Obesity and Physical Inactivity Are Related to Impaired Physical Health of Breast Cancer Survivors

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Abstract. *Aim: The aim of the present study was to examine the impact of obesity and physical activity on the health and wellbeing of patients with breast cancer shortly after the adjuvant treatments. Patients and Methods: A total of 537 women aged 35 to 68 years with newly-diagnosed breast cancer were enrolled into the exercise intervention study. The physical activity, physical performance (2-km walking test), cardiovascular risk factors, quality of life (EORTC-QoL-C30), co-morbidities and body-mass index (BMI) were measured after the adjuvant treatments. Results: Overall, 191 (39%) patients were overweight (BMI=25-30) and 85 (17%) obese (BMI≥30). Physical activity and performance (p<0.001 and p<0.001), QoL (p<0.001) and high density lipoprotein (HDL)-cholesterol decreased (p<0.001) whereas age (p=0.009), co-morbidities (p<0.001), hypertension (p=0.011), metabolic syndrome (p<0.001), low density lipoprotein (LDL)-cholesterol (p=0.0043), triglycerides (p<0.001), glucose (p<0.001) and insulin (p<0.001) increased linearly with BMI. Higher waist circumference (p=0.0011), triglyceride (p=0.020), insulin (p=0.0098), rate of metabolic syndrome (p=0.028), and lower HDL-cholesterol (p=0.012) and QoL (p<0.001) were associated with low physical activity. Physical activity and BMI were the most important determinants of physical performance (p<0.001 and p<0.001, respectively). Conclusion: Obesity and a sedentary lifestyle are related to poor physical performance, increased risk of cardiovascular diseases and impaired QoL, leading to a vicious circle, which impairs patients' physical health and QoL.*

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A passive lifestyle and obesity are among the greatest health risks in the Western world. Europe has the highest number of obese and overweight people in the world, over 130 million out of 730 million Europeans are obese [body-mass index (BMI) ≥30 kg/m^2] and 400 million are overweight (BMI >25 kg/m^2) (http://www.healthfirsteurope.org). Obesity and sedentary lifestyle are major risk factors for several diseases, such as diabetes, cardiovascular diseases and cancer, which are the leading causes of death in the Western world.

Over 420,000 women are diagnosed yearly with breast cancer in Europe (1). However, the prognosis of breast cancer has substantially improved during the last few decades and the number of breast cancer survivors has increased significantly.

While improving survival, adjuvant therapies may lead to long-term adverse effects and thus compromise the overall health benefit. Weight gain is one of the recognized consequences of adjuvant breast cancer therapies. Obesity increases the risk of type-2 diabetes and cardiovascular diseases (2). In addition, weight gain and obesity may have a negative impact on breast cancer outcome (3).

The level of physical activity in women decreases markedly after diagnosis of breast cancer (4). Epidemiological studies have demonstrated that physically active women not only have

a lower risk of breast cancer but also better breast cancer-specific survival as compared to sedentary women (5-10). In addition, the positive effect of physical activity on cholesterol and glucose levels, as well as on blood pressure, reduces the risk of cardiovascular disease and diabetes, and mortality in general (11-12). Therefore, metabolic parameters are important targets for intervention among patients with breast cancer. BREX (Breast Cancer and Exercise) is an open prospective randomized phase III trial on physical exercise training as a rehabilitation of patients with breast cancer after adjuvant treatment. The primary aim of the present article was to study the impact of obesity and physical activity on the health and wellbeing of patients with breast cancer shortly after the adjuvant treatments before the exercise intervention.

Patients and Methods

Patients. A total of 537 pre- and post-menopausal women aged 35 to 68 years with newly-diagnosed invasive breast cancer were enrolled into the one-year controlled prospective exercise intervention study (BREX), between September 2005 and September 2007 from Helsinki, Tampere and Turku University Hospitals, Departments of Oncology. Patients having finished adjuvant chemotherapy and/or radiotherapy for breast cancer within four months, or who had started endocrine therapy no more than four months earlier were eligible for the trial. The adjuvant treatment was carried out according to clinical guidelines. Chemotherapy regimens used were either six cycles of 5-fluorouracil 600 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (FE75C), three cycles of docetaxel 80 mg/m^2 and three cycles of FE75C or three cycles of docetaxel at 80 mg/m^2 with oral capecitabine (X) 1800 mg/m^2 per day for two weeks and three cycles of XE75C according to the FinXX trial (13). Endocrine therapy for pre-menopausal women comprised of tamoxifen for five years and for post-menopausal women an aromatase inhibitor, tamoxifen, or these agents given sequentially. Radiotherapy was given after breast-conserving surgery to the remaining breast tissue. Locoregional lymph nodes and operative scar after mastectomy were treated when needed. The randomization took place a median of 33 weeks from the surgery [interquartile range (IQR) 27, 40], 12 weeks (IQR 5, 17) from the end of the chemotherapy, 4 weeks from the radiotherapy (IQR -2, 10) and 9 weeks (IQR 3, 16) from the start of endocrine therapy.

