PAPERS AND ORIGINALS

Delay in diagnosis and long-term survival in breast cancer

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Summary and conclusions

The records of all 1591 women with a histologically confirmed primary breast neoplasm who received their primary treatment at the main referral centre in British Columbia and were diagnosed in the years 1945, 1950, 1955, 1960, 1965, 1970, or 1975 were reviewed. The interval from appearance of the first symptom to diagnosis decreased from 1945 to 1960, but no change was seen from 1960 to 1975. An analysis of survival from the date of first symptom showed that long-term survival was greater in patients with a shorter delay between the appearance of symptoms and diagnosis.

The demonstration that shorter delay does improve survival, even when assessed from the appearance of the first symptom, yet delay times have not been falling recently, suggests that educational efforts are inefficient.

Introduction

Earlier treatment is generally accepted to improve the prognosis in a woman with breast cancer, and so a prompt response by both patient and doctor to the finding of a breast lump is desirable and even worth the considerable expense of public and professional educational campaigns. Nevertheless, there is a lack of consistent evidence that such earlier diagnosis does improve survival. Several studies comparing patients whose treatment was delayed by several months with those whose treatment promptly followed the first symptom have shown either no difference[1-4] or a better survival in the long delay group,[5 6] while others have shown an improved survival associated with short delays.[7-9] In almost all studies survival is calculated from the date of diagnosis, and this may lead to a false conclusion of benefit for patients with short delays. For example, two groups of women experience symptoms at the same time but one group is diagnosed immediately and the other has a delayed diagnosis: if the natural history of the disease is not affected by the delay, the survival of each group from the date of first symptom will be the same, but survival from the date of diagnosis will be shorter in the group with a delayed diagnosis. Our study was designed to test whether prompt diagnosis of breast cancer improves survival as assessed from the date of the first symptom and whether the delay between the appearance of the first symptom and diagnosis has become shorter in recent years, as would be expected with the impact of public education.

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Patients and methods

Since 1938 the A Maxwell Evans Clinic in Vancouver has been the main radiotherapy and cancer referral centre in British Columbia. Standardised records, including lifelong follow-up information, have been maintained on all patients. From these we identified all women diagnosed in the years 1945, 1950, 1955, 1960, 1965, 1970, and 1975 with a primary breast tumour who were seen for consultation about primary treatment. Those referred only for treatment of recurrences or other later events were excluded, as were 48 patients with only a clinical diagnosis, leaving 1591 patients for study. Delay time was defined as the interval between the first recorded symptom and pathological diagnosis, and was available for 1545 patients (97%). It was recorded on the record cards in months. Thus one month's delay meant a delay of two to 6 weeks. Information was obtained on age, marital status, clinical stage (Manchester system[10]), pathological grade and type, site of tumour, outcome, interval to death or last follow-up, and patient's or spouse's occupation.

Results

We examined the trend in the distribution of delay time by year of diagnosis, combining 1945 and 1950 because of small numbers of patients. The results, summarised in table I, are presented as cumulative distributions of patients by delay time for each year in fig 1. A regular fall in delay time occurred from 1945-50 to 1960; the median delay time fell from 4·1 months in 1945-50 to 2·2 months in 1960, and the proportion of cases presenting within six weeks of the first symptom rose from 24% in 1945-50 to 46% in 1960. The statistical significance of the fall in delay time was shown by the logrank test for trend,[11] which yielded: $\chi^2 = 14{\cdot}5$; df = 1; $p < 0{\cdot}001$. There was, however, no regular change in delay time from 1960 to 1975 (fig 1;

$\chi^2 = 0{\cdot}0$, $p = 0{\cdot}96$). Thus the fall in delay time was restricted to the period before 1960.

