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FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ARM LYMPHEDEMA FOLLOWING BREAST CANCER TREATMENT: A MATCH PAIR CASE-CONTROL STUDY

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ABSTRACT

We examined factors that may influence the development of arm lymphedema following breast cancer treatment including the specific mode of therapy, patient occupation and life style. Medical record data and a questionnaire were used to collect information after surgery concerning such issues as wound seroma, infection, adjuvant treatment, vessel string (phlebitis), body mass index, smoking habits and stress. Occupational workload was assessed after surgery whereas housework, exercise, hobbies and body weight were assessed both before and after surgery. Seventy-one breast cancer treated women with arm lymphedema lasting more than 6 months but less than 2 years were matched to women similarly treated for breast cancer but without arm lymphedema (controls). The matching factors included axillary node status, time after axillary dissection, and age. In the lymphedema group, there was a higher body mass index at time of surgery ($p=0.03$) as well at time of study ($p=0.04$). No differences were found in occupational workload ($n=38$) or housework, but the lymphedema group reduced their spare time activities including exercise after surgery compared with the controls ($p<0.01$).

In conclusion, women treated for breast cancer with axillary node dissection with or without adjuvant radiotherapy could maintain their level of physical activity and occupational workload after treatment without an added risk of developing arm lymphedema. On the other hand, a higher BMI before and after operation increases the lymphedema risk.

Although an increasing number of patients are surviving long-term after surgery and often radiotherapy for management of breast cancer, some women develop post-treatment arm lymphedema. The incidence of this complication in Scandinavia varies widely from 0-60% (1-5) depending on how edema is defined. The risk of developing lymphedema, however, persists regardless of the time after operative treatment (6). Without treatment of the arm, swelling gradually worsens with time (7).

Most studies on lymphedema concentrate on its management, emphasizing the use of compression garments, bandaging, pumps, massage, and exercise (8-12), rather than on its prevention.

In Sweden, preoperative information is usually given to the patient with breast cancer including recommendations how to minimize the later development of arm lymphedema (13). The recommendations are often based on empiricism, only in part on scientific evidence, e.g., elevating the arm (14)

TABLE 1
Treatment Related Factors for Breast Cancer Patients with Arm Lymphedema and Without (Controls)

	Lymphedema n=17	Controls n=71	p-value
Age (mean±SD) years	58.2±10.5	58.1±9.4	n.s.
Surgery			
Time from operation (mean±SD) months	33.0±16.7	33.1±16.8	n.s.
Site, right/left, number	33/38	30/41	n.s.
Side, dominant/nondominant/ambidextrous number	36/34/1	40/28/3	n.s.
Type, partial/mastectomy, number	29/42	36/35	n.s.
Tumor size (mean±SD) mm	22.5±16.1	20.3±13.1	n.s.
Axillary nodes (mean±SD)			
number dissected	13.0±5.1	12.0±4.7	n.s.
number with metastasis	2.2±3.4	2.8±4.3	n.s.
Seroma			
Indwelling drain[a]			
(mean±SD) ml	233.0±284.4	247.0±263.6	n.s.
time, (mean±SD) days	2.9±1.8	3.2±2.8	n.s.
By puncture			
number of patients	28	21	n.s.
(mean±SD) ml	250.1±742.0	134.5±357.6	n.s.
number of suctions (mean±SD)	0.9±1.5	0.6±1.2	n.s.
time, (mean±SD) days first to last puncture	7.6±15.4	4.2±9.5	n.s.
Adjuvant treatment			
Radiotherapy			
breast and axilla, number	40	40	n.s.
breast only, number	19	24	n.s. p=0.06
no radiotherapy, number	12	7	n.s. p=0.06
Chemotherapy, number	22	27	n.s.
Tamoxifen, number	28	20	n.s.
Edema preventive information, number	45	36	n.s.

[a]64 pairs with complete data.

and propelling lymph flow by skeletal muscle contraction (15). As these recommendations have broad ramifications on the activities of daily living, they should be well grounded. There may also be other predisposing factors in lymphedema development not as yet included in the recommendations. Accordingly, we examined potential factors including specific form of breast cancer treatment, patient occupation and lifestyle associated with the development of arm lymphedema after breast cancer therapy.

