

National Action Plan on Breast Cancer Etiology Working Group: Workshop on Physical Activity and Breast Cancer

*Supplement to Cancer*

## Epidemiologic Issues Related to the Association between Physical Activity and Breast Cancer

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A workshop on physical activity and breast cancer was held in November 1997 to review previous epidemiologic research on this topic and to identify new areas for research. This article is the first of three summaries of the workshop's activities. The material reviewed included 21 studies that reported a measure of physical activity in relation to breast cancer outcomes and were published by December 1997. They were identified in a computerized literature search and a "by-hand" review of journals. The study designs, populations, data collection methods, and results were examined and the strengths and limitations of the studies identified. The strengths and limitations are discussed herein, as are recommendations for future research. Fifteen of the 21 studies suggested that physical activity reduces the risk of breast cancer, whereas four studies found no association and two studies found an increased risk of breast cancer associated with physical activity. Specific subgroups of the population may experience a greater decrease in breast cancer with increased levels of physical activity. These include women who are lean, parous, and premenopausal. Some examination of confounding and effect modification was undertaken. Hypothesized biologic mechanisms for this putative association include an effect of physical activity on endogenous hormones, energy balance, and the immune system. The overall evidence supports a reduction in breast cancer risk with increased physical activity. However, numerous questions remain regarding this putative association. These include the underlying biologic model and the parameters of physical activity that are associated with risk, such as the types of activity (occupational, recreational, and household), the components of activity (frequency, intensity, and duration), the time periods in life that are associated with risk reduction, and the important confounders and effect modifiers of this association. Use of intermediate endpoints for breast cancer may be useful in such investigations. *Cancer* 1998;83:600–10. © 1998 American Cancer Society.

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**A** number of recent epidemiologic studies have suggested that physical activity is related to breast cancer risk. Physical activity is a modifiable life-style characteristic and potentially a means for the primary prevention of breast cancer; hence, any link between physical activity and the most common cancer among women is significant to public health. Examining an association between physical activity and breast cancer is challenging because of the complexity in assessing physical activity and the multifactorial etiology of the disease. Experimental and epidemiologic data suggest that the effect of physical activity on breast cancer risk could be mediated through several biologic mechanisms,<sup>1–6</sup> including changes in endogenous hormones, body mass, energy balance, and immunologic parameters. From studies of migrants, it is apparent that life-style factors have

effects on risk that are less immediate for breast cancer than for colon cancer. Incidence rates for colon cancer approach the level of the new country within one generation of immigration to higher incidence countries, whereas incidence rates for breast cancer approach the same level in the second and subsequent generations.<sup>7-9</sup>

Given this background, researchers were invited to a workshop held in November 1997 that was organized under the auspices of the National Action Plan on Breast Cancer (NAPBC) to examine the association between physical activity and the risk of breast cancer. This is the first of three articles that summarize the presentations, discussions, and recommendations held and given at this workshop. The two other articles cover, in detail, the underlying biologic mechanisms operative in this association<sup>10</sup> and the methods and issues surrounding physical activity assessment.<sup>11</sup> In the current article, we describe the methods and results of previous investigations of physical activity and breast cancer. We then discuss the main methodologic issues that have arisen in these studies. They include 1) the need for an understanding of the underlying biologic model, 2) the appropriate measurement of exposure, 3) the assessment of and control for confounding in these studies, and 4) the evaluation of effect modification of the association by other important characteristics. Finally, we give some recommendations for future epidemiologic research in this area.

## EPIDEMIOLOGIC STUDIES OF PHYSICAL ACTIVITY AND BREAST CANCER

A systematic review of published literature available on MEDLINE and a "by-hand" search of relevant journals through December 1997 was conducted to identify all epidemiologic studies that reported a measure of physical activity in relation to breast cancer outcomes. Two studies were excluded because one was simply an extended follow-up of the same cohort<sup>12</sup> and one observed fewer than five breast cancer cases.<sup>13</sup> Thus, 21 studies are included in the current review.<sup>14-34</sup>

### Study Designs and Samples

The study designs, population samples, and measures of physical activity and outcome varied widely among these 21 investigations (Tables 1 and 2). They consisted of 1 record linkage study,<sup>19</sup> 3 retrospective cohort studies,<sup>14,15,18</sup> 5 prospective cohort studies,<sup>16,17,20-22</sup> and 13 case-control studies, 6 of which were hospital-based<sup>23,27-29,31,32</sup> and 6 population-based.<sup>24-26,30,33,34</sup>

