

		Week			
		1	2	3	4
Cisplatin	20 mg/m <sup>2</sup> per day i.v. (5 days)	↓ ↓ ↓ ↓ ↓		↓ ↓ ↓ ↓ ↓	
	40 mg/m <sup>2</sup> i.v. infusion × 1		↓		↓

*IPE*

Ifosfamide	1 g/m <sup>2</sup> per day i.v.	days 1–5
Cisplatin	20 mg/m <sup>2</sup> per day i.v.	days 1–5
Etoposide	100 mg/m <sup>2</sup> per day i.v.	days 1,3,5

*High-dose regimen*

Carboplatin total dose = AUC × (GFR + 25) mg i.v. Total dose given in five equal doses days 1–5.

Etoposide 240 mg/m<sup>2</sup> per day i.v. days 1–5. Total dose 1200 mg/m<sup>2</sup>. AUC, area under the serum concentration × time curve; GFR, glomerular filtration rate.



Pergamon

*European Journal of Cancer* Vol. 31A, No. 5, pp. 723–728, 1995  
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0959-8049/95 \$9.50 + 0.00

0959-8049(95)00046-1

# A Case–Control Study on Breast Cancer and Body Mass

E. Taioli, J. Barone and E.L. Wynder for the American Health Foundation—  
Division of Epidemiology

A hospital-based case–control study was carried out to examine the effect of body weight/fat and physical activity on risk of breast cancer on 617 newly diagnosed breast cancer cases and 531 controls matched to the cases by age ( $\pm 5$  years), race, year of interview ( $\pm 1$  year) and hospital of admission. Breast cancer was not found to be associated with height, while being overweight appeared to be protective in premenopausal women [odds ratio, OR = 0.4 (0.2–0.7) for cases who weighed  $\geq 72.7$  kg versus controls]. Increased body mass index (BMI) was protective in premenopausal women [OR = 0.4 (0.2–0.6) in breast cancer cases with BMI  $\geq 27$  versus controls], but not in postmenopausal women, for whom it was a risk factor [OR = 1.5 (1.0–2.3)]. Few women reported any strenuous physical activity from ages 15 to 22 years (22% of premenopausal, 13% of postmenopausal women), and no significant effect on breast cancer risk was observed.

**Key words:** breast cancer, body mass, physical activity

*Eur J Cancer*, Vol. 31A, No. 5, pp. 723–728, 1995

## INTRODUCTION

NUMEROUS STUDIES point to a relationship between body weight, body mass and breast cancer risk [1–30]. However, it is often difficult to compare these studies since they differ with regard to age of the subjects, how and at what age obesity or body fat is measured, and the mean weight categories used. Nevertheless, most [1–8, 12, 23, 24, 27–30], but not all [9–11, 21, 22, 25, 26, 29] of the studies find that the risk for breast cancer increases

postmenopausally with increases in body weight or body mass. The opposite seems to be true for premenopausal risk of breast cancer. A few studies have looked at the association between physical activity and breast cancer risk [31–36], finding a protective effect of college athletics and of non-sedentary jobs.

To our knowledge, none of the studies we reviewed examined the role of body weight/fat and breast cancer risk in relation to physical activity. The majority of studies looking at physical activity and breast cancer did not analyse the role of body size/weight, and presented only a small number of cases.

Our rationale for studying the relationship between physical activity, body weight and breast cancer includes evidence that female athletes are significantly lighter in weight and leaner than non-athletes [36, 37]. In those women who were athletic during

Correspondence to E. Taioli.

The authors are at the NYU Medical Center, Department of Environmental Medicine, 341 E 25th Street, New York, New York 10010, U.S.A.

Revised 15 Dec. 1992; accepted 15 Dec. 1994.

their early years, physical activity may be associated with leanness and less weight gain for a longer period of their life. Furthermore, heavier individuals may be less active and experience greater weight gain for longer periods of their life. The purpose of the present case-control study was to examine the effect of body weight/fat and physical activity on risk of breast cancer in a large subject population.

## MATERIALS AND METHODS

In this hospital-based case-control study, 617 consecutive, newly diagnosed breast cancer cases and 531 controls matched to the cases by age ( $\pm 5$  years), race, year of interview ( $\pm 1$  year) and hospital of admission were recruited during the period 1987–1990. All the cases had histologically confirmed cancer of the breast. Control patients were selected from persons admitted to the same hospital with non-tobacco-related, non-alcohol-related diseases. Discharge diagnosis for controls included non-neoplastic diseases (43.8%), benign neoplasms (13.2%), cancer of the skin, digestive tract, lymphohaematopoietic system (37.9%) or injuries (5.1%). Information was collected at the time of hospitalisation through a standardised questionnaire administered by trained interviewers. Demographic and anthropometric characteristics, medical and reproductive history, and leisure time physical activity were queried.