CLINICAL DESIGN

Subjects

The study included 103 women treated for breast cancer who developed arm lymphedema but without recurrence of the

TABLE 2
Sociodemographic Data for Breast Cancer Patients with Arm Lymphedema and Without (Controls)

	Lymphedema n=17	Controls n=71	p-value
Civil status (living alone/together)	13/58	12/59	n.s.
Number of children ≤ 14 years (none/at least one)	59/12	63/8	n.s.
Education level (low/medium/high)	24/28/19	31/24/16	n.s.
Sick leave after surgery			
number of patients			
(sick leave less than 2 weeks/			
sick leave more than 2 weeks/retired)	1/50/20	4/46/21	n.s.
months (mean±SD)[a]	6.0±5.3	5.0±9.3	n.s.

[a]Lymphedema group n=51, controls n=50

malignancy. The onset of edema had to be at least 3 months or more after operation, was noted in the medical record between January 1997 and June 1998 and had persisted for at least six months. Patients were identified through a physiotherapists's registry of lymphedema patients in 11 hospitals in the South Sweden Health Care Region. Permission from each patient was obtained through these physiotherapists. Two control patient groups treated for breast cancer (but without arm lymphedema) were identified for each subject through the Regional Tumor Registry. The determining factors for matching were in the following order: axillary node status (positive or negative for metastasis), time after axillary surgery (within a two month interval), and age (as close as possible) *(Table 1)*. Only one control group was used and was identified following the determining factors in the same order. To exclude women with unrecognized arm lymphedema in the control group, each woman was asked to provide information about arm swelling when returning the questionnaire. Sociodemographic data for the two groups are shown in *Table 2*.

The study was approved by the Research Ethics Committee, Lund University, 1998.

Data Collection

Data was collected from the medical records and from a questionnaire. The questionnaire was mailed to clinical subjects and controls in February 1999 with a single reminder. Questions were asked in relation to the time period before operation (1 year) for all individuals. The time period after surgical treatment was related to "since surgery" for the control group and "from surgery until onset of arm lymphedema" for the edema group.

In a pilot study, the questionnaire was tested for relevance of questions in 15 breast cancer treated women with arm lymphedema. The women were asked to complete the questionnaire and report if any question was unclear or irrelevant. Results revealed data making it possible to change opened questions into closed ones within the fields of housework, exercise, and hobbies.

Sociodemographic Data

Living conditions were reported in the questionnaire including marital status and number and age of children living in the household. Formal education was classified

as low if the woman had received only nine or less years basic education, and high if she had studied in a university or comparable institution. Sick leave (months) following the breast cancer treatment was reported by the women as full- time or part-time. Part-time sick leave was converted into full-time before final analysis.

Treatment Related Factors

The following information concerning treatment related factors was collected: type of operation and site, tumor size, number of excised lymph nodes and metastases in the axilla, postoperative seroma drainage and its evacuation by aspiration, wound infection, history of vessel string (phlebitis) (5), and cellulitis (erysipelas). Radiotherapy to the axilla was also codified. Other adjuvant pharmacological treatments registered included anti-estrogen drugs (Tamoxifen) or cytotoxic chemotherapy.

Factors Related to Occupational Workload

Women working outside their homes were asked to state their occupations and describe the occupational workload in terms of flexible/sedentary, monotonous/varied, heavy/easy, extra aids, etc. In 5 subjects, the answers had to be compiled by a telephone interview.

Physiotherapeutic assessment

One of the team (KO), a physiotherapist with experience within the ergonomic field, classified workload of the different occupations represented, according to a previous model (16). Five items were assessed concerning the upper extremity, namely: 1) lifting (practical nurse, child minder); 2) repetitive and/or static work (telephone operator, factory worker); 3) awkward working posture with respect to the neck and shoulder (medical secretary, hairdresser), 4) heavy work with hands and/or forearms (shop assistant, cleaner); 5) exposure to hand vibrations (bus driver, farmer). Each item was rated on a four point scale (0-3), with 3 as maximum exposure. Examples of occupations given the rating 2 are shown above within parentheses. The classification was performed blindly, that is, without knowledge of the subject's lifestyle.

