stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. *Cancer* 1988, **61**, 1719–1727.
5. Specht L, Nissen NI. Prognostic factors in Hodgkin's disease stage III with special reference to tumour burden. *Eur J Haematol* 1988, **41**, 80–87.
6. Specht L, Nissen NI. Prognostic factors in Hodgkin's disease stage IV. *Eur J Haematol* 1988, **41**, 359–367.
7. Specht L, Nissen NI. Hodgkin's disease and age. *Eur J Haematol* 1989, **43**, 127–135.
8. Specht L, Lauritzen AF, Nordentoft AM *et al.* Tumor cell concentration and tumor burden in relation to histopathologic subtype and other prognostic factors in early stage Hodgkin's disease. *Cancer* 1990, **65**, 2594–2601.
9. Kaplan HS. *Hodgkin's Disease*, 2nd edition. Cambridge, MA, Harvard University Press, 1980.
10. Kaplan HS, Rosenberg SA. The treatment of Hodgkin's disease. *Med Clin North Am* 1966, **50**, 1591–1610.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
12. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
13. Cox DR. Regression models and life-tables. *J R Stat Soc B* 1972, **34**, 187–220.
14. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York, Wiley, 1980.
15. Desser RK, Golomb HM, Ultmann JE, *et al.* Prognostic classification of Hodgkin's disease in pathologic stage III, based on anatomic considerations. *Blood* 1977, **49**, 883–893.
16. Rodgers RW, Fuller LM, Hagemeister FB, *et al.* Reassessment of prognostic factors in stage IIIA and IIIB Hodgkin's disease treated with MOPP and radiotherapy. *Cancer* 1981, **47**, 2196–2203.
17. Lukes RJ, Craver LF, Hall TC, Rappaport H, Ruben P. Report of the Nomenclature Committee. *Cancer Res* 1966, **26**, 1311.
18. Haybittle JL, Hayhoe FGJ, Easterling MJ, *et al.* Review of British National Lymphoma Investigation studies of Hodgkin's disease and development of prognostic index. *Lancet* 1985, **i**, 967–972.

Eur J Cancer, Vol. 28A, No. 12, pp. 1985–1988, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Evaluation of a Breast Cancer Screening Programme—The DOM Project

Corinne Collette, Hubertine J. A. Collette, Jacques Fracheboud, Bernard J. Slotboom and Frits de Waard

In several studies it has been shown that breast cancer screening by means of mammography reduces breast cancer mortality. To ensure that when organising a service screening programme the aim is reached, it is necessary to control and monitor the process. This is possible by several methods. In this study, disease-free intervals and survival rates were used as monitoring tools. The DOM project, a breast cancer screening programme for women aged 50–64 years old at intake, started at the end of 1974. All breast cancer cases diagnosed between 1973 and 1989 were followed up to 1991. It is clear that disease-free interval and survival rates are proper predictors of the effects of screening on breast cancer mortality.
Eur J Cancer, Vol. 28A, No. 12, pp. 1985–1988, 1992.

INTRODUCTION

MORTALITY REDUCTION as shown in randomised controlled trials [1–6], is the ultimate proof of the effectiveness of a breast cancer screening programme. However, when starting a new programme it is not acceptable to the population to be divided into a study and a control group. Moreover, it is more effective to monitor a population by being aware of signals that the expected effect will or will not be reached, so ways of monitoring have to be found. Monitoring has to be distinguished from quality control. Quality control deals with the test, both technical aspects and performance, in order to correct or improve it when necessary [7, 8]. Monitoring focusses on events that cannot easily be influenced, such as participation rate of women, changes in methods of treatment, incidence rates, etc. [9]. Up to now little attention has been paid to the influence of the screening programme itself on survival of the breast cancer cases. Survival alone cannot be proof of the effectiveness of screening, but in order to reduce mortality rate, increase of the survival rate is necessary (as screening is secondary and not primary prevention). So questions arise: 'Are screening activities reflected in survival rates?' and, 'Will longer survival and better survival rates be predicted by disease-free interval rates?'

Correspondence to H.J.A. Collette.
The authors are at the Department of Epidemiology, University of Utrecht, Radboudkwartier 261, 3511 CK, Utrecht, The Netherlands.
Revised 24 Mar. 1992; accepted 22 June 1992.

