The Ecology of Breast Cancer

The Promise of Prevention and the Hope for Healing

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Chapter 4

Exercise, physical activity, and breast cancer

Chapter summary

Humans evolved in the context of physical activity levels very different from today.* Sedentary living, more common now than ever before, is unhealthy and increases the risk of many diseases and earlier death. In fact, prolonged sitting itself is unhealthy, regardless of physical activity levels at other times.[1,2]

Physical activity benefits health across the entire lifespan. Stretching, resistance, and other aerobic fitness exercises influence immune and endocrine function, cardiovascular, pulmonary, and muscular health, body composition, and quality of life, including psychological well-being.

The American College of Sports Medicine recommends healthy adults and cancer survivors perform a minimum of 30-minutes of moderate-intensity exercise five days a week to promote health.[3,4] The American Institute for Cancer Research (AICR) and the World Cancer Research Fund recommend even more–60 minutes of moderate-intensity or 30 minutes of vigorous-intensity exercise daily to reduce cancer risk.[5]

In 1989, scientists from the National Cancer Institute examined the relationship between self-reported physical activity and cancer in the first NHANES cohort, originally assembled from 1971 to 1975, designed to represent

* Exercise is a form of physical activity that is usually planned, structured, and done to improve some aspect of fitness such as strength, flexibility, or aerobic endurance. Exercise also improves general health, well-being, and overall quality of life. Physical activity includes activity that is part of daily life. Household, workplace, and lifestyle physical activity are most common.

the general population, and followed for about 10 years.[6] They reported an increased risk of various kinds of cancer among inactive individuals compared to very active people (80 percent increased risk for men and 30 percent increased risk for women), even after correcting for smoking and BMI. The association was strongest for colorectal and lung cancer in men, and post-menopausal breast and cervical cancer in women.

Exercise, physical activity: breast cancer prevention

Strong evidence continues to show that increased physical activity helps to prevent post-menopausal breast, colorectal, and endometrial cancer.[7] Risk reduction ranges from 20 to 80 percent for post-menopausal breast cancer with increasing physical activity.[8] Evidence for prevention of pre-menopausal breast cancer is not as strong.

Most studies show that increasing levels and duration of physical activity increase the benefit. One review finds that moderate-to-vigorous intensity physical activity two to three hours/week is associated with an average breast cancer risk reduction of nine percent compared to 30 percent decreased risk with 6.5 hours/week or more.[9]

Studies that distinguish among kinds of physical activity find the greatest risk reductions for recreational activity (average 20 percent decrease), followed by walking/cycling for transportation (14 percent), household work (14 percent), and occupational activity (13 percent).[10]

Increased physical activity is beneficial at all life stages. A 15-year follow-up of 3940 former college athletes and their non-athlete classmates confirmed a significantly lower risk of breast cancer in the athletes. Among the entire group of former athletes, breast cancer risk was 40 percent lower than among the non-athletes. For women under age 45, former athletes experienced a striking 84 percent risk reduction.[11]

A prospective analysis of over 40,000 women participating in the Nurses' Health Study II found that increased amounts of physical activity in childhood, adolescence, and adulthood was associated with a decreased risk of developing proliferative benign breast disease—a condition generally considered an early stage in the development of breast cancer.[12] Women engaged in 39–50 MET-hrs/week of physical activity seemed to be at lowest risk. Thirty-nine MET-hrs/week is roughly equivalent to 13 hours/week of walking or 3.25 hours/week of running.

In general, higher lifetime levels are more consistently associated with decreased breast cancer risk than more recent measures. Nonetheless, increased physical activity after age 50 appears to reduce risks more than levels earlier in life. In studies that have examined the effects of exercise on breast cancer risk in various ethnic/racial groups, the largest risk reduction was observed in African-American and Asian women.

Exercise, physical activity: benefits after initial breast cancer treatment

Strong evidence, including results from randomized controlled trials, shows that regular exercise improves numerous measures of health, well-being, and quality of life from the time of a diagnosis of cancer throughout the pre-treatment and treatment periods and beyond. Most but not all studies show that women who regularly exercise after breast cancer treatment experience reduced all-cause and breast-cancer specific mortality compared to sedentary women over follow-up periods averaging four to eight years. In many studies, higher levels of physical activity or exercise before diagnosis are also associated with improved survival after diagnosis and treatment.

Biologic mechanisms linking physical activity and exercise to breast cancer risk

Multiple, inter-related biologic mechanisms probably explain how increasing physical activity levels help to reduce breast cancer risk and improve prognosis following diagnosis and treatment. They include:

- reduced adipose tissue,
- changes in metabolism,
- altered levels of various growth factors, hormones, and their metabolism,
- improved immune function,
- reduced chronic inflammation,
- altered gene expression.

Most but not all studies that examine whether BMI has an influence on the effect of physical activity levels find that increasing levels of exercise reduce breast cancer risk more in women with lower compared to higher BMI. But this is not a consistent finding. It is likely that increased levels of physical activity have benefits that are independent of BMI status.

