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Changes in breast cancer incidence and stage distribution in Modena, Italy: the effect of a mammographic screening program

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Abstract

Objective: Assessing changes in breast cancer (BC) incidence and stage distribution in the District of Modena, Italy, during the period 1992–1998, and their relationship to a mammographic screening program launched in 1995.
Methods: Demographic, clinical, and pathological data of all BC cases reported to the population-based Modena Cancer Registry between 1992 and 1998 were collected and linked to the screening database.
Results: A total of 3429 women were diagnosed with BC in the District of Modena between 1992 and 1998. In this period the incidence rate increased by 15.7% (from 134.3 in 1992 to 155.4 per 100,000 in 1998). The increase began in 1995 and exclusively included women aged 50–69; the incidence rose by 30.4%. Moreover, the rise was confined to early tumors, with more than half (54%) of all cases reported in 1998 diagnosed as stage 0 or I disease, compared with 42% in 1992. Screen-detected tumors were significantly smaller (13.2 mm) than other tumors diagnosed in women aged 50–69 (18.5 mm), with 46% of screen-detected tumors smaller than 10 mm. Overall, a decline in the average tumor diameter was shown (from 20.2 mm in 1992–1994 to 18 mm in 1996–1998).
Conclusions: Our data confirm that mammographic screening leads to an increase in the incidence of early-stage BC cancers.

Introduction

Breast cancer (BC) is by far the most common cause of cancer death among women living in developed countries. Age-standardized mortality rates per 100,000 women range from 25–26 in North America and northern Europe to 6–9 in Asia and Latin America, in Italy being 20.7 [1]. In the District of Modena the mortality rate for 1996–1997, age-adjusted to the world population, was 19 [2]. Nevertheless a reduction in BC mortality has recently been observed in countries with a high incidence of BC, such as the United States, Canada, and the United Kingdom. According to Peto and co-workers, over the period 1987–1997 the annual BC death rate per 100,000 women under age 70 decreased by 22% in the United Kingdom and by 18–19% in the United States; in older age groups a reduction, although smaller, was also observed (12% and 9%, respectively) [3]. Although with a different magnitude, the decline in death rates has been confirmed by several other authors, and the most recent report from the National Cancer Institute shows death rates from BC to have decreased by 1.6% annually from 1989 through 1995, and by 3.4% from 1995 through 1998, despite a continuous increase in BC incidence [4]. Survival rates support this trend toward a better prognosis: in England and Wales 5-year survival was 7% higher for women aged 50–69 years who were

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diagnosed with BC in 1993 than for those diagnosed in 1989 (78.3% *vs* 71.5%, respectively) [5]. The reason for such an improvement in BC prognosis has been much debated. There are two main factors which can affect BC survival and mortality: early detection and quality of treatment. On one hand there is consolidated evidence of the improved effectiveness of BC treatment, mainly related to the widespread use of systemic adjuvant therapies [6, 7]. On the other hand randomized, controlled trials have shown that screening for BC with mammography reduces BC mortality by 25–30% in women aged 50 years and over [8, 9]. However, this impact on mortality is estimated to become evident in the general population no earlier than 10 years after the start of a mass screening program [10]. Nevertheless, even before effects on mortality become evident, the effectiveness of screening programs in improving BC prognosis may be predicted by early indicators such as the increase in the rate of tumors diagnosed at an early stage of development. Stage at diagnosis is well known to be one of the most important prognostic factors for BC, and survival rates appear substantially lower in women diagnosed with advanced-stage disease than in women diagnosed at an early stage [11].

In Italy, if compared to the United States, Canada, and the United Kingdom, no substantial reduction in BC mortality has been demonstrated on the national level to date, even if regional disparities have been suggested by the evidence, for example, of a significant mortality drop in Tuscany [12]. However, in several Italian Districts mass screening programs have recently been started, which are likely to result in changes in BC incidence, stage distribution, and prognosis. This is supported by data from an early screening program carried out in the District of Florence, which show a significantly lower proportion of advanced-stage BC in women aged 50–70 diagnosed by screening, with respect to non-screen-detected patients [13].