The populations sampled in these investigations came from North America, western and eastern Eu-

rope, Australia, and Asia, and ranged from specific population groups—such as occupational cohorts,<sup>15,18</sup> educational cohorts,<sup>14,17</sup> or cohorts based on religious affiliation<sup>21</sup>—to hospital-based<sup>23,27-29,31,32</sup> or population-based samples.<sup>16,19,20,22,24-26,30,33,34</sup> Loss to follow-up was less than 20% in 5 of the 9 cohort and record linkage studies,<sup>15,18,19,21,22</sup> and the interview response rates among study subjects were greater than 75% in 6 of the 12 case-control studies.<sup>25,26,28,30,33,34</sup> Seventeen of the 21 studies reviewed herein included incident cases of breast cancer. The four exceptions were the studies based on breast cancer deaths,<sup>15,17</sup> self-reports of cancer,<sup>14</sup> or prevalent cases.<sup>31</sup> Histologic confirmation of the breast cancer diagnosis was clearly obtained in all but three studies.<sup>15,23,31</sup>

### Physical Activity Measurement Methods

The methods used for the measurement of physical activity in the epidemiologic studies reviewed herein varied considerably. Self-administered questionnaires were used to assess physical activity in six studies,<sup>21,22,25,28,31,32</sup> interview-administered questionnaires were employed in eight studies,<sup>16,20,24,26,27,29,30,33</sup> and classifications based on occupational title<sup>15,18,19,23,34</sup> or involvement in college athletics<sup>14,17</sup> were used in seven studies. No details are available on the physical activity information obtained for the case-control study from Serbia; hence, the following descriptions of the physical activity measurement methods used do not include this study.

In the studies that measured only recreational activity,<sup>14,17,24-28,30,32,33</sup> or both recreational and occupational activity,<sup>16,20-22,29</sup> individual assessments of physical activity were made. In contrast, the occupational studies determined physical activity according to job title.<sup>15,18,19,34</sup> Information on specific activities was obtained in seven studies.<sup>20-22,24,26,30,33</sup> The remaining studies surveyed subjects about categories of activities (e.g., heavy recreational activity) rather than individual activities (e.g., bicycling, walking, etc.). Most studies measured at least two of the three parameters of physical activity (i.e., frequency, duration, and intensity). To our knowledge, 7 of the 21 studies<sup>20-22,27,29,30,33</sup> assessed all 3 parameters in different ways.

Most studies measured physical activity prior to the diagnosis of breast cancer; the exceptions were three<sup>15,19,23</sup> of the five occupational studies that may have included activity that occurred after diagnosis. Direct inquiries<sup>24,26,27,29,30,33</sup> or inferences<sup>14,17</sup> regarding past physical activity were made in eight studies, and selected time periods of lifetime occupational activity were assessed in five other studies.<sup>15,18,19,23,34</sup> One study attempted to measure activity chronologi-

