Physical Activity, Heart Rate, Metabolic Profile, and Estradiol in Premenopausal Women

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ABSTRACT

EMAUS, A., M. B. VEIERØD, A.-S. FURBERG, S. ESPETVEDT, C. FRIEDENREICH, P. T. ELLISON, G. JASIENSKA, L. B. ANDERSEN, and I. THUNE. Physical Activity, Heart Rate, Metabolic Profile, and Estradiol in Premenopausal Women. Med. Sci. Sports Exerc., Vol. 40, No. 6, pp. 1024–1032, 2008. Purpose: To study whether physical inactive women with a tendency to develop metabolic syndrome have high levels of 17β-estradiol (E2) of importance for breast cancer risk. Methods: Two hundred and four healthy women of reproductive age were assessed for self-reported leisure-time physical activity (LPA), resting heart rate (HR), blood pressure (BP), anthropometry, and serum glucose, lipids, and insulin [Norwegian Energy Balance and Breast Cancer Aspect (EBBA) study]. E2 was measured in daily saliva samples throughout an entire menstrual cycle. A clustered metabolic risk score [z metabolic syndrome (zMS); total cholesterol–high-density lipoprotein-cholesterol (HDLC) ratio, insulin resistance, total fat tissue, BP, and triglycerides] was defined. Linear regression and linear mixed models were used, and confounding factors were tested. Results: Physically active women had lower fat percentage (P_trend = 0.003) and HRs (P_trend = 0.003) than sedentary women. We estimated an increase in E2 of 1.27 pmol·L⁻¹ [95% confidence interval (CI), 0.06–2.47] for each 11.7 beats·min⁻¹ (1 SD) increase in HR, and this corresponds to the 7% change in mean concentration of E2 for the total group. Associations with E2 were also found for fat tissue, total cholesterol–HDLC ratio, insulin resistance, and triglycerides. A dose–response relationship was observed among the three levels of LPA and HR and zMS (P_trend = 0.03 for LPA; P_trend = 0.004 for HR). Women in the highest tertile of the clustered metabolic risk score had average salivary E2 profiles that were markedly higher, throughout the cycle, than those of the other groups, with a cycle peak-day difference in E2 of 22–28%. Conclusion: LPA and HR were associated with metabolic risk score, and this score was associated with daily level of E2, pointing to important biologic mechanisms operating between a sedentary lifestyle and an increased breast cancer risk. Key Words: LEISURE-TIME PHYSICAL ACTIVITY, PULSE, 17β-ESTRADIOL, CLUSTERED METABOLIC SCORE

Sedentary lifestyle and high levels of estradiol are factors associated with increased breast cancer risk (34). The biological mechanisms underlying the relation between physical activity and breast cancer risk are complex and have not been fully identified (18). In contrast, estradiol is known to be associated with increased

mitogenic and proliferative effect in breast cells (16) and has been identified as an important factor in the development and the prognosis of breast cancer (18). However, reports on the association between estrogens and breast cancer risk among premenopausal women are sparse, partly due to the complexity of measuring hormonal levels throughout a menstrual cycle. Interestingly, in a recent publication from the Nurses’ Health Study II (7), the risk of breast cancer was more than doubled among premenopausal women in the highest quartile of the follicular free estradiol level compared with women in the lowest quartile.

Even though the biological mechanisms that act in the association between physical activity and breast cancer risk are currently not fully outlined, there are several plausible mechanisms, including, among others, a suppressive effect of physical activity on ovarian steroid hormone production (21,23,25) and an effect on energy balance (12,18). The
evidence for an inverse relationship between physical activity and breast cancer is stronger for postmenopausal than for premenopausal women (34). However, many case–control (2,11) and cohort studies (19,37) among various populations and on different continents have observed a beneficial effect of physical activity on premenopausal breast cancer risk and on biological mechanisms important for breast cancer risk (22). The magnitude of the observed risk reduction has been, on average, between 20% and 40% for the most physically active women compared with the least active, and there is evidence for a dose–response relationship (18,28,34).

