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ORIGINAL ARTICLE

Significant improvement in breast cancer survival through population-based mammography screening

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SUMMARY. The purpose of this study was to evaluate the effect of population-based mammography screening on survival. A total of 176 908 screening examinations were performed in 36 000 women aged 40–74 during the years 1987–1997. Screen-detected and interval primary invasive breast cancers ($n = 685$, screened) were more often smaller ($P < 0.0001$), localised ($P < 0.0001$) and histologically better differentiated (grade I vs II–III, $P < 0.0001$) than pre-screening cancers and cancers detected after the defined interval from the last screening ($n = 184$, clinical). Survival was far better in the 'screened' group than in the 'clinical' group ($P < 0.0001$, HR 2.55; CI 95% 1.77–3.67). Cox's multivariate analysis revealed axillary lymph node negativity ($P < 0.0001$), histological grade I ($P = 0.0005$) and size less than or equal to 20 mm ($P = 0.0118$) as explanations of the beneficial effect of screening. A new observation we recorded was that screening had a beneficial effect even in women whose cancer had already spread into the axillary lymph nodes.

Keywords: Breast cancer; Mammography; Screening; Survival; Histological type

INTRODUCTION

The Health Insurance Plan (HIP) of Greater New York during the years 1963–1966 demonstrated that a reduction of breast cancer mortality was achieved through breast cancer mammography screening.[1]

Subsequent randomised controlled trials in the 1970s and 1980s further confirmed reduced mortality among women invited to participate in mammography screening.[2–4] As a consequence of the excellent results in these early randomised studies organised population-based breast cancer screening programmes have been in place for women aged 40–74 in 22 countries since the late 1980s and early 1990s.[5] In Sweden, population-based service screening started in some counties in 1986. A 20% lower mortality rate from breast cancer was evident among women who attended screening in these counties than in women who lived in counties where the screening was initiated later.[6] The mean follow-up time was 8.4 years. In Finland, nationwide population-based breast cancer screening for women aged 50–59 was introduced gradually between 1987 and 1991. Mortality from breast cancer was 24% lower among the women offered screening, and 33% lower among those who were actually screened than in nonscreened women.[7] Mortality was expected to fall as a result of screening after 10 years, being 29% and 24% in the Netherlands and the United Kingdom, respectively.[8] Little attention has been paid to background factors, such as tumour size, histological type and grade of breast cancer, as reasons for the desired effect of population-based mammography screening. The present study is an

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evaluation of the correlation of different clinicopathological characteristics and survival in women aged 40–74 years with breast cancer found either through population-based mammography screening or by other means than screening and followed in the city of Turku, Finland during the years 1987–1997.

PARTICIPANTS AND METHODS

From 1987 to 1997 the average population of the city of Turku was 169 000, which included approximately 36 000 women aged 40–74 years. The population-based breast cancer mammography screening programme started in 1987, as described in detail elsewhere.[9] In short, women aged 40–49 born in even years were invited to attend for screening annually, and those born in odd years were invited to attend every third year. Women aged 50–74 were invited for screening every second year. In the years 1987–1997 a total of 176 908 two-view mammography examinations were independently read by two radiologists. The women were screened 1–10 times in the years 1987–1997, the median number of screening visits being 3. The attendance rate was excellent: 87%. During the 11-year study period, 913 cases of invasive breast cancer, 84 of in situ breast cancer (CIS) and two of Paget's disease were found. Patients with second primary breast cancer ($n=44$), CIS or Paget's disease were not included in the analyses. During the years 1987–1997 a total of 869 primary invasive breast cancers were found. Patients with screen-detected (n=531) and 'interval' (n=154) cancers are collectively referred to as the screened group. Of the 184 clinical breast cancers, 96 were detected before any screening and 88 after the defined interval from the last screening or in women who had refused screening.

The patients with breast cancer were followed up until the end of 1999. None of the 84 women with carcinoma in situ died of breast cancer. A total of 121 breast cancer deaths were verified among the total of 181 deaths during the follow-up periods of 1–13 years (median 6 years). All histological breast cancer specimens were re-evaluated by one pathologist (the late S. Toikkanen, M.D.), who had a special interest in breast pathology. The causes of death were obtained from Statistics Finland and from the Finnish Cancer Registry. The death certificates were checked for all patients, and other source data were evaluated as necessary with respect to the cause of death; this was done by two physicians working independently of each other (one oncologist and one forensic pathologist). The primary cause of death was changed after re-evaluation in eight (4.2%) cases. In some instances clinicopathological variables were missing; this was the case for patients in whom no axillary surgery was carried out owing to widespread cancer at presentation and for patients with no histological grading owing to a specific histological type of breast cancer.