We compared the demographic and clinical features of three delay time groups: short delay (one month or less, 696 patients), intermediate delay (2-11 months, 593 patients), and long delay (12 months or more, 256 patients). Within each of the two longer delay categories, the distributions according to delay time were highly skewed, with the mean delay larger than the median, and showed artefactual peaks at yearly and half yearly points (6, 12, 18, months etc). In the intermediate delay group the median delay was 3·4 and the mean 4·2 months; in the long delay group the median was 23·5 and the mean 35·4 months. The mean ages at diagnosis of the short, intermediate, and long delay groups were 55·4, 55·2, and 58·4 years respectively: the differences were largely due to the delay as the mean ages at time of first symptom were 55·3, 54·8, and 55·5 years respectively. Table II shows demographic and clinical features of the delay groups. Adjustments for age at diagnosis and for year of diagnosis made no differences to the conclusions.

Unmarried women were more likely to have longer delays than married women, and single, divorced, and separated women considered separately were very similar in this regard. There was a non-significant trend towards shorter delay in the higher socioeconomic groups, as defined by the occupation of the patient or her spouse.[12] Tumours affecting the whole breast occurred significantly more often in women with long delays, but otherwise there was no association between delay and site of tumour in terms of the quadrant of origin. Patients with long delays showed a much less favourable distribution by clinical stage. There were no differences between the delay groups in terms of whether the right or the left breast was affected, or in the pathological description of cell type. Information on pathological grading was available on only half the patients. Among those with known grading, the only difference was that the proportion of anaplastic tumours was 8% among patients in the long delay group and 3% among those in the short delay group.

TABLE I—*Distribution of patients studied according to year of diagnosis and delay time*

Year of diagnosis	No of patients	% Of patients with delay times of: ≥2 months	≥3 months	≥6 months	≥1 year	Median delay (months)
1945, 1950	109	76	61	39	23	4·1
1955	134	63	52	33	18	3·2
1960	231	54	37	26	17	2·2
1965	265	50	39	22	14	2·0
1970	347	55	44	30	21	2·4
1975	459	51	39	24	13	2·1

TABLE II—*Distribution of women with breast cancer according to delay time and demographic and clinical features. Results are numbers (and percentages) of patients*

	Delay time ≤1 month	2-11 months	≥12 months	Total	χ^2 Value
Marital status:					
Married	472 (45)	416 (40)	155 (15)	1043 (100)	7·6, df = 2, p<0·02
Unmarried	224 (45)	177 (35)	101 (20)	502 (100)	
Socioeconomic status:					
≤29 (low)	108 (44)	97 (40)	40 (16)	245	8·1, df = 6, p>0·1
30-39	179 (43)	160 (38)	78 (19)	417	
40-49	125 (51)	89 (36)	31 (13)	245	
≥50 (high)	165 (49)	122 (37)	47 (14)	334	
Unknown	119	125	60	304	
Site of tumour:					
Named quadrant or nipple area	619 (46)	520 (38)	212 (16)	1351	26·4, df = 2, p<0·001
Whole breast	12 (20)	25 (42)	23 (38)	60	
Unknown	65	48	21	134	
Clinical stage:					
I	401 (52)	275 (36)	95 (12)	771	68·2, df = 6, p<0·001
II	154 (46)	129 (39)	50 (15)	333	
III	45 (36)	50 (40)	31 (25)	126	
IV	40 (25)	69 (42)	54 (33)	163	
Unknown	56	70	26	152	

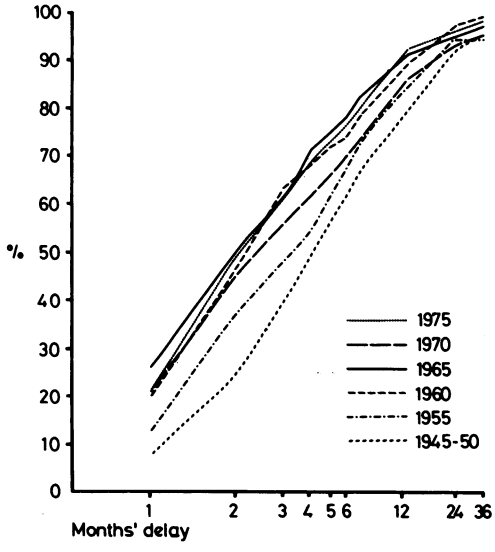

FIG 1—Cumulative proportion of patients with primary breast tumours according to elapsed delay time and year of diagnosis.