Before the commencement of organized mammographic screening programs, BC incidence in Italy was typical of an area at intermediate risk, although displaying geographical differences, with higher rates in the Northern, industrialized areas, and lower rates in the Southern, rural areas. In the period 1988–1992 the incidence rates per 100,000, age-adjusted to the world population, were reported to range from 69, on average, in the North, to 44 in the South [14]. In the District of Modena, Northern Italy, where annual BC incidence in 1988–1992 was 68.8, a mass mammographic screening was launched in 1995. Here we report the results of a population-based study aimed at analyzing the changes in BC incidence and stage distribution that occurred in the District of Modena in the period 1992–1998, and their relationship to the beginning of the screening program.

Materials and methods

The District of Modena is an highly industrialized area in Northern Italy with 616,585 inhabitants and a population density of 229 inhabitants per km^2 (Update: 31 December 1997).

Since 1988 the Modena Cancer Registry (MCR) has collected data on all cancer patients living in the District. Methods for data collection and registration have been described elsewhere [14].

All primary BC cases, identified as *International Classification of Diseases* (9th revision) rubric 174, registered by the MCR for the period 1992–1998, represent the population under study. For these cases (3429), detailed information on histology and stage at diagnosis were extracted from clinical records and collected in a specific database together with the information already available at MCR (demographics, age at detection, date of detection, and follow-up status). These data were linked with the records of the Institute of Pathology in order to check and complete information on histological type, tumor size, and nodal involvement. In 322 cases, lacking some information on tumor features, tumor specimens were reviewed by one of the authors (G.R.). For 73 cases (2%), for which no admissions were reported in the hospitals of the District, it was impossible to obtain clinical and pathological information. Final BC staging was based on the 1997 UICC-TNM classification [15].

In October 1995 a mass mammographic screening program was launched in the District of Modena as a part of a region-wide project. All women aged 50–69 years living in the District are actively recruited to the program, which offers biennial two-view mammography. The program started with the recruitment of the female residents in the municipality of Modena, and since 1997 has been extended to the other municipalities in the District. The first round in Modena was concluded in December 1997. The records of the screening program were linked to the population-based BC database in order to identify screen-detected and interval cases.

All data were analyzed with the Statistical Package for the Social Sciences (SPSS). Rates were expressed per 100,000 population and, when appropriate, were age-adjusted by the direct method to the 1991 Italian population. Pre-screening and post-screening incidence was estimated as the mean annual incidence rate of invasive cancer in the years 1992, 1993, 1994 (pre-screening), and in the years 1996, 1997, 1998 (post-screening).

Results

In the period 1992–1998 a total of 3429 women living in the District of Modena were diagnosed with BC: out of 3356 for whom clinico-pathological data were available, 3044 (91%) had an invasive and 312 (9%) an *in-situ* cancer.

Overall, an increase in incidence (+15.7%) was observed in the period under study, with the rate, adjusted to the Italian population 1991, rising from 134.3 in 1992 (95% CI 122.1–146.5) to 155.4 in 1998 (95% CI 142.4–168.3). Nevertheless, the analysis by year shows the rise to be confined to the years 1996 and 1997 (Figure 1).

The analysis by stage demonstrates that the increase did not involve advanced tumors, but only early tumors (Figure 2). *In-situ* (stage 0) and stage I cancers comprised respectively 102 (7.7%) and 490 (36.8%) out of 1332 diagnosed in the period 1992–1994, and 172 (10.6%) and 700 (43%) out of 1628 diagnosed in 1996–1998. By contrast, locally advanced (stage III) and metastatic (stage IV) disease showed a slight decline, from 76 (5.7%) and 88 (6.6%) in 1992–1994 to 51 (3.1%) and 60 (3.6%) in 1996–1998, respectively. Overall, more than half (54%) of all cases reported in 1998 were diagnosed as stage 0 or I disease, compared with 42% in 1992.

Moreover, among stage I tumors a relevant increase (from 26.9% in 1992 to 36.6% in 1998) was observed for smaller (≤1 cm), with respect to larger (1–2 cm) tumors (Figure 3). Overall the average tumor diameter changed from 20.2 mm in 1992–1994 to 18 mm in 1996–1998.