Women were asked to report their present weight, their weight 5 years before the diagnosis and at the age of 18, as well as their ages when they were at their maximum and their minimum weights.

Subjects were classified as 'exercisers' if they participated in regular, strenuous activity carried out for at least 20 min, three times a week, for 1 year or more, during which they perspire and become short of breath. Twenty-six activities were coded separately and up to two activities for three different age periods were recorded: 15–21, 22–44 and 45+ years. Therefore, each subject could report a maximum of six activities. For the present analysis, data relative to the period 15–21 years, and to any period of life were used.

Women were considered premenopausal if they reported regular cycles in the year before the interview, postmenopausal if they did not have cycles in the previous year or if they had surgically induced menopause.

### Statistical analysis

The average weekly caloric expenditure (WCE) was calculated according to the formula

$$\text{WCE} = X_{ij} H_i (M_i/12) Y_i / Y_i$$

where  $i$  ranges from one to six (the maximum number of reported activities was six),  $H_i$  = h/week,  $M_i$  = months/year,  $Y_i$  = number of years, and  $X_{ij}$  is a hourly caloric expenditure estimate for leisure time activity =  $j$ . These estimates ranged from 300 kcal/h for aerobic dancing and gymnastics, to 1200 kcal/h for running [38]. Quetelet index (QI) was calculated according to the formula:

$$\text{QI} = \text{weight (kg)} / \text{height (m)}^2$$

Demographic characteristics are presented as means and standard deviations. Logistic regression was used to compute odds ratios (OR), as estimates of relative risk, and their 95% confidence limits (CL). Adjustment for the matching factors and the possible confounding factors was performed.

## RESULTS

### Anthropometric variables

The general characteristics of the study population are presented in Table 1. No major differences were observed between premenopausal cases and controls.

Breast cancer was not found to be associated with height (Table 2), while being overweight appeared to be protective in premenopausal women [odds ratio, OR = 0.4 (0.2–0.7) for cases who weighed  $\geq 72.7$  kg versus controls]. Increased BMI was protective in premenopausal women [OR = 0.4 (0.2–0.6) in breast cancer cases with BMI  $\geq 27$  versus controls], but not in postmenopausal women, for whom it was a risk factor [OR = 1.5 (1.0–2.3)]. Gain in weight after the age of 18 was associated with a non-significant reduced risk in premenopausal women, and a non-significant increased risk in postmenopausal, but no trend was observed. Since increased body weight can reduce the probability of detecting the tumour in the breast, we analysed the effect of weight on breast cancer risk by stage of the disease (Figure 1). Overweight resulted in a significant protective effect only among premenopausal women.

### Physical activity

Relatively few women reported any strenuous physical activity from ages 15 to 22 years (22% of premenopausal, 13% of postmenopausal women; Table 3). The analysis of calories per week expended showed no significant effect on breast cancer risk. Premenopausal women who reported physical activity for three or more hours per week had a non-significant protective effect.

Physical activity at any age was also analysed; 60% of premenopausal and 80% of postmenopausal breast cancer patients and controls never exercised under our definition. No association was observed between length of physical activity (less than 3 hours a week; 3 or more hours a week; less than or equal to 3 years, more than 3 years) and breast cancer in either pre- or postmenopausal women.

## DISCUSSION

Our study confirmed the results from previous studies, showing a protective effect of overweight on breast cancer in premenopausal women, and a slightly increased risk in postmenopausal women. The majority of the studies examining premenopausal risk factors find that leanness is associated with an increased risk for breast cancer while a significantly reduced risk is found in those with heavier weights/body mass [2, 3, 5, 6, 13–18]. Some of these studies [1, 31, 35] find a dose-response gradient between body weight/mass and breast cancer risk; premenopausally there was a progressively reduced risk of breast cancer with increasing QI. Other studies provide evidence that weight or body mass at a particular stage of life is a risk factor for breast cancer [14, 16, 18, 19]; it was found that premenopausally there was a significantly inverse association between higher relative weight at 18 years old and breast cancer. Ballard-Barbash and associates found that the location of body fat increased risk of breast cancer in postmenopausal cases only [11]. Central or abdominal adiposity was associated with increased breast cancer risk. This result was confirmed by Folsom [19], who found that the mean waist:hip ratio was 2% higher in cases than controls, and Shapira [12] in which the OR for breast cancer progressively increased as the waist:hip ratio increased. Although Ballard-Barbash [20] found no association between baseline BMI and subsequent breast cancer, those in the upper tertile of body mass gain had an increased relative risk.

