

# The Response to Endocrine Therapy in Patients with Advanced Breast Cancer in Great Britain and Japan

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**Abstract**—A prospective study has been carried out to compare the response rates to endocrine therapy of Japanese and British women with breast cancer. Premenopausal women were treated by ovarian ablation, patients who were up to five years postmenopausal were prescribed androgen therapy and patients who were more than five years postmenopausal were treated with oestrogens. No differences in response rate, response time or survival could be detected in the three categories of patients. Significantly more Japanese patients presented with pulmonary metastases in the pre- and postmenopausal groups. In postmenopausal Japanese patients treated with oestrogens, those with pulmonary metastases survived significantly longer.

## INTRODUCTION

THE INCIDENCE of breast cancer is lower in Japan than in Western countries, particularly in postmenopausal women [1, 2], and the prognosis in patients with the early stages of the disease is said to be better [3]. Differences have been reported in the histological features of tumours in patients in Japan and the West [4-6], and it has also been suggested that there may be differences in endocrine function, both in patients and in normal women [7].

The present study was established to see whether the response to endocrine therapy in the advanced disease also differed in the two populations.

## MATERIALS AND METHODS

### Patients

From October 1968 onwards, all patients presenting with advanced breast cancer at the Breast Unit, Guy's Hospital, London, the National Cancer Center, Tokyo and the Aichi Cancer Center, Nagoya were considered for the investigation. Strictly consecutive patients were entered providing they had histologically proven carcinoma of the breast which was recurrent or disseminated, or had extensive local disease unsuitable for surgery or radiotherapy. The patients were divided into three treatment groups: (group A) premenopausal women who were treated by ovarian ablation; (group B) menopausal women who were treated by androgen therapy; and (group C) postmenopausal women who were treated by oestrogen therapy.

### Baseline assessment

All patients had the following clinical and laboratory investigations before endocrine treatment was started: (1) full clinical examination with grouping of all suitable lesions into

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systems (e.g. breast, lymphatic, cutaneous, skeletal, visceral). If possible, two perpendicular measurements of superficial lesions were obtained; (2) photographs were taken on a standard colour reversal film; (3) radiographs were taken of the chest, total spine and pelvis; (4) serum calcium, phosphate and alkaline phosphatase were measured.

#### *Follow-up assessment*

Each patient was seen at four-weekly intervals for the first year. If lesions remained static or were in regression for at least a year, the patients were thenceforward seen at three-monthly intervals. All clinical baseline features were measured again at each visit. Photographic and radiological records were repeated at three-monthly intervals.

#### *Group A—ovarian ablation*

Patients were included who were premenopausal—defined as having had a menstrual period within the previous six months. An artificial menopause was induced usually surgically by bilateral salpingo-oophorectomy, but in a few instances (patient preference, debility, severe pelvic involvement) ovarian irradiation was used. In the latter case the minimum central dose was 1200 rad and the maximum dose 1800 rad in four days. In all patients this resulted in complete cessation of periods. Assessment was from the date of the last dose of radiation or from the day of operation.

#### *Group B—androgen therapy*

In this group were included all patients whose last period was between six months and five years previously (i.e. to the end of the 5th postmenopausal year). Patients were treated by oral fluoxymesterone, 10 mg t.d.s. if they weighed 60 kg or more and 10 mg b.d. if they weighed under 60 kg. Treatment was stopped only if (a) there had been deterioration or no response after two months of uninterrupted therapy, (b) if the patient deteriorated so rapidly that it would have been unethical to continue treatment for two months, (c) excessive virilisation occurred and was distressing to the patient, (d) hypercalcaemia developed after treatment started or (e) jaundice became apparent during treatment.

#### *Group C—oestrogen therapy*

Patients were included whose last period was more than five years previously. There was no upper age limit. All patients were prescribed diethylstilboestrol 50 mg daily by mouth from the first attendance. If they were unable to

tolerate this dose, ethinyl oestradiol 1 mg daily was substituted. Treatment was stopped for the same reasons as detailed under (a) and (b) in Group B and, additionally, (c) if side-effects of nausea and vomiting were severe, (d) deep vein thrombosis or recurrent superficial thrombophlebitis occurred during treatment or (e) if oestrogen-induced fluid retention was severe enough to cause congestive cardiac failure that could not be controlled by oral diuretics.