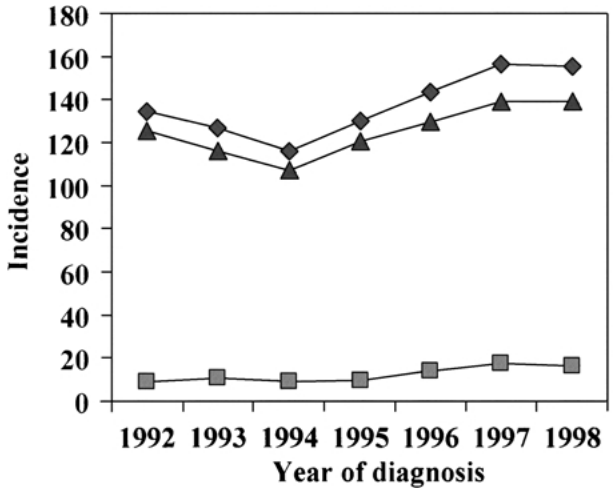

Fig. 1. Age-adjusted incidence of breast cancer (all, invasive, *in situ*) in the District of Modena by year. ◆, All; ■, *in situ*; ▲ invasive.

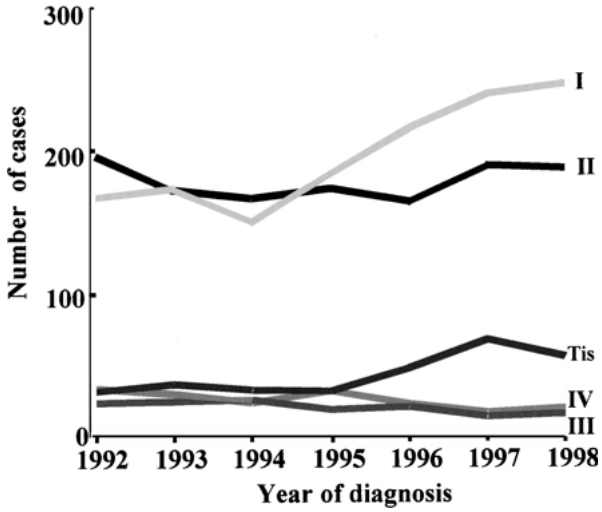

Fig. 2. Cases of breast cancer by stage (Tis, I, II, III, IV) and by year of diagnosis.

Incidence by age showed a relevant increase in the age group 50–69 after 1995, whereas no increase was reported in the other age groups (Figure 4). Among all cases registered in the period 1992–1998, 1631 were diagnosed in women aged 50–69: the percentage of tumors diagnosed in this age group ranged from 46% of total cases in the period 1992–1994 to 50.5% in the period 1996–1998, with an increase in incidence of 30.4% (from 233.3 to 304.2 per 100,000). The rise in incidence was observed in every subgroup (ranging 5 years) of the age group 50–69, in contrast to the absence of rise shown in the other groups (Figure 5). This could be considered an effect of the screening program, started in 1995: among the 25,208 women in the age range 50–69 living in the municipality of Modena, who had been all invited, 19,002 (75.4%) agreed to be screened in the first round. Abnormal mammograms comprised 1819 (9.5% of the total): biopsy was performed in 19% of these cases. Total cancer and invasive cancer detection rates per 1000 women screened were 11.2 and 9.3, respectively. Overall, among BC cases registered by RTM in the period 1992–1998, 276 were screen-detected, accounting for 17% of all cancers diagnosed in women aged 50–69 living in the District. Among the women aged 50–69 living in the municipality of Modena, screen-detected tumors accounted for 237 out of 660 cases (36%). Moreover, as shown in Figure 6, in women aged 50–69 a relevant decline in tumor size was registered, with the average diameter changing from 19.3 in the period 1992–1994 to 16.8 mm in 1996–1998. The decline mainly comprised screen-detected tumors, that were significantly smaller than non-screen-detected tumors (13.2 mm *vs* 18.5 mm;

