Review

Physical Activity and Postmenopausal Breast Cancer: Proposed Biologic Mechanisms and Areas for Future Research

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Abstract

Convincing evidence now supports a probable preventive role for physical activity in postmenopausal breast cancer. The mechanisms by which long-term physical activity affect risk, however, remain unclear. The aims of this review were to propose a biological model whereby long-term physical activity lowers postmenopausal breast cancer risk and to highlight gaps in the epidemiologic literature. To address the second aim, we summarized epidemiologic literature on 10 proposed biomarkers, namely, body mass index (BMI), estrogens, androgens, sex hormone binding globulin, leptin, adiponectin, markers of insulin resistance, tumor necrosis factor-α, interleukin-6, and C-reactive protein, in relation to postmenopausal breast cancer risk and physical activity, respectively. Associations were deemed ''convincing,'' ''probable,'' ''possible,'' or ''hypothesized'' using set criteria. Our proposed biological model illustrated the co-occurrence of overweight/obesity, insulin resistance, and chronic inflammation influencing cancer risk through interrelated mechanisms. The most convincing epidemiologic evidence supported associations between postmenopausal breast cancer risk and BMI, estrogens, and androgens, respectively. In relation to physical activity, associations were most convincing for BMI, estrone, insulin resistance, and C-reactive protein. Only BMI and estrone were convincingly (or probably) associated with both postmenopausal breast cancer risk and physical activity. There is a need for prospective cohort studies relating the proposed biomarkers to cancer risk and for long-term exercise randomized controlled trials comparing biomarker changes over time, specifically in postmenopausal women. Future etiologic studies should consider interactions among biomarkers, whereas exercise trials should explore exercise effects independently of weight loss, different exercise prescriptions, and effects on central adiposity. (Cancer Epidemiol Biomarkers Prev 2009;18(1):11–27)

Introduction

In 2004 the lifetime probability of developing invasive breast cancer for women in Canada was 11% or 1 in 9, more than any other cancer in women aside from nonmelanoma skin cancer (1). In 2004 in the United States, invasive breast cancer was the most commonly diagnosed cancer in women (age-adjusted incidence rate at 118 per 100,000 women; ref. 2). Although several risk factors are proposed for breast cancer, low levels of physical activity may be one of the most modifiable. Excess body weight and low physical activity together may account for one quarter to one third of all breast cancer cases (3). From the substantial epidemiologic literature on physical activity and breast cancer (3-6), convincing evidence now supports a ''probable'' preventive role for physical activity in postmenopausal women (4), whereby habitual activity may lower risk by approximately 20% (7). The evidence in premenopausal women has been generally weaker (4, 5). The mechanisms by which long-term physical activity lowers postmenopausal breast cancer risk, however, remain unclear. Mechanistic insight, ideally from biomarker studies (8), would add biological plausibility to the association, guide future epidemiologic research, identify new targets for interventions, and inform public health recommendations for lowering breast cancer risk.

The aims of our review were to propose a biological model whereby long-term physical activity lowers postmenopausal breast cancer risk and to highlight gaps in the epidemiologic literature. To address the second aim, we summarized the existing epidemiologic literature on the following 10 biologically plausible, candidate biomarkers (anthropometric and blood), in relation to postmenopausal breast cancer risk and physical activity, respectively: body weight or body mass index (BMI), estrogens, androgens, sex hormone binding globulin (SHBG), leptin, adiponectin, markers of insulin resistance (i.e. insulin, glucose, C-peptide, and glycosylated hemoglobin), tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). Although many

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candidate biomarkers exist (9-14), the plausibility of our chosen biomarkers has been discussed in recent literature (9, 13, 15) and their responses to exercise have been tested (16-20) or are currently under investigation (9) in various exercise intervention trials for postmenopausal breast cancer prevention. Insulin-like growth factor-1 was not included in our review because most previous studies in older women have not shown decreased insulin-like growth factor-1 with increasing physical activity (20, 21). Moreover, at least two reviews of the epidemiologic literature failed to show significantly altered breast cancer risk in postmenopausal women with higher insulin-like growth factor-1 levels (22, 23). Likewise, we excluded mammographic density from our biological model because recent research has generally shown no association between physical activity and breast density (24-30).

Materials and Methods

In February 2008 we searched the published literature using PubMed (NIH). To identify studies we queried medical subject headings (MeSH) for each hypothesized biomarker combined with terms for breast cancer (MeSH term ''Breast Neoplasms'') and physical activity (''physical activity'' or MeSH terms ''Motor Activity'' or ''Exercise''), respectively. Hypothesized biomarker information was retrieved using the following MeSH terms: ''Estrogens,'' ''Androgens,'' ''Sex-hormone binding globulin,'' ''C-reactive protein,'' ''Leptin,'' ''Adiponectin,'' ''Interleukin-6,'' ''Tumor necrosis factor-alpha,'' ''Insulin,'' "Insulin resistance," ''Glucose,'' ''C-peptide,'' ''Hemoglobin A, Glycosylated,'' ''Hyperinsulinism,'' ''Body weights and measures,'' ''Body composition,'' and ''Body weight.'' We limited our electronic search to English language publications in humans. Due to the extensive literature on physical activity and insulin resistance, physical activity and body weight, and breast cancer and body weight, we restricted the latter three searches to English language review articles and meta-analyses in adults. With respect to the remaining topics, we reviewed original articles reporting results explicitly for postmenopausal women. We excluded intervention trials in cancer survivors and studies in diseased women (unless they were type 2 diabetics, whom we included), trained athletes, or the severely obese. Studies presenting results only for women on hormone replacement therapy were also excluded. Furthermore, if postmenopausal status was ambiguous or results were not stratified by menopausal status, then the article was excluded. If menopausal status was not stated but the minimum age of participants was ≥55 y, however, the study was included. Acute exercise trials (<4 wk duration) or trials intervening in both exercise and diet were similarly excluded from our review in order to isolate the effects of long-term physical activity from weight loss. The review was not restricted to any particular type or intensity of physical activity.

We classified the epidemiologic evidence using a scheme adapted from the American Institute of Cancer Research/World Cancer Research Fund's recent comprehensive report on physical activity and cancer prevention (4). Unlike the report, however, we did not assess study quality or study heterogeneity within or among study types and we believed all of the associations to be biologically plausible. Furthermore, we did not assess physical activity methods or adjustment for potential confounders in the individual studies as these assessments were beyond the scope of this review. An association was deemed ''convincing'' if it was supported by at least two cohort studies or trials (i.e., randomized or nonrandomized) and the expected association was found consistently across all analyses, or if the association was generally supported by a large body of epidemiologic literature and/or public health guidelines. An association was considered ''probable'' if two or more cohort studies or trials were conducted and most of the analyses supported the same expected association. ''Possible'' described associations based on two or more cohort studies or trials or five or more case-control, nested case-control, or case-cohort studies and/or 50% of the analyses or less supporting the same expected association. An association was ''hypothesized'' if supported by a limited number of studies and/or very few analyses, if any, showed the expected association. We summarized each study's findings very simply in terms of ''positive'' or ''negative'' based on the direction of the association and whether or not the adjusted results reached statistical significance ($P \leq 0.05$).