MATERIALS AND METHODS

At the end of 1974 the DOM project, a population-based breast cancer screening programme was started in Utrecht, The Netherlands. All women born between 1911 and 1925, being between 50 and 64 years old at the start of the project, were invited; 72% participated (14697 women). The programme had a cohort design, which implied that only women having participated in the previous screening round were invited for the following screening. From 1974 to 1984 five screening rounds were performed, with different time intervals between two successive screening rounds [10, 11]. As a consequence of this design the screening activities in Utrecht were variable (Table 1).

At the start of the screening programme a breast cancer registry (including 1973) was established. Data from the population registry of Utrecht were collected making it possible to

Table 1. Number of screening examinations per screening round and calendar year in the city of Utrecht

Year	1	2	3	4	5	Total
1975	5.327					5.327
1976	6.940	4.248				11.188
1977	2.430	5.542	1.432			9.404
1978		2.077	4.620			6.697
1979			4.022	1.168		5.190
1980		372	134	7.449		7.955
1981				4		4
1982						—
1983						—
1984					6.118	6.118
1985					37	37
Total	14.697	12.239	10.208	8.621	6.155	51.920

follow the population at risk and to calculate incidence rates in the different subgroups of the cohort. Regarding the follow-up of all breast cancer cases, the hospitals and, when necessary, the general practitioners provided details about therapy, progression and cause of death.

In this paper the cancer cases from between 1973 and 1988 with a follow-up period up to the end of 1990 are the object of analysis.

Table 2 gives the total number of cancer cases (671 women) in the various subgroups according to their relation with the programme described below.

Cancer cases diagnosed in 1973 and 1974 were considered as a historic control group. As it took more than 2 years to invite all women born between 1911 and 1925, women with breast cancer diagnosed before receiving the invitation were classified as the 'before invitation group'. Women moving into Utrecht after 1925 were not invited. Women who dropped out of the programme after having participated at least once and who subsequently developed breast cancer were classified as 'non-compliance'. Non-participants are women who never attended the screening programme.

Figure 1 depicts the stage distribution of the different groups. Tumours were classified according to tumour diameter (either ≤ 2.0 cm or > 2.0 cm) and to axillary nodes (either negative or positive). The relatively large number of cancers with unknown stage in the historic control group is caused by the incompleteness of information at the start of the registration. In the other groups it concerns mainly small cancers as it is not usual to explore the axilla when the cancer is very small.

Table 2. Number of women with (first) breast cancer in several subgroups (LobCis excluded)

	Number of women with breast cancer (%)
Historic controls	110 (16.4)
Before invitation	53 } (11.0)
No invitation	21 }
Screen detected	
First screen	100 (14.9)
Following screens	84 (12.5)
Detected in an interval	77 (11.5)
Detected after non-compliance	102 (15.2)
Non-participants	124 (18.5)
Total	671 (100)

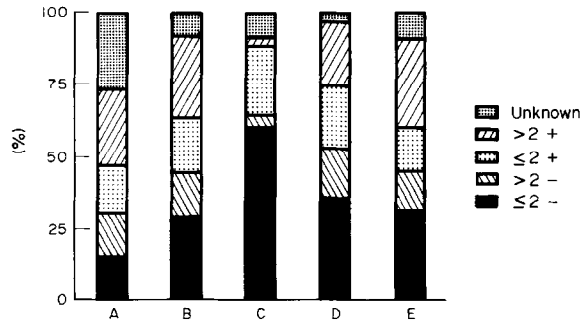

Fig. 1. Stage distribution per subgroup. A = historic controls; B = before/no invitation; C = screen detected; D = interval/non-compliance; E = non-participants.

Follow-up data were collected for all 671 women up to the end of 1990, so the period of follow-up differs from 1 to 18 years.

Survival analysis (with deaths from breast cancer only) was performed using the actuarial method (SPSS, significance test of Lee-Desu [12]). Survival time of women with screen-detected cancers was corrected for lead time, 2.5 years when detected at the first screen and half the length of the last interval when detected at a following screen. In this analysis, attention has been paid to stage of the disease, age at diagnosis and the relation to the screening programme, i.e. the above-mentioned subgroups. In addition, an analysis of the disease-free interval is given. Disease-free interval is defined as the period without progression after initial surgery.

Survival curves are given in Figs 2–5. Curves of disease-free interval in combination with survival curves are given in Figs 6 and 7.

RESULTS

It is clear that screening detects cancers at an early stage (Fig. 1). Figure 2 shows the survival of all cancers together according to the stage of the tumour at diagnosis. The differences between the stages are significant, as was expected.

