Chapter 6
Applying Physical Activity in Cancer Prevention

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6.1 Introduction

Over the past two decades, epidemiological research has generated compelling data describing the benefits of physical activity in relation to cancer risk. The evidence has been systematically reviewed by national (Physical Activity Guidelines Advisory Committee 2008) and international agencies (World Cancer Research Fund and the American Institute for Cancer Research 2007), and there is broad agreement that physical activity is associated with a reduced risk of colon, breast, and endometrial and possibly other cancer sites. Despite progress in understanding the cancer-protective effects of physical activity, uncertainty still exists regarding the type, timing, and amount of physical activity required for significant benefit. In this chapter, we provide an overview of the existing epidemiological evidence relating physical activity to cancer risk.

A related area of research that has received minimal attention to date is the effect of sedentary behavior on cancer risk. Sedentary behaviors involve prolonged sitting or reclining, the absence of whole-body movement, and low (≤1.5 metabolic equivalents) energy expenditure. Emerging epidemiological evidence suggests that sedentary behavior may increase the risk of colorectal, endometrial, and ovarian cancer, although only five cancer sites have thus far been studied (results for breast and renal cell carcinoma have been null) (Lynch 2010). Here we update this review of the epidemiological literature on associations of sedentary behavior with cancer risk.

An emerging literature is now examining the biologic mechanisms whereby physical activity influences cancer risk. Observational and randomized intervention trials are examining how adiposity, endogenous sex hormones, inflammation, and

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insulin resistance might explain the effect of physical activity and sedentary behavior on cancer risk. We provide an overview of the main findings on these mechanisms.

Finally, we highlight some of the public health implications of using physical activity as a means for cancer prevention by providing an overview of the current physical activity guidelines, the prevalence of physical inactivity, and the approaches that have been used to promote physical activity at a population level.

6.2 Epidemiological Evidence: Physical Activity and Cancer

6.2.1 Colon Cancer

The strongest evidence for an effect of physical activity on cancer prevention exists for colon cancer. To date, 85 separate studies have been published that have examined some aspect of physical activity and colon or colorectal cancer risk (Wolin and Tuchman 2011). Of these studies, 34 found a statistically significant reduced risk when comparing the most to the least active study participants, 38 studies observed a nonstatistically significant risk reduction, and 14 showed no effect of physical activity on colon cancer risk. The magnitude of the risk decrease ranges from 30% to 35%, and there is evidence of a linear dose–response with increasing physical activity and decreasing risk in 41 of 47 studies. The risk reduction is somewhat stronger in case–control studies than in cohort studies (Figs. 6.1 and 6.2). The effect of physical activity on colon cancer risk is seen equally in men and women, in different racial/ethnic groups, for all types of activity, and for activity done at different time points in life and at different intensities.

6.2.2 Breast Cancer

Nearly equally strong evidence for a role of physical activity exists for breast cancer as was found for colon cancer with 86 independent studies reported to date (Lynch et al. 2011a). A statistically significant reduced risk of breast cancer was observed in 36 studies and a nonstatistically significant reduction in 28 studies.

Only three studies found a slight, nonstatistically significant increased risk with increased physical activity levels, and 19 found no effect of activity on risk. The magnitude of the risk reduction was approximately 25% with a stronger association found in case–control than in cohort studies (Figs. 6.3 and 6.4). Breast cancer risk is decreased most with recreational and household activities and activity after the menopause. Both moderate- and vigorous-intensity activities contribute nearly equally to the risk reduction. Some effect modification by other factors has been investigated with a stronger association found in non-Caucasian populations, parous women, non-obese women, and those without a family history of breast cancer.

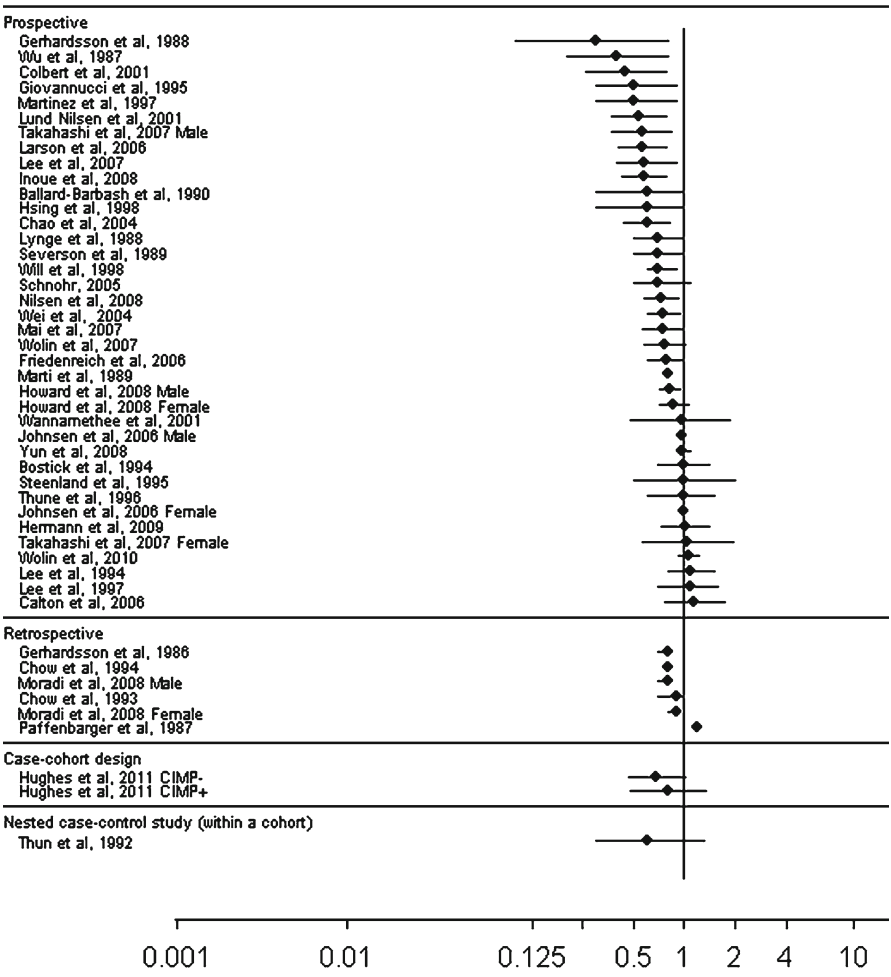

Fig. 6.1 Cohort studies of physical activity and colon cancer risk

6.2.3 Endometrial Cancer

Of the 28 studies on physical activity and endometrial cancer, half found a statistically significant risk reduction with increased activity levels and 9 of 28 a nonstatistically significant risk decrease (Cust 2011). The association is quite strong ranging from an average 38% decrease in case–control studies to a 25% decrease in cohort studies (Fig. 6.5). There is evidence for a dose–response association in 12 of 19 studies that examined this trend. There is no clear effect modification for this relationship by other factors. All types of activity, done at a moderate–vigorous intensity level, throughout lifetime, appear to be beneficial for reducing endometrial cancer risk.