Results

Body Weight Measures. A strong biological rationale and wealth of epidemiologic evidence now support a role for elevated body weight in increasing postmenopausal breast cancer risk. Overweight and obesity could lead to cancer through a number of pathways, including higher levels of circulating sex hormones, insulin resistance, chronic inflammation, and/or lower levels of SHBG and adiponectin (Table 1), although the exact mechanisms are unknown.

As expected, our search of the review literature supported a convincing positive association between postmenopausal breast cancer risk and elevated BMI (Table 2). A 2007 review of 24 cohort studies and 56 case-control studies in postmenopausal women (4) provided strong evidence of increased risk with increasing BMI based on consistent findings and clear dose-response relations. Similarly, a 2008 meta-analysis of 31 prospective studies found a 12% increase in risk of postmenopausal breast cancer for every 5 kg/m^2 increase in BMI [relative risk, 1.12; 95% confidence interval (95% CI), 1.08-1.16; ref. 31]. In general, earlier reviews reported higher risk with adult weight gain (32, 33) and increasing weight and/or BMI for postmenopausal women (3, 33-36). A 2001 meta-analysis of 13 studies in postmenopausal women showed a significantly increased risk of breast cancer by 2% per 1 kg/m^2 increase in BMI (37). Subsequently, a 2003 pooled analysis of eight prospective studies of postmenopausal women (38) found the relative risk of breast cancer to be 1.19 (95% CI, 1.05-1.34) for every 5 kg/m^2 increase in BMI. However, when adjusted for free estradiol, the risk approached unity (relative risk, 1.02; 95% CI, 0.89-1.17). In the same analysis, the mean concentration of estrogen metabolites in obese women (BMI ≥30.0) was between 60% and 219% higher than in thin women (BMI <22.5), showing the important, presumably causal path from body weight to circulating estrogen levels (Table 1).

Table 1. Possible mechanisms relating commonly proposed biomarkers to postmenopausal breast cancer risk and physical activity

Proposed biomarker	Possible role in postmenopausal breast cancer	Possible impact of physical activity in postmenopausal women
Estrogens	Adipose tissue contains higher levels of aromatase which converts androgens to estrogens (57). Estrogens are mitogens in the breast, stimulating mammary cell proliferation through estrogen receptor–mediated transcriptional activity and by activation of intracellular signaling pathways (48, 57).	Reduces adiposity thereby lowering the capacity for conversion of androgens to estrogens by aromatase and lowering circulating estrogen levels (10, 221). Reduces insulin levels thereby increasing SHBG levels (73-75) which may decrease estradiol bioavailability.
Androgens	Testosterone and androstenedione may increase risk upon conversion to estradiol and estrone, respectively, in adipose tissue (58, 222). Androgens also act directly on breast cells by binding to the androgen receptor (65), a ligand-dependent transcription factor expressed in the majority of breast cancers (223, 224). There may be synergy between estrogens and androgens in increasing breast cancer risk (69). The exact mechanism in postmenopausal breast cancer is unclear (69, 225). *In vitro*, androgens can directly stimulate or inhibit breast cancer cell proliferation depending on the cell line (69, 226, 227). Some clinical data support a protective role for androgens in breast cancer (227).	Decreases testosterone levels through loss of body fat. Decreased adiposity lowers levels of 17β-hydroxysteroid dehydrogenase enzyme which converts androstenedione to testosterone in s.c. and intra-abdominal fat (228), thereby lowering testosterone levels. Reduces adiposity thereby lowering the capacity for conversion of androgens to estrogens by aromatase and lowering circulating estrogen levels (10, 221). Reduces insulin levels thereby increasing SHBG levels (73-75) which may decrease testosterone bioavailability.
SHBG	SHBG binds to estradiol and testosterone (55) thereby reducing their bioavailabilities; may act as a negative modulator of estradiol (54).	Reduces insulin levels which increases circulating SHBG (73, 229), thereby decreasing the bioavailabilities of estradiol and testosterone.
Insulin Resistance	Hyperinsulinemia is associated with decreased plasma SHBG (73, 229), thereby increasing sex hormone bioavailability. Insulin exerts mitogenic effects in breast cancer cells *in vitro*; (230, 231) may synergize with estrogen (57, 232). Insulin resistance and hyperinsulinemia are strongly related to obesity,(233) and particularly intra-abdominal fat (73, 234). Insulin resistance has been associated with increased leptin, TNF-α, adipose tissue–derived IL-6, and decreased adiponectin, respectively (15, 117).	An acute bout of exercise enhances insulin sensitivity and glucose uptake mainly on account of skeletal muscle activity; however, the effects tend to dissipate within days (78). Prolonged high intensity exercise training can sustain insulin sensitivity (76, 78) and protect against development of type 2 diabetes (77) perhaps by reducing abdominal fat, increasing skeletal muscle mass, increasing glucose transport into the muscle,(235) or decreasing fatty acid synthesis (76, 78).
Body weight, BMI	Overweight and obesity generally results in: higher levels of sex hormones (71, 236, 237); higher levels of aromatase, which converts androgens to estrogens in adipose tissue, and therefore higher levels of total estradiol (57, 75, 238); more abdominal fat and thus more 17β-hydroxysteroid dehydrogenase, which regulates the conversion of androstenedione to testosterone (228); chronic release of free fatty acids from adipose tissue, resulting in reduced uptake of glucose by the tissues and consequently, increased circulating insulin (57, 238); lower levels of SHBG in response to hyperinsulinemia and thus, higher circulating levels of bioavailable estradiol and testosterone (57, 238); greater release of leptin, IL-6, and TNF-α from adipose tissue and decreased adiponectin (57, 111, 141, 238).	Reduces body weight (41) and decreases central adiposity in some populations (239) including postmenopausal women (17, 107, 108, 216, 240).

Not surprisingly, clinical practice guidelines for treatment of overweight and obesity in the United States (39) and Canada (40) support a convincing association between long-term physical activity and weight loss (Table 3). Although calorie restriction induces more weight loss than exercise alone (41), both countries advocate long-term regular exercise to induce modest weight loss in overweight and obese adults. Exercise is also recommended to maintain weight loss (40, 42, 43). A meta-analysis of 25 years of lifestyle weight loss programs specifically showed that aerobic exercise alone (mean, 15.6 weeks) decreased BMI by 0.8 and initial weight by 3.6% on average (41). In a meta-analysis of nine pedometer-based interventions, there was a strong dose-response relation whereby longer intervention duration was associated with greater weight loss (44). Another review of eight recent (2000-2006) exercise randomized control trials (RCT) suggested that longer duration of physical activity is optimal for decreasing body weight and adiposity (45).