Moreover, physical activity is one of the few risk factors for breast cancer that can be modified; it is also a promising preventive measure for many other chronic diseases because physical activity improves the metabolic risk profile (18,38). In addition, breast cancer has been linked to metabolic components including serum lipids and insulin, blood pressure (BP), and tissue fat (35,36). In a cohort study, we demonstrated that low high-density lipoprotein-cholesterol (HDL-C) is a potential marker of increased breast cancer risk among overweight women (14). In the Norwegian Energy Balance and Breast Cancer Aspect (EBBA) study (14), we confirmed the hypothesis that low HDL-C may be associated with increased levels of 17β-estradiol (E2) throughout the menstrual cycle. Furthermore, in Poland, not that much westernized population yet and in a parallel study to our EBBA study, Jasienska et al. (23) observed habitual physical activity to be associated with lower levels of E2 throughout Polish women’s menstrual cycles.

Because physical activity assessment is complex, a need exists to include objective measures of activity and energy expenditure when elucidating plausible biological mechanisms related to physical activity, E2, and later breast cancer risk. In the current study, we have used the resting heart rate (HR) and a set of metabolic factors related to the variation in physical activity as objective measurements. The aim of the present study was therefore 1) to study how self-reported leisure-time physical activity (LPA) and HR are related to levels of E2 and with the metabolic profile among premenopausal women and 2) to investigate how a set of metabolic risk factors (fat tissue, BP[(systolic BP + diastolic BP) / 2], insulin resistance, triglycerides, and total cholesterol–HDL-C ratio) are associated with E2 throughout an entire menstrual cycle.

MATERIALS AND METHODS

Participants and study design. Women who participated in the cross-sectional EBBA study during 2000–2002 were recruited through local media campaigns. A total of 204 women, 25–35 yr, were included and met the following eligibility criteria: self-reported regular menstruation (normal cycle length: 22–38 d within the previous 3 months), no use of steroid contraceptives and no pregnancy or lactation over the previous 6 months, no history of gynecological disorders, and no chronic medical conditions (e.g., diabetes, hypo- or hyperthyroidism).

Ethical considerations. All participating women signed an informed consent form, and the study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Questionnaires. We used both self- and interviewer-administered questionnaires to collect general information, including education, reproductive history, previous use of hormonal contraceptives, and lifestyle habits (smoking, alcohol). Recall aids including a lifetime calendar were used. We collected dietary data on seven different week days during the menstrual cycle (days 3–6 and 21–23) using a precoded food diary developed for the present study population based on a validated precoded food diary (29). The average daily intake of energy and nutrients was computed using a food database and software system developed at the Department of Nutrition, University of Oslo, Norway (29).

LPA, HR, and metabolic risk factors. In the general questionnaire, we asked about LPA over the last year. Leisure time was recorded and graded from 1 to 4 as follows:

1 = low or sedentary activities, including reading, watching television, or other sedentary activities
2 = moderate activities, including walking, bicycling, or physical activities for at least 4 h a week
3 = hard activities, including exercises to keep fit for at least 4 h a week
4 = very hard activities, defined as regular hard training or exercise for competition several times per week.

The study participants made three subsequent visits in a fasting state during the collection period: first visit (days 1–5 of the menstrual cycle), second visit (days 7–12), and third visit (days 22–25). The participants met on the first day possible, after onset of menstrual bleeding, for the first visit with clinical examinations, including height, weight, waist and hip circumference, resting HR, BP, and fasting blood sampling. All clinical procedures and measurements were conducted by trained nurses at the Department of Clinical Research, University Hospital of North Norway (UNN), Tromsø, Norway, at a scheduled time (14).

HR and BP were measured three times (PROPAQ 104), sitting in a resting position, with the mean of the final two measurements used in the analyses.

Anthropometric measurements were taken with participants wearing light clothing and no footwear: Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg on an electronic scale. Waist circumference was measured in a horizontal line 2.5 cm above the umbilicus; hip circumference was measured at the largest circumference, both measured to the nearest 0.5 cm.

Around the time of the second visit, participants underwent a whole-body scan using dual energy x-ray absorptiometry (DEXA—DPX-L 2288, Lunar Radiation Corporation, Madison, WI, USA), which was operated by...
Our nurse; the percentage total fat tissue was estimated using standard Lunar software.