#### *Exclusions*

The following categories were excluded: patients with previous or current malignancies at a different site; patients whose only criterion for assessment of response was a pleural effusion or ascites; patients who had received previous endocrine therapy or chemotherapy; patients who had had a hysterectomy and in whom the date of the natural menopause was unknown.

#### *Assessment of response*

Accrual of patients for this investigation was carried out between 1968 and 1977, before the U.I.C.C. criteria of response [8] had been formalised. The methods of assessment detailed below are defined in a similar way to these criteria and were in common use at that time. All patients were externally reviewed and an accurate comparison could be made between the two groups.

*Success rate.* Response was assessed according to the criteria described by Hayward [9] and subsequently modified by the British Breast Group [10]. This system categorised patients into three groups: (i) success: all visible, palpable and radiological lesions improve. The remission should last at least six months, during which time no new lesions should appear; (ii) failure: the disease is apparently unaffected by treatment. All visible, palpable or radiological lesions progress and new lesions may appear; (iii) intermediate: this group includes all cases in which response is in doubt. Three categories are recognised: (a) a mixed response: some lesions improve, others get worse; (b) a static response: all or most lesions remain stationary for a long period before slowly deteriorating; (c) a temporary response: here there may be a complete remission of all lesions but for a period of less than six months.

*The mean clinical value (MCV).* This is a numerical method of assessment which entails the monthly allotting of a mark to each lesion according to whether it has improved (2 marks), is the same (1 mark), or is worse (no marks) than before treatment. These marks are

added together, averaged, and multiplied by a factor of 6, so that a figure between 0 and 12 is given to the patient. A figure of 0 means that all lesions are worse, a figure of 12 means that all are better and an intermediate mark would mean that not all the lesions had responded in the same way. These MCVs are plotted on a chart at four-weekly intervals and a mean for all patients in each group can be obtained at any time after treatment and used for comparing response. It was described originally by Walpole and Paterson [11] and subsequently modified by Hayward [9].

**Survival.** Survival is expressed in months from the start of additive hormone therapy or completion of ovarian ablation.

#### External review

The categorisation of response was assessed biennially by a Japanese and British panel (two Japanese and one British for the Japanese results and two British and one Japanese for the British results). Each patient was considered by this panel and, from recorded notes, serial X-rays and photographs, a decision was made on the effects of treatment, as categorised above.

Table 1. Group A—ovarian ablation: cases withdrawn

	British	Japanese
Prior systemic therapy	8	1
Hormones given in addition to ovarian ablation	2	3
Lesions not assessable	6	4
Lost to follow-up	2	3
Total	18/118	11/111

#### Statistical analysis

The significance of differences between dichotomous variables was determined by the Chi-square test for trends and Student's *t* test for mean values. Durations of response and survival were analysed by the log rank method.

## RESULTS

#### Group A—ovarian ablation

One hundred and eighteen British and 111 Japanese cases were admitted to this group. Of these, 18 British and 11 Japanese cases were subsequently withdrawn for the reasons given in Table 1. This left 100 Japanese and 100 British cases available for comparison. Thirteen per cent of the British patients and 10% of the Japanese patients had ovarian ablation carried out by irradiation. Table 2 compares the response rate, MCV and survival data in the two groups of patients. No significant difference can be detected in any of these parameters. If the success cases only are compared, there is again no significant difference in MCV or survival (Table 3). Life tables were drawn of the survival experience and length of remission in the two groups of patients, and the curves were found to be almost identical.