**TABLE 1**  
**Summary of Published Cohort Studies of Physical Activity and Breast Cancer**

Study	Study population	Age range (yrs)	Cases	Physical activity measure	Results	Comments <sup>a</sup>
Frisch et al., 1985, U.S.A. <sup>14</sup>	Retrospective cohort; 5398 living alumnae of 10 colleges and universities who graduated 1925-1981; 2622 former athletes, 2776 nonathletes.	21-80	69 Hist+	Self-administered questionnaire on college athletics, precollege athletic training, and current exercise.	RR for nonathletes vs. athletes: 1.86 (95% CI = 1.00-3.47)	Protective effect. Adjustments for age, age at menarche, and family history of breast cancer. No confounding by age at FFTP, parity, OC and HRT use, BMI, or smoking.
Vena et al., 1987, U.S.A. <sup>15</sup>	Retrospective cohort; mortality of 25,000 females in Washington State for 1974-1979.	30-79	791 Hist-	Usual occupation during working life obtained from death certificate.	Highest activity jobs vs. lowest: PMR = 85, $P \leq 0.05$	Protective effect. No adjustment for confounding considered.
Albanes et al., 1989, U.S.A. <sup>16</sup>	Prospective cohort; NHANES I and NHEFS 7,413 women from throughout the U.S.	25-74	122 Hist+	Interview-administered questionnaire. Two questions on current recreational (R) and nonrecreational (O) activity.	RR for quite inactive vs. very active, all women: R: 1.0 (95% CI = 0.6-1.6) O: 1.1 (95% CI = 0.6-2.0) Premenopausal women: R: 0.6 (95% CI = 0.3-1.2) O: 0.4 (95% CI = 0.1-1.8) Postmenopausal women: R: 1.7 (95% CI = 0.8-2.9) O: 1.5 (95% CI = 0.7-2.8) No dose-response relation.	No overall effect. Adjustment made for age, age at FFTP, parity, menopausal status, family history of breast cancer, BMI, smoking, and dietary fat.
Paffenbarger et al., 1987, U.S. <sup>17</sup>	Retrospective cohort; 4706 female University of Pennsylvania students.	35-70	46 Hist+	Participation in college athletics, determined by college records.	RR for $\leq 5$ hrs/wk vs. $> 5$ 0.96 $P = 0.92$	No effect. No adjustment for confounding except age.
Pukkala et al., 1993, Finland <sup>18</sup>	Prospective cohort; 8619 language (L) and 1499 physical education (PE) teachers drawn from registers for all of Finland.	20-74	228 Hist+	Current occupational titles.	SIR for teachers vs. total Finnish female population, recreational activity: PE: 1.35 (95% CI = 0.95-1.87) L: 1.48 (95% CI = 1.27-1.69)	Lower risk among premenopausal PE teachers than L teachers. Age, age at menarche, age at FFTP, menopause, parity, hysterectomy, and oophorectomy considered but not adjusted for. Stratified by age.
Zheng et al., 1993, China <sup>19</sup>	Record linkage; 1982 Chinese census linked with cancer registry data for 1980-1984.	30+	2736 Hist+	Current occupational physical activity, determined by job title and index of sitting time and energy expenditure.	SIR for professionals vs. base population: Professionals: 158, $P \leq 0.01$ Long sitting time: 127, $P \leq 0.01$ Low energy expenditure: 131, $P \leq 0.01$	Protective effect among active women. No adjustment for confounding considered except age.
Dorgan et al., 1994, U.S. <sup>20</sup>	Prospective cohort; Framingham Heart Study, Massachusetts, 2298 women.	35-68	117 Hist+	Physician-administered questionnaire. No. of hrs spent at each type of activity during the day, weighted by relative oxygen consumption for each activity. Current activity.	RR for total physical activity index low vs. high quartile: 1.6 (95% CI = 0.9-2.9) Some indication of a dose-response relation.	Increased risk among active suggested after adjustments for age, age at FFTP, parity, menopausal status, alcohol intake, education, and occupation. Association restricted to leisure activity; no association for occupational or total activity.
Fraser et al., 1997, U.S. <sup>21</sup>	Prospective cohort; Adventist Health Study, California, 20,341 women.	24-90	218 Hist+	Self-administered questionnaire. Two questions on frequency of vigorous recreational and current occupational activity.	RR for low vs. high level of total physical activity: 1.46 (95% CI = 1.11-1.92)	Protective effect. Adjusted for age, age at FFTP, OC and HRT use, family history of cancer, BBD, and energy and fat intake. No confounding found.
Thune et al., 1997, Norway <sup>22</sup>	Population surveys; 3 counties in Norway involved in 1974-1978 and 1977-1983 survey (n = 25,624 women).	20-54 (entry) 36-68 (diagnosis)	351 Hist+	Self-administered questionnaire. Occupational (O) recreational activity (R) and total activity (Tot) in yrs preceding the surveys. Repeated assessments (Rep).	RR for sedentary vs. consistently active: R: 0.63 (95% CI = 0.42-0.95) O: 0.48 (0.95% CI = 0.25-0.92) Tot: 0.48 (95% CI = 0.27-0.86) Rep: 0.67 (95% CI = 0.40-1.10) Age at entry, recreational: <45: 0.38 (95% CI = 0.19-0.79) $\geq 45$ : 0.84 (95% CI = 0.51-1.39) BMI, recreational: <22.8: 0.28 (95% CI = 0.11-0.70) 22.8-25.7: 0.96 (95% CI = 0.45-2.01) >25.7: 0.83 (95% CI = 0.45-1.53) Dose-response relation.	Protective effect. Adjusted for age at entry, parity, BMI, height, and county of residence. No evidence of confounding for these factors. Also considered confounding by age at FFTP, menopausal status, smoking, energy intake, fat intake, and serum lipids/glucose. Stratified by age, menopausal status, and BMI. Found greater effect in women age <45 yrs, premenopausal, and BMI <22.8.

<sup>a</sup> All risk factors for breast cancer that were adjusted for in the multivariate model and all those considered as potential confounders are included.

PMR: proportional mortality ratio; RR: relative risk; SIR: standardized incidence ratio; Hist: histologic confirmation of breast cancer diagnosis (+: yes; -: no; ? : uncertain); FFTP: first full-term pregnancy; BMI: body mass index; OC: oral contraceptive use; HRT: hormone replacement therapy; BBD: history of benign breast disease. NHANES: US National Health and Nutrition Examination Survey; NHEFS: NHANES I Epidemiologic Follow-Up Study