Blood samples were drawn after overnight fasting (14). Serum concentrations of glucose, triglycerides, total cholesterol, HDL-C, and E₂ were measured in fresh sera at the Department of Clinical Chemistry, UNN. Serum glucose was measured enzymatically by the hexokinase method, serum triglycerides were assayed by enzymatic hydrolysis with lipase, and serum cholesterol was determined enzymatically using cholesterol esterase and cholesterol oxidase, with HDL-C quantified by a direct assay using polyethylene glycol-modified enzymes and dextran sulfate. Finally, serum concentrations of insulin were measured at the Hormone Laboratory, Aker University Hospital, Oslo, by RIA using kits from Linco Research, Inc (St Charles, MO, USA) (14).

Saliva Hormone samples and analysis. Women collected daily saliva samples at home for one entire menstrual cycle preferentially in the morning. They started on the first day of bleeding, according to previously established collection protocols developed at the Reproductive Ecology Laboratory at Harvard University, USA (31).

E₂ concentrations were measured in daily saliva samples for 20 d (reverse cycle days −5 to −24) of the cycle using an ¹²⁵I-based radioimmunoassay (RIA) kit (#39100, Diagnostic Systems Laboratory, Webster, TX, USA), along with published modifications to the manufacturer’s protocol (20).

The sensitivity and inter- and intra-assay variability of E₂ have been described previously (13,14). Of the 4080 potential samples, improper collection or loss during the assay procedure resulted in a loss of 6.9% of daily E₂ samples for the analyses.

Before statistical analysis, all cycles were aligned to the day of ovulation based on the identification of the E₂ drop at the midcycle (day 0), which provides a reasonable estimate of the day of ovulation, according to published methods (31). The E₂ values for 20 consecutive days during each woman’s cycle, aligned on day 0, were used in data analyses. Satisfactory identification of the midcycle E₂ drop could not be made for 14 women, and their cycles were not aligned. Overall average salivary E₂ (mean E₂) was calculated for all 204 women, whereas additional indices were calculated for the 190 women with aligned cycles. The following E₂ indices were calculated: “mean E₂” (mean of day −10 to +9), “mean follicular E₂” (mean of day −7 to −1), and “mean luteal E₂” (mean of day 0 to +11).

Statistical analysis. To study E₂ concentrations in relation to physical activity, HR, and a clustered metabolic risk score, linear regression and linear mixed models were used (SAS version 9.1).

As only 10 participants reported that they performed group 4 (very hard) activities, in the analyses, we combined activity groups 3 and 4. Hence, the study population was divided into three groups of LPA (low, moderate, and high activity).

As indicator of insulin resistance, we used the homeostasis model assessment (HOMA) score, calculated as the product of fasting glucose concentration (mmol·L⁻¹) and fasting insulin concentration (µU·mL⁻¹) divided by the constant 22.5 (26).

To create clustered metabolic risk scores, we computed the Z score (standard score) for selected individual risk factor variables associated with metabolic profile, broadly based on the World Health Organization definition of the metabolic syndrome. The Z score is calculated by subtracting the sample mean from the individual score (raw score) and by dividing the difference by the sample standard deviation. It is negative when the raw score is below the sample mean and positive when the raw score is above the sample mean, and lower Z scores indicate a more favorable metabolic profile. HOMA score, fasting triglycerides, and insulin were logarithmically transformed when used in the Z score due to their skewed distribution. The Z scores of the individual risk factors were then summed to construct clustered risk scores. The five risk factors included in the main clustered risk score (z metabolic syndrome; zMS) were the ratio total cholesterol–HDL-C, the logarithm of the HOMA score, the percentage of total fat as estimated from the DEXA scan, the BP, and the logarithm of the triglyceride levels. In parallel, we calculated a second clustered risk score containing the same variables without the obesity component (zMS-O).

Age-adjusted linear regression analyses were used to study the associations of average salivary E₂ concentration (overall, in the follicular and luteal phases of the menstrual cycle) and different variables related to the metabolic profile. We used a linear mixed model for repeated measures to study salivary E₂ concentrations throughout the menstrual cycle in relation to HR, level of LPA, and clustered risk scores. Different covariance structures were explored, and the results using a heterogeneous Toeplitz method are presented. Dunnett method was used for multiple comparisons, with examination of residuals. Age was included as a covariate in the final models. In addition, adjustment for birth weight, body mass index (BMI), energy intake, smoking, alcohol, previous use of hormonal contraceptives, education, and age at menarche gave similar estimates and are not presented. Possible interactions were studied.