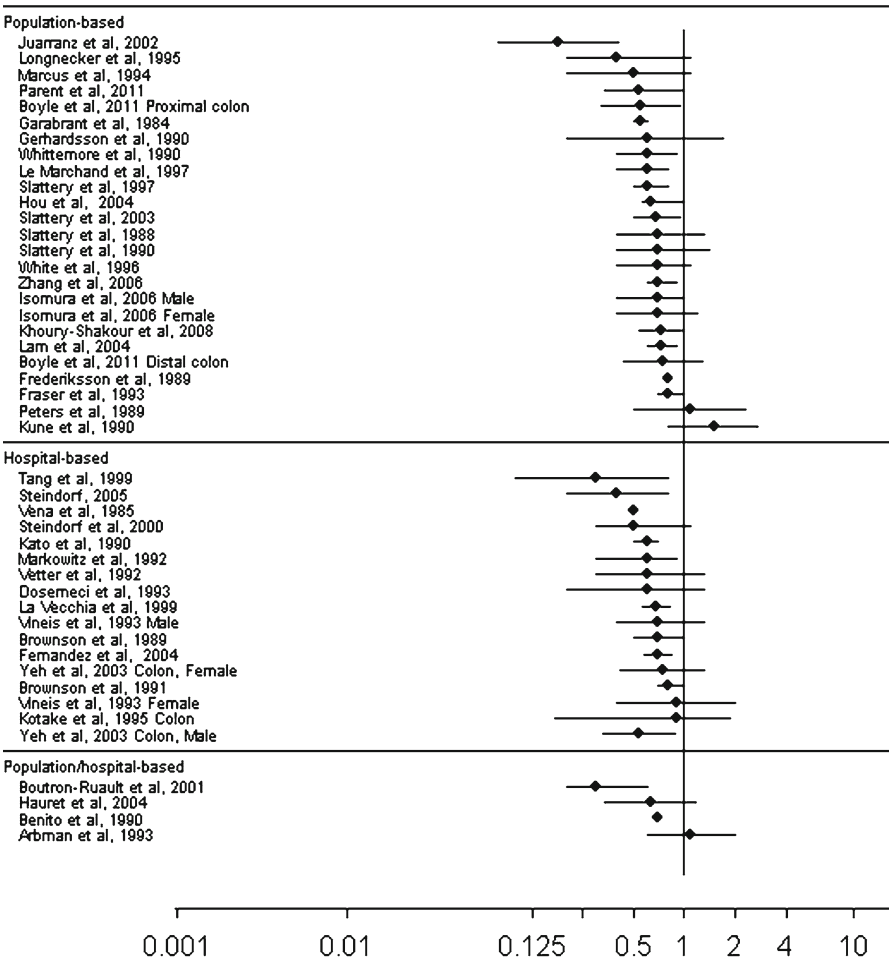

Fig. 6.2 Case–control studies of physical activity and colon cancer risk

6.2.4 Ovarian Cancer

In contrast to endometrial cancer, the epidemiological evidence for an association between physical activity and ovarian cancer is much weaker. Of the 23 studies published to date, only eight observed statistically significant risk reductions for ovarian cancer with higher levels of physical activity, four found nonstatistically significant decreases, eight showed no association, and three observed increased risks (Cust 2011). The risk reductions were, on average, less than 10%, and there was evidence for a dose–response effect in only nine of 11 studies (Fig. 6.6). There is only limited evidence thus far on any subgroup effects, and there is no clarity on whether any specific type, timing, or dose of activity is more beneficial for ovarian cancer risk reduction.