Exclusion criteria included severe cardiac disease [the New York Heart Association (NYHA) class III or more], myocardial infarction within 12 months, uncontrolled hypertension, verified osteoporosis, other serious illness or medical condition which could be a contraindication for exercise; patients incapable of training were also excluded. The recruitment rate of patients considered eligible for the study was 78%, comprising 54% from the potentially eligible patients and 31% from all those screened (14). The main reasons for excluding patients were age over 68 years and health problems that contraindicated physical training, *e.g.* musculoskeletal disorders.

The Ethical Committee of Helsinki University Hospital approved the study protocol and written informed consent was signed by all participants before the study entry. The trial is registered in the Helsinki and Uusimaa Hospital District Clinical Trials Register (www.hus.fi) (trial number 210590) and on the website, http://www.clinicaltrials.gov/ (identifier number NCT00639210).

Measurements. Cardiometabolic risk factors: Patients' height, weight, waistline, blood pressure, pulse and body-mass index (BMI), blood glucose and insulin, total cholesterol, low density lipoprotein (LDL)- and high density lipoprotein (HDL)-cholesterol and triglyceride were measured during the inclusion visit before randomization. The National Cholesterol Education Program (NCEP) definition for metabolic syndrome was used (waist circumference ≥88 cm, triglycerides ≥1.7 mmol/l, HDL-cholesterol <1.3 mmol/l, blood pressure >130/85 mmHg or use of antihypertensive medication and fasting glucose >5.5 mmol/l or use of medication for hyperglycemia) (15).

Quality of life: The data on quality of life of the study population has been reported elsewhere (16). The quality of life was measured by the EORTC QLQ-C30 (Version 3) (17-18), and fatigue by the FACIT-Fatigue scale (19) 34 used as a cut point (20). Depressive symptoms were assessed using the Finnish modified version of Beck's 13-item depression scale (RBDI): 0-4 points signifies no depressive symptoms, 5-7 mild, 8-15 moderate and 16-39 severe depressive symptoms (20-21).

Physical activity and performance: The history of leisure time physical activity (LTPA) before the diagnosis of breast cancer was classified as low (*e.g.* mostly watching TV, reading), moderate (*e.g.* walking or cycling at least four hours per week) or vigorous intensity (*e.g.* gym, ball games, swimming or jogging at least three hours per week). The current (after diagnosis and treatment) intensity of leisure-time physical activity was measured by a prospective two-week diary using metabolic equivalent of task (MET) hours (22): light intensity, <3 METs; moderate, 3 to 6 METs; vigorous, 6 to 9 METs; very vigorous intensity, >9 METs. The cardiovascular performance was tested by a two-kilometer walking test (UKK walk test, Tampere, Finland), where the participants were asked to walk the 2-km distance as quickly as possible (23-26). The reference walking time for women aged 31 to 40, 41 to 50, and ≥50 years of age are 16:08-16:23 (min:s), 16:15-16:59, and 17:34-18:31, respectively.

Statistical methods. The data are presented as means with standard deviations (SD), or ranges, or as counts with percentages. The most important outcomes are given with 95% confidence intervals (95 CI). The comparison between BMI groups for categorical variables was performed by the chi-square test. Dichotomous and ordered categorical variables were compared by using chi-square test or logistic or ordered logistic regression analysis. Analysis of variance and analysis of co-variance were used for continuous variables. In the case of violation of the assumptions, a bootstrap type version of the test for continuous variables was used instead. The linearity was tested by using an appropriate contrast in the model in question. Ordered logistic regression models were adapted in order to investigate for possible factors associated to physical performance. Forward selection was used in the multivariate regression model for all possible factors except age, which was not subjected to the selection and was included in the model.