#### Group B—androgen therapy

Ninety-six British and 34 Japanese patients were entered into this section of the investigation. Twelve British and 5 Japanese cases were subsequently withdrawn for the reasons given in Table 4. This left 84 British and 29 Japanese cases available for comparison. Tables 5 and 6 detail the success rate, MCV and survival experience in these two groups. Again,

Table 2. Group A—ovarian ablation

	British	Japanese
Total number admitted	100	100
Age:		
mean	42.9	41.7
range	27–55	26–52
Percentage castration by irradiation	13	10
Response:		
success	21 (21%)	27 (27%)
intermediate	25 (25%)	21 (21%)
failure	54 (54%)	52 (52%)
Mean MCV at 3 months	4.3	5.2
Length of remission (months):		
mean	5.3	7.2
range	0–54	0–63
Survival (months):		
mean	20.8	24.9
range	0.6–107.8	0.1–116.7(+)

Table 3. Group A—ovarian ablation: success cases

	British	Japanese
Number of success cases	21	27
Age:		
mean	42.6	43.1
range	27–52	31–52
Percentage castration by irradiation	14	11
Mean MCV at 3 months	10.8	11.5
Length of remission (months):		
mean	18.3	22.6
range	7(+)-54	6–63
Survival (months):		
mean	43.5	42
range	13.5(+)-107.8	10.3–116.7(+)

no significant difference can be detected in the results for the two countries. Moreover, life tables calculated for survival and remission again showed no significant difference.

#### Group C—oestrogen therapy

One hundred and twenty British and 71

Table 4. Group B—androgen therapy: cases withdrawn

	British	Japanese
Prior systemic therapy	6	1
Previous other cancer	1	
More than 6 years postmenopausal	1	
Chemotherapy given as well as androgens		1
Lesions not assessable	2	2
Lost to follow-up	2	1
Total	12/96	5/34

Table 5. Group B—androgen therapy

	British	Japanese
Total number admitted	84	29
Age:		
mean	52.5	51.2
range	31–67	44–57
Years postmenopausal:		
mean	2.8	2.5
range	0.5–6	0.5–6
Response:		
success	11(13.1%)	3(10%)
intermediate	18(21.4%)	13(45%)
failure	55(65.5%)	13(45%)
Mean MCV at 3 months	3.5	4.9
Length of remission (months):		
mean	2.5	3.4
range	0.3–31.0	0–34
Survival (months):		
mean	14.1	21.7
range	0.3–71.1	3.4–109.3(+)

Japanese cases were admitted to this group. Of these, 21 British and 11 Japanese cases were withdrawn for the reasons detailed in Table 7. In Table 8, details of the response, MCV and survival rates in the two groups of patients are given. Again, no significant difference can be detected in the results in either the total series or in those patients who had a successful response to treatment (Table 9). Similarly, life

Table 6. Group B—androgen therapy: success cases

	British	Japanese
Number of success cases	11	3
Age:		
mean	53	50
range	44–60	44–56
Years postmenopausal:		
mean	1.9	1.8
range	1–3	0.5–4.0
Mean MCV at 3 months	11.3	10.8
Length of remission (months):		
mean	13.5	19.7
range	7–31	11(+)-34
Survival (months):		
mean	34.6	45.4
range	20–71.1	11.4(+)-109.3(+)

Table 7. Group C—oestrogen administration; cases withdrawn

	British	Japanese
Previous other malignancy	2	
Previous hysterectomy	4	
Previous systemic therapy	3	1
Insufficient evidence of metastatic disease		3
Lesions not assessable	4	5
Lost to follow-up	4	1
Patient refusal	1	1
Side effects	2	
Died before treatment	1	
Total	21/120	11/71

tables of survival and remission experience showed no significant difference between the two races.

#### *Pattern of metastasis*

At entry into the trial, the sites of metastases in the two races were similar, except that there was a much higher incidence of pulmonary metastases in Japanese patients (Table 10). This increased incidence of pulmonary metastases in Japanese patients occurred in all categories and was significantly higher than the British in Groups A and C. When the remission experience of all patients with pulmonary metastases is compared, the Japanese patients survived slightly longer, although the difference is not significant (Fig. 1). On the other hand, if only patients receiving oestrogen therapy are considered, the Japanese patients

with lung metastases survived significantly longer than the British patients (Fig. 2). Moreover, postmenopausal Japanese patients with lung metastases survived significantly longer than those without lung metastases (Fig. 3). This difference does not hold for premenopausal or menopausal patients receiving ovarian ablation or androgen therapy.