Intra-reliability test for each of the 5 items was performed in 20 subjects randomly selected from the main 38 pairs. This test was performed two months after the first assessments were made in order to assure that no details from the first assessment was remembered. The test showed good correlation (Spearman's $r_s = 0.919$; $p<0.001$).

Self-assessment

Women were asked to self-assess their occupational workload. The following five weight categories were employed to assess lifting: "less than 1 kg," "1-5 kg," "6-20 kg," "20-50 kg," and ">50 kg." Further questions were asked regarding sudden unexpected loads (1 question), repetitive or static work (3 questions), and hand vibrations (1 question). A four-part scale with the levels never/rarely, sometimes, rather frequently and frequently was used. The questions were an excerpt from The Scandinavian Occupational Classification (17).

Life-Style Related Factors

Body weight, smoking and psychological stress

Information was collected regarding height and preoperative body weight at time of surgical treatment, from the medical record, and from the questionnaires. Body mass index (BMI) was calculated. A smoking history was catalogued including the number of cigarettes used daily. The following question concerning stressful events was posed: "The initial cancer treatment might cause a high level of psychological distress. Have there been any circumstances after the

operation also causing deep distress e.g., death of a close relative or friend, divorce, unemployment, economic problems or similar situations?"

Housework

The women were asked to what extent they took responsibility for housework in the period before and after surgery. The alternatives were: not at all, 25%, 50%, 75%, or all.

Exercise

Women were asked how many times a week they regularly exercised such as by walking, cycling, physical training and other activities (open question) for more than 30 minutes in each time period before and after surgery.

Hobbies

Women were queried if they did easy (e.g., weeding), medium or heavy work (e.g., digging) in the garden, and what kind of needlework or other hobbies (open question) they practiced regularly, both before and after surgery

Factors Influencing Arm Lymphedema

The women with arm lymphedema (n=71) were asked where the upper extremity was actually swollen at the time of the study. The choices given were hand, forearm, upper arm, and chest wall. They were also asked if they had noticed improvement or worsening of arm edema with housework, exercise or hobbies.

STATISTICS

Data from matched subjects were compared by McNemar's test for binary data, by the sign test for ordinal data, and by the paired t-test for continuous data (18). When response data was missing for some patients with lymphedema or without lymphedema (controls), only pairs with complete information were included in the statistical testing procedure.

RESULTS

Subjects

Two women initially placed in the control group reported having arm lymphedema and were excluded. The response rate was 78% for the entire group of subjects and 80% for matched pairs (n pairs=71). In 38 of the matched pairs both women were working at least half-time. One control and 3 women in the lymphedema group had decreased their occupational work to half-time after surgery. Other sociodemographic data are shown in *Table 2*. Data in the medical record was incomplete for body weight at time of operation for 5 subjects and for an indwelling drain for seroma in 7. Seventeen women did not recall if they had a vessel string (sign of phlebitis).

Treatment Related Factors

There were no significant differences in breast cancer treatment between the two groups concerning type of surgery or adjuvant therapy *(Table 2)*. However, there was a trend toward a higher number of women treated with radiotherapy to the breast only in the non-edematous (control) group (p=0.06) and also a trend toward a higher number of women who did not receive radiotherapy in the lymphedema group (p=0.06) *(Table 1)*.

There were no significant differences between the two groups concerning a vessel string (i.e., phlebitis), wound infection *(Table 3)*, or seroma formation treated by an indwelling drain or by suction *(Table 1)*. More women in the lymphedema group had a history of erysipelas compared with the control group *(Table 3)* but the difference was not statistically significant.

TABLE 3
Frequencies of Postoperative Wound Infection, Erysipelas and Vessel String (Phlebitis) in Matched Pairs of Breast Cancer Patients with Arm Lymphedema or Without (Controls)

	Wound infection n=71			Erysipelas n=71			Vessel string n=54		
	Lymphedema			Lymphedema			Lymphedema		
	+	-		+	-		+	-	
Controls +	0	2	2	0	1	1	22	12	34
Controls -	2	67	69	5	65	70	14	6	20
	2	69	71	5	66	71	36	18	54

Factors Related to Occupational Workload: Physiotherapeutic Assessment

Three control patients and 4 women in the lymphedema group had decreased their occupational workload after surgery. Comparisons were made between the edema group and the control group for each item of workload except for item 5, namely, exposure to hand vibrations, as this exposure was extremely rare in both groups (n=3 and n=1, respectively). The analyses showed no significant differences between the two groups in each queried workload item. Frequencies are shown in *Table 4A*.