Table 1. General characteristics of the study population

	Premenopausal women				Postmenopausal women			
	Cases		Controls		Cases		Controls	
	n	(%)	n	(%)	n	(%)	n	(%)
Total number	196		191		421		340	
Age (yrs)								
25-44	104	(53.1)	97	(50.8)	≤54	70	56	(16.4)
45+	92	(46.9)	94	(49.2)	55-64	162	142	(41.8)
					65+	189	142	(41.8)
Education years								
≤12	95	(17.9)	50	(26.2)	199	(47.4)	148	(43.6)
13-16	91	(46.4)	88	(46.1)	138	(32.8)	125	(36.9)
≥17	70	(35.7)	53	(27.7)	83	(19.8)	66	(19.5)
Marital status								
Married	135	(68.9)	125	(65.4)	251	(59.8)	216	(63.7)
Single	26	(13.3)	28	(14.7)	40	(9.5)	24	(7.1)
Divorced/separated	29	(14.7)	34	(17.8)	39	(9.3)	36	(10.6)
Widowed	6	(3.1)	4	(2.1)	90	(21.4)	63	(18.6)
Age at menarche (years)								
≤12	95	(48.5)	93	(48.7)	181	(43.5)	158	(46.9)
13	67	(34.2)	64	(33.5)	133	(32.0)	90	(26.7)
≥14	34	(17.3)	34	(17.8)	102	(24.5)	89	(26.4)
Age at first birth (years)								
(Parous women only)								
<22	30	(21.4)	31	(24.2)	64	(19.4)	58	(20.3)
22-25	49	(35.0)	37	(28.9)	109	(33.0)	90	(31.5)
≥26	61	(43.6)	60	(46.9)	157	(47.6)	138	(48.2)
Parity								
Yes	156	(80.0)	145	(75.9)	349	(83.3)	297	(87.9)
No	39	(20.0)	46	(24.1)	70	(16.7)	41	(12.1)

Totals may vary due to missing values.

Since the relationship between weight and breast cancer in premenopausal women can be biased by an easier detection of the tumour in thinner women, weight was analysed according to breast cancer stage. In premenopausal women, the association between weight and breast cancer was accentuated in stage 1 cancers, but was still present in stage 2 cancers. Therefore, even if stage at detection can influence the association between weight and breast cancer, the evidence is suggestive for an effect even in more advanced stages.

A marked gain in weight after the age of 18 years (more than 20 kg) was associated with a slightly protective effect in premenopausal women, and with a slight increased risk of breast cancer in postmenopausal women. As suggested [39], overweight in younger ages is associated with lower levels of progesterone and increased prevalence of amenorrhoea resulting in a lower proliferative activity of the mammary gland. Overweight in postmenopausal women is mostly due to excess deposition of adipose tissue, responsible for the synthesis of tumour-promoting oestrogens. In our data, the effect of overweight persisted after adjustment for possible confounding factors known to be associated with both weight and breast cancer, such as education, age and pregnancies. However, it is possible that other unknown factors confound the association, biasing the results towards an unknown direction. Hospital controls represent a selected population in terms of social class and dietary habits; furthermore, the diagnosis of admission is often a chronic

disease that can modify the weight. The selection bias introduced by the use of hospital controls can reduce the magnitude of the association. In our study, we analysed the mean weight and body mass in the different diagnostic categories of controls (cancers, chronic diseases, surgical procedures, trauma, acute infections) and among cases, without finding any significant difference. Furthermore, we used the information on weight in the previous year to reduce the possibility that thin patients had lost weight recently due to cancer.

Physical activity during adolescence or at any age was not associated with breast cancer in our study. However, the low prevalence of reported physical activity, as well as the low level of activity reported by persons who did exercise, decreases the possibility of finding any significant association in our population.