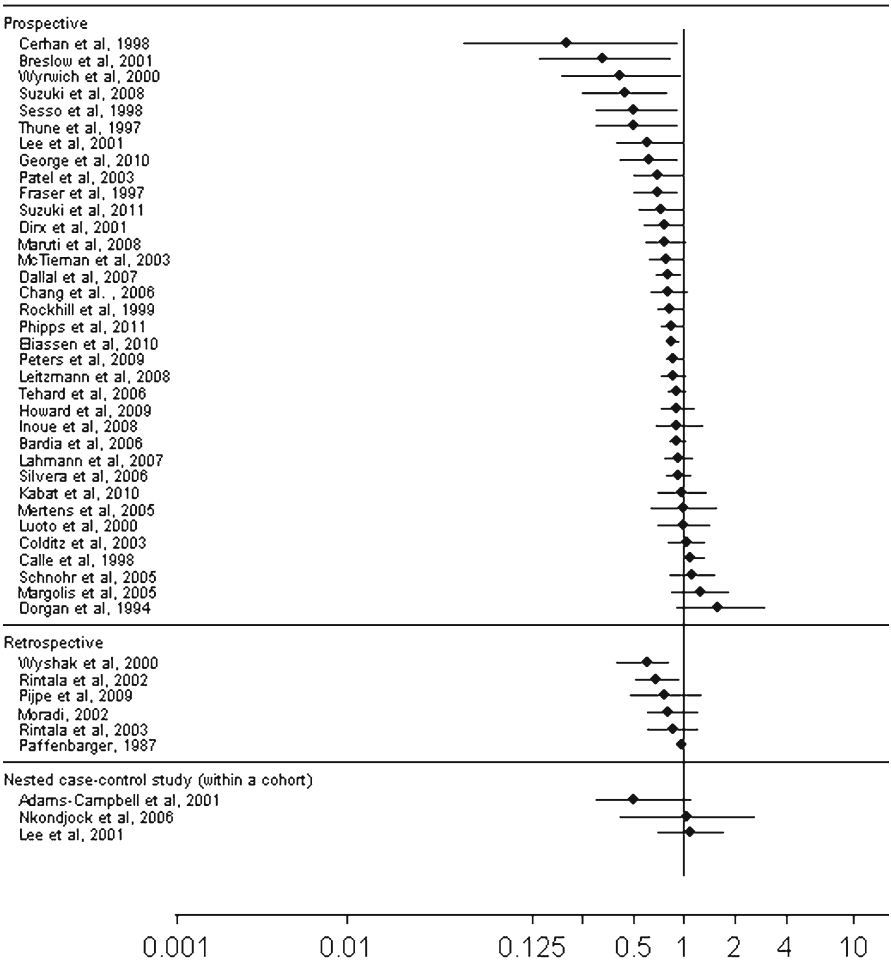

Fig. 6.3 Cohort studies of physical activity and breast cancer risk

6.2.5 Prostate Cancer

In total, 56 separate studies have been conducted on physical activity and prostate cancer risk (Figs. 6.7 and 6.8), of which 16 have found statistically significant risk reductions with increased activity levels, 10 nonstatistically significant decreases, 25 no effect, and five studies have detected an increased risk that was statistically significant in three studies (Leitzmann 2011). The magnitude of the risk decrease is on average about 10%. There are specific methodological challenges in studies of prostate cancer given the high prevalence of undetected prostate cancer in many men who would have served as controls in many of the case–control studies. Hence, there may have been some nondifferential misclassification bias that obstructed the ability to detect an association in these studies.

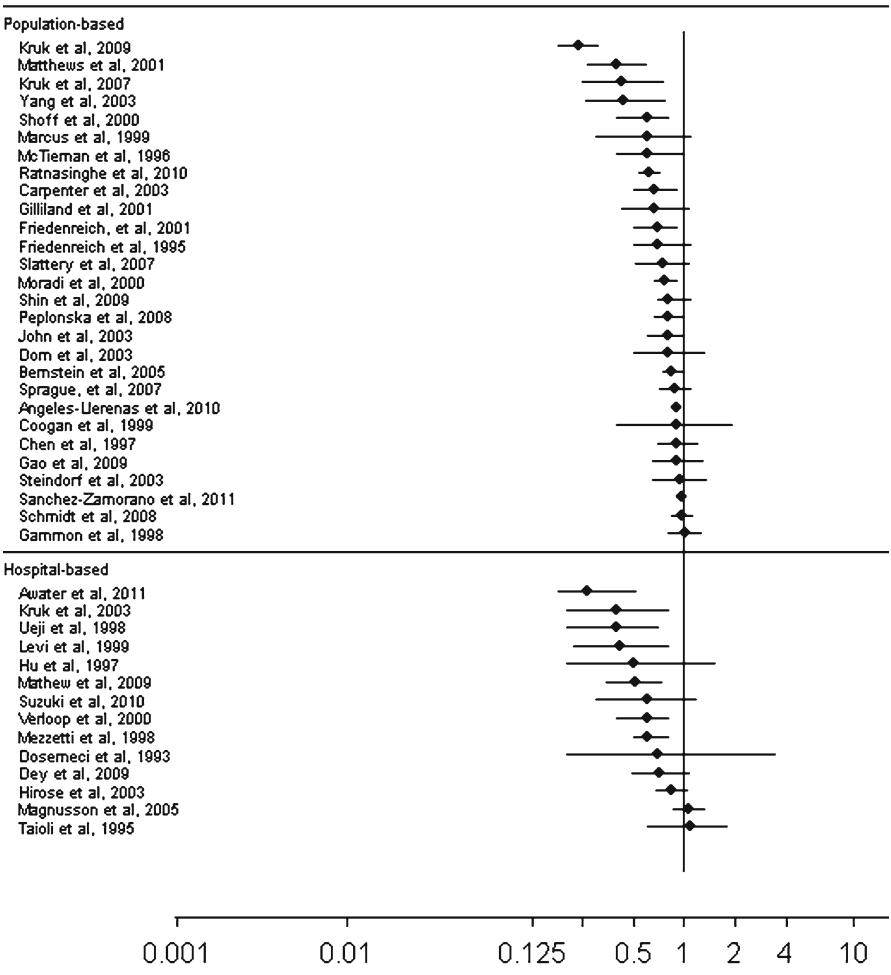

Fig. 6.4 Case–control studies of physical activity and breast cancer risk

There is not yet any clear evidence on the type, timing, and dose of activity needed to reduce prostate cancer risk nor is there any consistent evidence regarding associations specific to population subgroups.

6.2.6 Lung Cancer

Relatively few studies have been conducted on physical activity and lung cancer with 27 reported to date (Emaus and Thune 2011). Nearly half of the studies (13/27) showed a statistically significant risk reduction and six observed nonstatistically significant risk decreases among the most physically active men and women when compared to the least active. The magnitude of the risk reduction was about 25%