Self-assessment

Comparisons were made between the edema and the control group for each weight category and workload conditions. The analyses showed no significant differences between the groups in any item. Frequencies are shown in *Table 4B and 4C*.

Life-Style Related Factors

Body weight, smoking and psychological stress

BMI was higher in the lymphedema group than in the control group both at time of surgery and at time of study *(Table 5)*. No significant difference was found in weight gain during this period. There were no significant differences between the groups concerning smoking habits or stressful events *(Table 5)*. The most frequent examples of such events given by the women were severe illness or death of close relatives or friends (n=21) and worry about or crises with husband, children or parents (n=13).

Housework

Both groups significantly (p>0.001) reduced their responsibility for housework before surgery compared with after surgery. There were no significant differences between the groups either before or after surgery *(Table 6)*.

Exercise

Except for walking, cycling, and physical training that was specifically asked about, the patients mentioned other physical activities such as jogging, swimming, pool aerobics, tennis, badminton, table tennis, golf, boule,

TABLE 4A
Numbers of Matched Pairs (n=38) of Breast Cancer Patients with Arm Lymphedema and Without (Controls) in Different Kinds of Work-load Conditions (for details, see text) Rated by a Physiotherapist on a 0-3 Scale

	Heavy lifting				Repetitive/static				Neck/shoulder				Hand/forearm				Vibrations			
	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
Lymphedema	24	5	9	0	22	8	8	0	15	14	9	0	23	9	6	0	37	0	1	0
Controls	26	4	8	0	21	6	11	0	16	10	12	0	24	10	4	0	35	1	2	0

- = never/rarely; + = occasionally; ++ = sometimes; +++ = frequently

TABLE 4B
Numbers of Matched Pairs (n=38) of Breast Cancer Patients with Arm Lymphedema and Without (Controls) Rating Workload (for details, see text)

	Less than 1 kg				1-5 kg				6-20 kg				20-50 kg				>50 kg			
	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
Lymphedema	7	5	7	19	4	14	12	8	16	13	7	2	32	4	1	1	34	3	0	1
Controls	10	3	7	18	10	6	11	11	17	11	5	5	31	5	1	1	34	2	1	1

- = never/rarely; + = occasionally; ++ = sometimes; +++ = frequently

TABLE 4C
Numbers of Matched Pairs (n=38) of Breast Cancer Patients with Arm Lymphedema and Without (Controls) Rating in Different Kinds of Workload Conditions (for details, see text)

	Unexpected load				Lifted arms position				Repetitive movements				Static, exact work				Vibrations			
	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
Lymphedema	32	5	1	0	6	12	11	9	11	9	7	11	26	9	0	3	34	3	0	1
Controls	30	7	0	1	9	12	8	9	10	12	8	8	30	4	2	2	34	2	1	1

- = never/rarely; + = occasionally; ++ = sometimes; +++ = frequently

TABLE 5
Life-Style Related Factors for Breast Cancer Patients With Arm Lymphedema and Without (Controls)

	Lymphedema n=17	Controls n=71	p-value
BMI at time of operation, (mean±SD)[a]	26.4±4.0	25.0±4.3	p=0.04
BMI at time of study, (mean±SD)	26.6±3.8	25.0±4.5	p=0.03
BMI increase, (mean±SD)[a]	0.3±1.8	0.3±1.9	n.s.
BMI ≥ 30			
at time of operation,a number	11	8	n.s.
at time of study, number	15	9	n.s.
Smoking, number of patients (None/1-5 cig/5-20 cig/>20 cig/day)	59/3/8/1	58/2/9/2	n.s.
Stressful events number of patients (no/yes)	44/27	50/21	n.s.