**TABLE 2**  
**Summary of Published Case-Control Studies of Physical Activity and Breast Cancer**

Study	Study sample	Age range (yrs)	No. of cases/controls	Physical activity measurement/definition	Results	Comments <sup>a</sup>
Dosemeci et al., 1993, Turkey <sup>23</sup>	Oncologic treatment center in Istanbul, 1979-1984, for cases and controls.	?	241/244 Hist?	Occupational titles used to estimate time-weighted average energy expenditure and sitting time during work over lifetime.	RR for high vs. low activity: 0.7 (95% CI = 0.23-3.4)	Increased risk after adjustments for age, smoking, and socioeconomic status. Confounding by SES found. No other factors considered.
Bernstein et al., 1994, U.S. <sup>24</sup>	University of Southern California Cancer Surveillance Program and neighborhood controls.	<40	545/545 Hist+	Interview-administered questionnaire. Lifetime recreational activity.	RR for lowest vs. highest weekly activity quintile (none vs. >3.8 hrs/wk) overall: 0.42 (95% CI = 0.27-0.64) Parous women: 0.28 (95% CI = 0.16-0.50) Nulliparous women: 0.73 (95% CI = 0.38-1.41) Dose-response relation.	Protective effect after adjustments for age, age at menarche, age at FFTP, no. of FFTPs, breastfeeding, OC use, family history of breast cancer, and BMI. Only modest confounding for these factors. Others pregnancy related factors considered were not confounders.
Friedenreich et al. 1995, Australia <sup>25</sup>	Cancer registry in Adelaide and controls selected from electoral roll.	20-74	444/444 Hist+	Self-administered questionnaire. Current recreational physical activity converted into kilocalories expended per wk.	RR for low vs. highest quartile, overall: 0.73 (95% CI = 0.50-1.05) Premenopausal: 0.60 (95% CI = 0.30-1.17) Postmenopausal: 0.73 (95% CI = 0.44-1.20) Some indication of dose-response relation (N.S.).	Protective effect. Adjusted for age, BMI, and energy intake. No confounding found for these factors or for the others considered: age at menarche, age at FFTP, parity, menopausal status, history of bilateral oophorectomy, OC and HRT use, family history of breast cancer, BBD, smoking, and education.
Mittendorf et al. 1995, U.S. <sup>26</sup>	Cancer registries in Massachusetts, Maine, New Hampshire, and Wisconsin; controls age <65 yrs from drivers' licenses, age ≥65 yrs from Medicare lists.	17-74	6888/9539 Hist+	Telephone interview. Strenuous recreational physical activity at ages 14-18 and 18-22 yrs.	RR for no strenuous activity vs. every day of the yr, overall: 0.5 (95% CI = 0.4-0.7) Age <40 yrs: Parous: 0.8 (95% CI = 0.5-1.3) Nulliparous: 1.1 (95% CI = 0.4-2.6) Age ≥40 yrs: Parous: 0.5 (95% CI = 0.4-0.7) Nulliparous: 0.4 (95% CI = 0.1-1.0) Dose-response relation.	Protective effect. Adjusted for age, stage, age at menarche, age at FFTP, parity, age at menopause, menopausal status, type of menopause, family history of breast cancer, BBD, BMI, alcohol intake, interaction of BMI, and menopausal status. Not stated whether these factors were confounders. No difference between pre- and postmenopausal.
Taioli et al. 1995, U.S. <sup>27</sup>	American Health Foundation: one hospital source for cases and controls.	25-45+	617/531 Hist+	Interview-administered questionnaire. Strenuous recreational activity at ages 15-21, 22-44, and 45+ yrs.	RR for <3 vs. ≥3 hrs/wk of exercise: 1.0 (95% CI = 0.6-1.8) RR for <600 vs. >1750 kcal/wk: 1.1 (95% CI = 0.52-2.6)	No effect. Adjusted for age, age at menarche, parity, education, and BMI. Not stated whether these factors were confounders or whether other factors were considered.
Hirose et al., 1995, Japan <sup>28</sup>	Aichi Cancer Center Hospital: one center source for cases and controls.	20-80+	1186/23,163 Hist+	Self-administered questionnaire. Frequency of current recreational activity.	RR for none vs. ≥2 times/wk: Premenopausal: 0.64 (95% CI = 0.48-0.84) Postmenopausal: 0.71 (95% CI = 0.53-0.96)	Protective effect. Adjusted for age, age at menarche, age at FFTP, breastfeeding, BMI, height, smoking, alcohol intake, and some dietary components (e.g., meats and vegetables).
D'Avanzo et al. 1996, Italy <sup>29</sup>	Hospitals in six geographic areas were sources for cases and controls.	23-74	2569/2588 Hist+	Interview-administered questionnaire. Occupational and recreational activity at ages 15-19, 30-39, and 50-59 yrs.	RR for lowest vs. highest quartile: 15-19 yrs: R: 0.95 (95% CI = 0.77-1.18) O: 0.64 (95% CI = 0.37-1.11) 30-39 yrs: R: 0.76 (95% CI = 0.55-1.05) O: 0.54 (95% CI = 0.33-0.89) 50-59 yrs: R: 0.66 (95% CI = 0.41-1.06) O: 0.62 (95% CI = 0.30-1.25) Dose-response relation.	Protective effect. Adjusted for age, age at menarche, age at FFTP, parity, age at menopause, menopausal status family history of breast cancer, BBD, BMI, smoking, caloric intake, education, and treatment center. No confounding by BMI; modest confounding by other factors. Stronger inverse association for younger age (<60 yrs) at diagnosis.