A number of observational studies conclude that obesity is a risk factor for breast (post-menopausal only), colorectal, endometrial, esophageal, pancreatic, and kidney cancer. Only a few, however, examine whether weight loss lowers cancer risk. In patients who have undergone bariatric surgery, early evidence suggests that to be true. After nearly 11 years of follow-up, a Swedish study found that women undergoing the surgery had a 42 percent lower overall cancer risk and a 32 percent lower weight than those of controls.[13] Interestingly, men who underwent the surgery had no reduction of cancer risk during the same period. Another study reported that over an average of 12 years after surgery, women had a 27 percent lower total cancer incidence after a 31 percent reduction in weight compared with control subjects.[14] However, breast cancer incidence was not different between the groups. Again, men did not experience cancer risk reduction with the surgery.

Since elevated BMI is itself a risk factor for post-menopausal breast cancer, exercise should be combined with dietary modifications and other efforts to reduce overweight or obesity, particularly in post-menopausal women. After diagnosis and treatment of breast cancer, reducing overweight or obesity is beneficial in all women, regardless of menopausal status.

Interest in the influence of exercise on breast cancer risk began to rapidly grow in the 1980s after studies showed that increased physical activity was associated with fewer ovulatory menstrual cycles, particularly in adolescent girls.[15] A 1987 study monitored 169 high school girls for six months.[16] Increasing amounts of physical activity, including moderate levels of aerobic exercise about two hours weekly, was associated with higher likelihood of anovulatory menstrual cycles. The authors wondered if this might reduce breast cancer risk.

Numerous studies of differing design have examined the relationship of exercise or physical activity to breast cancer in detail. Some use comprehensive assessments of lifetime physical activity, while others use shorter-term measures. They also classify the intensity of physical activity in various ways. Many use metabolic equivalents (METs) as a measure. Metabolic equivalents describe activity intensity relative to a person's resting metabolic state, taking into account basal energy expenditure, age, size, and level of fitness (See Table 4.1).

Alternatively, physical activity intensity may be stratified by heart and breathing rates: vigorous (increases heart and breathing rates up to 80 percent or more of maximum), moderate (increases heart rate to 60-70 percent of maximum), and light (minor effects on heart and breathing rates).

Table 4.1: Intensity of physical activity expressed as metabolic equivalents

Physical Activity	MET
Light Intensity Activities	<3
sleeping	0.9
watching television	1.0
writing, desk work, typing	1.8
walking 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
walking 2.5 mph (4 km/h)	2.9
Moderate Intensity Activities	3 to 6
bicycling, stationary, 50 watts, very light effort	3.0
walking 3.0 mph (4.8 km/h)	3.3
calisthenics, home exercise, light or moderate effort, general	3.5
walking 3.4 mph (5.5 km/h)	3.6
bicycling <10 mph (16 km/h), leisure, to work or for pleasure	4.0
bicycling, stationary, 100 watts, light effort	5.5
Vigorous Instensity Activities	>6
jogging, general	7.0
calisthenics (e.g. pushups, situps, pullups, jumping jacks), heavy, vigorous effort	8.0
running jogging, in place	8.0
rope jumping	10.0

Individual studies of exercise and breast cancer risk

More than 70 cohort and case-control studies have examined the relationship between physical activity, exercise and breast cancer risk. Others have studied the relationship between physical activity levels and breast cancer prognosis after diagnosis and treatment. Most studies are done in countries with low average levels of occupational, household, and transport physical activity—thus, generally sedentary ways of life. Table 4.2 summarizes results of 17 large prospective cohort studies.

Summaries of published literature reviews

The most recent reviews have concluded that the evidence supporting a relationship between increased physical activity and decreased risk of breast cancer is convincing.[17,18,19]

Monninkhof, et al. reviewed 19 cohort studies and 29 case control studies and found strong evidence for post-menopausal breast cancer risk reductions ranging from 20-80 percent with increasing physical activity. The evidence for pre-menopausal breast cancer prevention was weaker.[20]

Friedenreich and Cust reviewed 34 case-control and 28 cohort studies finding reduced breast cancer risk with increased physical activity in three-quarters with greater risk reduction with more intense exercise.[21] Studies that distinguished among kinds of physical activity found the greatest risk reductions for recreational activity (average 20 percent decrease), followed by walking/cycling for transportation (14 percent), household work (14 percent), and occupational physical activity (13 percent). Increased physical activity seemed to be beneficial at all life stages, but higher lifetime amounts were more consistently associated with decreased risk than more recent measures. There was, however, a tendency for activity after age 50 to have a stronger risk reduction effect than activity earlier in life. Among the studies that distinguished results according to menopausal status, both pre- and post-menopausal women appeared to experience decreased risk with increased activity, but the decrease was larger and most consistent for post-menopausal women. Sixteen of the studies reviewed examined whether BMI had an influence on the effect of activity levels on breast cancer risk. Increasing physical activity reduced cancer risk more in women with low or normal BMI. This suggests that increased physical activity should be coupled with other efforts to reduce overweight or obesity, particularly in post-menopausal women in whom overweight is a risk factor for breast cancer. In studies that examined the effects of exercise in various ethnic/racial groups, the largest risk reduction was observed in African-American and Asian women.