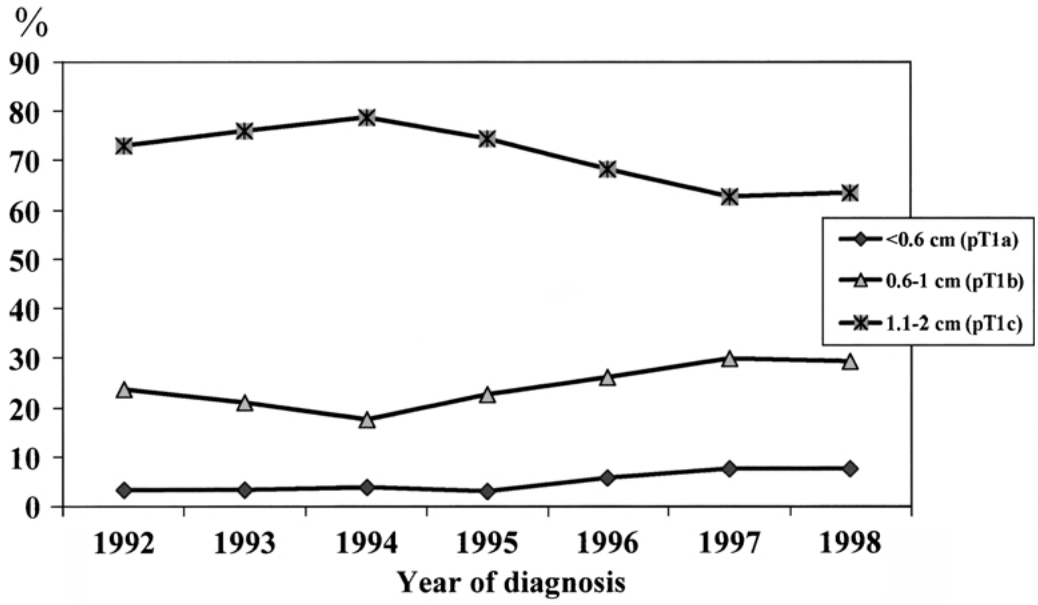

Fig. 3. Stage I breast cancer: distribution by tumor size.

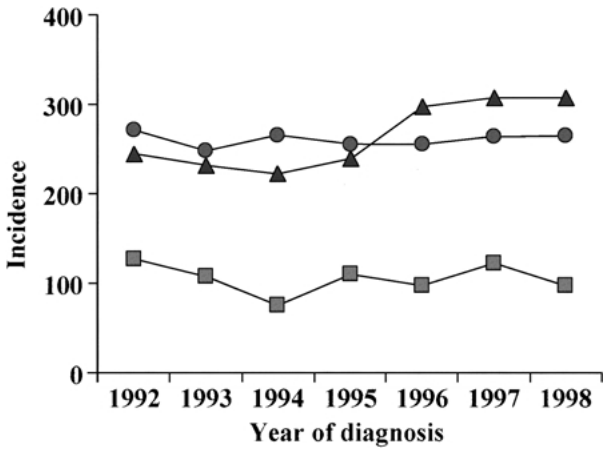

Fig. 4. Invasive breast cancer: age-specific incidence by year. ■, Age 30–49; ▲, 50–69; ●, 70+.

$p = 0.001$), with 46% of screen-detected tumors smaller than 10 mm (Figure 6).

Discussion

Our study shows an increase of 15.7% in BC incidence during the period 1992–1998 among women living in the District of Modena. This rise could be reasonably attributed to a mammographic screening program launched in 1995 which recruits all women aged 50–69 living in the District of Modena. The increase has been observed after the commencement of the program and exclusively involved women aged 50–69 (+30.4%), whereas no relevant increase was registered in the years before screening, nor was any difference observed among women in other age groups. In addition, among women aged 50–69 the greatest rise in incidence occurred in those living in the municipality of Modena, who were all invited to the screening program by 1997, compared to women living in other municipalities, in which recruitment was started, but not completed, in the period under study. A major contribution of the screening is also supported by changes in stage distribution, as the increase was entirely confined to early-stage tumors (stages 0 and I), whereas frequency of advanced tumors showed a slight decrease. Moreover, among tumors smaller than 20 mm (pT1), a relative increase of tumors of diameter 1–10 mm (pT1a and pT1b) with respect to tumors larger than 10 mm was observed. Overall, a decline in the average diameter of tumors was shown, which was mainly related to the significant smaller size (13.2 mm) of screen-detected tumors, with respect to non-screen-detected (18.5 mm) tumors, in women aged 50–69. An increase in BC incidence, as well as in the rate of small tumors, has been reported by several authors as a result of the introduction of mammographic screening [16–23]. Nevertheless, cancer detection rate at the first round was higher in our screening program than in previous reports (11.2 *versus* 5.3–6.5 for all cancers and 9.3 *versus* 5.0–5.3 for invasive cancers only) [21, 24], which cannot easily be explained.