Results

Main characteristics of the study population. All data were available on 494 out of 537 patients. The mean age of the patients was 52 years (range=35-68 years). A total of 263 (53%) of the patients were post-menopausal. Overall, 276 (56%) were overweight or obese and 266 (54%) had at least

Table I. *Demographic data, lifestyle habits and physical activity according to body-mass index (BMI).*

	BMI <25 n=218	BMI 25 -<30 n=191	BMI ≥30 n=85	*p*-Value† crude	*p*-Value† age-adjusted
Demographic					
Age, mean (SD)	51.0 (7.5)	54.2 (7.5)	52.4 (7.3)	0.0089	
Post-menopausal, n (%)	96 (44)	117 (61)	50 (59)	0.0025	0.026
Education years, mean (SD)	14.4 (3.3)	13.7 (3.4)	13.5 (3.2)	0.029	0.080
Lifestyle habits					
Smoking, n (%)	18 (8)	21 (11)	13 (15)	0.076	0.062
Alcohol consumption, mean (SD)	4.1 (4.4)	4.6 (7.1)	3.6 (4.2)	0.78	0.92
Physical activity and performance					
MET high, n (%)	119 (55)	93 (49)	35 (41)	0.033	0.029
MET hours per week, mean (SD)	28.6 (17.7)	25.2 (14.4)	23.4 (17.6)	0.010	0.0070
2-km Walking time, min, mean (SD)	17.8 (1.6)	18.6 (1.6)	20.4 (2.3)	<0.001	<0.001
LTPA, n (%)				<0.001	<0.001
Low	23 (11)	36 (19)	25 (31)		
Moderate	126 (59)	103 (56)	46 (57)		
High	65 (30)	46 (25)	10 (12)		

†*p*-Values are for linearity. LTPA: leisure time physical activity; MET: metabolic equivivalent of task; SD: standard deviation.

one chronic disease. The most common co-morbidity was hypertension in 96 (19%) cases. Fifty-two (11%) were randomly smokers. Lower- and upper-level employees (78%) dominated the sociodemographic distribution. The majority (92%) of the patients were treated with chemotherapy, while endocrine therapy was given to 82% and postoperative radiotherapy to 78% of the patients.

Body-mass index. A total of 218 (44%) patients had normal or lean body weight (BMI <25), 191 (39%) were overweight (BMI 25-30) and 85 (17%) were obese (BMI ≥30) (Table I). The mean weight (71.1 kg, SD 12.2 kg) of the patients was significantly higher at the entry to study (after adjuvant therapy) compared with the self-reported weight (68.4 kg, SD 11.7 kg) at the beginning of chemotherapy ($p<0.001$) (Figure 1).

Sociodemographic factors: Age and menopausal status were linearly associated with BMI ($p=0.0089$ and age-adjusted $p=0.026$, respectively) (Table I).

Lifestyle factors: Leisure-time physical activity before the diagnosis and current physical activity measured by METh/wk decreased linearly across BMI-groups (age-adjusted $p<0.001$ and $p=0.0070$ respectively) (Table I).

Tumour characteristics and treatments: No significant difference was found in tumour characteristics or treatments between the study groups, except for the proportion of mastectomies carried out (age-adjusted $p=0.032$ between BMI groups) (Table II).

Cardiometabolic risk factors: Co-morbidities increased linearly across BMI-groups (age-adjusted $p<0.001$). Hypertension (age- and tamoxifen-adjusted $p=0.011$) and metabolic syndrome ($p<0.001$) increased linearly, being the most frequent in obese patients. The frequencies of hypertension were 13%, 21% and 34%, and those of metabolic syndrome 10%, 39% and 71% in normal-weight, overweight and obese patients, respectively. In addition, HDL-cholesterol decreased ($p<0.001$) and LDL-cholesterol ($p=0.0043$), triglycerides ($p<0.001$), fasting glucose ($p<0.001$) and insulin increased linearly ($p<0.001$) across BMI-groups (Table III, Figure 2).

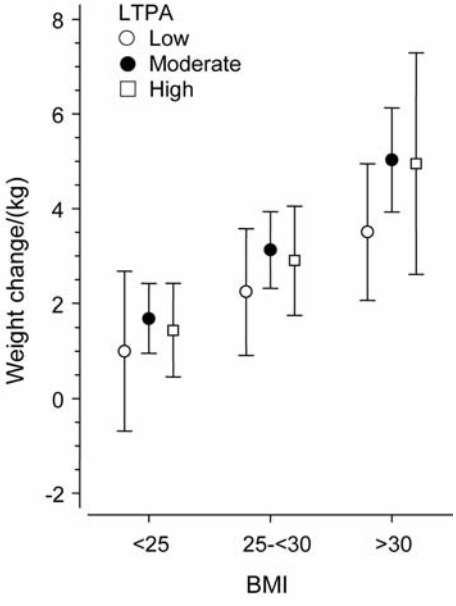

Figure 1. *Age-adjusted weight change during chemotherapy according to body-mass index (BMI) and leisure time physical activity (LTPA) classes. Data are means with 95% confidence intervals.*

Quality of life: There was a statistically significant linear relationship between the quality of life (EORTC-QLQ-C30) and the BMI groups (global health, adjusted $p<0.001$) (Table III).