Estrogens and SHBG. Endogenous estrogen status has become a well-established risk factor for postmenopausal breast cancer (46) regardless of individual risk (predicted

Table 2. Results from epidemiologic studies of proposed biomarkers and breast cancer risk in postmenopausal women

Proposed biomarker in blood	Type of study design, study results (±/NA) and number of analyses					
	Cross-sectional			Case-control		
	+	−	NA	+	−	NA
Estrone				2 (241, 242)		
Estradiol						2 (241, 242)
Testosterone				1 (242)		1 (241)
Androstenedione						1 (241)
SHBG						2 (241, 242)
Leptin				2 (125, 126)		4 (245-248)
Adiponectin					4 (125, 204, 245, 250)	2 (219, 251)
TNF-α						
Interleukin-6						
CRP						
Insulin	1 (85)			2 (86, 87)		3 (88, 92, 93)
Glucose				1 (88)		1 (93)
C-peptide				2 (89, 90)		3 (87, 92, 98)
Body weight, BMI	Reviews of the epidemiologic literature support positive associations between postmenopausal breast cancer risk and BMI and/or body weight (3, 4, 31, 33-38).					

NOTE: +, positive association and $P \leq 0.05$; −, negative association and $P \leq 0.05$; NA, no association and $P > 0.05$.
*Original studies included in pooled analyses were exclusive from studies referenced elsewhere in the table. The pooled analysis by Key et al. (59) included only prospective studies in postmenopausal women: six studies on estrone, nine on estradiol, seven on SHBG, seven on testosterone, and five on androstenedione. An update on one cohort included the pooled analysis (253) was subsequently published (254) but was not included in the table to avoid double counting.

by a modified Gail model, the Rosner and Colditz model, or family history of breast cancer; ref. 47) with possible influence on the initiation, promotion, and progression of breast cancer (48). Furthermore, the successful use of antiestrogenic drugs in reducing breast cancer incidence rates supports a role for estrogens in breast cancer etiology (49-51). Several estrogen metabolites may influence breast cancer risk (52) including estrone, estrone sulfate, and 17β-estradiol (estradiol), the most biologically active endogenous estrogen (53). Higher SHBG might lower risk by acting as a negative modulator of estradiol (54) and by reducing estrogen bioavailability (55). The most common hypothesis linking postmenopausal breast cancer to estrogens relates to adiposity (Table 1). The main source of circulating estrogens, for postmenopausal women who do not use hormone replacement therapy, derives from androgen aromatization in the peripheral tissues such as bone, muscle, brain, and most notably, adipose tissue (56-58).

As expected, our review of the literature revealed a convincing association between postmenopausal breast cancer and estrone and a probable association with estradiol (Table 2). Some of the strongest evidence stemmed from a pooled analysis of prospective studies in postmenopausal women (59), in which 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; for estrone the odds ratio was 2.19 (95% CI, 1.48-3.22). The evidence for SHBG was less convincing, deemed possible using our criteria, with the pooled analysis resulting in an odds ratio of 0.66 (95% CI, 0.43-1.00) reaching only borderline statistical significance (59).

In relation to physical activity, associations were rated probable for estrone but only possible for estradiol and SHBG (Table 3). Two RCTs examined estrone and estradiol in relation to physical activity with one RCT showing no association (60) and the other showing significant inverse associations with both metabolites (18). It is worth noting that most physical activity studies were cross-sectional in nature (5 of 8 studies on estrone, 7 of 10 studies on estradiol, 5 of 9 studies on SHBG), which is a limited study design because the temporal sequence of cause and effect cannot be shown.

It is unclear whether or not physical activity lowers estrogen levels independently of weight loss. Some cross-sectional studies have found significant inverse associations between physical activity and estrogen levels even after controlling for BMI or adiposity (61-64), suggesting an independent role for physical activity. Yet in a 12-month RCT (18), postmenopausal women assigned to an exercise group who lost ≥0.5% body fat experienced decreased estrone, estradiol, free estradiol and increased SHBG, whereas women who did not lose body fat experienced increased estrogen levels.

Androgens. As for estrogens, a growing body of epidemiologic evidence supports a positive association between androgen levels and postmenopausal breast cancer risk (46). Androgens are the most abundant sex steroid hormones in postmenopausal women, with testosterone being one of the most powerful natural forms (65). Before and after menopause, adrenal- or ovarian-derived androstenedione gives rise to testosterone (and its derivative, dihydrotestosterone) in the ovaries and in other tissues such as adipose and breast (65-68). As with estradiol, testosterone binds reversibly to SHBG rendering it biologically inactive (55). The aromatase enzyme converts testosterone to estradiol, and androstenedione to estrone, within the adipose tissue of postmenopausal women (56).

It remains unclear whether increased risk results from androgens increasing breast cell growth directly or indirectly via estrogen production (Table 1; ref. 69). For example, one prospective study in postmenopausal women found little association between androgens and breast cancer risk after controlling for estrogen levels

Table 2. Results from epidemiologic studies of proposed biomarkers and breast cancer risk in postmenopausal women (Cont'd)

Type of study design, study results (±/NA) and number of analyses									Classification
Nested case-control or case-cohort			Cohort			Pooled analysis*			
+	−	NA	+	−	NA	+	−	NA	
2 (70, 243)						1 (59)			Convincing
3 (70, 72, 243)		1 (244)				1 (59)			Probable
3 (70, 72, 243)		1 (244)				1 (59)			Probable
2 (70, 72)		1 (243)				1 (59)			Probable
	2 (70, 72)	2 (243, 244)					1 (59)		Possible
		1 (249)							Possible
	1 (252)								Possible
					1 (156)				Hypothesized
					1 (156)				Hypothesized
					2 (156, 205)				Hypothesized
					1 (94)				Possible
					2 (94, 95)				Possible
1 (91)		2 (96, 97)							Possible
									Convincing

(70). Likewise, respective adjustments for estrone, estradiol, and free estradiol (but not testosterone or androstenedione) substantially weakened associations between BMI and postmenopausal breast cancer risk in one nested case-control study (71). However, adjustment for estradiol levels only slightly attenuated the relative risk associated with testosterone in a pooled analysis of prospective studies (59) and at least one other cohort study (72), thus supporting an independent mechanism for androgens.