From 1960 to 1975 there was no association between delay time and year of diagnosis, so the data could be combined to examine the influence of delay time on survival. A conventional analysis, where survival is calculated from date of diagnosis to death or last follow-up, is shown in table III: in keeping with the much less favourable stage distribution, patients with long delays had a poorer survival from the date of diagnosis, with a relative survival rate at 5 years of 57% compared with 70% in the short delay group. Within stage categories, however, there were no consistent or statistically significant differences in survival between the long and the short delay groups.

To consider survival in terms of the natural history of the disease, or from the patients' viewpoint, it is more logical to assess it from the time of the first symptom, which will increase the survival of the long delay group. The difficulty with using the date of first symptom is that the patients did not come under observation at that time. As the long delay group were defined as such at the time of diagnosis, they were selected by having survived at least 12 months from the date of the first symptom. We can consider the long delay group as the survivors of a hypothetical cohort of women, defined by characteristics of their tumour, their personal features, and their medical care setting, who having developed a breast lump tended not to achieve a prompt diagnosis, due either to delay in seeking medical advice or to subsequent delay in obtaining a pathological diagnosis. Of this cohort some will remove themselves by seeking advice and being diagnosed within a year, and others may die from any cause

including breast cancer undiagnosed before death. It is impossible to estimate this drop out rate. We can, however, estimate the minimum drop out rate, which is the death rate expected in a group of women of that age group based on general population death rates. If we assume that the mortality of the hypothetical original cohort before diagnosis is equal to that expected in the general population and adjust the survival rate observed by this amount, we obtain a maximum estimate of the survival rates for this cohort of long delay patients from the date of first symptom. A comparison of this estimated survival for long delay patients with that of short delay patients, for those diagnosed in 1945-60 is shown in fig 2. Up to five years after the first symptom the long delay group appeared to have a better survival. As the curve was a maximum estimate, however, the true survival of long delay patients may not have been better than that of the short delay group, so no conclusion could be drawn. From six years onwards, however, the maximum estimate of the survival of the long delay group was significantly below that of the short delay group. The proportion of patients diagnosed in the earlier years was higher for the long delay group, which contributed a small proportion of the difference in survival, but even within specific years of diagnosis the patterns were very similar to that shown in fig 2.

The results for patients diagnosed in 1965-75 are shown in fig 3. The curve showing the maximum estimate of survival for the long delay group remained above that of the short delay group until eight years after the first symptom. After 10 years, the survival of the short

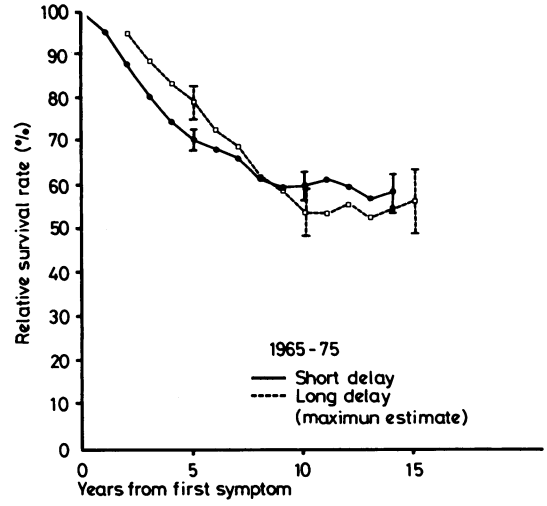

FIG 3—Relative survival rates by years from first symptom, for patients with breast cancer diagnosed in 1965 to 1975.

TABLE III—*Survival rates from date of diagnosis by clinical stage and delay group, patients diagnosed from 1960 to 1975*

	All stages		Stage I		Stage II		Stage III		Stage IV	
	Short‡	Long§	Short	Long	Short	Long	Short	Long	Short	Long
No of patients	609	201	391	88	139	40	41	29	38	44
5-year relative survival rate*(%)	70	57	78	84	65	47	49	39	26	24
Mortality ratio† ..	0·89	1·37	0·99	1·04	0·95	1·17	0·90	1·17	0·97	1·08
χ^2	15·56		0·05		0·80		0·82		1·10	
P value	0·0001		0·8		0·4		0·4		0·3	

*Actuarial survival rate at 5 years after diagnosis, divided by expected survival rate in a general population group of women of same age distribution.