### DISCUSSION

The results of this investigation show that the response to endocrine therapy of British and Japanese patients with advanced breast cancer does not differ to a significant extent. This is in spite of the fact that prognosis in the early disease appears to be better in Japanese patients [3]. The only difference that can be detected in the behaviour of the tumours in the two races is in the pattern of metastasis. Nearly twice as

Table 8. Group C—oestrogen therapy

	British	Japanese
Total number admitted	99	60
Age:		
mean	65.8	62.4
range	50–94	50–80
Years postmenopausal:		
mean	17.1	13.7
range	6–44	5–30
Response:		
success	24(24.2%)	14(23.3%)
intermediate	28(28.3%)	20(33.3%)
failure	47(47.5%)	26(43.3%)
Mean MCV at 3 months	5.2	5.8
Length of remission (months):		
mean	8.6	6
range	0–92(+)	0–31
Survival (months):		
mean	22.7	21.7
range	0.4–102.2(+)	1.6–92.6(+)

Table 9. Group C—oestrogen therapy: success cases

	British	Japanese
Number of success cases	24	14
Age:		
mean	65.3	62.1
range	56–86	57–72
Years postmenopausal:		
mean	16.6	14
range	7–40	8–25
Mean MCV at 3 months	11.5	11
Length of remission (months):		
mean	28.4	19.4
range	7–92(+)	8–31
Survival (months):		
mean	49.3	42.4
range	13–93.6	16.7–92.6(+)

Table 10. Pulmonary metastases

	Group A— ovarian ablation*	Group B— androgens	Group C— oestrogens†
Japanese	$\frac{32}{100}$ (32%)	$\frac{8}{29}$ (28%)	$\frac{22}{60}$ (37%)
British	$\frac{19}{100}$ (19%)	$\frac{17}{84}$ (20%)	$\frac{16}{99}$ (16%)

\* $\chi^2 = 4.45$ ,  $P < 0.05$ .

† $\chi^2 = 8.26$ ,  $P < 0.005$ .

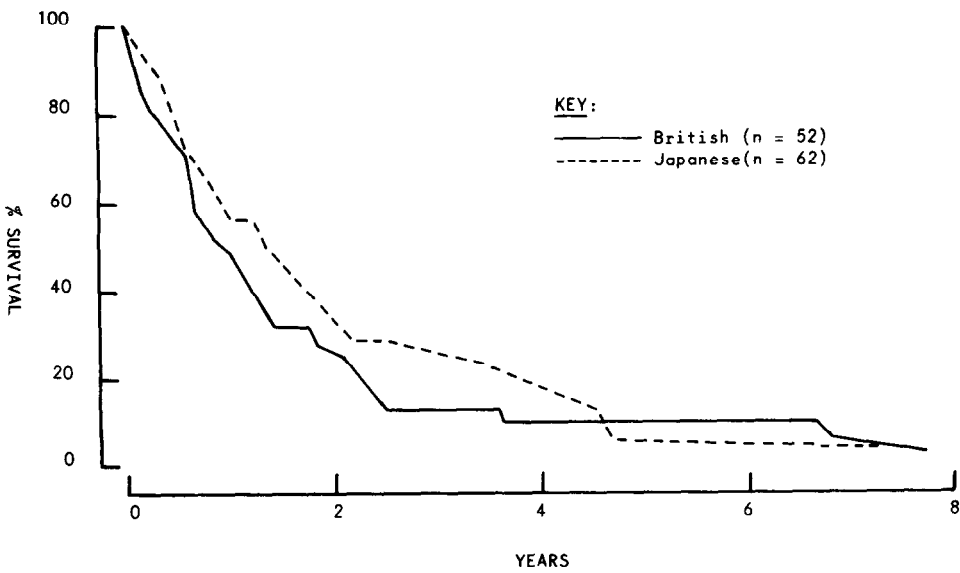


Fig. 1. Survival of British and Japanese cases with lung metastases.