An analysis for various age groups showed no influence of age at diagnosis, even after correcting for stage at diagnosis. Overall survival rate after 10 years is between 60 and 70% and after 15 years is approximately 50%.

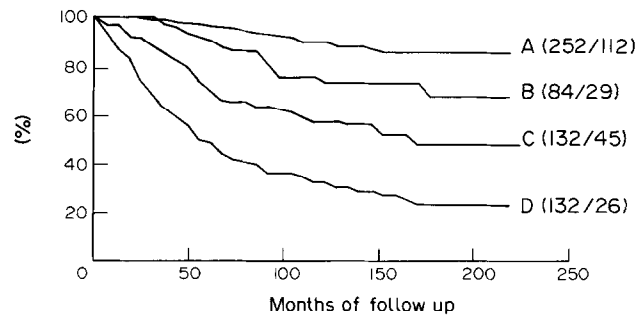

Fig. 2. Survival of breast cancer cases by stage. A $\leq$ 2 Ax−; B $>$ 2 Ax−; C $\leq$ 2 Ax+; D $>$ 2 Ax+. Number of breast cancer cases at start and after 10 years follow-up are in parentheses.

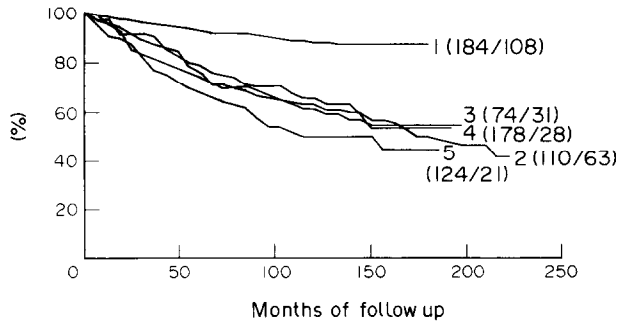

Fig. 3. Survival of breast cancer cases by group. 1 = screen detected (corrected for lead time); 2 = historic controls; 3 = before/no invitation; 4 = interval/non-compliance; 5 = non-particpants. Number of breast cancer cases at start and after 10 years follow-up in parentheses.

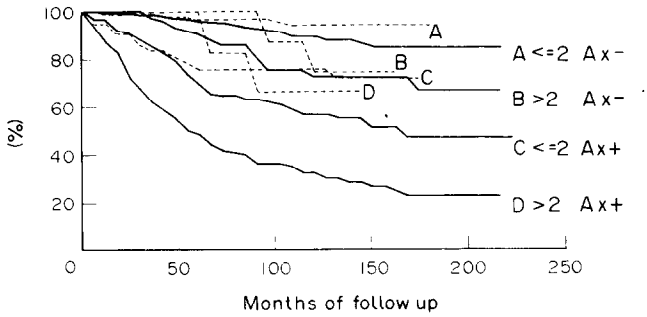

Fig. 4. Survival of breast cancer cases by stage. —ALL; --- screen detected.

In Fig. 3 a division is made between the subgroups mentioned in Table 2. The screen-detected cancers prove to have the best survival rates. In Fig. 4 survival curves according to stage distribution of all cancers are given together with those of the screen-detected cancers. The screen-detected cancers prove to have by far the best rates, regardless of the stage at diagnosis.

In Fig. 5 a distinction is made between pre and post intake. For evaluation purposes, the screening programme started at the first invitation to be screened for each individual. Thus, the terms pre-intake and postintake stand for preprogramme period and programme period, respectively. There proves to be a significant difference between both curves: all cancers, including cancers in the non-participants, having a better survival rate on the postintake curve.

Figure 6 depicts the survival and disease-free interval rates by stage at diagnosis. Survival curves follow the curves of the

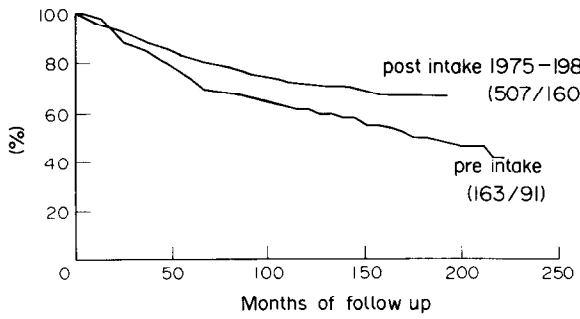

Fig. 5. Survival of breast cancer cases by intake. Number of breast cancer cases at start and after 10 years follow-up in parentheses.