Physical activity and performance. Factors associated with physical activity: Higher waist circumference (age- and tamoxifen-adjusted $p=0.0011$), triglycerides ($p=0.020$) and fasting insulin ($p=0.0098$), higher rate of metabolic syndrome ($p=0.028$) and lower HDL-cholesterol ($p=0.012$) and lower quality of life ($p<0.001$) were associated with low physical activity (Table III). No interaction was found between BMI and METh/wk in the analyses of cardiometabolic risk factors (Figure 2).

Physical performance: The time for completing the 2-km walking test was significantly associated with BMI-group (age-adjusted $p<0.001$) (Table I).

Factors associated with physical performance: Factors associated with the 2-km walking test divided into tertiles were investigated using both univariate- and multivariate-ordered logistic regressions. In univariate analyses adjusted for age LTPA before diagnosis ($p<0.001$), current physical activity ($p<0.001$) and longer education ($p<0.001$) were associated with better walking test results. High BMI, depression and co-morbidities were associated with significantly worse walking test results ($p<0.001$, $p<0.001$ and $p=0.002$, respectively). In forward stepwise multivariate analyses, LTPA before the diagnosis, current physical activity and BMI entered the model ($p<0.001$, $p<0.001$ and $p<0.001$, respectively) (Table IV).

Discussion

We found that overweight and obesity of breast cancer survivors were significantly associated with sedentary lifestyle and poor physical performance, comprising a vicious circle of impaired physical health and quality of life. In the present population, 57% of the women were overweight or obese.

The level of physical activity often diminishes after breast cancer diagnosis (27-32). Irwin *et al*. demonstrated that the total physical activity decreased on average by two hours per week within one year after diagnosis. The greatest declines in physical activity were observed among obese patients (32). Likewise, in the present study physical inactivity was most common among obese patients with a very low level of high-intensity activity.

Diminished physical activity is one of the primary factors responsible for further weight gain during adjuvant chemotherapy (27-31). In the present study, the average weight gain was 3 kg which is in line with the weight gain from 2.5 to 6.0 kg during the first year after breast cancer diagnosis presented in the previous literature (30-31,33). Likewise, physical inactivity and weight gain during chemotherapy were

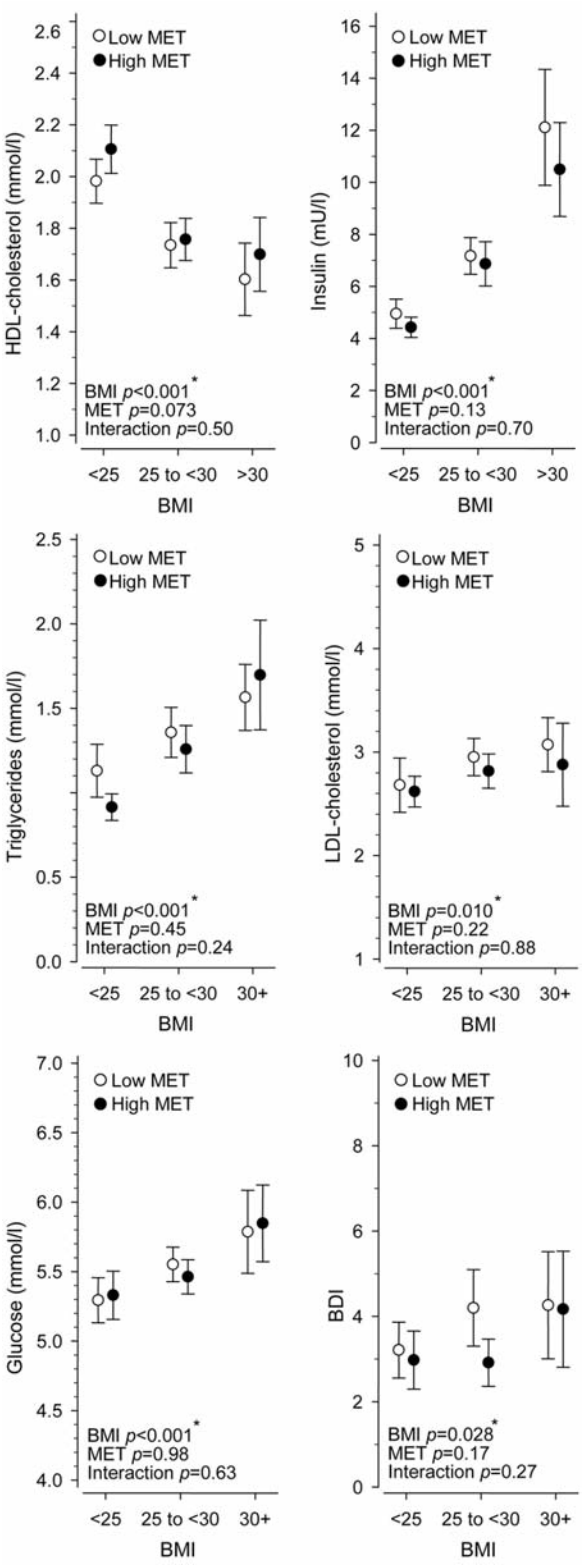

Figure 2. *Cardiovascular risk factors and quality of life according to body-mass index (BMI) and metabolic equivalent of task (MET). Data are means with 95% confidence intervals. *p-value is for linearity. HDL: high-density lipoprotein, LDL: low-density lipoprotein, BDI: Beck Depression Inventory.*