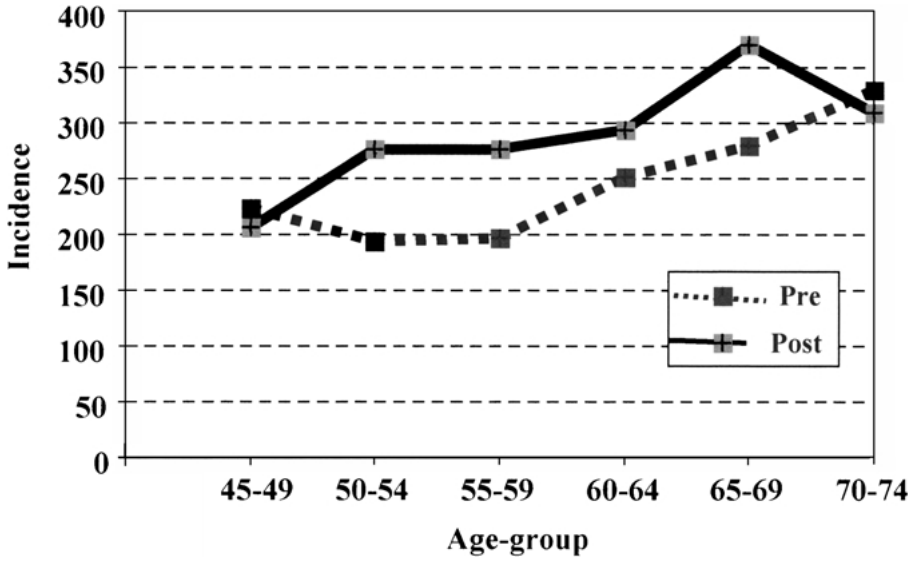

Fig. 5. Incidence in pre- and post-screening era by age group.

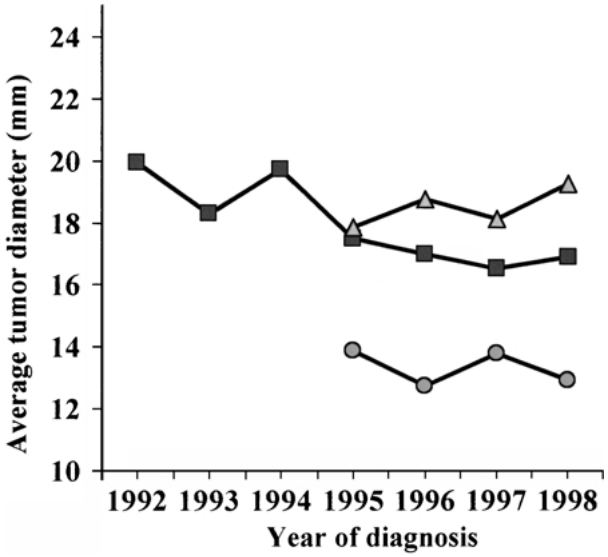

Fig. 6. Size of tumors diagnosed in women aged 50–69 by year of diagnosis (all cases, screen-detected, non-screen-detected). ■, All cases (age 50–69); ▲, non-screen-detected; ●, screen-detected.

The rise in early-stage cancers excludes the possibility that such a high detection rate is caused by the diagnosis of "old" prevalent tumors in a population with a lower use of mammography before organized screening with respect to other studies. This is also supported by the higher rate of tumors ≤10 mm among screen-detected cases in our experience (46%) compared to 33% and 42% in previous reports [16, 21]. One possible explanation is that, in addition to the apparent increase due to increased screen-related detection, there has also been a true increase in the underlying incidence. In addition, recent improvements in mammography performance may have played a role in increasing the cancer detection rate in comparison to screening programs carried out in the past, which raises the issue of an overdiagnosis of tumors with limited malignant potential. Monitoring of incidence rates will continue, in order to address this issue, and to better establish the long-term impact of the screening program.