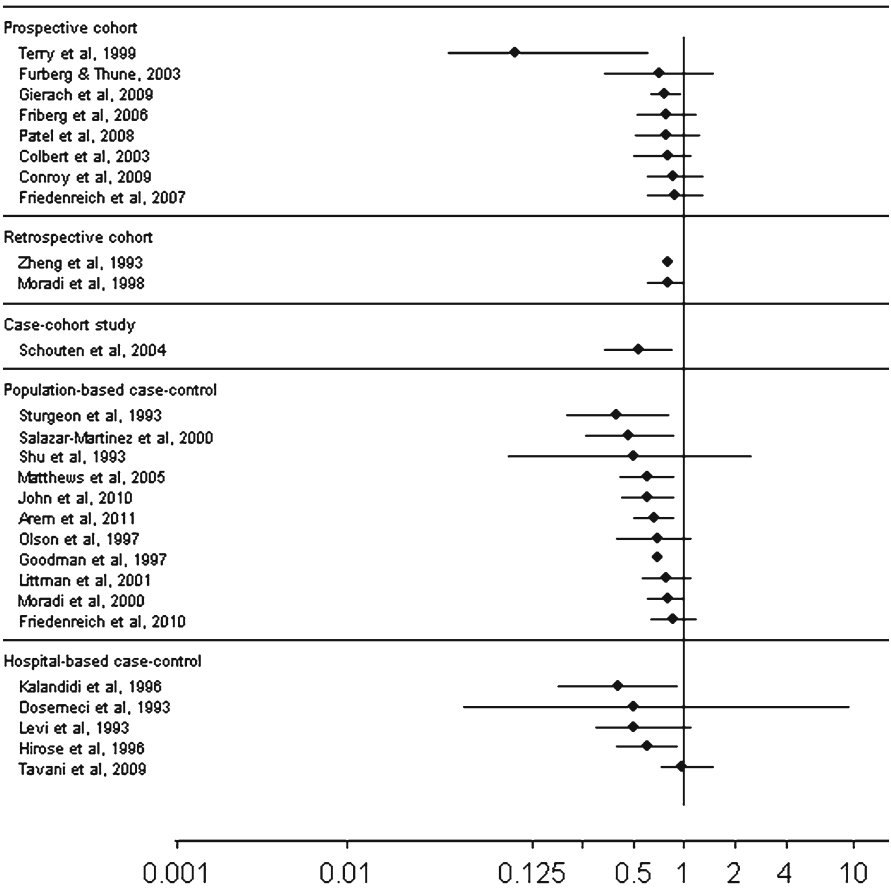

Fig. 6.5 Epidemiological studies of physical activity and endometrial cancer risk

and was observed equally in cohort and case–control studies (Figs. 6.9 and 6.10). A particular methodological issue in these studies is the ability to control for the possible confounding effect of smoking. Several of the studies examined the association separately for smokers and nonsmokers and found a stronger effect for current and former smokers compared to never smokers. Risk reductions appear to be of equal magnitude for different types of activity and for activity done at different time points in life or at different doses. There is no evidence yet of any specific effect modification within population subgroups.

6.2.7 Other Sites

For other cancer sites, such as the hematologic cancers (Pan and Morrison 2011), kidney, testicular, bladder cancers (Leitzmann 2011), and cervical cancers (Cust 2011),

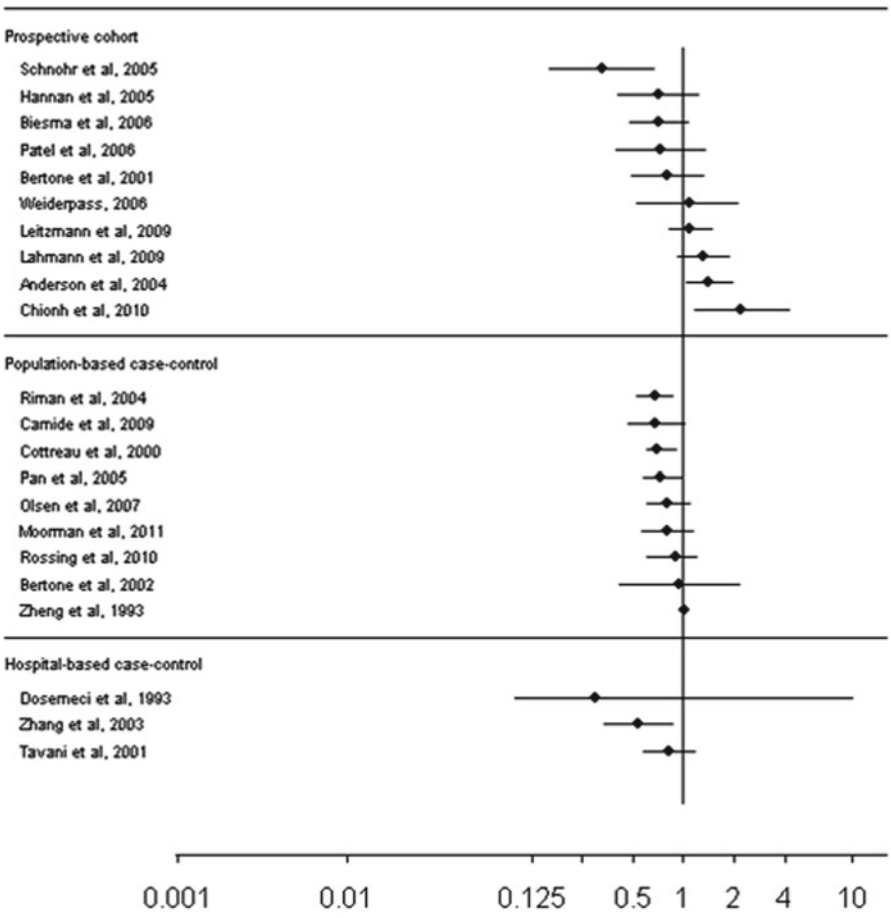

Fig. 6.6 Epidemiological studies of physical activity and ovarian cancer risk

there have been only a few studies published to date, and the data are insufficient to draw any conclusions at this time regarding the strength, dose–response, and consistency of the association between physical activity and risk of these other cancers.

6.3 Epidemiological Evidence: Sedentary Behavior and Cancer

6.3.1 Colorectal Cancer

Two studies have considered how sedentary behavior affects colorectal cancer risk (Howard et al. 2008; Steindorf et al. 2000). The National Institutes of