Statistical methods

The difference between the groups with regard to the distribution of baseline characteristics was analysed by cross-tabulation, and significances were tested by Pearson's chi-square test. The association between death rates and the predictive variables was studied by survival analysis. Survival curves produced by the Kaplan–Meier method and hazard ratios (HR) with 95% confidence intervals (95% CI) according to Cox proportional hazard models were used for age-adjusted survival analysis in the two groups.[10] P-values less than 0.05 were considered statistically significant. Computations were performed with the SAS System for Windows, release 8.2/2001.

RESULTS

The distribution of some characteristics relevant to screening is presented in Tables 1 and 2. Ductal invasive breast cancers predominated in the clinical group, whereas lobular cancers were more often found through screening. Five percent of the cancers found in women who attended screening were of the tubular type, whereas only 1.6% of cancers were of the tubular type among women who did not attend ($P=0.0405$, tubular vs all other types). None of the women who had tubular breast cancer died during the follow-up period. The cancers disclosed by screening were more often local (N0 vs N1–3, $P<0.0001$), smaller ($P<0.0001$) and well differentiated ($P<0.0001$) than the clinical cancers. There was no significant difference in histological grade, axillary lymph node status or size between breast cancers found in the first and in subsequent screening rounds (Table 3).

Univariate survival analysis shows that the women aged 40–74 who attended screening had a significantly higher survival rate ($P<0.0001$) than the women who did not attend (Fig. 1). After stratification into 10-year age groups the survival rate was still higher among the women who attended screening (Fig. 2).

The risk of death was further investigated after adjustment for clinicopathological variables and for age. Positive axillary nodal status ($P<0.0001$), poorer histological differentiation (P=0.0005) and increase in tumour size (P=0.0118) were independent risk factors in

death from breast cancer according to Cox multivariate analysis adjusted for age (Table 4). Because the axillary lymph node status appeared to be the most significant risk factor for death, we did Cox multivariate analysis for both the N0 and the N1–3 groups (Table 5). In local (N0) breast cancers higher histological grade and larger size are risk factors, whereas histological type and screening did not reach statistical significance. If the cancer had already spread into axillary lymph nodes (N1–3) by the time of diagnosis the risk of death tended to be lower in women who attended screening, although the difference was only marginally significant (P=0.0751). Higher histological grade remained a risk factor, whereas the size of the primary tumour had no effect on the probability of death if metastases were present in axillary lymph nodes.

Table 1 Distribution of clinical and histopathological variables of breast cancer among women in the screened group (with cancers, found through screening and during the interval phase) and the clinical group (women whose cancer was found in the prescreening phase or after the defined interval from the last screening and women who refused screening)

Variable	Screened, *n* (%)	Clinical, *n* (%)	P-value
Age (*n*=869)			<0.0001
40–49 years	147 (21.4)	47 (25.5)	
50–59 years	241 (35.2)	36 (19.6)	
60–69 years	237 (34.6)	52 (28.3)	
70–74 years	60 (8.8)	49 (26.6)	
Histological type (*n*=869)			0.0920
Ductal invasive carcinoma	490 (71.5)	150 (81.5)	
Lobular invasive carcinoma	102 (15.6)	16 (8.7)	
Tubular carcinoma	35 (5.1)	3 (1.6)	
Medullary carcinoma	6 (0.9)	3 (2.2)	
Mucinous carcinoma	14 (2.1)	4 (1.6)	
Apocrine carcinoma	9 (1.3)	3 (1.6)	
Papillary carcinoma	7 (1.0)	2 (1.1)	
Other types	17 (2.5)	3 (1.6)	
Tumour size (*n*=844)			<0.0001
1–10 mm	274 (40.9)	21 (12.1)	
10–20 mm	240 (35.8)	74 (42.5)	
>20 mm	156 (23.3)	79 (45.4)	
Axillary nodal status (*n*=859)			<0.0001
N0	523 (77.1)	104 (57.5)	
N1–3	155 (22.9)	77 (42.5)	
Histological grade (*n*=811)			<0.0001
I	220 (34.4)	25 (14.5)	
II–III	419 (65.6)	147 (85.5)	

DISCUSSION

The value of population-based breast cancer mammography screening in terms of improving breast cancer survival was examined with reference to important clinicopathological variables such as the size, histological type and grade of invasive breast cancer and also the axillary nodal status of the patients affected. From the beginning of this screening programme in 1987, the cohort of 36 000 women in a well-defined geographical urban area was followed up for a median of 6 and a maximum of 13 years. The female population has become familiar with the screening policy, and the attendance rate was high. Up to 1998 the screening was free of charge. In some age cohorts a screening fee has been shown to result in a low attendance rate from 1998 onward, and the years 1987–1997 were therefore chosen for the study.[11]

It is well known that mammography screening for breast cancer finds CIS lesions, which may, even though this is not invariably, so, develop into invasive breast cancer, if left untreated.[12] In our series, the major part of CIS cases were found through mammography examinations and none of the women with CIS died from breast cancer. Therefore, to exclude a bias in favour of screening we excluded all cases of CIS from the analysis.