Our review found probable associations between postmenopausal breast cancer risk and androstenedione and testosterone, respectively, because most studies supported positive relations (Table 2). 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 with women in the lowest quintiles (relative risk, 2.22; 95% CI, 1.59-3.10 for testosterone; relative risk, 2.15; 95% CI, 1.44-3.21 for androstenedione; ref. 59). In the same analysis, a doubling of androgen levels produced an estimated 20% to 40% increase in breast cancer risk.

Physical activity could lower testosterone levels by decreasing adiposity or by increasing circulating SHBG (refs. 73-75; Table 1). However, our literature review suggested only possible inverse associations between physical activity and serum testosterone and serum androstenedione (Table 3). Similar to the estrogen literature, much of this evidence was derived from cross-sectional studies (4 of 8 studies on testosterone, 4 of 6 studies on androstenedione) and hence, causal inference is limited.

Insulin Resistance. Insulin resistance describes the reduced effectiveness of insulin to regulate blood glucose, primarily via skeletal muscle (76, 77). When tissues cease to respond effectively to insulin, glucose uptake is reduced while the liver increases glucose biosynthesis, resulting in hyperglycemia. The pancreatic response to high blood glucose is increased insulin secretion, resulting in hyperinsulinemia (78-80). Although insulin resistance can coincide with normal or impaired glucose tolerance, it also increases risk of type 2 diabetes and is a key component of the metabolic syndrome, two conditions that are modifiable by physical activity (77, 81). Genetic and environmental factors contribute to both insulin resistance and the metabolic syndrome; obesity, however, and particularly intra-abdominal adiposity are also considered important determinants of risk (77, 82).

A causal link between insulin resistance and postmenopausal breast cancer risk is biologically plausible (Table 1). Furthermore, in one meta-analysis, diabetes mellitus (largely type 2) was associated with a significant (16%) increase in postmenopausal breast cancer risk (83). Our review suggested a possible increased risk of postmenopausal breast cancer with higher levels of serum insulin, glucose, and C-peptide (a marker of pancreatic insulin secretion; ref. 84), respectively (Table 2). Of the 14 studies measuring at least one of these markers in postmenopausal women, seven found at least one significant positive association (85-91), whereas the remainder showed no association (92-98). Also one large cohort study (99) revealed a weak inverse association between postmenopausal breast cancer risk and Hb_{A1C}, a measure of long-term blood glucose levels (100).

In contrast to its possible association with breast cancer risk, we classified the link between physical activity and insulin resistance as convincing (Table 3) based on the scientific consensus (7, 76, 101-104). Specifically, a statement by the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition (102), and others promote moderate weight loss via regular aerobic, and possibly resistance (103), exercise to improve insulin sensitivity (105) and prevent diabetes (7, 76, 102, 104). The effect of exercise may be strongest for those with impaired (versus normal) glucose tolerance (76) and when followed at higher doses (106), higher intensity (107), or when as combined aerobic/resistance exercise versus aerobic exercise alone (108).

Adipokines and Inflammatory Markers. Adipokines (adipocytokines) are a group of biologically active

Table 3. Results from epidemiologic studies of proposed biomarkers and physical activity in postmenopausal women

Proposed biomarker in blood	Type of study design, study results (±/NA) and number of analyses					
	Cross-sectional			Case-control		
	+	−	NA	+	−	NA
Estrone		3 (61, 63, 255)	2 (62, 256)		1 (257)	
Estradiol		2 (62, 255)	5 (61, 63, 64, 258, 259)			1 (257)
Testosterone		1 (62)	3 (61, 255, 256)			1 (257)
Androstenedione		2 (63, 255)	2 (61, 62)			
SHBG		1 (261)	4 (63, 258, 259, 262)			
Leptin						
Adiponectin						
TNF-α			2 (157, 158)			
Interleukin-6		2 (157, 173)	1 (158)			
CRP		2 (157, 214)				
Insulin, glucose, C-peptide	Reviews generally promote moderate weight loss with exercise to improve insulin sensitivity (101, 105) and prevent diabetes (7, 76, 102, 104).					
Body weight, BMI	Clinical guidelines for weight loss in the United States (39) and Canada (40) advocate long-term regular exercise to induce modest weight loss in overweight and obese adults.					

NOTE: +, −, and NA $P > 0.05$.
*The associations deemed ''+'' or ''−'' were based on the change observed in exercisers versus the change observed in controls with the exception of the RCT described by Giannopoulou et al. (129),which did not include a control arm; rather, the results at baseline were compared with the end of study within the exercise only arm.

polypeptides produced by adipocytes or adipose tissue; they include leptin, adiponectin, TNF-α, and IL-6 (109-111). CRP is not an adipokine but is produced in the liver in response to TNF-α and IL-6 levels (112), which are all considered common indicators of inflammation (113). Chronic inflammation is an acknowledged risk factor for several cancers (114), and obesity (112) and the metabolic syndrome (115) represent low-grade, systemic inflammatory states with elevated levels of inflammatory markers. The sustained proliferative activity, microenvironmental changes, and oxidative stress associated with chronic inflammation could act together to deregulate normal cell growth and development, thereby promoting initiated cells toward malignancy (116).

Postmenopausal breast cancer risk is positively associated with increased BMI (Table 2), and adipokines similarly exhibit strong positive correlations with BMI (15), hyperinsulinemia, insulin resistance, and type 2 diabetes (conditions related to overweight and obesity; refs. 15, 117). Several biological mechanisms implicate adipokines in breast cancer etiology (Table 4), but the extent to which adipokines influence breast cancer risk directly or act as biomarkers of increased adiposity, insulin resistance, and chronic inflammation, is unresolved.

Regular physical activity may reduce inflammation independently of fat loss (118), but the mechanisms are unknown. One RCT in postmenopausal women (118) found that a 6-month weight loss intervention, comprising a hypocaloric diet and exercise, significantly decreased plasma TNF-α, IL-6, and CRP whereas significant changes were not observed in the group receiving only the diet intervention. Interestingly, the two groups experienced similar losses in body weight and adipose tissue. Furthermore, a recent review article concluded that physical fitness generally decreases inflammatory markers even after adjusting for adiposity (119).

Leptin. Leptin is both a neurohormone and a member of the cytokine superfamily (120). Although first discovered in 1994 (121), its role in cancer etiology is only recently appreciated. Adipose tissue is quantitatively the most important source of leptin and the primary determinant of circulating leptin levels (122-124). Leptin is widely known for its ability to counteract obesity by inducing satiety and limiting caloric intake (123), but paradoxically, human obesity is associated with higher levels of circulating leptin, possibly signifying leptin resistance (57, 122). Considerable *in vitro* evidence implicates leptin as a risk factor for breast cancer (Table 4), either by direct mitogenic action on breast cells or perhaps indirectly, for example, by increasing estrogen production or by promoting insulin resistance.