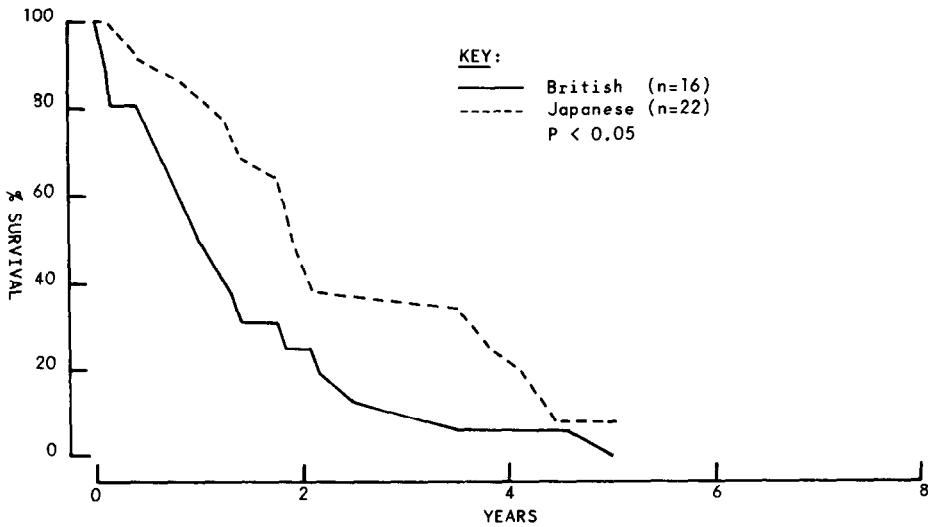


Fig. 2. Survival of oestrogen-treated cases with lung metastases.

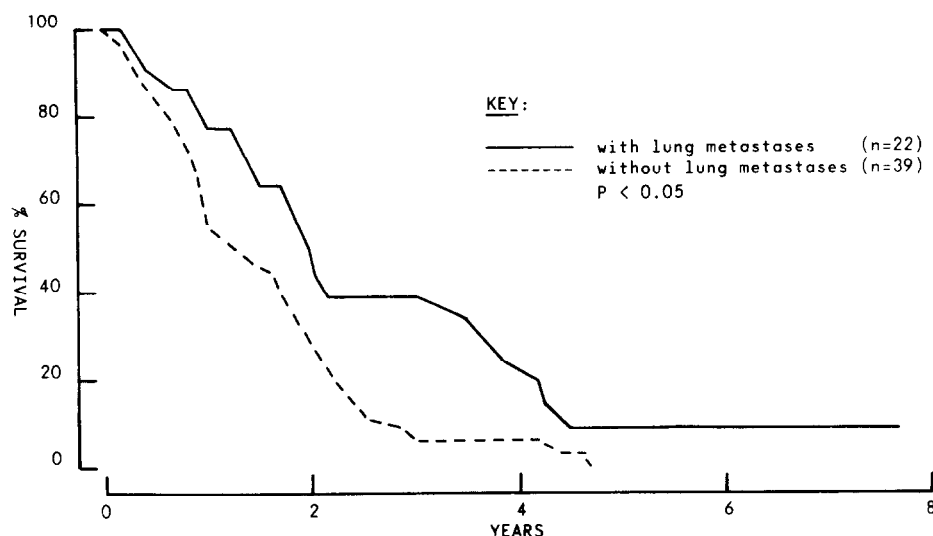


Fig. 3. Survival of Japanese oestrogen-treated cases.

many Japanese patients presented with pulmonary metastases than did British patients. Additionally, in postmenopausal Japanese women the presence of pulmonary metastases was associated with a better prognosis. It is interesting that this phenomenon should be noted only in postmenopausal women because it is in this group that the major difference in the incidence of breast cancer between the two races exists. The Breast Cancer Group in Japan [12], in a retrospective survey, also detected no difference in the effects of additive endocrine therapy or of adrenalectomy in Japanese patients when compared with similar groups of patients in the U.S.A. However, they also noted that their patients with pulmonary metastases survived longer than those with soft tissue or skeletal secondaries, although there was no comment on the relative incidence of pulmonary metastases.