Table 4.2: Individual prospective cohort studies

Study	Study Population (number of cases)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk (or Hazard Ratio) of Breast Cancer in Physically Active Women Compared with Inactive Women, RR or hazard ratio HR (95 percent CI)		
				Pre-menopausal	Post-menopausal	Pre- and post-menopausal combined
NIH-AARP Diet and Health Study[22, 23]	182,862 (6,609 cases)	7	At least 20 min. physical activity at least 5 times/ wk that caused increased breathing, heart rate, or sweating vs. inactive		0.92 (0.85-1.00)*	
Nurses' Health Study [24]	95,396 (4,782 cases)	20	27 or more vs. less than 3 MET hr/wk		0.88 (0.79-0.98)	
French E3N cohort [25]	90,509 (3,424 cases)	11.4	22.3-33.8 MET hrs/wk recreational activity vs. inactive			0.88 (0.79-0.98) [protective effect persisted regardless of family history, nulliparity, HRT use, BMI]
French E3N cohor	90,509 (3,424 cases)	11.4	33.8 or more MET hrs/wk recreational activity vs. inactive			0.81 (0.72-0.92)
EPIC [26]	218,169 (3,423 cases)	6.4	Recreation: At least 42 vs. less than 14 MET hrs/wk of recreational activity Household activity: > 90 vs < 23 Met hrs/wk	0.94 (0.76-1.15) 0.71 (0.55-0.90)	0.96 (0.85-1.08) 0.81 (0.70-0.93)	
California Teachers Study[27]	110,599 (2,649 cases)	6.6	5 or more hrs/wk moderate physical activity vs. inactive			ER- tumors 0.53 (0.33-0.85); ER+ tumors 0.98 (0.82-1.16)
Iowa Women's Health Study[28]	36,363 (2,548 cases)	15.3	High vs. low level of physical activity		0.91 (0.82-1.01) 0.66 (0.46-0.94) for ER+/PR- tumors	
National Breast Cancer Screening Study-Canada[29] ##	40,318 (2,545 cases)	16.4	At least 1 hr/day vigorous physical activity vs. inactive	0.87 (0.68-1.09)	1.00 (0.78-1.29)	0.93 (0.78-1.10)
Cancer Prevention Study II (CPS II)[30]	72,608 (1,520 cases)	5	At least 42 vs. less than 7 MET hrs/wk physical activity		0.71 (0.49-1.02) Non-recreational activity not associated with BC risk	

Study	Study Population (number of cases)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk (or Hazard Ratio) of Breast Cancer in Physically Active Women Compared with Inactive Women, RR or hazard ratio HR (95 percent CI)		
				Pre-menopausal	Post-menopausal	Pre- and post-menopausal combined
Norwegian-Swedish Women's Lifestyle and Health Cohort Study[31]	99,504 (1,166 cases)	9.1	Vigorous physical activity vs. no physical activity	1.24 (0.85-1.82)‡ (7 percent of cohort post-menopausal at enrollment) A change from being inactive to active at age 30; RR 0.66 (0.44-0.96)		
Women's Health Initiative[32]	74,171 (1,780 cases)	4.7	Strenuous physical activity 3X/wk; (enough to sweat, make heart beat fast); at ages 35 and at 50		0.82 (0.68-0.97); similar risk reduction for exercise at age 35 and 50; less effect with exercise at age 18	
Breast Cancer Detection Demonstration Project Follow-up Study[33]	32,269 (1,506 cases)	8.4	Most vigorous vs. lower level of physical activity		0.87 (0.74-1.02); effect largest in normal weight women	
Netherlands Cohort Study[34]	62,537 (1,208 cases)	7.3	More than 90 minutes/day of physical activity vs. less than 30 minutes/day		0.76 (0.58-0.99); more marked risk reduction in women with higher BMI	
U.S. Radiologic Technologies cohort[35]	45,631 (864 cases)	8.9	At least 97 vs. less than 9.5 MET hrs/wk physical activity			0.91 (0.74-1.13)
U.S. Radiologic Technologies cohort	45,631 (864 cases)	8.9	Walking/hiking at least 10 hrs/wk vs. never walking/hiking	0.37 (0.16-0.84)		0.57 (0.34-0.95)
Nurses' Health Study II[36]	110,468 (849 cases)	10	27 or more vs. less than 3 MET hrs/wk; running or jogging > 2 hrs/wk; lifetime physical activity > 39 MET hrs/wk	1.04 (0.82-1.33)[§] 0.71 (0.45 – 1.12) 0.77 (0.64-0.93)		
PLCO Cancer Screening Trial[37 #]	27,541 (764 cases)	4.9	3 hrs/wk recreational activity vs. inactive		1.02 (0.79-1.30)	

Study	Study Population (number of cases)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk (or Hazard Ratio) of Breast Cancer in Physically Active Women Compared with Inactive Women, RR or hazard ratio HR (95 percent CI)		
				Pre-menopausal	Post-menopausal	Pre- and post-menopausal combined
PLCO Cancer Screening Trial	27,541 (764 cases)	4.9	4 or more hrs/wk recreational activity vs. inactive		0.78 (0.61-0.99)	
Japan Public Health Center-based Prospective Study; case-control design[38]	53,578 (652 cases)	14.5	Leisure-time physical activity at least 3 days/wk vs. 3 or fewer days/month[###]	0.66 (0.40-1.09)	0.78 (0.52-1.17)	0.73 (0.54-1.00)
Swedish Twins Cohort[39]	9,539 (506 cases)	20	Regular vs. very little physical activity		0.6 (0.4-1.0) regular leisure physical activity	
Shanghai Women's Health Study[40]	73.049 (717 cases)	9	Non-occupational and occupational physical activity levels	HR 1.25, (0.77-2.01) for women exercising more than 8 MET h/wk/yr in past 5 yrs	HR 0.73, (0.57-0.92) for women exercising more than 8 MET h/wk/yr; effect greater in women with BMI > 24	

* Additional analyses of 97,039 postmenopausal women (2,866 cases) found that women whose daily routines included activities such as walking or heavy lifting/carrying had a lower risk of breast cancer compared to women who sat all day.