Table II. *Tumour characteristics and treatments according to body-mass index (BMI).*

	BMI <25 n=218	BMI 25 - <30 n=191	BMI ≥30 n=85	*p*-Value† crude	*p*-Value† age-adjusted
Tumour size /mm, mean (SD)	22.3 (13.0)	23.8 (17.8)	26.2 (14.3)	0.088	0.054
Node-positive, mean (SD)	2.00 (3.52)	1.83 (3.08)	3.22 (5.72)	0.11	0.11
Nodes investigated, mean (SD)	13.3 (7.8)	13.1 (8.0)	15.3 (8.1)	0.080	0.11
Tumour grade, n (%)					
1	42 (19)	23 (12)	7 (8)	0.088	0.076
2	90 (42)	90 (48)	38 (45)		
3	84 (39)	76 (40)	39 (46)		
Histology n (%)				0.91	
Ductal	149 (68)	131 (69)	58 (68)		
Lobular	45 (21)	42 (22)	16 (19)		
Other	24 (11)	18 (9)	11 (13)		
ER-positive, n (%)	185 (85)	153 (80)	69 (81)	0.43	0.37
PR-positive, n (%)	154 (71)	121 (63)	61 (72)	0.21	0.38
Breast operation, mastectomy n (%)	129 (59)	84 (44)	44 (52)	0.009	0.032
Axillary operation, evacuation, n (%)	160 (73)	137 (72)	69 (81)	0.24	0.25
Chemotherapy, n (%)	195 (89)	175 (92)	82 (96)	0.14	0.14
Herceptin, n (%)	38 (17)	35 (18)	11 (13)	0.53	0.45
Radiotherapy, n (%)	164 (75)	153 (80)	70 (82)	0.30	0.31
Endocrine therapy, n (%)				0.44	
None	35 (16)	37 (19)	15 (18)		
Tamoxifen	60 (28)	63 (33)	29 (34)		
Aromatase inhibitor	123 (56)	91 (48)	41 (48)		

†*p*-Value between groups. ER: estrogen receptor; PR: progesterone receptor; SD: standard deviation.

the most common among obese patients, increasing the risk for future impairment of physical ability.

In the present study, adverse health behaviour and several cardiovascular risk factors were associated with obesity and overweight. As expected, the prevalence of metabolic syndrome was significantly higher in obese (68%) and overweight (39%) patients as compared to those with normal weight (11%). Of note, pre-existing cardiovascular risk factors are known to predict the development of therapy-induced cardiovascular injury among patients with breast cancer (34). Obesity was also related to co-morbidities, particularly hypertension, in our study. This is especially alarming as patients with breast cancer and co-morbidities, such as cardiovascular problems or diabetes, are known to have a poorer prognosis (35). In a Norwegian study including 1,364 patients with breast cancer, obese women (BMI>30), sedentary women and women with the highest values of total cholesterol had a 30-50% increased risk of total and breast cancer-specific mortality compared to healthier women (36). Likewise from our observations, the profile of cardiovascular risk factors was less favorable not only in obese women, but also in women with a lower level of physical activity independently of BMI. It is of concern that the study subjects were already a pre-selected group as health problems contraindicating exercise training were exclusion criteria of the study.

In line with existing literature, we found a non-significant trend towards more advanced disease in overweight and obese patients as tumor size, nodal status and grade were greater among these women (37). In addition to this, epidemiological studies have shown a clear dose-response relation between physical activity and breast cancer mortality (7). The association between physical inactivity and breast cancer risk has been related to weight control and sex hormone regulation, but also to insulin resistance (38). Notably, in our study, obesity and physical inactivity were significantly related to hyperinsulinemia.

We earlier reported that quality of life of the patients with breast cancer shortly after the adjuvant treatments was significantly impaired as compared with the general population (16). Every fourth patient was depressed. In the current study, we found a strong association between high BMI and impaired quality of life. Thus, obesity does not only alter physical health but also psychosocial wellbeing and quality of life. Interestingly, as we previously reported, physical activity is the only factor positively-correlating to quality of life (16).

