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Energy balance and breast cancer risk: a prospective cohort study

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Key words: body mass index, breast neoplasms, energy balance, energy intake, physical activity

Summary

While there is evidence that breast cancer risk is positively associated with body mass index (in postmenopausal women) and energy intake and inversely associated with physical activity, few studies have examined breast cancer risk in association with energy balance, the balance between energy intake and expenditure. Therefore, in the cohort study reported here, we studied the independent and combined associations of vigorous physical activity, energy consumption, and body mass index (BMI), with breast cancer risk. The investigation was conducted in 49,613 Canadian women who were participants in the National Breast Screening Study (NBSS) and who completed self-administered lifestyle and food frequency questionnaires between 1980 and 1985. Linkages to national mortality and cancer databases yielded data on deaths and cancer incidence, with follow-up ending between 1998 and 2000. During a mean 16.4 years of follow-up, we observed 2545 incident breast cancer cases. Due to exclusions for various reasons, the analyses were based on 40,318 subjects amongst whom there were 1673 incident cases of breast cancer. Participation in vigorous physical activity and body mass index were not independently associated with breast cancer risk in the total cohort. A statistically significant positive trend was observed, however, between energy intake and breast cancer risk ($P_{trend} = 0.01$). Although there was some variation in risk associated with vigorous physical activity, and BMI when the analyses were stratified by menopausal status, these interactions were not statistically significant. The interaction between menopausal status and energy intake, however, was of borderline statistical significance ($P_{interaction} = 0.06$), with a statistically significant increased risk of breast cancer associated with highest versus lowest quartile of energy intake among premenopausal women (Hazard Ratio [HR] = 1.45, 95% confidence interval [CI] = 1.13–1.85, $P_{trend} = 0.001$). There was evidence of an increased risk of breast cancer associated with a relatively high body mass index among postmenopausal women in the highest quartile level of energy intake (Hazard Ratio [HR] = 1.72, 95% confidence interval [CI] = 1.01–2.93, $P_{trend} = 0.05$). In addition, there was evidence of an increased risk of breast cancer among premenopausal, physically inactive, overweight/obese women who consumed ≥1972 kcal/day compared to physically active normal weight women who consumed <1972 kcal/day (HR = 1.60, 95% CI = 1.08–2.37). Our data suggest that obese premenopausal women with relatively high energy intake may be at increased risk of breast cancer. In addition, energy imbalance, represented by a relatively high energy intake, lack of participation in vigorous physical activity, and a relatively high body mass index, may be associated with increased breast cancer risk, particularly among premenopausal women.

Background

Energy imbalance results in a change in body energy stores due to an excess or deficit of energy intake in comparison to energy expenditure [1]. Energy intake, body size (the primary determinant of energy expenditure), and physical activity (the major determinant of variation in energy expenditure between individuals of similar age and sex [1]), are important components of energy balance. There is evidence from animal studies that disturbances in energy balance might influence breast cancer risk via alterations in the production of ovarian steroid hormones [1,2], particularly estradiol, which has been shown to be positively associated with breast cancer risk [3,4]. Each of these components of energy balance (namely, energy intake, physical activity, and body mass index) has been examined separately in relation to breast cancer risk. Specifically, low energy consumption and relatively high levels of physical activity have been shown in some studies to be associated with decreased breast cancer risk [5–11], and a relatively high body
mass index has been associated with increased risk, particularly among postmenopausal women [11–13]. There is also some evidence that energy intake [14,15] and body mass index [15] modify the association between physical activity and breast cancer. To our knowledge, however, few studies have attempted to examine these various components of energy balance simultaneously in relation to breast cancer risk [14,15]. Such analyses might shed light on the incremental effect of one factor given levels of one or both of the other two. In view of the paucity of such data, we examined the independent and combined associations of physical activity, energy intake, and body mass index with risk of subsequent breast cancer.

Methods

Study population

The study, which has been described in detail elsewhere [16], was conducted amongst participants in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer [17]. A total of 89,835 women aged 40–59 years with no history of breast cancer were recruited into the trial between 1980 and 1985.