E₂ measurements at the start and end of the cycles have higher coefficients of variation and higher rates of missing as a result of variation in cycle length; we therefore included E₂ measurements from day of cycle −10 to +9. Sample size estimation has shown that a sample size of 20–25 is sufficient to detect significant differences in indices of ovarian function between groups.

RESULTS

The participating 204 healthy women of reproductive age were, on average, 30.7 yr; 15.7% reported low LPA, 59.3%
reported moderate LPA, and 25.0% reported high LPA. Descriptive analyses were stratified by reported LPA (Table 1). Women with a high level of reported LPA had lower total fat percentage (P_trend = 0.003) and lower HR (P_trend = 0.003) and tended to have a lower total cholesterol–HDL-C ratio (P_trend = 0.09) and a higher HDL-C (P_trend = 0.12) than women with a more sedentary level of LPA (Table 1). There were no statistically significant differences in overall average salivary hormones or HOMA score between the three groups.

We studied estimated changes in overall average, follicular, and luteal salivary E2 concentrations by changes in the selected metabolic risk factor variables (Table 2). We estimated that an increase (of 1 SD) in total fat tissue, glucose (mmol L⁻¹) 114.5 (10.7) 112.7 (10.4) 113.8 (13.3) 0.90
Diastolic blood pressure (mm Hg) 71.4 (8.95) 70.8 (7.39) 70.8 (8.91) 0.81
Saliva hormone concentrations (pmol L⁻¹)
Overall average Estradiol 17.9 (8.93) 17.2 (8.86) 17.1 (8.90) 0.003
Overall average Progesterone 121.2 (61.1) 129.3 (72.4) 137.8 (62.7) 0.28
Estradiol follicular index 18.7 (9.63) 16.9 (8.70) 19.7 (8.86) 0.45
Estradiol luteal index 19.0 (9.54) 18.2 (9.92) 19.7 (8.98) 0.66
Serum concentrations
Total cholesterol: HDL-cholesterol ratio 3.17 (0.71) 3.02 (0.81) 2.87 (0.83) 0.09
HDL-cholesterol (mmol L⁻¹) 1.45 (0.29) 1.55 (0.32) 1.57 (0.39) 0.12
Total cholesterol (mmol L⁻¹) 4.45 (0.67) 4.49 (0.77) 4.34 (0.88) 0.42
Fasting triglycerides (mmol L⁻¹) 0.90 (0.55) 0.86 (0.90) 0.87 (1.37) 0.93
Fasting glucose (mmol L⁻¹) 5.06 (0.54) 5.06 (0.62) 4.92 (0.42) 0.20
Insulin (µU mL⁻¹) 13.3 (10.2) 11.7 (6.35) 12.0 (7.58) 0.55

**Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Overall Average E2 Change Mean (SD)</th>
<th>Average E2 Change (Follicular Index)</th>
<th>Average E2 Change (Luteal Index)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat tissue (%)</td>
<td>34.2 (7.8)</td>
<td>1.43 (0.23, 2.63)*</td>
<td>1.40 (0.14, 2.66)*</td>
<td>1.02 (−0.34, 2.38)</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol L⁻¹)</td>
<td>5.02 (0.56)</td>
<td>0.84 (−0.39, 2.06)</td>
<td>0.93 (−0.33, 2.2)</td>
<td>0.44 (−0.90, 1.80)</td>
</tr>
<tr>
<td>Insulin (µU mL⁻¹)</td>
<td>12.0 (7.35)</td>
<td>1.00 (−0.21, 2.21)</td>
<td>0.82 (−0.46, 2.10)</td>
<td>1.34 (−0.02, 2.72)</td>
</tr>
<tr>
<td>HDMA score</td>
<td>2.67 (1.71)</td>
<td>1.25 (0.03, 2.46)*</td>
<td>1.07 (−0.21, 2.35)</td>
<td>1.55 (0.19, 2.93)*</td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>113.3 (11.2)</td>
<td>0.12 (−1.10, 1.34)</td>
<td>0.07 (−1.23, 1.37)</td>
<td>0.02 (−1.37, 1.41)</td>
</tr>
<tr>
<td>DBP</td>
<td>92 (9.01)</td>
<td>−0.11 (−1.33, 1.10)</td>
<td>−0.15 (−1.44, 1.15)</td>
<td>−0.32 (−1.70, 1.06)</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total C-HDL-C ratio</td>
<td>3.0 (0.8)</td>
<td>2.46 (1.26, 3.66)**</td>
<td>2.29 (1.01, 3.57)**</td>
<td>2.35 (0.97, 3.72)**</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.77 (0.39)</td>
<td>1.62 (0.40, 2.85)**</td>
<td>1.49 (0.23, 2.75)*</td>
<td>1.60 (0.25, 2.96)*</td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>69.0 (11.5)</td>
<td>1.27 (0.06, 2.47)*</td>
<td>1.29 (0.03, 2.55)*</td>
<td>1.31 (−0.04, 2.66)</td>
</tr>
</tbody>
</table>