‡ This study also found no link between physical activity at age 30 and breast cancer risk (vigorous activity vs. no activity 1.20 (0.77-1.95), nor between physical activity at age 14 and breast cancer risk (vigorous activity vs. no activity, RR was 1.05 (0.72-1.54).

§ Among 64,777 premenopausal women in this study, average lifetime physical activity was found to decrease risk of breast cancer. Women who averaged at least 39 MET hours of physical activity a week during their lifetime had lower risk of breast cancer compared to inactive women, RR was 0.77 (0.64-0.93).

This study also examined post-menopausal breast cancer risk associated with total energy intake (as estimated by food frequency questionnaire), BMI in combination with various levels of exercise. Women with highest quartile of total energy intake, BMI >30, and less than 4 hrs/wk of exercise had a 2.2-fold increased risk of breast cancer (RR 2.1; 1.27-3.45) compared to women in the lowest quartile of energy intake, with BMI <30, and who exercised >4 hrs/wk. The relationship of energy intake to breast cancer risk was not dependent on BMI or activity level.

This study found increased cancer risk in premenopausal women with highest energy intake, independent of BMI (for BMI <25, RR 1.44 (1.13–1.82); for BMI >25, RR 1.49 (1.12–1.99)). This increased risk was identified across exercise levels. This suggests that energy intake and BMI may have different effects on pre-menopausal breast cancer risk, and BMI is not necessarily a good surrogate for energy intake.

In this study, most marked risk reduction for pre- and post-menopausal breast cancer seen with strenuous activity at age 12 and moderate activity at age 20 and within the past 5 years.

Lynch, et al. reviewed 33 cohort and 40 case-control studies.[41] Forty percent of the studies found a statistically significant decrease in breast cancer risk when comparing the highest with the lowest physical activity levels. An additional 11 percent had a borderline statistically significant risk reduction. Across all studies, there was a 25 percent risk reduction with higher amounts of physical activity. Thirty-three of 41 studies that looked found increasing risk reduction with increased amounts of exercise. In studies that distinguished menopausal status, risk reduction was slightly greater for post-menopausal than pre-menopausal breast cancer. Duration seemed to have a greater effect than intensity of physical activity. Moderate-to-vigorous intensity activity two to three hours/week was associated with an average risk reduction of nine percent, compared to 30 percent decreased risk with 6.5 hours/week or more.

Chandran, et al. reviewed the role of diet, exercise, and BMI in breast cancer risk in African-American women.[42] In four case-control studies increasing physical activity tended toward being protective against pre- and post-menopausal breast cancer. Studies including African-American and white women suggested an even stronger protective effect of exercise in African-American women.

Physical activity or exercise before and after diagnosis of breast cancer: quality of life, recurrence, and survival

Strong evidence, including results from randomized controlled trials, also shows that regular exercise improves numerous measures of health and well-being from the time of a diagnosis of cancer throughout the pre-treatment and treatment periods and beyond.[43,44,45] Most but not all studies show that regular exercise improves quality of life and reduces all-cause and breast- cancer specific mortality over an average follow-up of four to eight years.

Physical activity/exercise at the time of diagnosis and initial treatment

For breast cancer specifically, physical activity levels, both before and after diagnosis and treatment, can influence the likelihood of recurrence and the risk of death—from breast cancer or any cause. Even short-term (12-week) involvement in a supervised exercise program during and after treatment can improve quality of life and outcomes over the long term.[46]

Many controlled and uncontrolled studies of the effects of exercise soon after the diagnosis and during the treatment of breast cancer have been published.[47,48] In a recent meta-analysis of 82 controlled trials of exercise in people recently diagnosed with cancer, 66 were considered of high quality and 83 percent were conducted in breast cancer survivors.[49] The majority found significant benefits from exercise interventions. Early on, upper and lower body strength and self-esteem improved. Following initial treatment, participants experienced significant benefits in aerobic fitness, upper and lower body strength, flexibility, lean body mass, overall quality of life, vigor, fatigue reduction, and measures of hormone and immune parameters (insulin-like growth factor 1 (IGF-1), IGF binding protein-3, cellular immunity, and inflammatory markers).

The majority of exercise interventions were longer than five weeks—about half were more than three months. Aerobic or combined activity interventions were the most common and typically moderately or vigorously intense, three-five times per week, for 30 – 45 minutes per session, both during and after initial cancer treatment.