Questionnaires

At recruitment into the study, participants completed a self-administered questionnaire that sought information on demographic characteristics, lifestyle factors, menstrual and reproductive history, and use of oral contraceptives and replacement estrogens. Starting in 1982 (that is after some participants had completed their scheduled visits to the screening centers), a self-administered food frequency questionnaire (FFQ) was distributed to all new attendees at all screening centers and to women returning to the screening centers for rescreening [18]. Completed dietary questionnaires were received from 49,613 women. The FFQ contained questions on the frequency of consumption and usual portion size of 86 food items. Photographs of various portion sizes were included to assist participants with quantification of intake. In addition, women were queried about vigorous physical activity using a question that asked ‘On an average weekday and weekend day, how much time did you spend on the following activities during the past one month: vigorous exercise (jogging, running, brisk walking, vigorous sports, bicycling, and heavy housework)?’

Calculation of energy intake, physical activity and body mass index

Data from the food frequency questionnaire were used to calculate daily total energy intake, and intakes of various nutrients and alcohol, using a database developed by modifying and expanding food composition tables from the United States Department of Agriculture to include typically Canadian foods [19,20]. Self-reported vigorous physical activity was defined as the number of hours per day of participation in the activities listed above. Body mass index was defined as weight (kg)/height (m²); height and weight were measured at baseline [21]. Height and weight were measured the nurses who did the initial examinations (i.e., at the time of enrollment and randomization in the trial) and who were instructed in the process by the center coordinators.

Ascertainment of incident breast cancer cases and deaths

Cases were women who were diagnosed during follow-up with incident breast cancer, ascertained by means of computerized record linkage to the Canadian Cancer Database. Deaths from all causes were ascertained by means of record linkage to the National Mortality Database and this information was utilized as a censoring variable. Both of these databases are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality to December 31, 2000 for women in Ontario, to December 31, 1998 for women in Quebec, and to December 31, 1999 for women in other provinces in Canada. Among the women for whom dietary data were available, we identified 2545 incident breast cancers.

Statistical analysis

Of the 49,613 women with dietary data, we excluded women with extreme energy intake values (at least three standard deviations above or below the mean value for log10 calorific intake; i.e., kcal/day < 730 or > 5389) (n = 502), those who were missing information on body mass index (n = 494), and women for whom information on participation in physical activity was missing (n = 5864) or extreme (at least three standard deviations above the mean log10 value for hours per day of vigorous physical activity; i.e., > 2.72 h/day) (n = 3085). These exclusions (not mutually exclusive) left 40,318 women available for analysis, amongst whom there were 1673 incident cases of breast cancer.

Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between breast cancer risk and participation in vigorous physical activity (any versus none and quartiles of duration in minutes/day), energy intake (in kcal/day, categorized by quartiles), and body mass index (categorized as normal (< 25 kg/m²), overweight (25–29 kg/m²), or obese (≥30 kg/m²)). For these analyses, study participants were considered at risk from their date of enrollment until the date of diagnosis of their breast cancer, termination of follow-up (the date to which cancer incidence data were available for women in the corresponding province) or death, whichever occurred.
earlier. Multivariate models included the variables listed in the footnote of Table 2. To test for trend in the categorical variables of interest, study participants were assigned the median value of their category, and the resulting variable was fitted as a continuous variable in the regression models; the statistical significance of the coefficients were evaluated using the Wald test [22]. We examined the main effects of the associations as well as their two- and three-way interactions. Stratum-specific multivariate models included the variables listed in the footnotes to Tables 3–5. Tests for interaction were based on likelihood ratio tests comparing models with and without product terms representing the variables of interest. Use of the lifetest procedure in SAS showed that the proportional hazards assumption was met in this dataset. All analyses were performed using SAS version 9 (SAS Institute Cary, NC).

**Results**

The average duration of follow-up for cohort members was 16.4 years, corresponding to a total of 660,110 person-years of follow-up. The mean (± SD) age at diagnosis for the cases was 59.6 (± 7.4) years. For the cohort as a whole, the mean (± SD) energy intake, minutes per day of vigorous physical activity, and body mass index at baseline were 2,064 (± 639) kcal/day, 42.6 (± 40.4) min/day, and 24.8 (± 4.4) kg/m², respectively. Compared to non-cases, breast cancer cases were slightly older at baseline, were less likely to have ever used oral contraceptives, and were more likely to have a history of breast disease, a family history of breast cancer, and to be nulliparous (Table 1). No appreciable difference between cases and non-cases was observed for mean body mass index, mean energy intake, participation in vigorous physical activity, smoking and alcohol consumption, use of hormone replacement therapy, age at menarche, parity, or menopausal status.