The current study had some limitations that should be considered when interpreting its findings. The study population was selected from the exercise intervention trial. Even though the recruitment rate was as high as 78%, older patients and patients with major health problems were excluded. The study population represents only 30% of all screened patients. This,

Table III. *Cardiometabolic risk factors according to body-mass index (BMI) and physical activity (METh/week).*

	BMI			*p*-Value†	MET		*p*-Value*
	<25 n=218	25 - <30 n=191	≥30 n=85		Low ≤27 h/wk n=247	High >27 h/wk n=247	
Clinical							
Waist, cm, mean (SD)	79.4 (7.5)	91.3 (7.2)	104.1 (9.1)	<0.001	89.9 (12.0)	86.5 (11.4)	0.0011
Weigth, kg, mean (SD)	61.6 (6.6.)	73.6 (5.6)	88.7 (10.4)	<0.001	71.8 (12.4)	70.0 (11.6)	0.093
Blood pressure, mmHg, mean (SD)							
Systolic	131 (19)	139 (18)	140 (17)	<0.001	134 (18)	137 (19)	0.21
Diastolic	83 (10)	87 (11)	89 (11)	<0.001	85 (10)	86 (11)	0.27
NCEP, n (%)	23 (11)	75 (39)	57 (68)	<0.001	88 (36)	67 (27)	0.028
Biochemical, mean (SD)							
Total-cholesterol, mmol/l	5.08 (1.17)	5.25 (1.00)	5.37 (1.12)	0.12	5.17 (1.19)	5.12 (1.00)	0.15
HDL-cholesterol, mmol/l	2.04 (0.50)	1.76 (0.42)	1.65 (0.47)	<0.001	1.81 (0.47)	1.92 (0.50)	0.012
LDL-cholesterol, mmol/l	2.61 (1.08)	2.91 (0.91)	3.01 (1.06)	0.0043	2.87 (1.13)	2.73 (0.91)	0.13
FP-glucose, mmol/l	5.29 (0.92)	5.53 (0.65)	5.81 (0.98)	<0.001	5.49 (0.84)	5.45 (0.86)	0.59
FP-insulin, mU/l	4.59 (2.42)	7.10 (3.86)	11.45 (7.02)	<0.001	7.28 (5.25)	6.20 (4.16)	0.0098
Triglycerides, mmol/l	1.00 (0.62)	1.33 (0.73)	1.62 (0.82)	<0.001	1.31 (0.76)	1.16 (0.70)	0.020
Depressive, n (%)	48 (23)	44 (24)	27 (33)	0.063	67 (28)	52 (22)	0.18
Fatigue, n (%)	39 (18)	37 (20)	22 (27)	0.096	53 (22)	45 (19)	0.44
EORTC QHS, mean (SD)	72.3 (18.7)	69.4 (17.8)	64.3 (20.1)	<0.001	66.8 (19.2)	72.9 (17.8)	<0.001

†*p*-Value for linearity across body mass index (BMI) groups, age- and tamoxifen- adjusted. **p*-Value between metabolic equivivalent of task (MET)-groups, age- and tamoxifen-adjusted. NCEP: The National Cholesterol Education Program; HDL: high-density lipoprotein; LDL: low-density lipoprotein; EORTC QHS: Health score of EORTC-QLQ-C30 QoL questioinnaire for cancer patients; SD: standard deviation.

Table IV. *Factors associated with the UKK 2-km walking test results divided into tertiles [0=19.12-27.62 min (n=175), 1=17.63-19.10 min (n=175), 2=13.75-17.62 min (n=173)] using ordered logistic regression models.*

	Univariate*		Multivariate†	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	0.94 (0.92 to 0.96)	<0.001	0.93 (0.91 to 0.96)	<0.001
Chemotherapy	0.68 (0.37 to 1.23)	0.20		
LTPA		<0.001‡		<0.001‡
Low	1 (reference)		1 (reference)	
Moderate	3.36 (2.08 to 5.45)		2.28 (1.31 to 3.97)	
High	9.06 (5.17 to 15.85)		4.72 (2.49 to 8.96)	
MET	1.32 (1.22 to 1.43)	<0.001	1.26 (1.16 to 1.38)	<0.001
BMI		<0.001‡		<0.001‡
<25	1 (reference)		1 (reference)	
25 - <30	0.48 (0.33 to 0.69)		0.63 (0.42 to 0.95)	
≥30	0.09 (0.05 to 0.15)		0.10 (0.05 to 0.19)	
Co-morbidity present	0.59 (0.42 to 0.83)	0.002		
Depression present	0.53 (0.36 to 0.77)	<0.001		
Education years	1.09 (1.04 to 1.14)	<0.001	1.08 (1.02 to 1.14)	0.010

*Age is included in the model as a covariate. †Forward selection. Only those variables are shown which entered the model. Age is included in the model and not subjected to selection. ‡*p*-Value for linearity. LTPA: leisure time physical activity; MET: metabolic equivivalent of task; BMI: body mass index.

however, makes our findings even more worrying as such a significant number of physical and psychosocial problems were observed among the participants. Another limitation is that both physical activity and weight before breast cancer diagnosis were reported by the patients. The strength of this study lies in the large size and comprehensive assessment of the physical and mental wellbeing including quality of life, physical activity, physical performance and cardiometabolic risk factors.