[a]66 pairs with complete data

TABLE 6
Part of Responsibility for Housework (Number of Patients) for Breast Cancer Patients with Arm Lymphedema and Without (Controls)

	Not at all	25%	50%	75%	all	p-value
Lymphedema, before/after surgery	0 / 0	2 / 4	9 / 16	15 / 19	45 / 32	p<0.001
Controls, before/after surgery	0 / 0	0 / 6	7 / 12	26 / 22	38 / 31	p<0.001

TABLE 7
Number of Physical Activities per Week, Median (Range), for Breast Cancer Patients with Arm Lymphedema and Without (Controls)

		Before surgery	After surgery	p-value
Lymphedema	n=71	4 (0-15)	2 (0-14)	<0.001
Controls	n=71	4 (0-22)	4 (0-24)	n.s.

TABLE 8
Numbers of Breast Cancer Patients with Arm Lymphedema and Without (Controls) with Different Kinds of Hobbies Before (b) and After (a) Surgery

		Gardening									
		easy		medium		heavy		Needle work		Other hobbies	
		b	a	b	a	b	a	b	a	b	a
Lymphedema	n=71	27	31	31	17**	19	4***	27	16***	18	12
Controls	n=71	31	34	26	20	10	7	31	27	12	14

**: p=0.003; ***: p<0.001

bowling, body building, work-outs, dancing, and riding. The number of activities per week for each patient was totaled. There was no significant difference in numbers of physical activities between the two groups before and after surgery, although the patients with arm lymphedema reduced the number of exercise activities after surgery (p<0.001) *(Table 7)*. Even when walking and cycling (regarded as "no arm activity") was excluded, the outcome was the same (p<0.017).

Hobbies

The data collected was binary (yes/no). As to gardeners there was no significant difference between the groups in any of the categories (easy, medium or heavy) before or after surgery. The edema group reduced their medium and heavy garden work (p=0.003 and p<0.001, respectively) after surgery compared with beforehand *(Table 8)*. The kind of needlework mentioned by the women were embroidery, sewing, knitting, crocheting, and weaving. There was no significant difference between the groups in number of women performing needlework before and after surgery. After surgery the number was reduced in the edema group (p<0.001) *(Table 8)*.

Factors Influencing Arm Lymphedema

Twenty-two of the women with arm lymphedema that still were working (n=38) considered that their occupation worsened the edema. Most frequently mentioned activities was working at computer or word processor (n=8) and heavy lifting (n=7).

Thirty-five of the patients in the lymphedema group considered housework to aggravate the arm edema. The five activities most often cited were window cleaning (n=14), vacuum cleaning (n=10), floor wiping (n=7), carrying (n=7), and ironing (n=7).

Fourteen of the patients with arm lymphedema considered exercise to have a negative impact on the arm edema, whereas 10 thought it helped. Examples of a negative impact were walking or cycling with the arm hanging (n=8), heavy exercise, work-outs, bodybuilding, riding, golf, boule, and cross-country skiing. A positive influence was found in light exercise/Qigong (n=8), and pool aerobics/swimming (n=3).

Eighteen patients with arm lymphedema thought hobby activities exerted a negative influence on the edema and one found a positive influence. The most frequent negative examples cited were gardening (n=13) and sewing/embroidery (n=6). Weaving was considered beneficial.

DISCUSSION

Professionals often advise women treated for breast cancer to rest the arm and "be careful" to avoid arm lymphedema (19-21). Such advice promotes the idea that inactivity is beneficial. In the present study, we found no support for this admonition. Rather, an unchanged level of physical activity after treatment seems preferable.

Another suggestion to minimize arm edema is to avoid heavy lifting. This advice makes some women hesitate to return to heavy work such as that in the health care sector. To our knowledge, there has been no previous attempt to determine if there are any differences in work load during occupational work or spare time activities for women who develop arm lymphedema after treatment of breast cancer. Most questionnaires do not take these issues into consideration. Because in our clinical experience such questions were included using parts of a tested questionnaire (17) created primarily to assess loading on musculoskeletal structures, they were considered relevant to this study. In this regard, there was no statistical difference objectively *(Table 4A)* or subjectively *(Table 4B,4C)* between those women with or without arm lymphedema after treatment for breast cancer.