†Ratio of observed mortality to that expected assuming equal mortality in each delay group; and corresponding χ^2 statistic on 1 df given by logrank test.

‡Delay time ≤1 month. §Delay time ≥12 months.

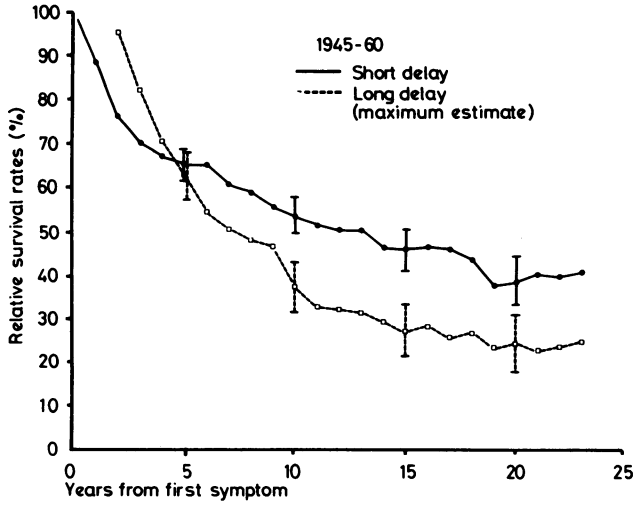

FIG 2—Relative survival rates according to years from first symptom, for patients with breast cancer diagnosed in 1945 to 1960. Vertical bars show one standard error on either side of the estimate.

delay patients was higher than the maximum estimate of survival in the long delay group, although the difference was not statistically significant. Nevertheless, as the true survival of the long delay patients may have been considerably below the maximum estimate shown, the short delay patients may have had the better long term survival.

The results are shown here as relative survival rates, based on all causes of death in the patients and then adjusted for the expected mortality in an age-matched group of women. Curves based on mortality from all causes without this adjustment, and curves based only on deaths certified as being due to breast cancer, both showed patterns very similar to the relative survival curves.

Discussion

This study shows that women with breast cancer who have a short delay between the appearance of the first symptom and diagnosis have better long-term survival rates than those with long delays, even when survival is assessed from the date of the first symptom. While this finding supports a commonly held view, few other studies have shown this. One reason for this is suggested by our data on survival from diagnosis within stage categories, which shows that comparison of patients with long and short delay times within stage categories shows no difference in survival. Accordingly, if only patients with limited disease are studied no difference in survival is to be expected. Thus in a study of all the patients seen at his clinic McWhirter showed a lower five-year survival rate from diagnosis in long delay patients, but when only operable patients were studied no difference was seen.[8] In many studies only operable or early stage tumours are included.[3 4 6 7 9] For a given extent of disease at diagnosis, a longer interval between first symptom and diagnosis implies a more slowly growing tumour. If delay time is considered as a prognostic factor, its effect should be assessed within stage categories and survival measured from the date of diagnosis. Such studies show that delay time, allied to observations on the occurrence of change in symptoms, does have prognostic value beyond that given

by disease staging.[13] Nevertheless, in studying the natural history of disease and the impact on this of the timing of diagnosis and treatment, stage of disease is determined at least in part by delay time and therefore the only applicable comparison is between patients defined by different delay periods, irrespective of the stage of disease at diagnosis.

The recorded information on the date of first symptom is open to question as this event may be difficult to define and patients may consciously or unconsciously report the date incorrectly. Our comparisons, however, were between the shortest and the longest delay groups: inaccuracies may mean that the short delay group included some patients with longer delays and the long delay group some with shorter delays, but such errors can only decrease any true difference in survival rates and thus make our conclusion conservative.