(continued)

TABLE 2  
Continued

Study	Study sample	Age range (yrs)	No. of cases/controls	Physical activity measurement/definition	Results	Comments <sup>a</sup>
McTiernan et al. 1996, U.S. <sup>30</sup>	Washington State Cancer Registry and RDD controls.	50-64	537/492 Hist+	Interview-administered questionnaire. Recreational activity between ages 12-21 yrs and 2 yrs before interview.	RR for no exercise vs. $\geq 3$ hrs/wk in high-intensity exercise: 0.6 (95% CI = 0.4-1.0) Postmenopausal: 0.6 (95% CI = 0.3-0.9) Dose-response relation.	Protective effect. Adjusted for age and education. Other factors considered were not confounders: age at menarche, age at FFTP, parity, menopausal status, OC and HRT use, family history of breast cancer, BBD, BMI, dietary fat intake, education, and mammography screening history.
Kocić et al., 1996, Serbia <sup>31</sup>	Oncology hospital in Niš, Serbia, for cases; two orthopedic and rehabilitation hospitals in Niš for controls.	?	106/106 Hist?	Self-administered questionnaire. Physical activity (not specified what information was asked).	Student's <i>t</i> test for difference in means of physical activity performed: $t = 2.72, P = 0.008$	Protective effect. No multivariate analyses performed. No adjustment for confounding.
Hu et al. 1997, Japan <sup>32</sup>	Gihoku General Hospital in central Japan for cases and breast screening program for controls.	26-75	157/369 Hist+	Self-administered questionnaire. Recreational activity in adolescence and in twenties.	RR for no vs. upper tertile of energy expended (Pre-, then postmenopausal): Adolescence: 0.72 (95% CI = 0.38-1.38) 1.39 (95% CI = 0.61-3.13) Twenties: 1.01 (95% CI = 0.54-1.87) 0.53 (95% CI = 0.19-1.52) No dose-response relation.	Protective effect. Adjusted for age, age at menarche, age at FFTP, parity, breastfeeding, and BMI. Stratified by menopausal status.
Chen et al. 1997, U.S. <sup>33</sup>	Seattle-Puget Sound SEER registry, RDD controls.	21-45	747/961 Hist+	Interview-administered questionnaire. Recreational activity 2 yrs before interview and at ages 12-21 yrs.	RR for no activity vs. $\geq 4$ hrs/wk 2 yrs before diagnosis: 0.92 (95% CI = 0.71-1.22) Age 12-21 yrs: 1.21 (95% CI = 0.80-1.81) No dose-response relation.	No effect. Adjusted for age. Other factors considered were not confounders: age at menarche, age at FFTP, parity, family history of breast cancer, BMI, smoking, alcohol intake, education, family income, and county. No effect modification by age at diagnosis, menopausal status, family history of breast cancer, and BMI.
Coogan et al., 1997, U.S. <sup>34</sup>	State cancer registries in Maine, Wisconsin, Massachusetts, and New Hampshire, RDD controls.	75	4863/ 6783 Hist+	Telephone interview. Usual occupation during lifetime and recreational activity at 14-22 yrs.	RR for sedentary jobs vs. heavy activity jobs, overall: 0.82 (95% CI = 0.63-1.08) Premenopausal: 0.64 (95% CI = 0.32-1.28) Postmenopausal: 0.87 (95% CI = 0.64-1.18) Nulliparous: 0.27 (95% CI = 0.09-0.79) Parous: 0.91 (95% CI = 0.68-1.21) BMI $\leq 23.6$ : 0.75 (95% CI = 0.41-1.05) BMI $> 23.6$ : 0.95 (95% CI = 0.67-1.34) Dose-response relation.	Protective effect. Adjusted for age, age at menarche, age at FFTP, menopausal status, family history of breast cancer, BBD, BMI, education, and alcohol intake, state. Only modest confounding for these factors.

<sup>a</sup> All risk factors for breast cancer that were adjusted for in the multivariate model and all those considered as potential confounders are included.

PMR: proportional mortality ratio; RR: relative risk; SIR: standardized incidence ratio; RDD: random digit dialing; Hist: histologic confirmation of breast cancer diagnosis (+: yes; -: no; ?: uncertain); FFTP: first full-term pregnancy; BMI: body mass index; OC: oral contraceptive use; HRT: hormone replacement therapy; BBD: history of benign breast disease. SEER: Surveillance, Epidemiology, and End Results program.

cally, from childhood/adolescence until age 40 years.<sup>24</sup> Other studies that examined past physical activity focused on particular age groups (e.g., 12-20 years, 30-39 years, etc.).<sup>26,27,29,30,32,33</sup> One study used a

global question on the usual occupational activity in which the subjects were engaged over their lifetimes.<sup>34</sup>

Of the nine cohort studies, only two<sup>14,20</sup> measured current activity in addition to physical activity at the

time of the study initiation. Neither of these studies adjusted the original exposure classification for current activity levels in the analysis or examined the relation between current physical activity and breast cancer risk. One cohort study examined the effects of repeated assessment of physical activity.<sup>22</sup> No study systematically measured total (i.e., recreational, occupational, and household) physical activity throughout a woman's life.