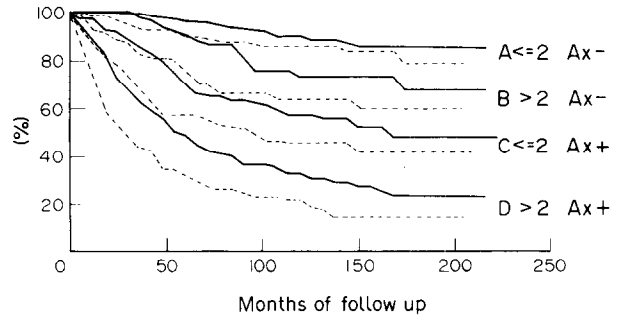

Fig. 6. Survival and disease-free interval by stage. — survival; --- disease-free.

disease-free interval after a longer or shorter period. The same holds true when comparing these rates per subgroup, as mentioned in Table 2 (Fig. 7).

DISCUSSION

In this study, the follow-up data of 671 women with breast cancer, diagnosed when a breast cancer screening programme was operational, are analysed. These women were divided into several subgroups. When analysed according to stage at diagnosis (Fig. 6), disease-free interval and survival appear to be strongly related to stage at diagnosis: survival curves follow the disease-free interval curves after a longer or shorter period. As both types of curves per subgroup do not end at the same level, more deaths from breast cancer are expected to occur in the near future.

Age at diagnosis does not influence the outcome. These results are independent of the stage at diagnosis. Adami *et al.* [13], using the nationwide cancer registry, analysed the follow-up of more than 55 000 women with breast cancer. He found a difference between age groups in survival rates, namely women 40–49 years old having the best prognosis and women over 75 years the worst prognosis, in particular after a longer follow-up period (15 years). The other age groups did not differ. Breast cancer cases in Norway (more than 10 000) follow the same pattern [14]. Our cohort mainly consists of women between 50 and 70 years old; the findings concerning these women are in accordance with those of Adami [13] and in Norway [14]. The time of follow-up for women aged 70 and over is only 10 years, so if these women resemble Swedish and Norwegian women their survival will become worse in the coming years.

The prognosis is strongly related to the motive for the breast examination, namely asymptomatic (screening) or not (Fig. 3). The screen-detected group shows by far the best prognosis.

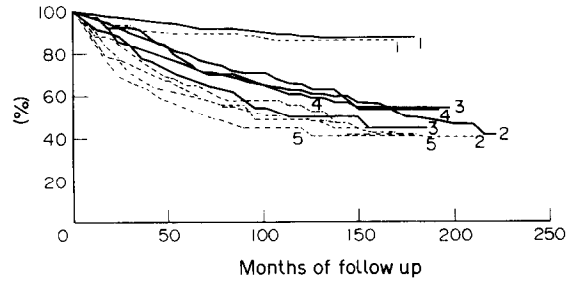

Fig. 7. Survival and disease-free interval by group. 1 = screen detected (corrected for lead time); 2 = historic controls; 3 = before/no invitation; 4 = interval/non-compliance; 5 = non-participants. — survival; --- disease free.

Moreover, it is highly probable that women with screen-detected breast cancer who are alive after 10 years are cured as both curves, namely disease-free interval and survival, run parallel at the end at virtually the same level for up to 15 years of follow-up, in contrast with curves of the other subgroups (Fig. 7).

When looking at the curves per subgroup by stage it turns out that the curves of the screen-detected group run at a higher level than those in the other groups. An explanation may be the rather broad classification (four groups only): screen-detected cancers may have more small cancers in each group. Inspection and comparison of the ranges proved this to be true: in the screen-detected group 40% of the cancers were < 1.0 cm and 85% were > 2.0 and < 3.0 cm, compared with 19 and 53%, respectively, in the rest.

A point of criticism not yet mentioned is the length bias. From a theoretical point of view screening preferentially picks up slow growing cancers which have a better prognosis. In an earlier analysis we compared survival rates of cancers detected on the first screen with those from following screens, as in the latter mainly newly arising cancers should be detected and length bias will therefore be minimal. There was no significant difference [15].