Many participants were fearful of harm from exercise, particularly related to anemia, weight loss, and lymphedema in their arms. With few exceptions, aerobic and upper body resistance exercises were well tolerated with no evidence of adverse effects on the development or worsening of lymphedema. One study did not exclude participants with anemia and found no adverse effects of vigorous aerobic exercise even after recent hospital discharge following high dose chemotherapy and stem cell transplantation.[50] However, a number of authors caution against prolonged, repetitive high-intensity exercise in cancer survivors near the end of treatment when immune function may be compromised because of the potential for added adverse immune system impacts, as have been noted even in healthy people who exercise excessively.[51]

Exercise also helps to diminish depression associated with the diagnosis and treatment of cancer.[52] Depression is not only important psychologically but also can increase inflammation and alter some immune system functions.[53] This can promote conditions for tumor growth, invasion, and metastasis.

One systematic review examined evidence that tai chi may be beneficial for BC survivors.[54] Tai chi combines physical exercise with mindful meditation and breathing control and is claimed to have positive effects on psychological health, quality of life, mood, flexibility, and balance. The review included three randomized clinical trials in the U.S. and four controlled clinical trials in Korea involving a total of 201 participants. Duration of treatment varied from six to twelve weeks, with one to three supervised sessions weekly. None of the trials found that tai chi improved quality of life or mood compared to controls. One trial found improved range of motion of the shoulder joint, upper limb function, and daily life activity. Three found favorable effects on pain and range of motion of the shoulder, but not on hand grip strength, flexibility, and upper limb function compared with no treatment. No adverse effects were reported.

Physical activity/exercise after the initial treatment period

Beyond the initial treatment period, increased exercise also appears to reduce both breast cancer – specific and overall mortality over the longer term.[55] The evidence is particularly strong for post-menopausal breast cancer. Some evidence shows increased risk reduction with increasing exercise levels. In general, highly significant reduction in risk of mortality over the follow-up period of a number of studies is associated with exercise levels equivalent to about two-three hours of brisk walking weekly (roughly nine MET hours/week). Evidence that exercise reduces the risk of breast-cancer recurrence or that increased activity is more or less beneficial for certain sub-groups of individuals—for example, women with higher (or lower) BMI, hormone receptor status of tumors, stage of disease—is inconsistent.

Table 4.3 summarizes the results from a number of large cohort and population-based case control studies examining the relationship between pre-diagnosis physical activity levels and outcomes following diagnosis and treatment. Table 4.4 summarizes results of studies looking at outcomes associated with varying levels of physical activity post-diagnosis and treatment.

Literature reviews of pre- and post-diagnosis exercise levels and breast cancer outcomes

Ballard-Barbash, et al. systematically reviewed available observational studies and randomized trials of physical activity and cancer-specific and all-cause mortality and relevant biomarkers in cancer survivors.[56] None of the studies reported that higher levels of physical activity were associated with an increased risk of death from breast cancer or any cause. For breast cancer–specific mortality, four studies reported no association with physical activity, seven studies observed non – statistically significant decreased risk of death that ranged from 13 to 51 percent when comparing the highest with the lowest physical activity categories, and six studies observed statistically significant decreased risks of breast cancer-specific mortality that ranged from 41 to 51 percent. With regard to the association between physical activity and mortality from any cause, two studies reported no effect, five studies reported non – statistically significant reduced risks, and seven studies reported statistically significant reduced risks.

Several possible reasons may explain inconsistencies in study results. Study participants may not be comparable. For example, women in the Nurse's Health Study were generally leaner than those in LACE. Measures of physical activity levels are not the same among studies. There may also be unaccounted for differences in the severity of disease, tumor types, or other interventions, such as dietary changes.

Table 4.3: Association of pre-diagnosis exercise on post-diagnosis outcomes

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	**All-cause mortality**	**Breast-cancer specific mortality**
Population-based case control study; Alberta, CA[57]	1231; 60 percent post-menopausal	minimum of 8.3 years for any cancer progressions, recurrences, new primaries; minimum of 10.3 years for deaths	Lifetime level of physical activity; highest vs lowest quartile	Moderate intensity recreational activity decreased the risk of recurrence, progression or new primary cancer RR 0.66; (0.48–0.91)	No association with total physical activity; Highest vs lowest recreational activity HR 0.54, (0.36–0.79)	No association with total physical activity; Moderate recreational activity: HR 0.56, (0.38–0.82) Vigorous recreational activity: HR 0.74 (0.56–0.98)
WHI[58]	4,643 post-menopausal	Physical activity assessment pre-diagnosis average 4.3 yrs. Physical activity assessment post-diagnosis 1.8 yrs Follow-up average 3.3 yrs.	>9 MET-h/week compared to inactive same		HR 0.61; (0.44–0.87) HR 0.54; (0.38–0.79)	HR 0.61; (0.35–0.99)
Population-based case control study; NJ or Atlanta[59]	1264; age 20-54; 85 percent per-menopausal	Follow-up average 8.5 yrs.	Physical activity estimates at age 13, 20, and the year prior to diagnosis		Reduced mortality associated with high physical activity during the previous year in women with BMI >25; HR 0.70 (0.49–0.99)	
Population-based case control study; Australia[60]	451 cases; age 20-74	Average follow-up 5.5 yrs.	Assessed association of physical activity in the year before diagnosis			No significant association with physical activity: pre- or post-menopausal cases
CA teachers study[61]	3,539 cases; age 26-94 yrs; average 59 yrs	Median follow-up of women who died 38.5 mos; medium follow-up of women who survived 64 mos.	Long-term (high-school-age to age 54) and recent exercise (last 3 yrs); Strenuous and moderate exercise; moderate exercise by quartile		Higher long-term exercise RR 0.73 (0.55-0.96); association mostly in women with BMI>25; other levels no effect	Intermediate long-term exercise RR 0.65 (0.45-0.93); high long-term exercise RR 0.53 (0.35-0.80). Recent exercise-no association