Despite biological plausibility, we classified the epidemiologic evidence relating leptin to postmenopausal breast cancer risk as possible (Table 2). Of the seven studies we reviewed, only two case-control studies (125, 126) found significant positive associations. We did not identify any cohort studies in postmenopausal women. In contrast, the relation between higher physical activity and decreased leptin was deemed probable in our review (Table 3). Although only five studies were identified, all five were prospective trials and four (16, 127-129) produced significant decreases in leptin. Moreover, reviews have suggested that the greatest impact on leptin is achieved by exercise training of longer duration, extending beyond 12 weeks, and at higher intensities (130, 131).

Adiponectin. Adiponectin was first described in 1995 as the most abundant gene product of human adipocytes (132). It is now gaining recognition as a predictive indicator of abdominal fat and obesity-related sequelae such as the metabolic syndrome (133) and now, possibly, breast cancer. Although adiponectin is produced only by adipocytes (57, 134), unlike other adipokines, it has a strong inverse correlation with adiposity (135); consequently, weight loss increases adiponectin levels (136, 137). The relation may occur in part because IL-6 and TNF-α, which increase in obesity (138), are potent

Table 3. Results from epidemiologic studies of proposed biomarkers and physical activity in postmenopausal women (Cont'd)

Type of study design, study results (±/NA) and number of analyses						Classification
Trial			RCT*			
+	−	NA	+	−	NA	
				1 (18)	1 (60)	Probable
				1 (18)	1 (60)	Possible
	2 (240, 260)			1 (19)		Possible
					2 (19, 60)	Possible
	2 (240, 263)	1 (260)			1 (18)	Possible
	2 (127, 128)	1 (264)		2 (16, 129)		Probable
		1 (147)			1 (129)	Hypothesized
		1 (128)			1 (129)	Hypothesized
						Hypothesized
	1 (265)			1 (129)		Convincing
						Convincing (general population)
						Convincing (general population)

inhibitors of adiponectin expression and secretion (ref. 139). Generally, adiponectin is acknowledged to be anti-inflammatory and antiatherogenic (140-143), and lower levels of adiponectin are strongly associated with insulin resistance (144, 145), perhaps more strongly than obesity or adiposity (146).

Although lower levels of adiponectin may imply increased risk for postmenopausal breast cancer, we found only a possible association based on our literature review (Table 2). Five of seven studies in postmenopausal women showed negative associations, but none were prospective in nature and therefore these data are limited for assessing causality. In relation to physical activity, only a hypothesized association exists at this time (Table 3). We identified only two studies of exercise and adiponectin in postmenopausal women (129, 147); both were prospective trials, but neither found any statistically significant effect.

The effect of exercise on adiponectin in other populations (i.e., not exclusively postmenopausal women) has been reviewed previously (148, 149). Despite three of eight exercise trials producing significantly increased adiponectin levels in one review (148), the overall evidence on chronic exercise was inconclusive because many factors were uncontrolled for, namely, weight change, diet, and the effects of cytokines. Furthermore, regression analysis of 15 exercise trials found no significant relation between changes in body weight and adiponectin (148). According to another review (149), chronic exercise that improves fitness, increases insulin sensitivity, and reduces body weight will increase adiponectin levels if the training volume is sufficiently high and lasts longer than 2 months. Whether exercise influenced adiponectin through weight loss alone was unclear from these studies (149).

TNF-α. TNF-α is a cytokine produced mainly by macrophages that infiltrate adipose tissue in obesity (109) but also by a variety of tumor cells, including breast carcinoma (114, 150). TNF-α is well known for its critical roles in host defense, inflammation, and organogenesis (151). The relation of TNF-α to cancer, however, is less straightforward. Although TNF-α can induce apoptosis and necrosis, as its name implies, chronic moderately elevated levels of TNF-α seem to promote nearly all steps leading to cancer, from cellular transformation to metastasis (Table 4; refs. 114, 151, 152). Because TNF-α mRNA and TNF-α protein are released by adipose tissue (153-155), weight loss may decrease circulating TNF-α.

To our knowledge, only one epidemiologic study has evaluated TNF-α in postmenopausal breast cancer (ref. 156; Table 2). This cohort study followed 2,438 older adults (ages 70-79 years) for an average of 5.5 years. Despite biological plausibility, no association was found between circulating TNF-α and breast cancer incidence. Similarly, of four studies investigating physical activity and TNF-α (128, 129, 157, 158), none found a statistically significant association, although lower TNF-α levels corresponded with increased physical activity in one study (cross-sectional; ref. 157) and TNF-α levels decreased after 14 weeks of exercise in another (RCT; ref. 129). Consequently, we classified both associations as hypothesized (Tables 2 and 3).

IL-6. IL-6 is a cytokine that occurs predominantly in circulating form (159) originating from a number of sources (160) including fibroblasts, macrophages, lymphocytes (145), skeletal muscle (161), and adipose tissue (162). Obesity is strongly associated with elevated circulating IL-6 (161), although it is estimated that adipocytes *per se* account for only 10% of IL-6 released from adipose tissue (163). Because TNF-α stimulates the release of IL-6, it is suggested that moderate increases in systemic IL-6 and CRP may actually reflect chronic TNF-α production (164, 165). IL-6 has a broad range of regulatory functions involving inflammation and immune responses (15) but might also increase breast cancer risk by IL-6–induced insulin resistance (145) and aromatase activity (Table 4; ref. 166).

Our review identified only one study examining IL-6 levels relative to postmenopausal breast cancer risk; no significant association was found (156) and so we deemed this association hypothesized (Table 2). Interestingly, other studies not exclusive to postmenopausal women have showed higher IL-6 levels in breast cancer cases relative to controls (167-171), and some have implicated IL-6 as a negative prognosticator in breast

Table 4. Possible mechanisms relating recently proposed biomarkers to postmenopausal breast cancer risk and physical activity