A second pitfall is lead time bias, we corrected for this when analysing the follow-up. The third possible bias is participation/selection bias. We compared incidence rates in the historic group and in the non-participants group; there were no significant differences [16]. An analysis of breast cancer risk factors and survival of the disease did not reveal any biasing factors either (not published). We also looked at compliance for control in the hospitals: no difference appeared to be present between the historic group and the non-participants, thus making it unlikely that there is a difference in health behaviour of participants and non-participants.

Moreover, the differences between screen-detected cancers and those diagnosed by other means is so large as to make it very unlikely that they could be fully explained by any sort of bias.

As the DOM project was a research project with a specific design and not a service screening, the screening activities in Utrecht were deliberately unequal over the years (Table 1). 88% of the breast examinations were performed in the first 6 years. Thus, any effect of the project on prognosis of breast cancer cases will be more visible in cancers detected in those 6 years than in later years. This was visible in the follow-up: the survival rates are better for the first period (1975–1980) than for the whole period (1975–1988; data not shown). The same holds true for the disease-free interval. As a consequence, the difference between the pre- and postintake groups is in favour of the first 6 years. Thus, these results of the DOM project are in accordance with other results regarding mortality reduction [17].

CONCLUSION

Screening activities are reflected in both the disease-free interval and survival rates. An effect of screening cannot formally be proved in this way but these rates can be used when monitoring a programme, as a reduction in mortality is not very likely without a better prognosis of screen detected breast cancers.

1. Shapiro S, Venet W, Strax Ph, Venet L, Roeser R. Ten-to-fourteen-year effect of screening on breast cancer mortality. *J Natl Cancer Inst* 1982, **69**, 349–355.
2. Andersson I, Aspegren K, Janzon L, *et al.* Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. *Br Med J* 1988, **297**, 943–948.
3. UK trial of early detection of breast cancer. First results on mortality reduction in the UK trial of early detection of breast cancer. *Lancet* 1988, **ii**, 411–416.
4. Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *J Epidemiol Community Health* 1989, **43**, 107–114.
5. Roberts MM, Alexander FE, Anderson TJ, *et al.* Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990, **335**, 241–246.
6. Frisell J, Eklund G, Hellström L, Lidbrink E, Rutqvist LE, Somell A. Randomized study of mammography screening—preliminary report on mortality in the Stockholm trial. *Breast Cancer Res Treat* 1991, **18**, 49–56.
7. Hendriks JHCL, Verbeek ALM. Population screening for breast cancer by mammography in the Netherlands. *Diagn Imag Clin Med* 1985, **54**, 186–191.
8. Verbeek ALM, Ban van den MC, Hendriks JHCL. A proposal for short-term quality control in breast cancer screening. *Br J Cancer* 1991, **63**, 261–264.
9. Day NE, Williams DRR, Khaw KT. Breast cancer screening programmes: the development of a monitoring and evaluation system. *Br J Cancer* 1989, **59**, 954–958.
10. Waard de F, Collette HJA, Rombach JJ, Baanders-van Halewijn EA, Honing C. The DOM project for the early detection of breast cancer, Utrecht, The Netherlands. *J Chron Dis* 1984, **37**, 1–44.
11. Collette HJA, Rombach JJ, Waard de F, Collette C. An update of the DOM project for the early detection of breast cancer. In: Day NE, Miller AB, eds. *Screening for Breast Cancer*. Toronto, The International Union Against Cancer, 1988.
12. Lee ET, Desu MM. A computer program for comparing K samples with right-censored data. *Computer Programs in Biomedicine* 1972, **2**, 315–321.
13. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. *N Engl J Med* 1986, **315**, 559–563.
14. The Cancer Registry of Norway, Oslo. Survival of cancer patients, cases diagnosed in Norway 1968–1975. 1980, 99–102.
15. Collette HJA, Collette C, Rombach JJ, Waard de F. Het DOM-project voor de vroege opsporing van borstkanker te Utrecht, deel 4 (in press).
16. Collette HJA, Rombach JJ, Day NE, Waard de F. Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case-control study. *Lancet* 1984, **i**, 1224–1226.
17. Collette HJA, Waard de F, Rombach JJ, Collette C, Day NE. Further evidence of benefits of (a non-randomised) breast cancer screening programme, the DOM project. *J Epidemiol Community Health* (in press).

Acknowledgements—We thank our assistants for all the work concerning the registration and figures and David Beijerinck for his comments. Also, clinicians, general practitioners, local authorities and the Central Bureau for Statistics for their cooperation in collecting the data. This study was funded by the Praeventiefonds.