In summary, overweight and obesity of patients with breast cancer are related to a sedentary lifestyle and poor physical performance, increased risk of cardiovascular diseases, and impaired quality of life. Obesity and reduced physical activity lead to a vicious circle, which impairs patients' physical health and quality of life. More attention should be paid to obesity and physical inactivity among patients with breast cancer and survivors.

Ethical Approval

The Ethical Committee of Helsinki University Hospital approved the study protocol (approval # 210590).

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References

1 Ferlay J, Parkin DM and Steliarova-Foucher E: Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer *46*: 765-781.

2 Haslam DW and James WP: Obesity. Lancet *366*: 1197-1209, 2005.

3 Lorincz AM and Sukumar S: Molecular links between obesity and breast cancer. Endocr Relat Cancer *13*: 279-292, 2006.

4 Irwin ML, Crumley D, McTiernan A, Bernstein L, Baumgartner R, Gilliland FD, Kriska A and Ballard-Barbash R: Physical activity levels before and after a diagnosis of breast carcinoma: The Health, Eating, Activity, and Lifestyle (HEAL) Study. Cancer *97*: 1746-1757, 2003.

5 Gammon MD, John EM and Britton JA: Recreational and occupational physical activities and risk of breast cancer. J Natl Cancer Inst *90*: 100-117, 1998.

6 McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N and Ockene J: Recreational physical activity and the risk of breast cancer in postmenopausal women: The Women's Health Initiative Cohort Study. JAMA *290*: 1331-1336, 2003.

7 Holmes MD, Chen WY, Feskanich D, Kroenke CH and Colditz GA: Physical activity and survival after breast cancer diagnosis. JAMA *293*: 2479-2486, 2005.

8 Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, Baron JA, Egan KM and Willett WC: Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev *17*: 379-386, 2008.

9 Sternfeld B, Weltzien E, Quesenberry CP Jr., Castillo AL, Kwan M, Slattery ML and Caan BJ: Physical activity and risk of recurrence and mortality in breast cancer survivors: Findings from the lace study. Cancer Epidemiol Biomarkers Prev *18*: 87-95, 2009.

10 Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, Baumgartner RN, Baumgartner KB and Bernstein L: Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: The health, eating, activity, and lifestyle study. J Clin Oncol *26*: 3958-3964, 2008.

11 Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ and Fairey AS: Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. J Clin Oncol *21*: 1660-1668, 2003.

12 Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW and Mackey JR: Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: A randomized controlled trial. Cancer Epidemiol Biomarkers Prev *12*: 721-727, 2003.

13 Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R, Jukkola-Vuorinen A, Tanner M, Asola R, Kokko R, Ahlgren J, Auvinen P, Hemminki A, Paija O, Helle L, Nuortio L, Villman K, Nilsson G, Lahtela SL, Lehtio K, Pajunen M, Poikonen P, Nyandoto P, Kataja V, Bono P, Leinonen M and Lindman H: Adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for breast cancer: An open-label, randomised controlled trial. Lancet Oncol *10*: 1145-1151, 2009.

14 Penttinen H, Nikander R, Blomqvist C, Luoto R and Saarto T: Recruitment of breast cancer survivors into a 12-month supervised exercise intervention is feasible. Contemp Clin Trials *30*: 457-463, 2009.

15 Grundy SM, Brewer HB Jr., Cleeman JI, Smith SC Jr. and Lenfant C: Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation *109*: 433-438, 2004.

16 Penttinen HM, Saarto T, Kellokumpu-Lehtinen P, Blomqvist C, Huovinen R, Kautiainen H, Jarvenpaa S, Nikander R, Idman I, Luoto R, Sievanen H, Utriainen M, Vehmanen L, Jaaskelainen AS, Elme A, Ruohola J, Luoma M and Hakamies-Blomqvist L: Quality of life and physical performance and activity of breast cancer patients after adjuvant treatments. Psychooncology *20*: 1211-1220, 2010.

17 Kaasa S, Bjordal K, Aaronson N, Moum T, Wist E, Hagen S and Kvikstad A: The EORTC core quality of life questionnaire (QLQ-c30): Validity and reliability when analysed with patients treated with palliative radiotherapy. Eur J Cancer *31A*: 2260-2263, 1995.