Proposed Biomarker	Possible role in postmenopausal breast cancer	Possible impact of physical activity in postmenopausal women
Leptin	Induces aromatase and stabilizes estrogen receptor-α (57, 122, 124, 266-268). Although leptin can improve insulin sensitivity (145), elevated leptin levels are associated with insulin resistance (117). Hypothalamic actions of leptin could theoretically decrease systemic insulin sensitivity and adiponectin production (269). Expression is induced by high levels of estrogens and insulin (124, 141, 268). Mitogen in breast cancer cells (15); inhibits apoptosis; pro-angiogenic (111, 122, 124, 141).	Weight loss decreases body fat, which is the main source of circulating leptin (122-124).
Adiponectin	Gene expression and secretion from adipocytes are reduced by TNF-α and IL-6 (57, 142); production might also be reduced partially by leptin (269). Promotes and enhances insulin sensitivity (140, 142, 144, 270); reduced adiponectin leads to insulin resistance and compensatory hyperinsulinemia (271). Antiangiogenic (272); antimitogenic, and anti-inflammatory (111). In one breast cancer cell line adiponectin had no effect on apoptosis but did inhibit cell proliferation (273).	Fat loss decreases IL-6 and TNF-α (138), which are potent inhibitors of adiponectin expression and secretion (139). Hence, weight loss may increase circulating adiponectin levels. Chronic physical activity may lower inflammation (e.g., circulating IL-6, TNF-α) independently of fat loss (118); however, the mechanisms for this effect are unknown.
TNF-α	A key regulator of IL-6 synthesis (57). Stimulates estrogen biosynthesis via aromatase induction (166). Induces insulin resistance (109, 164). Paradoxical action: inhibits tumor cell proliferation (274) but also acts as a tumor promoter (151, 152, 275). Can cause direct DNA damage; antiapoptotic and mitogenic (151); promotes invasion, angiogenesis and metastasis of tumor cells (114, 150, 152).	Fat loss may decrease TNF-α levels given that TNF-α mRNA and TNF-α protein are released from adipose tissue in obesity (153-155). Chronic physical activity may reduce the number of mononuclear cells in the blood thereby depleting a source of TNF-α (138).
IL-6	Release is stimulated by TNF-α; has been speculated that systemic IL-6 reflects ongoing production of TNF-α (164, 165); IL-6 in turn, exerts inhibitory effects on TNF-α (165). Plays a primary role in stimulating hepatic production of CRP (159). Produces insulin resistance in adipocytes (276, 277); possible role in type 2 diabetes (160). Stimulates estrogen biosynthesis by the induction of aromatase activity (166). Promotes breast cancer cell motility suggesting a role in metastasis (167). Complex role of IL-6 in breast cancer cells *in vitro*. Up-regulates antiapoptotic and angiogenic proteins in tumor cells but also induces apoptosis in estrogen receptor–positive mammary carcinoma cell lines (172).	Although the acute effects of exercise on IL-6 levels have been studied widely (160), the mechanisms whereby chronic physical activity alter IL-6 levels are unclear (161). Reduced adiposity may decrease IL-6 levels given that IL-6 originates from adipose tissue (162), among other sources. Chronic physical activity may reduce the number of mononuclear cells in the blood thereby depleting a source of IL-6 (138).
CRP	A prototypical marker of inflammation (174). Production is promoted by TNF-α and IL-6 (112). Independently associated with leptin in healthy individuals, possibly via induction of IL-6 by leptin (278). CRP production is strongly, positively related to insulin resistance and can change with insulin levels independently of changes in obesity (279).	Long-term physical activity may decrease CRP by reducing adiposity, by reducing cytokine production (i.e., IL-6 and TNF-α) in muscle and mononuclear cells, or by other means (179).

cancer patients (172). Therefore, a similar relation in postmenopausal women remains plausible.

We classified the relation between physical activity and IL-6 in postmenopausal women as hypothesized (Table 3). Only cross-sectional studies were identified, and two (157, 173) of the three showed significant inverse associations. In both studies, statistical significance was maintained even after adjusting for BMI. Thus, although weight loss can reduce IL-6 (138), exercise might modify IL-6 levels through an independent mechanism.

CRP. CRP is a hepatocyte-derived, acute phase protein considered to be the prototypical marker of inflammation in humans (174) and might also affect postmenopausal breast cancer risk. CRP levels correlate positively with weight (175, 176) and weight gain (177) and have been

similarly related to type 2 diabetes risk (178). Because physical activity confers benefits in each of these conditions, one might expect it similarly to decrease CRP levels.

We identified only two studies of CRP levels and postmenopausal breast cancer risk. Due to the limited epidemiologic literature, we deemed the association to be hypothesized (Table 2). It is noteworthy, however, that both were cohort studies and neither found a statistically significant association. In contrast, an association between CRP and physical activity has been more widely studied and is quite persuasive (Table 3). We identified four studies in postmenopausal women, including one prospective trial and one RCT; all four found that higher levels of physical activity corresponded to lower levels of circulating CRP. We regarded this association as convincing in postmenopausal women. Reviews in other populations support this conclusion. One review of 17 cross-sectional studies of regular physical activity showed consistent evidence of lowered serum CRP in the highest versus the lowest physical activity levels (179). In another review, longitudinal studies showed reduced CRP levels with exercise training (180).

In postmenopausal women it remains unclear whether exercise or weight loss modifies CRP levels (119, 138). One review concluded that CRP levels decline whether weight loss is achieved through exercise or diet (181), implying weight loss is most important. A meta-analysis of five RCTs of long-term exercise training in men and women found statistically significant decreases in body weight and adiposity but only a nonsignificant reduction in CRP levels, suggesting neither exercise nor weight loss is effective (182); however, not all subjects had high CRP levels at baseline and only one study focused on postmenopausal women (183). In the latter RCT of breast cancer survivors, the mean CRP level decreased in the exercise group, but relative to controls this decrease was not statistically significant ($P = 0.066$).

Proposed Biological Model. An overview of our proposed mechanisms for breast cancer (Tables 1 and 4) and