Table 2 shows that in age-adjusted models, there were no associations between body mass index and risk of breast cancer. There was, however, an inverse trend of borderline statistical significance with duration of vigorous physical activity (Ptrend = 0.05). In addition, women consuming ≥2406 kcal/day were at greater risk of breast cancer compared to women who consumed <1630 kcal/day (HR = 1.18, 95% CI = 1.02–1.36, Ptrend = 0.02). After multivariate adjustment (including mutual adjustment of each factor for the other components of energy balance), the hazard ratios for energy intake remained essentially the same, but the hazard ratios for vigorous physical activity became essentially null.

Among premenopausal women, the highest versus lowest quartile level of energy intake was associated with a 45% increase in risk (HR = 1.45, 95% CI = 1.13–1.85, Ptrend = 0.001), but there was no association between energy intake and risk among postmenopausal women (χ²(3) = 7.59, Pinteraction = 0.06) (Table 3). In contrast, while there was no association between body mass index and breast cancer risk among premenopausal women, a positive trend was observed among postmenopausal women (Ptrend = 0.08). Upon formal testing, however, the test for interaction between menopausal status and body mass index was not statistically significant (χ²(2) = 1.91, Pinteraction = 0.38). There was no evidence of effect modification of the association between physical activity and breast cancer risk by menopausal status (Table 3).

Among premenopausal women there was evidence of some variation in breast cancer risk with BMI when the analyses were stratified (separately) by participation in vigorous physical activity (any versus none) and by quartiles of energy intake. However, none of the point estimates was statistically significant and the associated tests for interaction were not statistically significant (χ²(3) = 2.88, P = 0.24 and χ²(6) = 6.69, P = 0.35, respectively) (Table 4). Among postmenopausal women, although there was some variation in the risk of breast cancer associated with BMI across quartiles of energy intake, and in particular, increases in risk in obese women with relatively low and relatively high energy intake, the interaction between energy intake and body mass index was not statistically significant (χ²(6) = 10.22, P = 0.12) (Table 4). The association between body mass index and breast cancer risk among postmenopausal women did not differ between strata defined by participation in vigorous physical activity (Table 4).

Table 5 shows breast cancer risk for combined levels of body mass index, energy intake, and participation in

<table>
<thead>
<tr>
<th>Energy balance and breast cancer risk</th>
<th>Non-cases</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td>38,645</td>
<td>1673</td>
</tr>
<tr>
<td>Mean age at baseline in years (SD)</td>
<td>48.5 (5.6)</td>
<td>49.5 (5.7)</td>
</tr>
<tr>
<td>Mean body mass index (SD)*</td>
<td>24.8 (4.4)</td>
<td>24.8 (4.2)</td>
</tr>
<tr>
<td>Mean energy intake (kcal/day)</td>
<td>2063</td>
<td>2095</td>
</tr>
<tr>
<td>Vigorous physical activity (% any)</td>
<td>71.1</td>
<td>68.8</td>
</tr>
<tr>
<td>Mean duration of vigorous physical activity (min/day)*</td>
<td>57 (33)</td>
<td>55 (32)</td>
</tr>
<tr>
<td>Alcohol consumption (% ever drinker)</td>
<td>26.3</td>
<td>26.1</td>
</tr>
<tr>
<td>Smoking history (% ever smoker)</td>
<td>48.6</td>
<td>49.7</td>
</tr>
<tr>
<td>Oral contraceptive use (% ever)</td>
<td>59.6</td>
<td>55.3</td>
</tr>
<tr>
<td>HRT (% ever)*</td>
<td>47.2</td>
<td>46.8</td>
</tr>
<tr>
<td>History of breast disease (% yes)</td>
<td>15.1</td>
<td>20.4</td>
</tr>
<tr>
<td>Family history of breast cancer (% yes)</td>
<td>31.6</td>
<td>39.4</td>
</tr>
<tr>
<td>Age at menarche (% ≥ 12 years)</td>
<td>59.0</td>
<td>58.1</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>14.9</td>
<td>16.8</td>
</tr>
<tr>
<td>Mean age at 1st live birth (SD)</td>
<td>24.3 (4.7)</td>
<td>24.9 (4.8)</td>
</tr>
<tr>
<td>Postmenopausal at baseline (%)</td>
<td>43.1</td>
<td>44.7</td>
</tr>
</tbody>
</table>

*BMIm = Body mass index (kg/m²).
*Among women who participated in vigorous physical activity.
*HRT = hormone replacement therapy; among postmenopausal women only, as recorded at baseline.
*Among parous women.