### Overall Results

Fifteen of the 21 published studies observed decreased risk of breast cancer for women who were physically active in their recreational and/or occupational activities compared with inactive women.<sup>14,15,18,19,21,22,24–26,28–32,34</sup> No overall association between physical activity and breast cancer was found in four studies,<sup>16,17,27,33</sup> although a decreased risk of breast cancer was observed for postmenopausal women in one of these latter studies.<sup>16</sup> Increased risk of breast cancer was associated with higher levels of physical activity in the Framingham cohort study<sup>20</sup> and with increased energy expenditure in the Turkish case-control study.<sup>23</sup> There was a statistically significant reduction in overall or subgroup risk estimates associated with high levels of physical activity in 12 studies,<sup>15,18,19,21,22,24,26,28–31,34</sup> and reduction in these risk estimates was of borderline statistical significance in 1 study.<sup>14</sup>

It is important to note that the methods used across studies have been quite heterogeneous, which rules out the possibility of providing an overall quantitative estimate of risk. The magnitude of the overall association ranged from a 10–60% reduction in risk for the highest activity levels measured in 12 studies<sup>14,15,18,19,22–26,29,30,32</sup> to a 30–40% increased risk in 2 studies.<sup>20,23</sup> The possibility of a dose-response relation was examined in 12 of the studies;<sup>16,20,22–26,29,30,32–34</sup> in 6 studies, a trend of decreasing risk of breast cancer with increasing physical activity levels was observed.<sup>22,24,26,29,30,34</sup>

More studies measured recreational than occupational activity, and the largest decreases in risk (58% and 50%, respectively) were observed in 2 case-control studies that measured only recreational activity.<sup>24,26</sup> However, the Norwegian cohort study,<sup>35</sup> in which occupational and recreational activity were of equal importance in decreasing risk (i.e., by 52%), suggested that the type of activity may not be critical to a beneficial effect. Furthermore, this study<sup>35</sup> suggested that women who are physically active both in their occupations and their recreational activities are at lower risk for breast cancer than women who are physically active in only one of these areas.

As noted above, the time period(s) in life for which physical activity patterns were assessed varied across the investigations. The majority of studies inquired only about usual or current practices (i.e., prior to diagnosis). Some of the studies that assessed physical activity during adolescence and/or young adulthood<sup>14,17,24,26,27,29,30,32,33</sup> observed reductions in subsequent breast cancer risk.<sup>14,17,29</sup> Mittendorf et al. observed a decreased risk of breast cancer in relation to higher activity for both age groups considered (younger and older than 40 years),<sup>26</sup> whereas others did not observe any influence of physical activity during young adulthood on pre- or postmenopausal risk of breast cancer.<sup>30,33</sup> There is some suggestion that lifelong and sustained high levels of activity have a stronger protective effect than a short period of activity early in life.<sup>22,24</sup>

Also relevant to public health policy development is whether threshold effects on breast cancer risk exist in relation to the duration, frequency, or intensity of the performed activity. Preliminary evidence for such a threshold effect is available from 3 of the previous 21 studies.<sup>22,24,30</sup> In two of these studies,<sup>22,24</sup> a much stronger risk reduction was observed in the highest levels of recreational activity as compared with the lower levels. In these studies, the highest activity levels represented about 4 hours per week of activity of at least moderate intensity. In the study by McTiernan et al.,<sup>30</sup> a steady risk reduction occurred until a level of 5 or more hours per week was attained; at higher levels, no further risk reduction was observed.

### Population Subgroup Results

Findings specific to population subgroups are relevant to the development of public health guidelines, formulating mechanistic hypotheses, and designing and analyzing future investigations. For example, does the association between physical activity and breast cancer vary according to menopausal status or age at diagnosis? Most studies that included both pre- and postmenopausal women considered the influence of menopausal status, age at diagnosis, or both. Among the nine studies that stratified their results by menopausal status,<sup>16,21,22,25,26,28,30,32,34</sup> evidence for effect modification was found in five studies,<sup>16,21,22,25,32</sup> with no evidence for effect modification found in the other studies.<sup>26,28,30,34</sup> Albanes et al. found a suggestion of an increased risk of breast cancer among postmenopausal women in the low exercise group with an opposite association premenopausally.<sup>16</sup> A decrease in the risk of breast cancer among the physically active women was more evident in the premenopausal women in the four remaining studies.<sup>21,22,25,32</sup> These

results indicate the importance of stratifying the data by menopausal status in future investigations.

Some studies<sup>18,21,22,26,29</sup> stratified the data by age as well as menopausal status. In the Italian case-control study, D'Avanzo et al. reported a more pronounced protective association among women younger than 60 years at diagnosis.<sup>29</sup> In the Norwegian cohort study, Thune et al. observed a more markedly decreased risk for women younger than 45 years versus those older than 45 years of age; this decrease was independent of menopausal status.<sup>22</sup> Pukkala et al., in the Finnish cohort study, found elevated standardized incidence ratios in inactive women older than and younger than 50 years.<sup>18</sup> Mittendorf also found risk reductions of equal magnitude among women younger than and older than 40 years.<sup>26</sup>