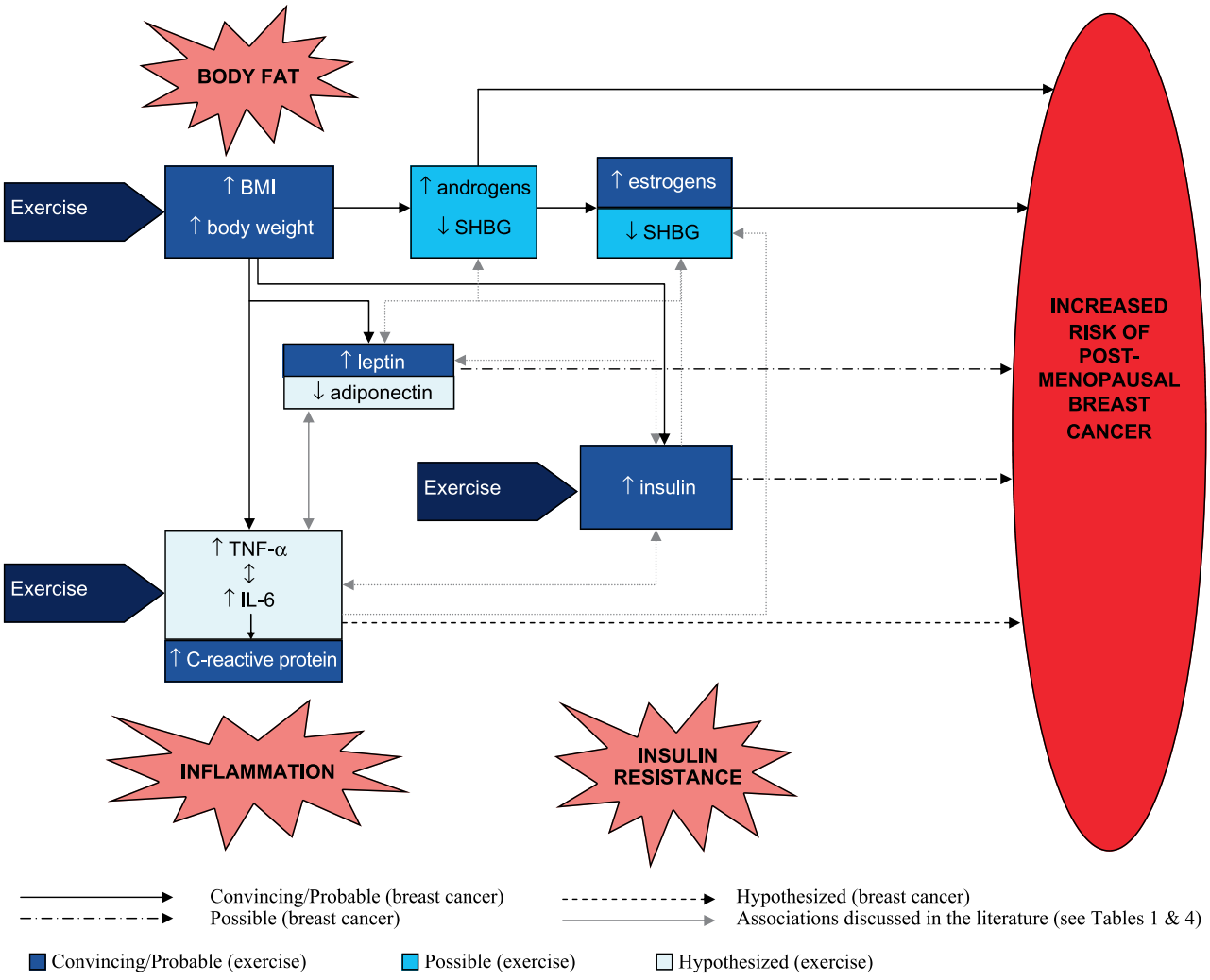

Figure 1. Biological model relating proposed biomarkers to long-term exercise (*shading*) and postmenopausal breast cancer risk (*arrows*).

a summary of findings from our literature review (Tables 2 and 3) are illustrated in Fig. 1. This figure suggests that the co-occurrence of overweight/obesity, insulin resistance, and chronic inflammation may increase postmenopausal breast cancer risk through several complex biological mechanisms. As shown, the most convincing epidemiologic evidence supports associations between breast cancer risk and body weight, estrogens, and androgens, respectively. In relation to physical activity, associations were most convincing for body weight, estrone, leptin, insulin resistance, and CRP levels. Only body weight and estrone were convincingly (or probably) associated with breast cancer risk and physical activity. The least amount of evidence supported roles for TNF-α and IL-6 in this model based on the epidemiologic evidence to date.

This review focused on postmenopausal women and thus, we can only speculate on the effects of these influences over the life course. Hypothetically, cumulative lifetime levels of some biomarkers (e.g., related to insulin resistance or inflammation) might affect postmenopausal breast cancer risk, and sustained physical activity could modify lifetime exposure. However, the epidemiologic evidence relating physical activity and body size to breast cancer is less convincing for premenopausal women (4, 5, 184) and hence, the proposed biological model probably becomes more important after menopause. This finding might reflect a mechanism involving adiposity and sex hormones, for example, because only after menopause, when ovarian production of estrogens has ceased, does adipose tissue become the primary source of circulating estrogens.

Discussion and Future Research Directions

This review provides an overview of three commonly proposed mechanisms relating physical activity to postmenopausal breast cancer risk; namely overweight and obesity, insulin resistance, and chronic inflammation. As illustrated in our model, several mechanisms potentially act simultaneously to increase postmenopausal breast cancer risk with opposing, promoting, and possibly synergistic pathways at play. Considering the complexity of the model, it is not surprising that epidemiologic findings have been inconsistent for some candidate biomarkers. Several questions remain regarding the biological mechanisms that mediate the association between physical activity and breast cancer. Which biomarkers are most predictive of risk? Which are direct versus indirect consequences of exercise? The proposed model also has important implications for the design and analysis of future etiologic studies. It is conceivable, for instance, that the combined effects of elevated sex hormones, insulin resistance, and elevated inflammatory markers present greater risk than any one factor individually; future etiologic studies should explore potential interactions among biomarkers. The notion that interacting pathways connect physical activity to breast cancer risk was proposed by Hoffman-Goetz et al. ten years ago (10), but since then most epidemiologic researchers have continued to study candidate biomarkers in isolation.

As shown in our model, all of the proposed biomarkers are, at least indirectly, related to body size. Therefore, the effect of exercise could be entirely or only partially dependent on weight loss. The available literature does not adequately address whether fitness or decreased fatness is more important for lowering postmenopausal breast cancer risk. However, the Nutrition and Exercise in Women (NEW) Trial led by Dr. Anne McTiernan will address this issue in an ongoing RCT involving over 500 postmenopausal women (13). Additionally, Holt et al. (185) recently explored the effect of fit versus fat on insulin sensitivity in a study of 25 men. The independent effects of adiposity, physical fitness, and physical activity energy expenditure were compared. Multiple regression analysis revealed significant relations between adiposity and whole body insulin sensitivity, and between physical activity energy expenditure and liver insulin sensitivity. We encourage similar studies in the future, designed specifically to compare the effects of physical activity and weight loss and to measure biomarkers prospectively during interventions.

The generalizability of our model is tempered by potential effect modification. It is possible, for instance, that the proposed mechanisms contribute only in certain high-risk subgroups of postmenopausal women (e.g., obese women with BMI $\geq$30 and/or insulin resistance) for whom, according to our model, exercise might confer the greatest benefits. Additional factors such as genetic polymorphisms, family history, race, diet, and medications might further modify the roles of the proposed biomarkers on breast cancer risk. For example, weight gain and BMI only increase postmenopausal breast cancer risk in never users of hormone replacement therapy (186-191). The effect of exercise on breast cancer risk may be similarly modified by hormone replacement therapy use. Two (192, 193) of at least four (192-195) observational studies that examined effect modification of this kind found a stronger protective effect of physical activity among never hormone replacement therapy users as compared with ever users. Furthermore, one cross-sectional study of postmenopausal women showed a two-fold increased median CRP level in hormone replacement therapy users compared with nonusers with control for potential confounders (196). Besides hormone replacement therapy, several other CRP-altering medications have been identified (197). Finally, dietary composition and smoking could hypothetically modify the benefits of exercise by influencing insulin resistance and inflammation (198-200). Given the multitude of potential effect modifiers in our model, the notion that physical activity decreases breast cancer risk generally in postmenopausal women cannot be practically applied to individuals.