The average size of invasive breast cancer at presentation had decreased continuously over the decades even before the screening era in Turku, and tumours detected by mammography are even smaller.[9,13]

Table 2 Distribution of invasive breast cancers by histology and method of detection

		Screening			
Histological type of invasive cancer	Prescreening, *n* (%)	First, *n* (%)	Subsequent, *n* (%)	Interval cancer, *n* (%)	Clinical, *n* (%)
Ductal	81 (84.4)	103 (70.1)	274 (71.4)	113 (73.4)	69 (78.4)
Lobular	7 (7.3)	29 (19.7)	55 (14.3)	23 (14.9)	9 (10.2)
Tubular	0 (0)	5 (3.4)	25 (6.5)	5 (3.2)	3 (3.4)
Medullary	1 (1)	1 (0.7)	2 (0.5)	3 (1.9)	2 (2.2)
Mucinous	1 (1)	1 (0.7)	10 (2.7)	3 (1.9)	3 (3.4)
Apocrine	3 (3.1)	6 (4.1)	3 (0.8)	0 (0)	0 (0)
Papillary	1 (1)	0 (0)	4 (1.1)	3 (1.9)	1 (1.1)
Other	2 (2.1)	2 (1.4)	11 (2.9)	4 (2.6)	1 (1.1)

Table 3 Distribution of breast cancers by histological grade I vs II–III, axillary lymph node status N0 vs N1–3 and tumour size 1–10 mm or more than 10 mm in diameter in the first and subsequent screens

	Method of detection		
	First screen, *n* (%)	Subsequent screens, *n* (%)	P-value
Histological type			
Grade I	55 (38.2)	137 (38.1)	0.9945
Grade II–III	89 (61.8)	222 (61.9)	
Axillary lymph node status			
N0	119 (80.9)	303 (79.9)	0.7951
N1–3	28 (19.1)	76 (20.1)	
Tumour size			
1–10 mm	62 (42.5)	184 (48.9)	0.1838
>10 mm	84 (57.5)	192 (51.1)	

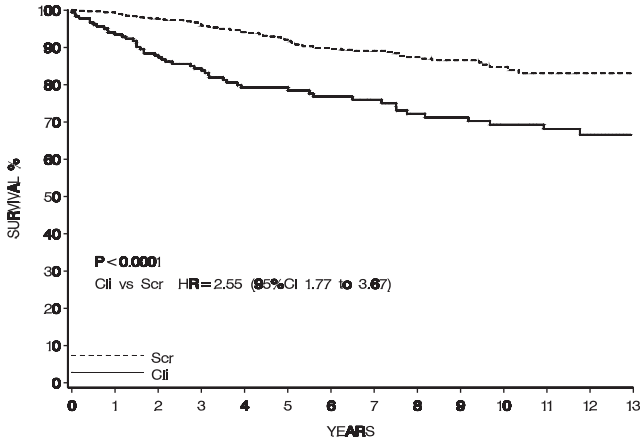

Fig. 1 Kaplan–Meier survival curves of women aged 40–74 years with invasive breast cancer. Scri [HS1]indicates women whose breast cancer was detected through mammography screening or during the defined interval. Cli indicates women whose breast cancer was detected before any screening or after the defined interval from the previous screening or who had refused screening.

Univariate survival analysis indicates that women aged 40–74 obtained significant benefit from screening. According to Kaplan–Meier analysis a survival advantage was obvious in all 10-year age groups (Figs 1 and 2). Since the first promising results showing the benefit of screening mammography in terms of reduced mortality from breast cancer in 1977, several reports have confirmed the survival advantage among women aged 50–74 who have been invited to participate in screening for breast cancer.[1,2,14–16] Our findings are in line with these results. There has been a lot of debate and concern about the value of screening of women aged 40–49. However, our results suggest that women aged 40–49 may also have a survival advantage from breast cancer screening by mammography, as shown by other authors as well.[3,17–21]

In this particular study a pathologist who had special interest in breast tumours reclassified all the breast cancers, hence excluding any classification bias. The most common histological types are ductal and lobular, and these together account for most of all breast cancers. Slow-growing tubular cancers outnumbered other types in the screened group, whereas there was no significant difference between the percentages of other specific types of breast cancer. In a series of patients with tubular T1N0 breast carcinoma followed up for a median of 18 years there were no recurrences.[22] Although the tubular type of breast cancer was over-represented among women who attended screening, there was no statistical difference in survival between the screened and the clinical groups with respect to ductal and lobular vs special types of cancer. Furthermore, histological type was not a risk factor for death in the Cox multivariate analysis in women with either N0 or N1–3 breast cancer. However, the number with specific types was quite low compared with the number with ductal and lobular histology.