18 Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, Franzini L, Williams A, de Haes HC, Hopwood P, Cull A and Aaronson NK: The European organization for research and treatment of cancer breast cancer-specific quality-of-life questionnaire module: First results from a three-country field study. J Clin Oncol *14*: 2756-2768, 1996.

19 Yellen SB, Cella DF, Webster K, Blendowski C and Kaplan E: Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. J Pain Symptom Manage *13*: 63-74, 1997.

20 Van Belle S, Paridaens R, Evers G, Kerger J, Bron D, Foubert J, Ponnet G, Vander Steichel D, Heremans C and Rosillon D: Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: Proposal for use as a screening tool. Support Care Cancer *13*: 246-254, 2005.

21 Elämänhallinta sosiaalipolitiikan tavoitteena. Raitasalo R (ed). Kansaneläkelaitos Helsinki, 1995.

22 Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr., Schmitz KH, Emplaincourt PO, Jacobs DR, Jr.and Leon AS: Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc *32*: S498-504, 2000.

23 Suni JH, Miilunpalo SI, Asikainen TM, Laukkanen RT, Oja P, Pasanen ME, Bos K and Vuori IM: Safety and feasibility of a health-related fitness test battery for adults. Phys Ther *78*: 134-148, 1998.

24 Suni JH, Oja P, Laukkanen RT, Miilunpalo SI, Pasanen ME, Vuori IM, Vartiainen TM and Bos K: Health-related fitness test battery for adults: Aspects of reliability. Arch Phys Med Rehabil *77*: 399-405, 1996.

25 Suni JH, Oja P, Miilunpalo SI, Pasanen ME, Vuori IM and Bos K: Health-related fitness test battery for adults: Associations with perceived health, mobility, and back function and symptoms. Arch Phys Med Rehabil *79*: 559-569, 1998.

26 Suni JH, Oja P, Miilunpalo SI, Pasanen ME, Vuori IM and Bos K: Health-related fitness test battery for middle-aged adults: Associations with physical activity patterns. Int J Sports Med *20*: 183-191, 1999.

27 Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J, Sidlofsky S, Trudeau M, Hood N and Redwood S: Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol *17*: 120-129, 1999.

28 Goodwin P, Esplen MJ, Butler K, Winocur J, Pritchard K, Brazel S, Gao J and Miller A: Multidisciplinary weight management in locoregional breast cancer: Results of a phase II study. Breast Cancer Res Treat *48*: 53-64, 1998.

29 Rock CL, Flatt SW, Newman V, Caan BJ, Haan MN, Stefanick ML, Faerber S and Pierce JP: Factors associated with weight gain in women after diagnosis of breast cancer. Women's healthy eating and living study group. J Am Diet Assoc *99*: 1212-1221, 1999.

30 Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, Blackwell K and Rimer BK: Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol *19*: 2381-2389, 2001.

31 McInnes JA and Knobf MT: Weight gain and quality of life in women treated with adjuvant chemotherapy for early-stage breast cancer. Oncol Nurs Forum *28*: 675-684, 2001.

32 Irwin ML, McTiernan A, Baumgartner RN, Baumgartner KB, Bernstein L, Gilliland FD and Ballard-Barbash R: Changes in body fat and weight after a breast cancer diagnosis: Influence of demographic, prognostic, and lifestyle factors. J Clin Oncol *23*: 774-782, 2005.

33 Demark-Wahnefried W, Rimer BK and Winer EP: Weight gain in women diagnosed with breast cancer. J Am Diet Assoc *97*: 519-526, 529; quiz 527-518, 1997.

34 Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS and Mackey JR: Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol *50*: 1435-1441, 2007.

35 Patterson RE, Flatt SW, Saquib N, Rock CL, Caan BJ, Parker BA, Laughlin GA, Erickson K, Thomson CA, Bardwell WA, Hajek RA and Pierce JP: Medical comorbidities predict mortality in women with a history of early stage breast cancer. Breast Cancer Res Treat *122*: 859-865, 2010.

36 Emaus A, Veierod MB, Tretli S, Finstad SE, Selmer R, Furberg AS, Bernstein L, Schlichting E and Thune I: Metabolic profile, physical activity, and mortality in breast cancer patients. Breast Cancer Res Treat *121*: 651-660, 2009.

37 Dirat B, Bochet L, Escourrou G, Valet P and Muller C: Unraveling the obesity and breast cancer links: A role for cancer-associated adipocytes? Endocr Dev *19*: 45-52, 2010.

38 Neilson HK, Friedenreich CM, Brockton NT and Millikan RC: Physical activity and postmenopausal breast cancer: Proposed biologic mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev *18*: 11-27, 2009.

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