**Notes:**

- **Numbers may vary as a result of missing information.**
- **Linear regression or χ² test.**
- **Blood sampling first visit (days 1–5).**

**Table 1. Characteristic of the study population by level of self-reported leisure time activity among premenopausal women: means (SD)* or proportions (from the Norwegian EBBA study; n = 204).**

**Table 2. Estimated changes in salivary overall average E2 with 95% CI by 1 SD increase in the subcomponents of the clustered metabolic risk score (n = 204).**

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HOMA score, total cholesterol–HDL-C ratio, triglycerides, and HR was associated with an age-adjusted increase in E₂ concentrations (Table 2). The mean daily saliva concentration of E₂ throughout the menstrual cycle was 17.9 pmol·L⁻¹ (SD 8.8) (data not presented). An age-adjusted increase in the overall level of E₂ of 1.27 pmol·L⁻¹ [95% confidence interval (CI), 0.06–2.47] was observed for each 11.7 beats·min⁻¹ (1 SD) increase in HR, and this corresponds to the 7% (1.3 of 17.9 pmol·L⁻¹) change in mean overall concentration of E₂ for the total group. For each 0.8 (1 SD) increase in the total cholesterol–HDL-C ratio, the mean age-adjusted increase in overall E₂ is 2.46 pmol·L⁻¹ (95% CI, 1.26–3.66), which equals a 13.7% change in mean overall concentration of E₂ for the total group.

Figure 1A shows the association between the clustered metabolic score (zMS) and the LPA. An inverse dose–response relationship was observed ($P_{\text{trend}} = 0.03$). Likewise, Figure 1b shows that zMS is directly related to HR in a dose-dependent manner ($P_{\text{trend}} = 0.004$).

We examined the average E₂ concentrations by cycle day throughout the whole menstrual cycle by tertile of HR (Fig. 2A; $P$ between levels = 0.15) and at the three levels of LPA (Fig. 2B; $P$ between levels = 0.48), without finding a clear pattern, even when stratifying by birth weight (data not shown). No interaction was found between HR and day of E₂ measurement ($P = 0.89$) or level of activity and day of E₂ measurement ($P = 0.18$).

In contrast, when we examined the E₂ concentration by cycle day throughout the whole menstrual cycle in tertiles of the clustered risk score, zMS, a clear pattern was observed; women in the highest tertile of the zMS had age-adjusted average salivary E₂ profiles that were markedly higher, throughout the cycle, than those of the other groups (Fig. 3). Using a linear mixed model for repeated measures, we examined how, in women in the group of the highest tertile of the zMS, the average E₂ concentration by cycle day differed from that in the other groups of women described, and we observed significant age-adjusted differences for all comparisons (Fig. 3; age-adjusted $P$ values:...
tertiles III–I, \(P = 0.001\); tertiles III–II, \(P < 0.001\). The same pattern was observed when the obesity component was removed (i.e., zMS-O, not shown).