The association between body mass index and breast cancer is different for pre- and postmenopausal women,<sup>36</sup> and it may be an intermediary factor between physical activity and breast cancer. Most studies considered the influence of body mass index on risk, and six performed stratified analyses by body mass index.<sup>22,24,29,30,33,34</sup> Two studies noted stronger effects of physical activity among lean versus overweight women.<sup>22,34</sup> In the study of Thune et al.,<sup>22</sup> the reduced effect of physical activity was restricted to women with body mass indices less than 22.8, a relation observed for both pre- and postmenopausal women. Other studies, however, did not find that the effects of physical activity varied by body size.<sup>24,29,30,33</sup>

A few studies examined whether the effect of physical activity on the risk of breast cancer varied by parity.<sup>24,26,29,34</sup> Bernstein<sup>24</sup> and D'Avanzo<sup>29</sup> observed stronger effects of recreational physical activity among parous women than among nulliparous women. Other studies, however, found either the opposite effect (of a stronger effect of occupational physical activity among nulliparous women)<sup>34</sup> or no evidence of effect modification by parity.<sup>26</sup>

Other factors considered but not shown to alter the effects of physical activity have included a family history of breast cancer,<sup>30,33</sup> oral contraceptive use,<sup>24</sup> and use of hormone replacement therapy.<sup>30</sup>

## **METHODOLOGIC ISSUES**

A number of important methodologic issues need to be considered when previous studies of physical activity and breast cancer are reviewed and when future research protocols are designed. These issues include the need to understand the underlying biologic model that may be operating in this putative association; the problem of measuring the exposure accurately, reliably, and with the appropriate parameters (i.e., type of activity, frequency, intensity, and duration of activity);

and the effects that confounding and effect modification may have on this relation.

## **Biologic Model**

Despite the fact that our understanding of the biology and pathogenesis of breast cancer is incomplete, physical activity might reduce the risk of breast cancer through one or more of several plausible biologic mechanisms. These mechanisms include alterations in endogenous hormones, energy balance, and immune function.

First, considerable epidemiologic evidence has accumulated indicating that breast cancer is hormonally mediated. Breast cancer risk is influenced by factors that are related to endogenous hormone profiles. These include age at menarche, number of ovulatory menstrual cycles, age at first pregnancy, and type and age at menopause.<sup>37,38</sup> It has been suggested that if physical activity modified breast cancer risk, it might do so through a hormone-related pathway—for example, by reducing the cumulative exposure to ovarian hormones, by delaying menarche, or by reducing the number of ovulatory cycles.<sup>1,39–45</sup>

Second, physical activity may affect breast cancer risk through its observed influence on energy balance and prevention of obesity and weight gain. Obesity during postmenopausal years and weight gain over a lifetime have been shown to increase breast cancer risk.<sup>46–48</sup> However, obesity is associated with a decreased risk of breast cancer among premenopausal women.<sup>49,50</sup> In premenopausal years, fat stores reduce the level of ovarian hormones because of an increased frequency of anovulation,<sup>51</sup> whereas in postmenopausal women, endogenous ovarian production of estrogens is reduced, which increased the importance of their synthesis in peripheral adipose tissue.<sup>51</sup> Thus, in overweight postmenopausal women, it is hypothesized that there may be increased conversion of precursor substrates to estrogens in adipose tissue.<sup>52</sup>

The third plausible biologic mechanism is that physical activity may enhance the immune system by improving the capacity and numbers of natural killer cells,<sup>53</sup> which may influence breast carcinogenesis. No single, well-defined biologic model currently exists for the association of physical activity with breast cancer or with the pathogenesis of the disease.

## **Exposure Measurement**

Physical activity is defined as bodily movement produced by skeletal muscles that results in a quantifiable form of energy expenditure.<sup>54</sup> The use of high quality, validated instruments designed to capture complete information on the frequency, duration, and intensity of all types of physical activity is essential to the

proper epidemiologic investigation of this association.<sup>55,56</sup> Because the effect of physical activity on breast cancer risk is likely to be modest or vary throughout life, measurement of physical activity needs to be very accurate to minimize the possibility that an effect will not be observed because of measurement error (nondifferential misclassification bias). A better understanding of the probable biologic mechanisms and critical life periods during which activity may exert its influence will further enhance our ability to target and ascertain the appropriate exposure information.

Some of the inconsistencies observed in these investigations could be attributed to problems with exposure measurement. For example, in the studies that used job titles to classify study participants into categories of physical activity, exposure misclassification was more likely because no individual assessment was made of the actual duration, frequency, and intensity of the activity performed. Likewise, in the studies that did not observe an association between physical activity and breast cancer,<sup>27,33</sup> the absence of an effect may have reflected a limited range of activities, with few women being physically active.

Another problem with exposure assessment in these investigations is the lack of information on physical activity throughout life. Insufficient data exist thus far to conclude which age periods are most important in reducing the risk of breast cancer. Studies are needed that measure activity and assess risk throughout life before recommendations can be made regarding which time period(s) are most etiologically relevant.