Table 1. Baseline characteristics of the NBSS study population by outcome
vigorous physical activity stratified by menopausal status. Among premenopausal women, those who were physically inactive, overweight/obese, and had a relatively high energy intake had a 60% increased risk of breast cancer compared to normal weight, physically active women with relatively low energy intake (95% CI = 1.08–2.37). This association was not observed among postmenopausal women (HR = 1.12, 95% CI = 0.83–1.16).

Discussion

In the prospective study reported here, there was a statistically significant positive association between energy intake and breast cancer risk, but no association between body mass index or participation in vigorous physical activity and breast cancer risk over a 16 year follow-up period in the total study population. There was evidence that risk was positively associated with energy intake among premenopausal women and that risk was positively associated with body mass index among postmenopausal women in the highest quartile of energy intake. Furthermore, there was some evidence of variation in risk according to combined levels of physical activity, energy intake, and body mass index among premenopausal women. Specifically, premenopausal physically inactive overweight/obese women who had a relatively high caloric intake were at increased risk of breast cancer compared to that for premenopausal women who undertook vigorous physical activity, were relatively lean, and who had relatively low caloric intake.

Total energy intake has been shown to be positively associated with mammary cancer in mice [23] and there is evidence of an increased risk of breast cancer associated with relatively high energy consumption among humans [24]. In addition, there is evidence from animal studies that calorie restriction is associated with a reduction in the occurrence of spontaneous mammary tumors [25], tumor multiplicity, and tumor burden [26]. A majority of the cohort studies of calorie restriction that have been conducted in humans also tend to support a beneficial association with breast cancer risk [5–8,27,28]. Of the four that focused on the effects of the war-time famine on breast cancer risk in Norway [6,7] and the Netherlands [27,28], two [6,7] showed reductions in risk with exposure to calorie restriction, one [28] showed no association, and one [27] showed a positive association. In addition, the two studies that examined the association between anorexia nervosa prior to age 40 and subsequent risk of breast cancer both showed reductions in risk [5,8]. However, these studies did not collect information on individual energy intake, and given the specificity of the study populations, these results cannot be directly compared to the findings.
presented here. In addition, these studies were unable to account for differences in physical activity and body size, important determinants of total energy intake [1].

Variations in energy expenditure are largely determined by physical activity [1]. Intervention studies [29,30] have shown inverse associations between physical activity and ovarian steroids in postmenopausal women, thereby supporting a possible inverse association between physical activity and breast cancer risk. While previous epidemiologic studies of physical activity and breast cancer have yielded mixed results, the majority supports an inverse association [10], in contrast to our finding of no association in the overall study population. Differences in study findings may be due, in part, to the use of different methods for measuring and categorizing physical activity [31].

Body size, which affects the amount of energy required for resting metabolic activity and physical activity, is a component of energy balance [1]. The relationship between body mass index and breast cancer has been examined in a number of cohort studies [12]. In contrast to previous cohort studies [12,13,32], we found no association between BMI and breast cancer risk among premenopausal women. In keeping with the literature, however, which supports a positive association [15,33–41] between body mass index and breast cancer risk among postmenopausal women, we observed a 26% increased risk for obese versus normal weight postmenopausal women, although this finding was not statistically significant. The increased risk associated with obesity among postmenopausal women is consistent with evidence that obesity is associated with higher serum estrogen concentrations in postmenopausal women [42,43]. Given evidence that physical activity is inversely associated with serum estrogen levels [29], we examined whether physical activity further modified the association between body mass index and breast cancer risk. While we found that while obese postmenopausal women who did not participate in vigorous physical activity were at slightly higher risk of breast cancer than obese postmenopausal women who participated in any vigorous physical activity, the difference was not statistically significant, suggesting that given BMI, physical activity may not have a strong impact on breast cancer risk among postmenopausal women.