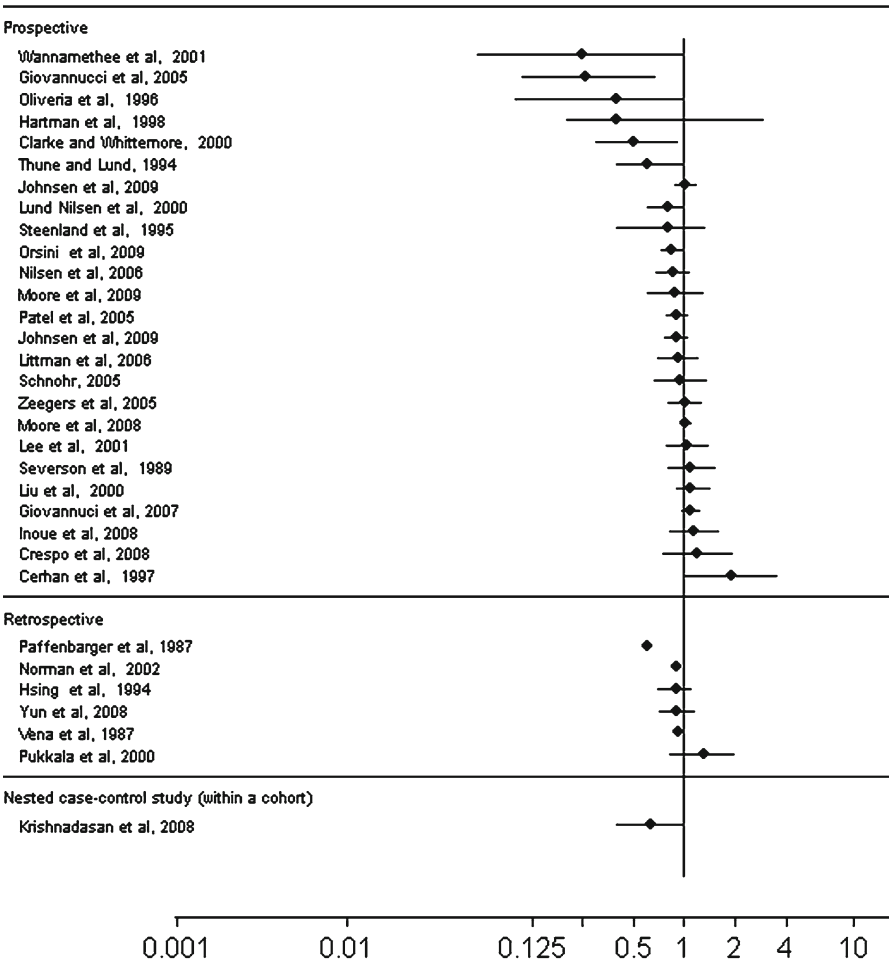

Fig. 6.7 Cohort studies of physical activity and prostate cancer risk

Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study examined the associations of television viewing time and total sitting time with colorectal cancer risk in 300,673 men and women. Colorectal cancer risk increased significantly by more than 50% for men with longer television viewing times (≥9 vs. <3 h/day; RR = 1.56, 95% CI: 1.11, 2.20); for women, the risk was somewhat lower and of borderline significance (RR = 1.45, 95% CI: 0.99–2.13). About a 20% nonstatistically significant increased risk for longer total sitting time (≥9 vs. <3 h/day) was observed for both men and women (Howard et al. 2008). In a small case–control study of Polish women, Steindorf et al. (2000) found a statistically significant increased risk of colorectal cancer between the top and bottom tertiles (≥2 vs. <1.14 h/day) of television viewing (OR = 2.22, 95% CI: 1.19–4.17).

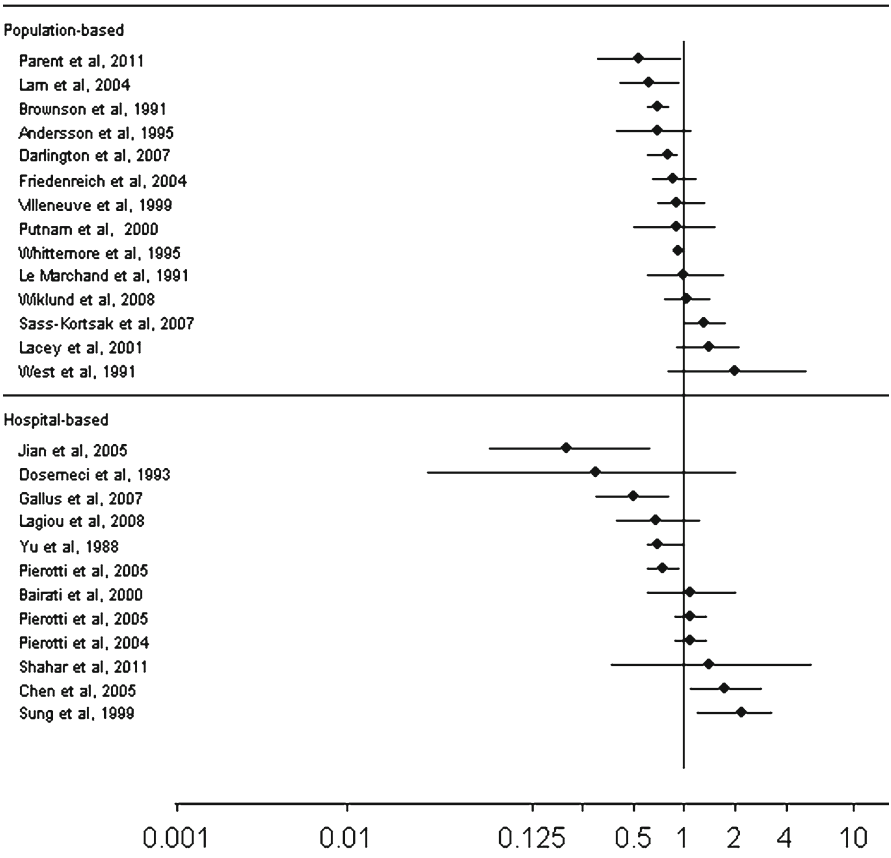

Fig. 6.8 Case–control studies of physical activity and prostate cancer risk

6.3.2 Endometrial Cancer

To date, three cohort studies (Friberg et al. 2006; Moore et al. 2010; Patel et al. 2008) and two case–control studies (Friedenreich et al. 2010a; Arem et al. 2011) have examined the association between sedentary behavior and endometrial cancer risk. Statistically significant increased risks were found in one cohort study (for ≥5 vs. <5 h/day television viewing RR = 1.66, 95% CI: 1.05–2.61) (Friberg et al. 2006) and in both case–control studies: OR = 1.52 (95% CI: 1.07–2.16) for ≥8 versus <4 h/day total sitting time (Arem et al. 2011) and OR = 1.11 (95% CI: 1.01–1.22) for every 5 h/week/year of lifetime occupational sitting (Friedenreich et al. 2010a). A borderline increased risk was shown in the NIH-AARP study: RR = 1.23 (95% CI: 0.96–1.57) for ≥7 versus <3 h/day total sitting time (Moore et al. 2010). A slightly increased nonsignificant risk was found in the Cancer Prevention Study II (CPS II) Nutrition Cohort for ≥6 versus <3 h/day total sitting time (Patel et al. 2008).