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References

1. Mettlin C (1999) Global breast cancer mortality statistics. *CA Cancer J Clin* **49**: 138–144.
2. Federico M, Mangone L, Maiorana A, De Girolamo G (2001) *I tumori in provincia di Modena nel biennio 1996-97*. Modena: Progress.
3. Peto R, Boreham J, Clarke M, Davies C, Beral V (2000) UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. *Lancet* **355**: 1822.

4. Howe HL, Wingo PA, Thun MJ, *et al*. (2001) Annual Report to the Nation on the Status of Cancer (1973 through 1998), featuring cancer with recent increasing trends. *J Natl Cancer Inst* **93**: 824–842.
5. Coleman MP (2000) Trends in breast cancer incidence, survival and mortality. *Lancet* **356**: 590–591.
6. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of randomised trials. *Lancet* **351**: 1451–1467.
7. Early Breast Cancer Trialists' Collaborative Group (1998) Polichemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* **352**: 930–942.
8. Tabàr L, Fagerberg G, Gad A, *et al*. (1985) Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish national Board of Health and Welfare. *Lancet* **1**: 829–832.
9. Kierlikowske K, Grady D, Rubin SM, Sandrock C, Ernster V (1995) Efficacy of screening mammography. A meta-analysis. *JAMA* **273**: 149–154.
10. Day ME, Williams DRR, Khaw KT (1989) Breast cancer screening programmes. The development of a monitoring and evaluation system. *Br J Cancer* **59**: 954–958.
11. Ries LAG, Eisner MP, Kosary CL, *et al*. (2001) *SEER Cancer Statistics Review, 1973–1998*. Bethesda, MD: National Cancer Institute.
12. Barchielli A, Paci E (2001) Trends in breast cancer mortality, incidence and survival, and mammographic screening in Tuscany, Italy. *Cancer Causes Control* **12**: 249–255.
13. Paci E, Ciatto S, Buiatti E, Cecchini S, Palli D, Rosselli del Turco M (1990) Early indicators of efficacy of breast cancer screening programmes. Results of the Florence Screening Programme. *Int J Cancer* **46**: 198–202.
14. Parkin DM, Whelan SL, Ferlay J, *et al*. (1997) *Cancer Incidence in Five Continents*, Vol. VII. Lyon: International Agency for Research on Cancer; IARC Scientific Publication No. 143, pp. 542–545.
15. Sobin LH, Wittekind CH, eds. International Union Against Cancer. (1997) *TNM Classification of Malignant Tumours*, 5th edn. New York: Wiley.
16. Fagerberg G, Baldetorp L, Gröntoft O, Lundström B, Månson JC, Nordenskjöld B (1985) Effects of repeated mammographic screening on breast cancer stage distribution. *Acta Radiol* **24**: 465–473.
17. White E, Yul Lee C, Kristal AR (1990) Evaluation of the increase in breast cancer incidence in relation to mammography use. *J Natl Cancer Inst* **82**: 1546–1552.
18. Lantz PM, Remington PL, Newcomb PA (1991) Mammography screening and increased incidence of breast cancer in Wisconsin. *J Natl Cancer Inst* **83**: 1540–1546.
19. Quinn M, Allen E (1995) Changes in incidence and mortality from breast cancer in England and Wales since the introduction of screening. *BMJ* **311**: 1391–1395.
20. Brewster D, Everington D, Harkness E, Gould A, Warner J (1996) Incidence and mortality from breast cancer since the introduction of screening. *BMJ* **312**: 638–639.
21. McCann J, Wait S, Séradour B, Day N (1997) A comparison of the performance and impact of breast cancer screening programmes in East Anglia, U.K. and Bouches Du Rhône, France. *Eur J Cancer* **33**: 429–435.
22. McCann J, Stockton D, Day N (1998) Breast cancer in East Anglia: the impact of the breast screening program on stage at diagnosis. *J Med Screen* **5**: 42–48.
23. Harmer C, Staples M, Kavanagh AM (1999) Evaluation of breast cancer incidence: is the increase due entirely to mammographic screening? *Cancer Causes Control* **10**: 333–337.
24. Fracheboud J, De Koning HJ, Beemsterboer PM, *et al*. (1998) Nation-wide breast cancer screening in the Netherlands: results of initial and subsequent screening 1990–1995. National Evaluation Team for Breast Cancer Screening. *Int J Cancer* **75**: 694–698.