Dirx et al. [14], Patel et al. [44], and Malin et al. [15] conducted analyses of physical activity stratified by energy intake. In keeping with our observation of no

<table>
<thead>
<tr>
<th>Menopausal status at baseline</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b818/327,994</td>
<td>b662/2244,616</td>
</tr>
</tbody>
</table>

**Vigorous physical activity**

- None: 1.00
- Any: 0.91

**Vigorous physical activity (min/day)**

- 0–30: 1.02
- 31–60: 0.88
- >60: 0.87

**Energy intake (kcal/day)**

- <1630: 1.00
- 1630–1978: 1.12
- 1979–2405: 1.41

**Body mass index (kg/m²)**

- <25: 1.00
- 25–29: 1.11
- ≥30: 1.01

| p for interaction | 0.60 | 0.78 | 0.38 |

**Table 3. Adjusted hazard ratios and 95% CIs for the association between participation in vigorous physical activity, energy intake, and body mass index and risk of breast cancer stratified by menopausal status**

- Adjusted for age (time to event variable), alcohol (zero plus three levels), smoking history (never, former, current), use of oral contraceptives (ever versus never), use of hormone replacement therapy (ever versus never), age at menarche (<12, 12, 13, >13), parity (0, 1–2, 3–4, >4), age at first live birth (<25, 25–29, ≥30), family history of breast cancer (yes/no), history of breast disease (yes/no), study center, and randomization group.
- Number of cases/person-years.
- Also adjusted for energy intake (quartiles) and BMI.
- Also adjusted for participation in vigorous physical activity (any versus none) and BMI.
- Also adjusted for participation in vigorous physical activity (any versus none) and energy intake (quartiles).
interaction between physical activity and energy intake (data not shown), Patel et al. [44], in an analysis of data from the American Cancer Society Cancer Prevention Study II (CSP-II), a prospective study in the United States (1420 incident cases), observed no interaction between recreational physical activity and caloric intake.
(p-interaction = 0.96) among postmenopausal women. Dirx et al. [14], in a prospective study in the Netherlands (1208 incident cases), found no association between duration of recreational physical activity among postmenopausal women in the lowest quintile level of energy intake, but they did observe inverse trends among postmenopausal women in the upper four quintile levels of intake. Malin et al. [15], in a case-control study conducted in Shanghai, observed a 4.7-fold increased risk in postmenopausal women who did not participate in adult exercises/sports and who had a BMI > 25 kg/m², and a 2.7-fold increased risk in postmenopausal women who did not participate in adult exercises/sports and who were in the highest quartile level of energy intake. These studies each differed from ours in that age at baseline was lower in our study population, and they also differed from ours (and each other) with respect to categorization of energy intake and duration of physical activity [14,15,44]. We found no evidence of effect modification of the association between caloric intake (using the cut points indicated by Patel et al. [44]) and breast cancer risk by quartiles of duration of physical activity (derived from the distribution of duration of physical activity in our study population). Likewise, we examined the association between duration of physical activity, using the cut points indicated by Dirx et al. [14], and breast cancer risk by quintile levels of energy intake (based on energy intake in our study population, given that Dirx et al. [14] did not provide information on cut points used in their analysis) among postmenopausal women. In contrast to Dirx et al. [14], we found no association between duration of physical activity and breast cancer risk among any of the strata of energy intake (quintile levels) (data not shown). The differences between our results and those of Dirx et al. [14] may be due, in part, to differences in energy intake between these study populations.

McKeown-Eysen proposed that a metabolic profile that reflected a combination of risk factors associated with an increased risk of cancer (obesity, Western diet, low physical activity) may provide a growth-promoting environment for cells, particularly neoplastic cells, possibly through influences on insulin resistance [45]. Given evidence that hyperinsulinemia is associated with increased breast cancer risk [46,47], it is plausible that this metabolic profile has a greater influence on cancer risk than do the individual effects of body size, obesity, or physical activity [45]. The combined effects of energy intake, BMI, and physical activity were investigated in two recent studies [14,15]. Dirx et al. [14] examined the interaction between energy intake and recreational physical activity and breast cancer risk among postmenopausal women stratified by BMI, as part of a case-cohort analysis using data from the Netherlands Cohort Study (1208 incident cases), and found a statistically significant inverse trend associated with longer duration of physical activity among postmenopausal overweight (BMI = 25–30 kg/m²) women with relatively high caloric intakes (Pₜrend = 0.002). Malin et al. [15] reported results from a case-control study in China. As did they, we found evidence of an increased risk of breast cancer among premenopausal women who were physically inactive, overweight/obese, and had a relatively high energy intake. Unlike Malin et al. [15], however, we did not observe an association between energy balance and risk among postmenopausal women.