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
Breast cancer family registry[62]	4,153 cases; ages < 35 - >60 yrs.	Median follow-up 7.8 yrs.			HR 0.77 (0.60-1.00) for recreational physical activity of >38.2 vs 0 MET-h/wk within last 3 yrs.; effect mostly in ER+ tumors; beneficial effects also at < 9 MET hrs/wk; No significant effect of earlier physical activity levels	
Population-based survival study; Norwegian Counties Study [63]	1,364 cases; ages 27-79 yrs. at diagnosis	Mean follow-up 8.2 yrs.	Level of leisure physical activity in the year prior to study entry		HR 1.47, (1.08–1.99) for pre-diagnostic BMI > 30 compared to BMI 18.5-25*; Active compared to inactive women: HR 0.60, (0.36–0.99)	
Population-based case control study; So. CA[64]	717 cases; all pre-menopausal	10.4 yrs.	Lifetime recreational exercise history; from menarche to one yr. before diagnosis			No association of exercise with breast cancer survival

*effect stronger in pre/perimenopausal women. Women with BMI < 25 kg/m2 and age of diagnosis > 55 years had a 66 percent reduction in overall mortality if they regularly exercised before diagnosis compared with sedentary women; HR = 0.34 (0.16–0.71). Women with the highest total cholesterol had a 29 percent increase in mortality compared to women with the lowest cholesterol (HR = 1.29, [1.01–1.64]). Women with the highest blood pressure had a 41 percent increase in mortality compared to women with the lowest BP. (HR = 1.41, [1.09–1.83]).

Table 4.4: Association of post-diagnosis exercise on outcomes

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
Nurse's health study[65]	3,846 cases; average age at diagnosis 58 yrs.	Median length of follow-up 83 months, and maximum length of follow-up 321 months.	Level of physical activity after diagnosis			Decreasing risk associated with increasing amounts of physical activity (by quintile) RR 0.53 (0.39-0.71); 0.36 (0.26- 0.51); 0.28 (0.19- 0.41); 0.17 (0.11-0.27)

Study	Study Population (number of participants)	Follow-up (years)	Levels of Physical Activity Compared	Relative Risk of Recurrence or Mortality in Physically Active Women Compared with Inactive Women, RR (95 percent CI)		
				Recurrence	All-cause mortality	Breast-cancer specific mortality
WHI	4,643 post-menopausal; average follow-up 3.3 yrs.		Physical activity assessment post-diagnosis 1.8 yrs		Activity > 9 MET hr/wk; HR 0.54; (0.38–0.79)	Activity > 9 MET hr/wk; HR 0.61; (0.35–0.99)
China; Shanghai Breast Cancer Survival Study[66]	4826 cases, mean age 53.5 yr; mostly Asian; pre- and postmenopausal; interviewed 6, 18, 36 mos. after diagnosis	Median median follow-up 4.3 yrs.	Exercise determined at interview 6, 18, 36 mos. after diagnosis		HR 0.65 (0.51-0.84) for exercise ≥ 8.3 MET-h/wk vs. no exercise	HR 0.59 (0.45-0.76) at 36 mo. after diagnosis with exercise of ≥ 8.3 MET-h/wk vs. no exercise
Life After Cancer Epidemiology Study, U.S. [67] (LACE)	Cohort study of cancer survivors; 1970 cases, ages 18–79 yrs; mostly white	Median follow-up 7.25 yrs.	Interviewed at study entry; mean 1.9 yrs. post-diagnosis; occupational, household care giving, leisure-time, transportation-related physical activity, in MET-hr/wk, during the preceding 6 mo	HR 0.91 (0.61-1.36) for recurrence for physical activity of ≥ 62 vs <29 MET-h/wk =	HR 0.76 (0.48-1.19) for death from any cause for physical activity of ≥ 62 vs <29 MET-h/wk	HR 0.87 (0.48-1.59) for death from breast cancer for physical activity of ≥ 62 vs <29 MET-h/wk
Health, Eating, Activity, and Lifestyle (HEAL) Study; U.S.[68]	Cohort study of cancer survivors; 933 cases; mean age 55 yrs; multiethnic; pre- and post-menopausal cases	Mean follow-up 7.25 yrs.	frequency and duration of leisure, occupational, household, physical activity; in MET hr/wk		HR 0.33 (0.15 to 0.73) for leisure activity ≥ 9 vs 0 MET-h/wk	HR 0.65 (0.23-1.8) for leisure activity > 9 vs 0 MET-h/wk
Women's Healthy Eating and Living Study (WHEL) [69]	A dietary RCT in which physical activity also assessed; 2361 cases; mean age 54 yrs; multiethnic; pre- and post-menopausal;	Mean follow-up 5.6 yrs.	frequency, duration, and intensity of physical activity, in MET-h/wk, interviewed after treatment at baseline and 1 yr later	HR 0.74 (0.50 to 1.10) for 24–107 vs 0–2.5 MET-hr/wk	HR 0.47 (0.26-0.84) for 24–107 vs 0–2.5 MET-hr/wk =	
Collaborative Women's Longevity Study; U.S. [70]	4482 cases; mean age 61.7 yrs; mostly white; pre- and post-menopausal 88 – 2001; pre- and postmenopausal; interviewed 2 y after diagnosis		Frequency and duration of weekly leisure physical activity		HR 0.44 (0.32-0.61) for physical activity of ≥ 21 vs <2.8 MET-h/wk	HR 0.49 (0.27-0.89) for physical activity ≥ 21 vs <2.8 MET-h/wk