It is also conceivable that the proposed biomarkers increase risk for only certain tumor types; namely, hormone receptor–positive or hormone receptor–negative tumors. Interactions with estrogen receptor status have been explored previously, for instance, in relation to breast cancer risk and body weight (186, 191, 201), adiposity (202), sex hormone levels (203), impaired glucose metabolism (99), serum adiponectin (204), and IL-6 levels (171). Furthermore, a recent review provided preliminary evidence that physical activity produces a somewhat greater risk reduction for hormone receptor–negative tumors (estrogen receptor negative/progesterone receptor negative) than for hormone receptor–positive tumors (estrogen receptor positive/progesterone receptor positive; ref. 6). Future etiologic

studies should similarly consider tumor characteristics to advance the interpretation of our model.

Despite the potential importance of frequency, duration, or intensity, surprisingly little evidence exists for defining an effective exercise prescription to reduce postmenopausal breast cancer risk (4). One might expect particular types of physical activity to target abdominal fat and perhaps greater levels of energy expenditure to achieve greater weight loss. Some authors propose that exercise of greater duration, intensity, or volume may also be most effective for decreasing leptin (130, 131) and increasing adiponection (149). Hence, it would be very useful for future exercise intervention trials to compare the effects of different exercise prescriptions in the context of our biological model.

Our review revealed several noteworthy gaps in past epidemiologic research. First, there is clearly a lack of prospective exercise trials examining sex hormone changes in postmenopausal women undergoing physical activity modification. Thus, it is unclear whether or not exercise is causal in reducing androgen and estrogen levels. This is important to note because sex hormones are currently the most compelling candidate biomarkers, given their probable/convincing associations with breast cancer risk (Table 2). Second, the biomarkers designated as hypothesized in this review are hypothetical due largely to a lack of research. Only one study on TNF-α and IL-6 (156) and two on CRP (156, 205) related specifically to postmenopausal breast cancer risk. Furthermore, the soluble receptor for IL-6 (sIL-6R) is a known agonist of IL-6 activity whereas higher levels of TNF soluble receptors (sTNFR1, sTNFR2) inhibit TNF-α activity (206); these could additionally contribute to our proposed model. Therefore, in the context of postmenopausal breast cancer, more epidemiologic research into inflammatory markers and their soluble receptors is warranted.

Despite biological plausibility, our review of four independent studies (128, 129, 157, 158) suggested no relation between TNF-α and physical activity level (128, 129, 157, 158). This finding may indicate that greater levels of concurrent weight loss (or weight disparities in observational studies) are required before differences in TNF-α levels are detectable. Alternatively, changes in TNF-α might be confounded by dietary composition, which is also associated with chronic inflammation (200). Finally, it is possible that compensatory mechanisms to proinflammatory factors or perhaps soluble TNF receptors varied with exercise, but these factors were not studied and/or were excluded from our review. Given these possibilities, excluding TNF-α from our model at this stage might be premature.

To maximize the pool of literature for review, we selected BMI and body weight as our surrogate measures of adiposity. BMI predicts total body fat with varying accuracy depending on the study population (207, 208) but is generally comparable with alternative measures (BMI – % body fat, r = 0.69-0.75 (208, 209) and r = 0.81 for postmenopausal women (210); BMI – abdominal fat assessed by computer tomography, r = 0.8 ref. 207). Therefore, BMI is an acceptable measure for guiding public health recommendations. Abdominal fat, however, may be more etiologically relevant to breast cancer mechanistic research given its inverse association with SHBG levels (211) and insulin sensitivity (212) and positive associations with circulating insulin (213) and CRP levels (214) in postmenopausal women.

Positive associations have been found in many, but not all, studies of waist-hip ratio, waist circumference, or other measures of central adiposity and breast cancer risk in postmenopausal women (3, 32, 33, 36, 75). Abdominal fatness was deemed a probable risk factor for postmenopausal breast cancer in the World Cancer Research Fund/American Institute for Cancer Research 2007 report (4). However, current North American guidelines claim there is only limited evidence supporting the effectiveness of physical activity for abdominal fat loss (ref. 40; also concluded by ref. 215) and only modest reductions in abdominal fat to be expected, if at all (39). It remains plausible, however, that postmenopausal women could be amenable to significant abdominal fat loss given the most effective exercise prescription (e.g., evidenced by refs. 17, 108, 216). Thus, further exercise trials and etiologic studies are needed, ideally using more accurate measures of abdominal fat such as dual energy X-ray absorptiometry. Perhaps more accurate, targeted anthropometric measures will clarify the role of central adiposity.

Our model focuses primarily on mechanisms related to the promotion of postmenopausal breast cancer, but physical activity could influence risk at several points along the cancer continuum (8). Markers associated with detoxification pathways, DNA repair mechanisms, oxidative stress, and various aspects of immune function could all be relevant to postmenopausal breast cancer and also modifiable by exercise (6, 8-10). Moreover, recently proposed biomarkers may be integrated into our model as new research is conducted. For example, resistin is an adipose tissue–derived polypeptide associated with (and named for) insulin resistance in rodents, but its role in humans remains controversial; it might induce insulin resistance or could play a proinflammatory role (217, 218). Resistin is an emerging risk factor for breast cancer with significantly increased serum levels in postmenopausal cases relative to controls in two recent studies (125, 219). However, two recent studies suggested resistin is not modifiable by exercise (129, 220). Still, based on the limited evidence to date, more research is warranted to elucidate resistin's response to exercise and its possible role in postmenopausal breast cancer.

In summary, the current review provides a conceptual framework for future research into the biological mechanisms surrounding physical activity and postmenopausal breast cancer risk. BMI and sex hormones have so far been the most commonly cited biomarkers relating physical activity to decreased risk, but emerging evidence now suggests that insulin resistance and chronic inflammation could play pivotal roles. The important interrelations between these mechanisms must be considered when analyzing data or planning future studies. Two general types of prospective studies are required to validate our model: cohort studies relating the proposed biomarkers to cancer risk, and exercise RCTs comparing biomarker changes at several time points over the long term, specifically in postmenopausal women. Convincing findings from both fields of study, with account for effect modification, would strengthen the existing epidemiologic evidence, and would ultimately guide breast cancer prevention strategies for postmenopausal women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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