The women with arm lymphedema restricted exercise and hobby activities after operation *(Table 7, 8)*. This finding may relate to greater pain (22), depression (23), or professional advice. Nonetheless, the fact remains that they were less physically active after operation but this inactivity was not advantageous in preventing the onset of lymphedema. It seems that more directed help (e.g., follow-up programs and personal advice) to continue physical activity level unchanged may be the wisest course. As for increased physical activity, Harris et al (24) examined 20 breast cancer treated women taking part in an upper-extremity strengthening and aerobic condition program to prepare and carry through Dragon Boat racing. At the end of the racing season (7-8 months), no woman showed a significant difference in circumference between the operated and non-operated arm. This finding suggests that even vigorous physical activity is unlikely to promote arm lymphedema. In the present study, we did not examine the risk associated with various exercise and hobby programs but such studies need to be prospectively examined as physical activity affects the production, metabolism, and excretion of "female" hormones which may be linked to a lower risk of breast cancer in active women (25,26). Exercise may also contribute to recovery from the impact of breast cancer treatment by resetting the sympathetic tone of lymphatic vessels (27), activating lymphangions and propelling lymph flow by skeletal muscle contraction (15), improving range of motion (28), and stimulating the immune system (29).

Previous studies have suggested that obesity contributes to arm lymphedema after treatment of breast cancer (2,30,31). This conclusion is supported by our findings showing BMI to be higher in the women who developed arm lymphedema *(Table 5)*. We also found, however, that the BMI of those that developed arm lymphedema was already higher at time of surgery or at the time the arm was without edema. Thus, it seems appropriate to instruct women who are obese to lose weight including the already determined safety of maintaining or even increasing physical activity. Because weight gain was similar in the control group and in the lymphedema group, the contribution of arm edema as opposed to the influence of increased body weight in development and progression of arm lymphedema seems negligible.

For actual treatment related factors to the development of arm lymphedema, there was no difference between the groups as to the specific regional treatment performed *(Table 1)* as found in previous studies (32,33). Soft tissue infections were more common in the lymphedema group *(Table 3)* but not

statistically significant with a very small number of subjects. Segerström et al (2) previously noted the development of soft tissue infection in the arm as a contributor to the development of arm lymphedema.

In a retrospective questionnaire, accuracy of data collection depends on human factors, such as memory and perception, that are inherently subject to distortion (34). Aseltine et al (35), for example, examined the recollection among patients treated for benign prostatic hyperplasia. Whereas they found that retrospective changes in how patients felt showed good agreement with prospective symptomatic assessment, they also showed that a patient's retrospective report of change in overall health was more favorable than objective benefit before and after treatment. Litwin et al (36) also showed that men treated for prostate cancer tended to remember their baseline health-related quality-of-life before surgery as being better than it actually was. Other studies suggest that for recall of sociodemographic data (37), the bias may not have as great an impact and may stabilize over time (38). Our study questionnaire was more related to sociodemographic data, and thus the bias is probably less than if it had been quality-of-life related. Litwin et al also noted that recall bias decreased with better education but did not vary with age or time after operation. Because there were no differences between the two groups in our study concerning time after operation, age and education, any potential bias was dissipated.

In the matching procedure, two subgroups of patients were defined, one with and the other without axillary radiotherapy. Women receiving radiotherapy to the *breast only* or no radiotherapy were not divided, because earlier studies have shown no difference in later arm lymphedema in these two subgroups (5). Nonetheless, an increased risk of developing arm lymphedema for patients receiving radiotherapy to the *axilla* has been well documented (1,2,5,32); accordingly, these women were analyzed separately.

In the matched pairs of patients there was a similar time frame from surgery to study *(Table 1)*, although during this interval only some women developed arm lymphedema. Thus, time for exposure to risk factors was longer for the women in the control group (i.e., they did not as yet develop arm edema). The fact that these women did not develop arm lymphedema supports the findings that occupational workload and life-style related factors were not significant risk factors for later development of arm lymphedema.

In summary, women with arm lymphedema showed a higher BMI compared with women without arm lymphedema both before and after development of arm swelling making a higher BMI an increased risk for this complication. Despite the fact that women without arm lymphedema displayed a similar level of occupational workload to those of the lymphedema group shows that work is not itself a contributor to its development. Indeed, the lymphedema group had also decreased their overall level of physical activity after surgery compared with those who did not have arm lymphedema. Thus, the soundest advice for a woman treated for breast cancer by axillary node dissection with or without adjuvant radiotherapy, seems to be to continue with her occupational workload and maintain her level of physical activity after therapy.

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