In summary, the authors concluded that there is fairly consistent evidence that increased physical activity either before or after breast cancer diagnosis is associated with a reduction in both breast cancer – specific mortality and overall mortality, with some evidence suggesting increased risk reduction with increasing activity levels.

Mechanisms by which physical exercise may reduce breast cancer risk and improve prognosis following diagnosis

Multiple, inter-related biologic mechanisms probably explain how increasing activity levels help to reduce breast cancer risk and improve prognosis following diagnosis and treatment. They include:

- reduced adipose tissue accumulation,
- changes in metabolism,
- altered levels of various growth factors, hormones, and their metabolism,
- improved immune function,
- reduced chronic inflammation,
- altered gene expression. A recent randomized exercise intervention study reported that 6 months of moderately vigorous regular exercise modified methylation patterns on a number of genes, including reducing methylation of a tumor suppressor gene, allowing it to be more strongly expressed.[71]

In addition to estrogen and insulin, two additional hormones, leptin and adiponectin have attracted considerable attention with respect to their role in post-menopausal breast cancer. Leptin is a protein hormone manufactured primarily in adipose tissue. It is a key regulator of appetite, food intake, and body weight and plays a role in energy balance and metabolism. Elevated leptin levels are associated with overweight, obesity, and inflammation-related diseases. A reduction in elevated leptin concentrations can lead to an improvement in blood lipid levels, blood pressure, and insulin sensitivity.[72] Adiponectin is an insulin-sensitizing, anti-inflammatory hormone, also produced primarily in adipose tissue. It plays a central role in energy homeostasis, as well as lipid and glucose metabolism. The Nurses' Health Study reported that higher levels of adiponectin were associated with lower postmenopausal breast cancer risk.[73] A systematic review concluded that measurement of adiponectin might serve as a means for predicting risk of obesity-related cancers.[74]

Pre-menopause

The effects of exercise on levels of hormones and related growth factors in pre-menopausal women are not entirely clear. Most studies show little or no relationship between exercise and IGF-1 or IGFBP-3 levels in pre-menopausal women.[75,76,77,78]

With regard to sex hormones, it is important to note that, unlike hormone-receptor-positive, post-menopausal breast cancer, the relationship between endogenous estrogen levels, estrogen metabolites, and premenopausal breast cancer risk is less certain.[79] Nonetheless, the effect of exercise on estrogen levels in premenopausal women is at least plausibly related to breast cancer risk. However, results of studies of this relationship in premenopausal women have been inconsistent.

A recent study of 318 women (165 exercisers, 153 controls), using 24-hour urine collections at the mid-follicular phase of the menstrual cycle, found that the ratio of 2-hydroxyestrone:16α-hydroxyestrone was significantly increased in women who engaged in 30 minutes of aerobic exercise five days a week for 16 weeks.[80] This estrogen metabolic profile may reduce breast cancer risk since the 2-hydroxy metabolite of estrogen is less genotoxic than the 16α-hydroxy metabolite.[81] However, a smaller study of 32 women found no difference in estrogen metabolites between participants who engaged in aerobic exercise 30-40 min. four days/week for 12 weeks and controls.[82] In this study, estrogen metabolites were measured in a morning urine specimen once during the luteal phase of each menstrual cycle during the trial.

Inconsistent findings may be due in part to the wide variability of estrogen levels during the menstrual cycle, making it difficult to estimate total exposure to endogenous estrogen from single or even a few measures during monthly cycles. A recent small study addressed this problem by measuring hormone levels of seven healthy women 25-35 years old before and after an exercise program intervention.[83] Participants were healthy but believed to be at high risk of breast cancer because of BRCA-status or family history. Urinary estrogen and progesterone metabolite levels were monitored daily at baseline during two menstrual cycles and after the introduction of an exercise program to a maintenance level of 300 minute/week to 80-85 percent of aerobic capacity. This approach provided a more accurate estimate of hormone levels throughout the menstrual cycles. Average total estrogen exposure declined by 18.9 percent and total progesterone exposure by 23.7 percent after the maintenance level of exercise was achieved. The declines were mostly due to decreased luteal phase (post-ovulation) levels.

Post-menopause

After menopause, when the ovaries are no longer producing estrogen, the enzyme aromatase continues to facilitate estrogen synthesis in adipose tissue. This is likely to contribute to increased post-menopausal hormone-receptor-positive breast cancer risk. It also helps to explain why reduced adipose tissue lowers the risk of post-menopausal breast cancer. Although exercise will help with weight loss, other mechanisms are also probably involved.

