future epidemiologic research. There is a need for prospective observational epidemiologic studies relating new and proposed biomarkers to breast cancer risk (particularly pertaining to insulin resistance and inflammation). As well, additional randomized, controlled exercise intervention trials that evaluate biomarker changes with different types and doses of physical activity are needed to further elucidate how activity influences breast cancer risk.

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