### Confounding

Without a clear understanding of the underlying biologic model and mechanism(s) operative in the association between physical activity and breast cancer, epidemiologic studies need to incorporate broadly and test potential confounders. Residual confounding may have influenced a few of the previously conducted studies that did not assess confounding completely.<sup>15,17,19,23,27,31</sup> However, most previous studies assessed important potential confounders, and no major confounding of the association between physical activity and breast cancer was found.

The main risk factor that was not measured and controlled for in the majority of the studies was dietary intake. Total caloric intake may confound the association because high calorie intake may increase breast cancer risk.<sup>57</sup> However, for the seven studies that did measure dietary intake,<sup>16,21,22,25,28–30</sup> there was little or no confounding by either total dietary energy or fat intake. These results suggest that dietary factors may

not be important confounders of the association between physical activity and breast cancer, although they could still act as effect modifiers. High total caloric intake occurs in different subgroups of the population—the overweight and inactive as well as the lean and highly active. Hence, disentangling the influence of total caloric intake on breast cancer risk in assessing the impact of physical activity becomes difficult but could be of importance.

### Effect Modification

The challenge in epidemiologic investigations is to differentiate between confounders, effect modifiers, and factors in the causal pathway, because bias can be introduced into a study when adjustment is made for a factor that is a consequence of the exposure of interest.<sup>58,59</sup> Obesity is an example of a risk factor that may be a confounder, an effect modifier, or on the causal pathway between physical activity and breast cancer risk. Epidemiologic evidence exists that obesity is associated with an increased risk of breast cancer in postmenopausal women.<sup>48,50</sup> There is also some evidence to suggest that the pattern of body fat distribution—specifically, a high waist-to-hip ratio—is particularly predictive of postmenopausal breast cancer.<sup>60–63</sup> Exercise reduces obesity;<sup>64,65</sup> therefore, physical activity may reduce breast cancer risk through its influence on obesity.

Some of the discrepancies in the study results may be due to underlying differences in the characteristics of the subjects included. Thus, it is important to consider modifying effects of physical activity in light of other patient characteristics. Future investigations should carefully examine the effects of physical activity within defined strata of other breast cancer risk factors, especially because such analyses may provide insights into etiologic mechanisms. In addition to body size (and perhaps body fat distribution patterns), it would be useful to examine relationships according to exogenous hormone use histories, especially given recent findings of substantial interactive effects of body size and the use of estrogen replacement therapy on breast cancer risk.<sup>48</sup> Studies of interactive effects, however, will be needed to assure that there is sufficient statistical power within the subgroups to enable meaningful interpretations.

### RECOMMENDATIONS FOR FUTURE RESEARCH

Although epidemiologic research suggests that increased physical activity reduced breast cancer risk, in many respects the evidence is sufficiently incomplete to warrant further targeted research. A better understanding of the underlying biologic model is necessary so that epidemiologic studies can be designed to mea-

sure exposures at the appropriate time periods in life and using the appropriate parameters (i.e., intensity, frequency, and duration of activity). Biomarkers for breast cancer risk are needed for use in future epidemiologic investigations, particularly prospective ones, to assess risk. These markers might include endogenous hormones and mammographic density. Future research should examine the change in endogenous hormone levels as physical activity levels change. Intervention studies might be especially useful in monitoring hormone level changes resulting from controlled exercise regimens.

The validity of different physical activity assessment methods needs to be improved and the reliability of these methods assessed. Some experimentation with new physical activity assessment methods should also be undertaken. Physical activity assessment methods could be improved by designing instruments using methods already tested in nutritional research, such as recall diaries, 24-hour recalls, etc. Future studies need to measure all *types* of physical activity (occupational; recreational, including aerobic activity and resistance training; and household) and all *components* of physical activity (frequency, intensity, and duration) across *entire lifetimes*. Inactivity as well as activity should be measured because inactivity itself may be a risk factor for breast cancer. Where possible, self-reported physical activity assessments should be augmented with more direct measurements of activity and physical fitness, such as heart rate measurement and activity monitors. New research on assessment methods should consider the underlying biologic mechanisms in the design and evaluation of these tools.

Important confounders need to be identified and controlled. For confounders that can change with time, such as dietary intake, repeated assessments over time with the best instrument available are necessary, so that the information is from the appropriate time periods. Subgroups of the population need to be examined separately to assess effect modification. These could include subgroups based on menopausal status, weight and body mass index, exogenous hormone use, and ethnicity. A better understanding of the causal pathway between physical activity and breast cancer risk is needed. Physical activity may itself be a biomarker of a healthful life-style. Hence, future investigations need to distinguish between physical activity as both a risk factor and part of an entire life-style.

## CONCLUSIONS

There is epidemiologic evidence from 15 of the 21 previously published studies that physical activity re-

duces breast cancer risk. It is unclear, however, exactly what the magnitude of the effect is; what intensity, duration, and frequency of activity are required for a reduction in risk; what time period(s) in a woman's life are important in such a risk reduction; whether there is confounding and effect modification by other factors; and, equally importantly, what the underlying biologic mechanisms are for such an association. Given the number of unanswered questions regarding this potential association, more research on this topic is warranted.

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