Since the studies showing a negative association between physical activity and breast cancer were conducted among highly trained women and/or athletes, it is possible that a higher level of activity is required for any effect to be detected on breast cancer risk. Frisch found a significant reduction in breast cancer risk in postmenopausal women who participated in college athletics compared with non-athletes [34-36]. Such a protective effect, however, was not found by Paffenbarger and associates [32]. In studies of occupational physical activity, non-sedentary jobs have been associated with a significant reduction of breast cancer risk while women in sedentary occupations had a slightly

Table 2. Odds ratio (OR) of breast cancer with height, weight and body mass

	Cases (n = 196)	Premenopausal Controls (n = 191)	Adjusted OR* (95% CL)	Cases (n = 421)	Postmenopausal Controls (n = 340)	Adjusted OR* (95% CL)
Height (cm)						
<160	47	42	1.0	146	102	1.0
160–162.5	24	26	0.8 (0.4–1.7)	64	38	1.2 (0.8–1.8)
162.6–167.6	80	75	1.0 (0.6–1.6)	149	148	0.7 (0.5–1.0)
≥167.7	45	48	0.8 (0.5–1.5)	62	52	0.8 (0.5–1.3)
Weight (kg) 1 year before diagnosis						
≤57.2	69	46	1.0	102	85	1.0
57.3–63.5	47	39	0.8 (0.4–1.3)	78	71	1.0 (0.6–1.5)
63.6–72.6	41	39	0.7 (0.4–1.2)	118	86	1.2 (0.8–1.8)
≥72.7	39	67	0.4† (0.2–0.7)	123	98	1.1 (0.7–1.6)
BMI 1 year before diagnosis						
<21	54	39	1.0	59	56	1.0
21–23	72	59	0.8 (0.5–1.4)	127	101	1.2 (0.8–2.0)
24–26	35	23	1.1 (0.5–2.1)	94	93	1.0 (0.6–1.6)
≥27	35	70	0.4‡ (0.2–0.6)	141	90	1.5 (1.0–2.3)
Change in weight after the age of 18 years						
Reduced or unchanged	51	40	1.0	86	74	1.0
+1–9.9 kg	61	65	0.7 (0.4–1.3)	107	94	1.0 (0.6–1.6)
+10–19.9 kg	57	45	1.1 (0.7–1.9)	136	100	0.8 (0.6–1.8)
+20+ kg	27	41	0.5§ (0.3–1.0)	92	72	1.2 (0.8–2.0)

\* Adjusted for age (continuous), education (≤12, 13–16, 17+ years), age at menarche (≤12, 13, ≥14 years), pregnancies (yes/no), physical activity at the age 15–22 years (yes/no). †  $\chi^2 = 11.9$ . ‡  $\chi^2 = 11.8$ . §  $\chi^2 = 2.2$ . CL, confidence limits; BMI, body mass index.

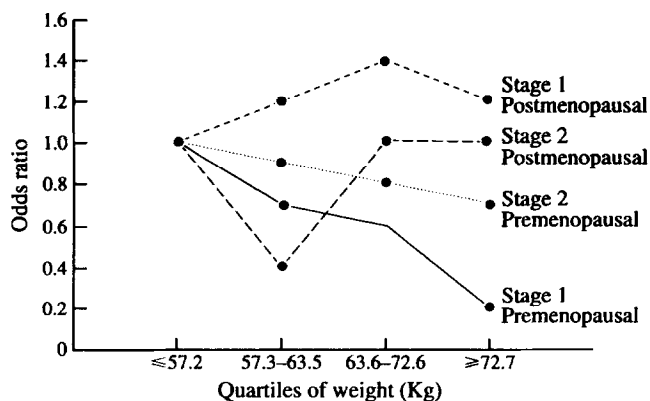


Figure 1. Risk of breast cancer by weight according to stage and menopausal status.

higher risk for breast cancer [31]. Similarly, Albanes [33] found a slightly increased risk for breast cancer in women who were inactive non-recreationally, but no association between breast cancer risk and recreational activity. When the data were analysed according to menopausal status, the authors found an increased risk among those least active (non-recreational and recreational), but among premenopausal women the effect was the opposite, i.e. increased risk among those who were most active [33]. The association of increased all-site cancer risk and low level of non-recreational activity was most notably found in those women of low to moderate relative weight/BMI.

An attempt was made to rule out the possibility that other factors related to breast cancer risk confound the association with physical activity, adjusting the data for age, education, some reproductive variables and body mass. It is possible, however, that the lack of association we found is related to measurement error, since it is difficult, especially for older women, to recall the amount and duration of exercise during adolescence.