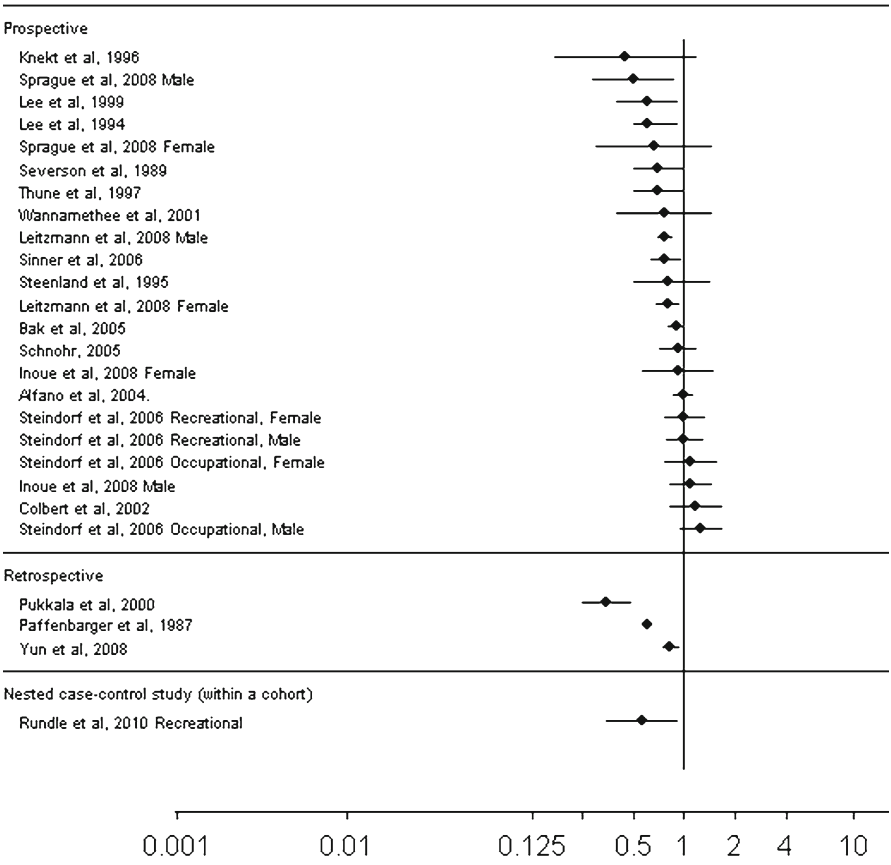

Fig. 6.9 Cohort studies of physical activity and lung cancer risk

6.3.3 Ovarian Cancer

Two studies have examined the role of sedentary behavior in ovarian cancer risk; both found a statistically significant association. Total sitting time (≥6 vs. < 3 h/day) was associated with an RR of 1.55 (95% CI: 1.08–2.22) among women in the CPS II Nutrition Cohort (Patel et al. 2006). In a Chinese case–control study, television viewing time (>4 vs. <2 h/day) was significantly associated with ovarian cancer risk (OR = 3.39, 95% CI: 1.0–11.5), as was total sitting time (>10 vs. <4 h/day, OR = 1.77, 95% CI: 1.0–3.1) and occupational sitting time (>6 vs. <2 h/day, OR = 1.96, 95% CI: 1.2–3.2) (Zhang et al. 2003).

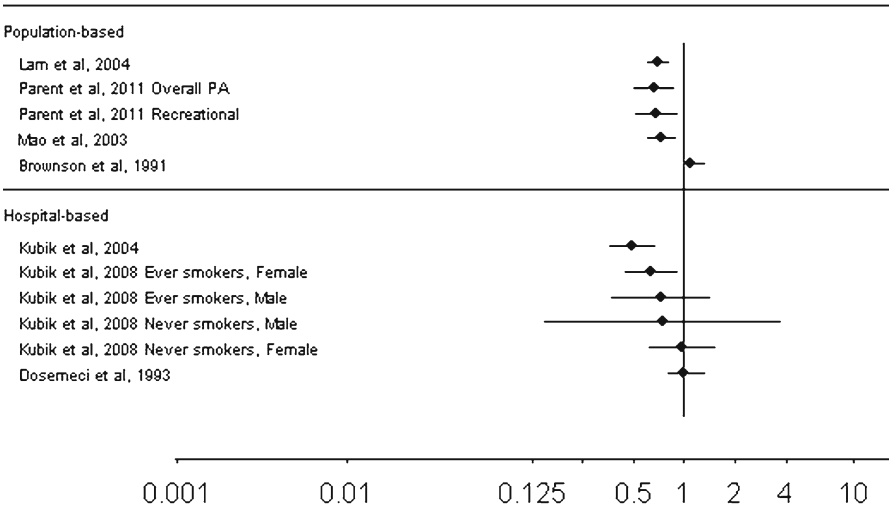

Fig. 6.10 Case–control studies of physical activity and lung cancer risk

6.3.4 Other Sites

Neither television viewing nor overall sitting time was associated with breast cancer (George et al. 2010) or with renal cell carcinoma (George et al. 2011) in the NIH-AARP Diet and Health study. Similarly, no association between television viewing and breast cancer was found in a case–control study of Indian women (Mathew et al. 2009).

6.4 Proposed Biologic Mechanisms

A number of biologic pathways relating physical activity and sedentary behavior to the development and progression of cancer have been proposed (McTiernan 2008; Friedenreich 2010; Lynch 2010) (Fig. 6.11). It is likely that these mechanisms are interrelated and that their relative contributions vary by cancer type. To become firmly established in a causal pathway, each proposed mechanism must relate significantly both to cancer risk and to physical activity/sedentary behavior.

6.4.1 Adiposity

Adiposity may facilitate carcinogenesis directly or through a number of pathways including increased levels of sex and metabolic hormones, chronic inflammation, and altered secretion of adipokines (Neilson et al. 2009; van Kruijsdijk et al. 2009).

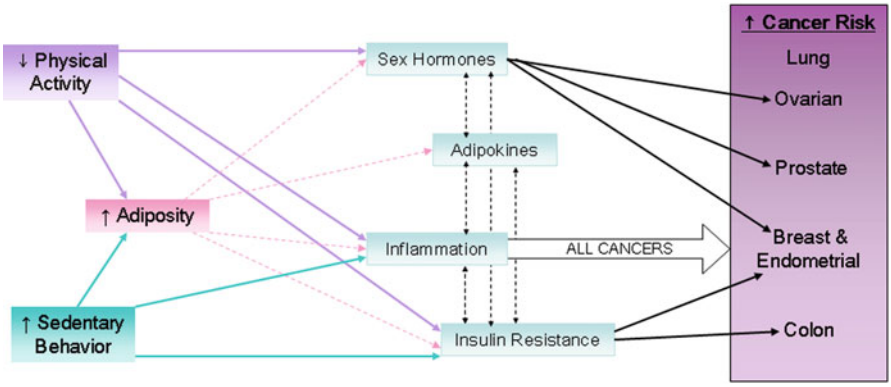

Fig. 6.11 Hypothesized biologic model relating proposed biomarkers of cancer risk to long-term physical activity and sedentary behavior

There is convincing evidence that adiposity increases colon, postmenopausal breast, endometrial, kidney, and esophageal cancer risk and cancer-related mortality (Reeves et al. 2007; Renehan et al. 2008).