When studying the peak day (the day before the drop day of the menstrual cycle), we observed that the mean peak-day levels of \(E_2\) in tertiles of zMS were as follows (Fig. 3): lowest tertile 28.7 pmol L\(^{-1}\), medium tertile 26.3 pmol L\(^{-1}\), and highest tertile 36.6 pmol L\(^{-1}\) \(\left(P_{\text{trend}} = 0.001\right)\), which corresponds to a 22% and a 28% difference between the highest tertile of the clustered metabolic risk score and the lowest and medium tertiles, respectively.

**DISCUSSION**

Among 204 healthy premenopausal women, we observed that those women with high LPA and women with lower HR had a more favorable clustered metabolic risk score, zMS, with a dose–response relationship than those of inactive women. In addition, we observed that this clustered risk score of metabolic factors was strongly associated with the daily level of free biologically active \(E_2\) throughout an entire menstrual cycle, with a cycle peak-day difference of 22–29% between the tertiles of zMS.

The observation that healthy women of reproductive age in the current study showed a clear association between LPA and zMS and that zMS was associated to levels of estradiol is of great interest and support previously hypothesized biological mechanisms operating between physical activity and breast cancer (14,21,24). Furthermore, western lifestyle, characterized by physical inactivity, is also associated with obesity and metabolic imbalance, including unfavorable lipids, high BP, and insulin resistance—factors that are also associated with increased breast cancer risk (15,18,30,37). Additionally, several studies have observed a stronger protective effect of physical activity among lean women in comparison with normal-weighted women (21,37). Furthermore, several recent studies provide support for the role of physical activity in the prevention of the metabolic syndrome (1,5). Randomized controlled trials have shown that exercise training has a mild or a moderately favorable effect on many metabolic risk factors (27), whereas others have shown less association after controlling for obesity (17). Moreover, the metabolic syndrome is a cluster of risk factors that predisposes individuals to type 2 diabetes, and individuals with metabolic syndrome have an increased risk of all-cause mortality (27).

Recently, the association between metabolic syndrome and its components (especially insulin) has been observed to predispose individuals to breast cancer. Hence, if physical activity can improve the metabolic risk profiles (3,38), it might indirectly reduce breast cancer risk. Importantly, we have recently pointed to sex hormones and insulin as important pathways toward the development of breast cancer (13). In the current study, we observed an association between the clustered metabolic risk score and the level of LPA, but the association was not there for all the single factors alone. There could be not only an additive effect but also a multiplicative effect when several metabolic risk factors are put together in a cluster score based on biological effects. Another explanation may be that a clustered risk score may compensate for fluctuations in the single risk factors, or there could be less error variation in the clustered risk score compared with each single risk factor. However, this observation underlines the fact that physical activity may influence several factors often hypothesized (14,21), which independently and/or together influence the level of \(E_2\) and then lead to an increase in breast cancer risk.

In our study, the clustered risk score was positively associated with daily levels of \(E_2\) during the entire menstrual cycle: A high clustered metabolic risk score gave a high level of \(E_2\). Interestingly, this observation was similar when the obesity component was excluded from the metabolic risk score, indicating that the protective effect of physical activity is not entirely mediated by changes in adiposity also supported by others (7). In a recent study, Ekelund et al. (6) observed that an increase in physical activity is associated with reduced metabolic risk, independent of changes in fitness and fitness. However, in another study, Campbell et al. (4) found that a 12-wk aerobic exercise training intervention improved aerobic fitness and body composition but did not alter the urinary estrogen metabolites in premenopausal women. These
results regarding metabolites cannot be compared with our measurements of the free biologically active E₂ throughout
the menstrual cycle.

Despite the HR not showing any clear pattern with level of E₂ throughout the menstrual cycle, when analyzing it as a single factor it clearly is associated with a clustering of metabolic factors in the same way as leisure-time activity. Previous studies have shown that HR has a clear association both with fitness and leisure-time activity. These findings underline the role of HR as an objective measurement in clinical studies both in relation to metabolic profile and leisure-time activity (38).