The NIH-AARP Diet and Health study (90 percent Caucasian) found that post-menopausal breast cancer risk was reduced by about 13 percent in women who reported the highest levels of relatively recent physical activity at baseline after 7 years of follow up.[84] The risk reduction was not entirely explained by BMI and was somewhat more pronounced for ER-negative tumors. This has also been reported in some but not all other studies that distinguished tumor hormone-receptor status.[85] Thus exercise may also reduce post-menopausal breast cancer risk through non-estrogenic mechanisms.

In a study of over 1,000 post-menopausal women from the National Health and Nutrition Examination Survey, increased activity was associated with reduced insulin resistance and lower levels of markers of chronic inflammation.[86] Even light-intensity activity reduced markers of inflammation, while increased sedentary time increased levels, independent of levels of exercise at other times. Chronic inflammation is increasingly well-established as a promoter of carcinogenic processes.[87]

Three prospective, randomized, controlled trials examined biologic pathways that might connect physical activity with post-menopausal breast cancer risk. A study of 173 post-menopausal women from the Seattle area (87 intervention, 86 control) assessed the effect of at least 45 minutes of moderate-intensity exercise, 5 days/week for 12 months on serum hormone levels and other markers.[88] It showed that exercise can lower levels of circulating estrogens and increase levels of sex hormone binding globulin in previously sedentary, overweight/obese postmenopausal women. Loss of adipose tissue in addition to exercise was necessary to see the changes.

The Sex Hormones and Physical Exercise (SHAPE) study randomly prescribed a 12-month strength and aerobic training program of approximately 150 minutes per week to 189 sedentary post-menopausal women from the Netherlands. (96 intervention, 93 controls) At the end of the year, estrogen levels were reduced an average of 17 percent in participants who lost at least two percent of their body weight, whether or not they were in the exercise-intervention group.[89] Androgen levels (testosterone, androstenedione) also declined in that group.

The Alberta Physical Activity and Breast Cancer Prevention (ALPHA) trial (320 participants; 160 exercise, 160 controls) involved a moderate- to vigorous-intensity physical activity intervention of approximately 225 min per week over 12 months. After one year, C-reactive protein (CRP) levels—a marker of inflammation—were significantly lower in the exercise-intervention group, though the effect seemed to be primarily mediated by weight loss and higher levels of dietary fiber. Two other markers of inflammation (IL-6, TNF-alpha) were unchanged. Other studies have not observed the same effect on CRP but this may be attributable to lower intensity and amounts of exercise in those trials.[90,91]

The HEAL study of pre- and post-menopausal women with breast cancer (see table 4.4) reported statistically significantly lower levels of leptin, IGF-1, and CRP with increasing levels of physical activity.[92] The study found no association between activity levels and mammographic breast density (mammograms taken one year before or 1-2 years after diagnosis), insulin-like growth factor binding protein-3 (IGFBP-3), or the ratio of IGF-1 to IGFBP-3.

A recent study of 439 overweight/obese healthy 50-75 year old post-menopausal women examined the effect of a 12-month intervention of a reduced calorie, weight loss diet, exercise, or diet + exercise on levels of leptin and adiponectin.[93] Eighty-five percent of the women were non-Hispanic white, seven percent African-American, and the remainder Asian and Hispanic. The diet had a total energy intake goal of 1200-2000 kcal/day and <30 percent daily energy intake from fat. The weight loss goal was 10 percent by 6 months, with maintenance thereafter. The exercise intervention goal was 45 minutes of moderate-to-vigorous intensity exercise five days/week for 12 months. Adiponectin increased by 9.5 percent in the diet group and 6.6 percent in the diet + exercise group, both significantly greater than in a control group. Compared with controls, leptin significantly decreased with all interventions (diet + exercise, -40.1 percent; diet, -27.1 percent; exercise, -12.7 percent). The results were not influenced by the baseline BMI. Thus combinations of diet, exercise, and weight loss may be particularly effective at beneficially altering concentrations of these hormones, at least in this population of women.

A recent review[94] of four primary prevention and five tertiary prevention (exercise intervention following diagnosis and treatment) trials found:

- Primary prevention: All trials showed weight loss; three of 4 showed reduction in estradiol levels; one showed reduction in insulin levels, insulin resistance, and leptin in inactive, overweight, post-menopausal women. All of these trials were 12 months long and met the ACSM recommendations for intensity and duration of exercise. None met AICR recommendations.

- Tertiary prevention: Trials involved combinations of aerobic and resistance exercises. Two did not meet ACSM guidelines for cancer survivors. Most participants were post-menopausal cancer survivors. The two trials that met ACSM guidelines showed reduction in insulin levels. Two trials showed decreased IGF levels. The two studies that examine immune function showed significant improvements, including increased natural killer cell (NKC) activity. C-reactive protein, a marker of inflammation, also moderately decreased.

In summary, multiple biologic mechanisms probably explain how exercise helps to reduce pre-menopausal and post-menopausal breast cancer risk and improve prognosis following diagnosis. They include mechanisms that may influence the likelihood of malignant transformation of cells as well as mechanisms involved in tumor growth and progression. These findings support a conceptual model of breast cancer in which the *milieu intérieur* (the environment within) plays an important role in the origins and progression or remission of breast cancer.

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