There is now evidence from three randomized controlled exercise intervention trials that physical activity reduces adiposity, all of which found statistically significant reductions in adiposity levels with increased aerobic exercise as well as a dose–response effect on all body fat measures with increasing adherence to the exercise intervention (Irwin et al. 2003; Friedenreich et al. 2010c; Monninkhof et al. 2009).

Time in sedentary behavior generally displaces time spent in light-intensity physical activity (Owen et al. 2010); such a shift reduces overall cumulative daily energy expenditure. Sedentary behavior and adiposity are consistently associated in cross-sectional studies; however, results from cohort studies are mixed (Lynch 2010).

6.4.2 Sex Hormones

Exposure to biologically available sex hormones is a risk factor for hormone-related cancers, particularly breast, endometrial, and prostate cancers (McTiernan 2008; Friedenreich 2010). Sex hormone-binding globulin (SHBG) may also affect cancer risk by binding to sex hormones, rendering them biologically inactive (Neilson et al. 2009). Both physical activity and sedentary behavior may be associated with endogenous sex hormones via adiposity. In postmenopausal women, the main source of circulating estrogen is from conversion of androgens within adipose tissue (Kendall et al. 2007); hence, adiposity directly influences levels of total and bioavailable estrogen (Kaaks et al. 2002). Visceral adipose tissue is also important in the production of adipokines, which influence estrogen (Pou et al. 2007) and androgen biosynthesis (Böttner et al. 2004).

There is evidence from randomized intervention trials that exercise can reduce the level of estradiol and increase SHBG but limited evidence for an effect on estrone, testosterone, and androstenedione (McTiernan et al. 2004; McTiernan et al. 2006;

Monninkhof et al. 2009; Tworoger et al. 2007; Friedenreich et al. 2010b; Chubak et al. 2004).

Only one study has considered whether or not sedentary behavior directly affects sex hormone levels. A cross-sectional study of 565 postmenopausal women examined associations of sitting time with various estrogens, androgens, and SHBG and found no statistically significant associations (Tworoger et al. 2007).

6.4.3 Insulin Resistance

Associations between insulin levels and colorectal, postmenopausal breast, pancreatic, and endometrial cancers have been demonstrated in epidemiological studies, while fasting glucose levels have been directly associated with pancreatic, kidney, liver, endometrial, biliary, and urinary tract cancers (Becker et al. 2009). Neoplastic cells use glucose for proliferation; therefore, hyperglycemia may promote carcinogenesis by providing an amiable environment for tumor growth (Xue and Michels 2007). High insulin levels increase bioavailable insulin-like growth factor-I (IGF), which is involved in cell differentiation, proliferation, and apoptosis (Nandeesha 2009). Decreasing blood insulin levels also results in increased hepatic synthesis of SHBG; hence, insulin indirectly increases bioavailability of endogenous sex hormones (Kaaks 2001; Xue and Michels 2007).

Exercise intervention trials have found that insulin, glucose, and insulin resistance as assessed by the HOMA score are all reduced with aerobic exercise (Friedenreich et al. 2011a; Mason et al. 2011). No effect has been found for exercise on any of the IGF family of proteins (Friedenreich et al. 2011a; Irwin et al. 2005; McTiernan et al. 2005).

Sedentary behavior could plausibly affect metabolic function via increased adiposity and decreased skeletal muscle mass. The sustained periods of muscular inactivity that occur during sedentary behavior may reduce glucose uptake (Hamilton et al. 2007; Tremblay et al. 2010). Although cross-sectional studies mostly demonstrate significant associations between sedentary behavior and biomarkers of metabolic dysfunction, no clear evidence of an association has emerged from the limited prospective research to date (Thorp et al. 2011; Proper et al. 2011).

6.4.4 Adipokines and Inflammation

Chronic inflammation is acknowledged as a risk factor for most types of cancer (McTiernan 2008; Neilson et al. 2009). Inflammation may induce cell proliferation, microenvironmental changes, and oxidative stress, which in turn could deregulate normal cell growth and promote progression and malignant conversion (Coussens and Werb 2002). Obesity is considered a low-grade, systemic inflammatory state (Lee et al. 2007). Adipose tissue is a complex metabolic and endocrine organ that secretes multiple biologically active polypeptides known collectively as adipokines (Kershaw and Flier 2004; Antuna-Puente et al. 2008), including leptin, adiponectin,

tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). C-reactive protein (CRP) is an acute phase protein produced in the liver in response to TNF-α and IL-6 levels; each of these factors is a biomarker of inflammation.

The release of adipokines may play a central role in the development of insulin resistance (Antuna-Puente et al. 2008), and elevated levels of adipokines might also increase cancer risk by affecting estrogen biosynthesis and activity (Pou et al. 2007).

Exercise intervention trials have demonstrated a direct effect of exercise on CRP but no effect on TNF-α or IL-6 levels (Friedenreich et al. 2011b; Tworoger et al. 2007; Irwin et al. 2009; Campbell et al. 2009). Likewise, no direct effect on adiponectin was observed; however, the ratio of leptin/adiponectin was associated with increasing exercise levels (Friedenreich et al. 2011a).

There have been few epidemiological studies linking sedentary behavior with biomarkers of inflammation. One prospective study found a significant, positive association between average television time (four assessments over 6 years) and leptin but no association with CRP (Fung et al. 2000). In contrast, data from the National Health and Nutrition Examination Survey has demonstrated statistically significant, cross-sectional associations between accelerometer-assessed sedentary time and CRP in postmenopausal women (Lynch et al. 2011b) and in the broader adult population (Healy et al. 2011).

6.5 Public Health Implications

Despite compelling evidence for the health benefits of physical activity, including a reduced risk of several cancers, many individuals do not meet recommended activity levels. Several key areas need to be addressed to translate scientific knowledge on the health benefits of physical activity that include education of the public on these benefits through evidence-based guidelines, increased health promotion activities, coordinated efforts at different jurisdictional levels, public engagement, partnerships between governmental and nongovernmental organizations, changes in fiscal policies, and urban and rural planning (Global Advocacy for Physical Activity (GAPA) 2010).