We have no explanation for this difference in the incidence of pulmonary metastases and the effect on survival. Friedell and his colleagues

[13], in a study of the pathology of lymph nodes taken from British and Japanese patients treated by radical mastectomy, noticed a much higher incidence of sinus histiocytosis in the uninvolved lymph nodes in Japanese patients than was the case in British women and suggested that this might be a measure of the patient's immune response to her tumour. It has been postulated [13] that one of the factors involved in oestrogen treatment of breast cancer is an enhancement of immune response. There is at least a possibility, therefore, that the striking remission rate of pulmonary metastases in Japanese postmenopausal women following oestrogen therapy may involve an immunological component.

Nevertheless, whatever differences exist in aetiological factors in the two countries and in the histology and biological characteristics of the primary tumours, response in the advanced disease to hormonal therapy in Japanese and British women is very similar.

## REFERENCES

1. SEGI M, KURIHARA M, MATSUYAMA T. *Cancer mortality for selected sites in 24 countries*. No. 5: (1964-1965). Sendai, Tohoku University School of Medicine, 1969.
2. DOLL R, MUIR C, WATERHOUSE J. *Cancer Incidence in Five Continents, II*. Berlin, Springer-Verlag (UICC publication), 1970.
3. WYNDER EL, KAJITANI T, KUNO J, LUCAS JC, DE PALO A, FARROW J. A comparison of survival rates between American and Japanese patients with breast cancer. *Surg Gynecol Obstet* 1963, **117**, 196-200.
4. MACMAHON B, MORRISON AS, ACKERMAN LV, LATTES R, TAYLOR HB, YUASA S. Histologic characteristics of breast cancer in Boston and Tokyo. *Int J Cancer* 1973, **11**, 338-344.
5. CHABON AB, TAKEUCHI S, SOMMERS SC. Histologic differences in breast carcinoma of Japanese and American women. *Cancer* 1974, **33**, 1577-1579.

6. ROSEN PP, ASHIKARI R, THALER H *et al.* A comparative study of some pathologic features of mammary carcinoma in Tokyo, Japan and New York, U.S.A. *Cancer* 1977, **39**, 429–434.
7. WYNDER EL, BROSS IJ, HIRAYAMA T. A study of the epidemiology of cancer of the breast. *Cancer* 1960, **13**, 559–601.
8. HAYWARD JL, CARBONE PP, HEUSON J-C, KUMAOKA S, SEGALOFF A, RUBENS RD. Assessment of response to therapy in advanced breast cancer. *Eur J Cancer* 1977, **13**, 89–94.
9. HAYWARD JL. Assessment of response to treatment at Guy's Hospital Breast Clinic. In: HAYWARD JL, BULBROOK RD, eds. *Clinical Evaluation in Breast Cancer*. London, Academic Press, 1966, 131–140.
10. BRITISH BREAST GROUP. Assessment of response to treatment in advanced breast cancer. *Lancet* 1974, **ii**, 38–39.
11. WALPOLE AL, PATERSON E. Synthetic oestrogens in mammary cancer. *Lancet* 1949, **ii**, 783–786.
12. BREAST CANCER GROUP IN JAPAN. The effect of endocrine treatment on advanced breast cancer in Japan. *Jap J Clin Oncol* 1973, **6**, 13–18.
13. FRIEDEL CH, SOTO EA, KUMAOKA S, ABE O, HAYWARD JL, BULBROOK RD. Sinus histiocytosis in British and Japanese patients with breast cancer. *Lancet* 1974, **ii**, 1228–1229.
14. MAGAREY CJ, BAUM M. Oestrogen as a reticulo-endothelial stimulant in patients with cancer. *Br Med J* 1971, **2**, 367–370.