While our first conclusion, that shorter delay gives better survival, implies that public education about the importance of early investigation of a breast lump should be beneficial, our results show no reduction in delay in recent years. Although our data came from one referral centre rather than including all new cases in an entire population, it is unlikely that this would obscure a reduction in delay over time. The proportion of all newly diagnosed breast cancers in the province which are referred to this centre has increased, as has the proportion of stage I cancers: whereas the referral rate was probably highest for patients with advanced tumours in the earlier years studied, those referred more recently were less highly selected. This bias would lead us to overestimate any true improvement in delay patterns in all patients in the province, so our failure to see such a trend is strong evidence against its existence.

Public education about cancer has been pursued by the Canadian Cancer Society in British Columbia since 1938, and films about breast self-examination were used as early as 1956. National surveys in Canada have reported that the proportion of women stating that they regularly examine their breasts rose from 20% in 1960 to 38% in 1971 and to 63% in 1975 and that those using self-examination have shorter delay times.[14] Our failure to observe a corresponding improvement in delay time since 1960 suggests that further examination of the impact of education on behaviour is warranted. Nevertheless, the limitations of our sample make it impossible to conclude firmly that public education is of no benefit. As our information on delay time was given only to the nearest month, a slight improvement in delay time within the short delay category is impossible to exclude, although it seems unlikely: the proportion of patients recorded as having 0 months delay rather than 1 month showed no change between 1960 and 1975. Between 1960 and 1975 the stage distribution of breast tumours improved in each delay time category, and some of this improvement may have been due to methods such as breast self-examination, which should lead to an earlier recognition of the first symptom. While this is consistent with the improving stage distribution in short delay patients, it is difficult to account for the similar improvement in staging in long delay patients, without any change in delay times, and so we conclude that the differences in staging are likely to have been due to changing referral patterns.

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ONE HUNDRED YEARS AGO SIR,—It may be of interest to some of your readers to know how useful the ordinary hypodermic syringe may be as an aspirator. Lately, I had a case of ganglion which I treated by forcing the hypodermic needle into the sac, and then exhausting the contents by drawing the piston upwards. Almost nothing but a little blood made its appearance in the syringe. From that date, the swelling, which was on one of the tendons of the extensor communis digitorum, gradually disappeared, and in a week or two the hand was quite normal. The puncture and exhaustion were followed by a slight swelling, which lasted for some hours. In performing this operation, it might be better to draw the skin tightly over the swelling and then puncture, so that the hole in the skin and in the sac would not be opposite one another, and thus prevent septic mischief; or a little dressing of antiseptic gauze might be fastened on by means of collodion, as I have seen Mr. Lister frequently do in cases of wen in the scalp. But this may almost be discarded, for if the punctures of the large needles of Dieulafoy's aspirator are followed by no mischief, the small hypodermic needle will certainly not cause trouble, especially as we can see that the puncture is sealed almost immediately after the withdrawal of the needle by a plug of lymph. I have also used the hypodermic syringe as an aspirator on such cases as those of ecchymosis and of inflammatory induration of the cellular tissue. I had a case lately of a "black eye," presumably from a blow, where I made a puncture with the needle and used the syringe as an exhauster, and then withdrew the needle. The puncture bled freely for some minutes, at the end of which time the colour of the skin was of the natural hue, whereas a few minutes before it was swollen and ecchymosed. Of course, this method can only be applied in recent cases, where the blood has not begun to clot. In a case of inflammatory induration of the cellular tissue, following hypodermic injection of morphia, I have adopted the same course as in the above case of ecchymosis, and by relieving the intense hyperaemia of the part by the escape of the blood, have kept off a bad abscess. I have never used the hypodermic syringe as an aspirator in cases of abscess; but a medical friend of mine, lately resident in this district, told me that he had used it to exhaust superficial abscesses, and also to withdraw the serum from the prepuce in cases of phimosis or paraphimosis before reducing the lesion.

In conclusion, there is no doubt that many other cases suitable for this method of treatment will suggest themselves to the observing practitioner. For instance, in cases of gum-boil the abscess could be exhausted and the pus removed without the patient getting a mouthful of it, as he must necessarily do where the knife is used. In doubtful cases, where there is a difficulty between a collection of fluid and a solid tumour, the introduction of the needle and the subsequent exhaustion by the syringe would prove what is really the matter.—I am, etc., JOHN A. ERSKINE STUART. (*British Medical Journal*, 1880.)