6.5.1 Physical Activity Guidelines

Global recommendations for physical activity for health issued by the World Health Organization (WHO) currently recommend that adults 18–64 years of age engage in at least (1) 150 min of moderate intensity aerobic physical activity, or (2) 75 min of vigorous intensity aerobic physical activity, or (3) an equivalent combination of moderate and vigorous intensity activity, in intervals of 10 min or greater over the course of a week. Additional moderate–vigorous aerobic activity (of up to 300 min for moderate, 150 min for vigorous, or an equivalent combination of moderate and vigorous

activities) and muscle strengthening on two or more occasions may be performed over the week for additional health benefits (World Health Organization 2010).

Through endorsements from the WHO, national physical activity guidelines have become available in many countries (World Health Organization 2008; United Nations General Assembly 2011). National guidelines in Canada (Canadian Society for Exercise Physiology 2011) and the United States (U.S. Department of Health and Human Services 2008) are similar but differ from available cancer prevention-specific guidelines from the American Cancer Society that recommends at least 30 min of moderate–vigorous activity on at least 5 days/week for adults (Kushi et al. 2006) and the World Cancer Research Fund/American Institute for Research on Cancer that recommends that adults be "physically active everyday in any way for at least 30 min" (World Cancer Research Fund and the American Institute for Cancer Research 2007).

Despite widespread and long-standing guidelines, the majority of Canadians (Bryan and Katzmarzyk 2009; Colley et al. 2011) and Americans (Troiano et al. 2008) do not meet recommended activity levels. It is estimated that if recommended all Canadians followed activity guidelines, up to 20% of colon cancer deaths and 14% of breast cancer deaths in Canada could be prevented (Warburton et al. 2007).

6.5.2 Population-Based Strategies to Increase Physical Activity Levels

Physical activity guidelines are not produced under the intention of directly eliciting behavior change, but rather offer evidence-based targets that if adhered to are associated with reduced risks of disease. To encourage uptake and adherence, physical activity guidelines must be supplemented with effective public health messaging and, where possible, population-based physical activity programs or interventions.

Effective public health messaging should address not only why physical activity is important but also how recommended levels may be achieved. Messaging should be informative and persuasive and be disseminated to the public through a multiphase social marketing campaign to target the largest possible audience (Brawley and Latimer 2007). Evaluations of messaging strategies have demonstrated only modest and short-term changes to physical activity levels with this approach alone (Kahn et al. 2002).

Publicly accessible activity programs and/or interventions may be a more direct and effective means to physical activity promotion, but available resources limit implementation. Several trials have assessed intervention-based strategies for encouraging uptake and adherence to physical activity guidelines. A critical review of this research revealed that many interventions had only modest effects on changing activity levels and that few strategies had the capacity to elicit behavioral changes that are adequate to fulfill currently recommended guidelines (Hillsdon et al. 2005).

Measurement error is one optimistic explanation for the minimal changes to physical activity levels observed with these strategies, as many studies have employed self-reported measures of activity that may not be sufficiently sensitive to

detect meaningful differences between study groups. Further, it may take people time to change physical activity, and so they may occur beyond the follow-up period of a typical study. Given these limitations, comprehensive evaluation of activity promotion should also consider changes in awareness, understanding, motivation, and self-efficacy to pursue physical activity (Brawley and Latimer 2007).

An important consideration for physical activity intervention trials is the feasibility of interventions on a population level. In their review of the literature, Hillsdon et al. observed that the most effective interventions were those that included professional advice and ongoing support and which took place in a community or health-care center (Hillsdon et al. 2005). Such interventions may be too costly and complex to apply beyond the research setting. To facilitate this bridge from research to community, future trials should consider consultation with key stakeholders such as community organizations and policy makers.

The subtle changes to physical activity levels observed with public health messaging and activity interventions highlight the importance of the underlying sociocultural, environmental, and policy influences of inactive and sedentary lifestyles, which may require transformation in order to achieve the greatest possible changes to physical activity levels. The 2010 Toronto Charter for Physical Activity and its supporting action document provide an international consensus regarding the specific steps that should be taken to promote and support physical activity on a global scale (Bull 2011). Recommendations advise that governments and organizations working to improve physical activity levels address the determinants of physical inactivity in all relevant sectors including programs targeting education, transport, sports and recreation, primary health-care systems, and urban planning.

Overall, improving physical activity participation in the future requires a concerted effort from many parties. While approaches to increasing population physical activity levels have been identified and endorsed, implementing these strategies requires serious political commitment and strong investments (Bull 2011). Continued dissemination and advocacy for the Toronto Charter and its specific recommendations and continued efforts to secure support from key governmental agencies are key priorities to increasing global physical activity levels and, ultimately, preventing cancer.

6.6 Conclusions

There is now consistent and strong evidence that physical activity reduces the risk of colon and breast cancers and fairly consistent evidence for endometrial cancer as well (Table 6.1). The evidence is somewhat weaker for lung and prostate cancers and currently insufficient for ovarian and other cancer sites.

There is also emerging evidence for an etiologic role of sedentary behavior in increasing the risk of several cancer sites. Several hypothesized biologic mechanisms have emerged for these associations of physical activity and sedentary behavior and cancer risk with the strongest evidence for a role of adiposity, insulin resistance, inflammation, and endogenous sex hormones. More research is needed,

Table 6.1 Summary of epidemiological evidence on physical activity and cancer prevention by cancer site

Cancer site	Number of studies	Number of studies with statistically significant risk reduction	Magnitude of risk reduction	Dose–response effect	Overall classification of evidence
Colon	85	72 (34)	30%	Yes	Convincing
Breast	86	64 (36)	25%	Yes	Convincing
Endometrial	28	23 (14)	30–35%	Yes	Probable
Ovarian	23	12 (4)	<10%	Limited	Weak
Prostate	56	26 (15)	10%	Limited	Weak
Lung	27	19 (7)	25%	Some	Possible

ideally from randomized controlled trials, to improve understanding of the effects of different doses and types of physical activity and sedentary behavior on the various biologic pathways. Translation of this knowledge on cancer prevention benefits to the general population has not yet occurred; concerted and coordinated efforts are needed at several jurisdictional levels to increase physical activity levels before benefit with respect to cancer risk reduction will be realized.

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