Table 3. Odds ratio (OR) of breast cancer with reported physical activity at ages 15–22 years

	Cases	Controls	Adjusted OR	95% CL*	Cases	Controls	Adjusted OR	95% CL†
No exercise	162	152	1.0	(Ref)	378	303	1.0	(Ref)
Calories/week‡								
≤600	6	12	0.5	(0.2–1.3)	3	10	0.2	(0.1–0.9)
601–1012	10	7	1.3	(0.5–3.5)	13	8	1.3	(0.5–3.2)
1013–1750	9	10	0.9	(0.3–2.2)	7	5	1.2	(0.4–4.0)
>1750	8	10	0.6	(0.2–1.6)	14	11	1.1	(0.5–2.6)
Hours of exercise/week‡								
<3	8	8	0.8	(0.3–2.3)	2	5	0.3	(0.1–1.8)
≥3	26	31	0.7	(0.4–1.4)	37	31	1.0	(0.6–1.8)

Totals may vary due to missing values. \* Adjusted for age (continuous), education (≤12, 13–16, 17+ years), body mass index (continuous), age at menarche (≤12, 13, ≥14 years), pregnancies (yes/no). † Data not available for one premenopausal case and three postmenopausal controls. ‡ Data not available for one postmenopausal control. OR, odds ratio; CL, confidence limits; Ref, reference value.

Recall bias is one of the limitations of case-control studies; however, if it was present in our population, we do not believe that it acted differently among cases and controls, since no data were available to the public at that time about the risk of breast cancer associated with overweight and being sedentary. The possible misclassification would be non-differential, and therefore would bias the data toward the null value.

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Pergamon

*European Journal of Cancer* Vol. 31A, No. 5, pp. 728–734, 1995  
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 0959-8049/95 \$9.50 + 0.00

0959-8049(94)00531-1

# Quality Assurance in Cervical Cancer Screening: The Icelandic Experience 1964–1993

K. Sigurdsson

Monitoring of the effectiveness of a screening programme is vital to ensure optimal use of public resources. This report correlates the results of the Icelandic cervical cancer screening programme with the results of monitoring the programme since 1964. Screening has significantly decreased both the incidence and mortality rates and greatly affected the stage distribution of squamous cell carcinomas, but not of adeno- and adenosquamous carcinomas. In the 25–64 years age group, 84% were screened, 80% of whom were in the organised screening. Smears taken outside the guidelines amounted to 10%. Sensitivity at 1 year was 93% for all smears. At 3 years it was 81% for squamous cell carcinomas, and 42% for adeno- and adenosquamous carcinomas. The rate of unsatisfactory smears was 1.3% for all smears, and 4.5% of the women had abnormal smears (7.7% in the 20–24 years age group). The specificity of the smears test was 98%. It is concluded that monitoring is vital for optimal screening results and although screening is effective in the targeted age group of 25–64 years it should preferably start sooner after age 20 years with a screening interval of 2–3 years.

**Key words:** quality assurance, health care, sensitivity and specificity, mass screening, cervix neoplasms, vaginal smears, incidence, mortality, organisation, adenocarcinoma, squamous cell carcinoma

*Eur J Cancer*, Vol. 31A, No. 5, pp. 728–734, 1995

## INTRODUCTION

VIEWED GLOBALLY, invasive cervical cancer accounts for approximately 15% of all cancer in women, the second most prevalent after breast cancer which accounts for approximately 18% [1]. In many countries, cervical cancer is the leading cancer in women. In the U.S.A. (SEER Programme), during the period 1983–1987, the average world-adjusted incidence among Caucasian females was approximately 7 cases per 100 000 women

and among black females approximately 12 cases per 100 000 per year. The incidence is, however, highest in the developing areas of the world with approximately 40 to 55 cases per 100 000 women per year in some areas of Latin America and Asia [2].

In the Nordic countries, during the period 1981–1985, cervical cancer was the sixth most common malignancy in women with an average world-adjusted incidence rate of 11 per 100 000 women per year. The age-specific incidence rose from 3.1 at the ages of 20–24 years to 21.8 at the ages of 45–49 years, reached a maximum of 31.2 at the ages of 65–69 years and then decreased to 20.3 at the ages of 90–94 years. Although the disease is rare below the age of 25 years, the incidence is increasing in the 20–24 years age group in all the Nordic countries except Finland [3,4].

Correspondence to K. Sigurdsson at the Cancer Detection Clinic of the Icelandic Cancer Society, P.O. Box 5420, IS-125 Reykjavík, Iceland.  
 Received 11 Aug. 1994; accepted 19 Dec. 1994.