Current evidence supports an inverse relationship between physical activity and breast cancer risk (18), and one of the biologic mechanisms proposed to explain the protective effect is reduced exposure to E₂ (2) based on the suppressive effect of physical activity on ovarian steroid hormones (18,23,25). Endurance training as well as general physical activity has been reported to give low levels of E₂ (23,33); in a recent parallel study, a strong association was observed between habitual physical activity and level of E₂ among premenopausal women in Poland (23). In addition, when stratifying by birth weight, Polish women who were relatively fat babies did not exhibit ovarian suppression in response to moderate levels of physical activity at adulthood in contrast to women who were skinnier babies (22). This suggests that ovarian responsiveness may depend on conditions during fetal life. In comparison, in the present study among Norwegian women, we observed that women with the most unfavorable metabolic profile (highest tertile zMS) had higher level of E₂ throughout the menstrual cycle corresponding to a higher HR and lower leisure activity compared with other women. This result suggests that ovarian responsiveness also may interact with normal physiology throughout adulthood of importance for premenopausal E₂ levels throughout an entire menstrual cycle. In the present study, we did not observe a clear association between level of E₂ and level of LPA or between level of E₂ and level of HR as a single factor, even when stratifying by birth weight. These findings suggest that Norwegian and Polish women may have different ovarian responsiveness to physical activity or that other factors may have an influence.

The evidence for an inverse relationship between physical activity and breast cancer is stronger for postmenopausal than for premenopausal women (34). The women in our study were premenopausal, and there is no clear reason why physical inactivity is often less strongly related to increased risk of breast cancer among premenopausal women. The main source of E₂ in premenopausal women is the ovaries, although it is also produced in adipose tissue. For postmenopausal women, the main site for E₂ production is adipose tissue. Thus, physical activity may influence premenopausal and postmenopausal breast cancer risk differently through different physiological and hormonal mechanisms, as seen with obesity (9). To elucidate in detail the influence of physical activity, it might be necessary to do subgroup analyses of birth characteristics, obesity, and parity, which more often is performed and underlined, as well as different aspects of the activity: type, intensity, frequencies, duration, and age at exposure (10).

Our study has several strengths, including daily saliva sampling for estimation of daily E₂ concentrations throughout an entire menstrual cycle. We used well-developed and validated methods and assays to characterize the women’s exposure to free, biologically active, ovarian steroids and performed comparisons of levels by aligned cycle days (31). This recommended approach of examining all women at the same time during the menstrual cycle is rarely achieved because of its logistic complexity (24). However, it is a major strength of this study, given the large intracycle fluctuations in levels of ovarian hormones and the wide interindividual variation in cycle length in menstruating women. Furthermore, salivary levels of E₂ were quite stable within participants over time (8). In addition, one trained nurse traced all the participants in the study and met them in the same clinical research department at a university hospital. This standardization enhanced the quality of our data and allowed us to sample all clinical variables within the same narrow frame of the cycle for each participant by using uniform procedures. To limit any potential influence of season, women did not participate during the winter months when there is no daylight (December and January). When adjusted for potential confounders such as age at menarche, parity, birth weight, energy intake, and use of alcohol, smoking, and previous oral contraceptives, we observed only small modifications of the interrelationships of clustered metabolic risk score and level of E₂, which did not change the result.

Assessment of physical activity is difficult, and self-reported physical activity is less precise than objective measurements of physical activity. In addition, we used recorded LPA data over the last year, so the effect of physical activity in different periods of life on E₂ has not been examined in the current study. However, the self-reported LPA questionnaire that we used has previously been validated (32,39), found to be associated with HR and to be a valid measure of physical fitness; 5869 women, 20 to 49 yr, who both sustained high levels of physical activity and changed from sedentary to higher levels of physical activity, relative to sedentary women, improved their metabolic risk profiles (lipids, BMI) and HR (38), and the level of LPA and physical fitness and HR and physical fitness were positively related (32). We used information about LPA and not total activity, which includes habitual and occupational activity.

CONCLUSION

In conclusion, our data suggest that higher physical activity and lower HR are associated with a healthier
metabolic risk profile, which furthermore is positively associated with levels of E₂ throughout the menstrual cycle among healthy premenopausal women. These associations point to possible biological pathways operating in the inverse relationship between physical activity and breast cancer, but the interactions of these possible pathways are complex. Physical activity may influence the carcinogenesis of breast cancer by having a suppressive effect on ovarian steroid hormones as well as through reduced exposure to insulin and by reducing obesity.

REFERENCES