As noted above, high energy intake and low energy expenditure have been shown to be associated with increased ovarian steroid hormone production [2,48], and obesity is also associated with higher concentrations of free plasma estradiol via an inverse association with circulating sex hormone-binding globulin (SHBG) [49]. In addition to these effects, there are several other possible mechanisms by which disturbances in energy balance might influence breast cancer risk. Friedenriech [49] postulated that individuals with greater fat tissue may be exposed to higher levels of carcinogens given that fat tissue has the capacity to store toxins. In addition, Hursting et al. [50], in a review of the effects of caloric restriction and cancer risk, noted that caloric restriction is associated with decreased oxidative stress, possibly via decreased oxidant production, enhanced antioxidant capacity, and decreased inflammation. Caloric restriction has also been shown to maintain antioxidant defense systems [51], and to decrease the rate of DNA replication and enhance apoptosis, thereby reducing tissue susceptibility to damage by carcinogens [50]. Finally, energy imbalance may affect breast cancer risk through effects on circulating levels of insulin and IGF-I, which have been positively associated with breast cancer risk [52]. There is evidence that energy restriction is associated with lower circulating IGF-I levels [53–56] and some evidence of a positive association between IGF-I and obesity [57]. IGF-I has been shown to regulate circulating levels of total and bioavailable sex steroids [52] and there is evidence that IGF-I stimulates cell proliferation and inhibits apoptosis in various cell types [58–60] including breast epithelial cells [61]. However, while chronic energy restriction is strongly inversely associated with circulating IGF-I levels, there is evidence that physical activity does not generally decrease total circulating IGF-I levels and that when controlling for energy intake, obesity does not increase total IGF-I levels in comparison to the non-obese state [52]. Hence changes in IGF-I levels might account only partially for the association between energy balance and cancer risk.

Our data are limited by the possibility of error with respect to the measurement of diet and the calculation of energy intake. A pilot version of this questionnaire, however, was validated against an interviewer-administered diet history questionnaire and reported correlation coefficients of 0.63 for total caloric intake [18]. Measurement error may have influenced the results of previous studies of energy intake and breast cancer as well. Our measure of vigorous physical activity was somewhat limited in that the questionnaire asked only about the average time spent per day over the last month in the
following activities: jogging, running, brisk walking, vigorous sport, bicycling, or heavy housework. Furthermore, inclusion of housework in the question may have contributed to the relatively high duration of physical activity that we observed compared to that reported in general population surveys [62]. Biased measurements of energy intake and physical activity may also have arisen because of the known underreporting of energy intake and over-reporting of energy expenditure among heavier individuals, particularly in women [63,64]. In our study population, however, overweight and obese women (BMI $\geq 25$ kg/m$^2$) reported slightly higher average energy intake ($p < 0.0001$) and slightly lower duration of vigorous physical activity ($p < 0.01$) than did lean women (BMI $< 25$ kg/m$^2$) (data not shown). Additional limitations of our study include the fact that information on menopausal status was collected only at baseline. Given that the minimum age at baseline was 40 and that participants were followed up for an average of 16 years, it is likely that most of those who were premenopausal at enrolment would have become postmenopausal during the course of follow-up. Thus it is likely that our results for premenopausal women are largely accounted for by a mix of breast cancers diagnosed postmenopausally. In addition, approximately 22% of the study subjects overall, and 30% of breast cancer cases, were missing information on physical activity. A comparison of those missing information on physical activity to those for whom physical activity information was available, however, showed little difference between them with respect to baseline characteristics in the overall study population or among breast cancer cases. Finally, although we adjusted our estimates for a wide range of potentially confounding variables, uncontrolled confounding by dietary and other factors cannot be excluded.

The main strengths of this investigation are its prospective study design, which eliminates the possibility of recall bias. As well, the essentially complete follow-up of the cohort [65,66], based on linkage to national cancer incidence and mortality databases, reduces the likelihood that our results reflect bias due to differential follow-up.

In conclusion, the results of this study suggest that breast cancer risk may vary according to various combinations of the components of energy balance. In particular, our results suggest that relatively high caloric intake may be associated with an increased risk of breast cancer, particularly among premenopausal women. In addition, obese postmenopausal women with relatively high energy intake may be at increased risk of breast cancer, and that among premenopausal women, energy imbalance, represented by a relatively high energy intake, lack of participation in vigorous physical activity, and a relatively high body mass index, may be associated with increased breast cancer risk. These results, which require confirmation in other prospective studies, add to the growing body of knowledge concerning the potentially deleterious effects of energy imbalance.

Acknowledgements

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