It has been claimed that mammography screening detects breast cancers in their preclinical phase, thus giving a 'lead time' with a consequent survival advantage for women with screen-detected breast cancers. We cannot deny this. In addition it has been claimed that screening detects less aggressive breast cancers that are growing so slowly (i.e. length bias) that they will never be a threat to the affected women's lives. If this is true, the first screening round should detect many less aggressive tumours. According to our results, there was no statistically significant difference in histological type or grade, axillary lymph node status or size of breast cancer between the cancers found in the first and in later screening rounds. Therefore, the claim, that mammography screening more often detects slow-growing and less aggressive tumours that without screening would never surface during the women's lifetimes to threaten their lives, does not seem plausible. One explanation for the difference in survival may be the so-called selection bias. The women whose breast cancer is found through screening or during the interval phase, are presumably those who accept and attend for screening; they may be generally more aware of their health and better placed economically than women who do not attend for screening.

An additional important factor affecting survival is cancer treatment. The women in the present study all live in the city of Turku and were all treated according to the same treatment guidelines. Consequently, the treatment modality does not explain the survival differences between women who attended and who did not attend for screening.

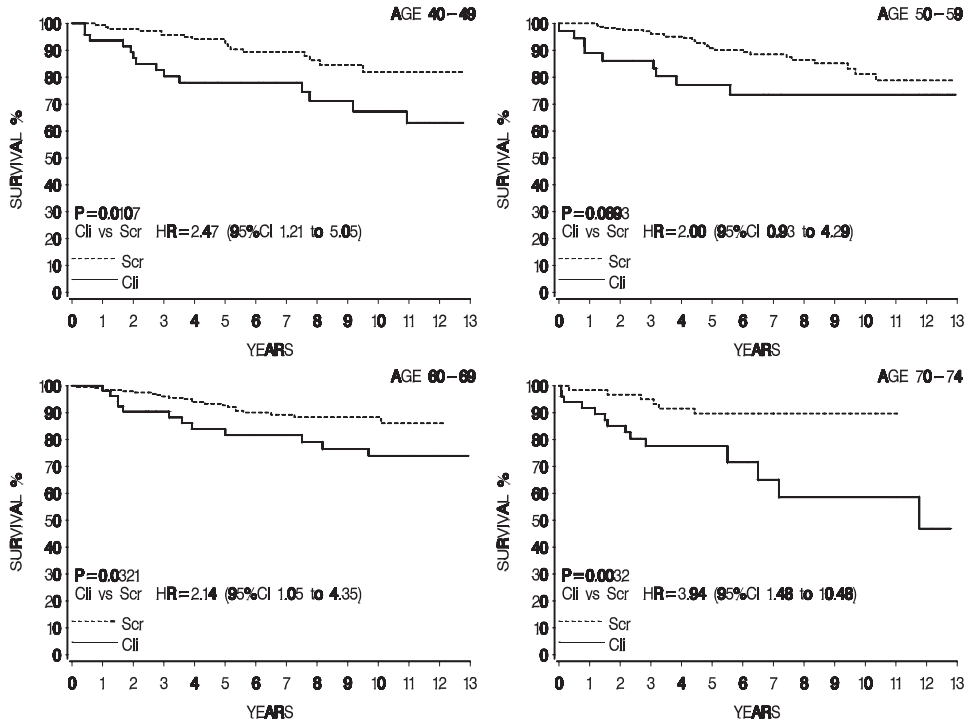

Fig. 2 Kaplan–Meier survival curves of women in four age groups with invasive breast cancer. Abbreviations as in Fig. 1.

Table 4 Multivariate survival analysis by Cox proportional hazard model: 786 patients with invasive breast cancer

Variable	P-value	HR	95% CI
Screening history	0.1660		
Clinical vs screened		1.36	(0.88–2.02)
Axillary lymph node	<0.0001		
N1–3 vs N0		4.32	(2.85–6.54)
Histological grade	0.0005		
Gr II–III vs Gr I		3.67	(1.77–7.69)
Tumour size	0.0118		
>20 mm vs 1–20 mm		1.68	(1.12–2.53)
Histological type	0.3103		
Ductal and lobular vs specific types		1.69	(0.61–4.63)

Clinicopathological variables analysed together with history of mammography screening in the model. HR = hazard ratio. 'Screened' and 'clinical' used as defined in Table 1.

Table 5 Multivariate survival analysis by Cox proportional hazard model of 786 women divided into groups with axillary node negative (N0) and positive (N1–3) breast cancer. Otherwise as in Table 4

Variable	P-value	HR	95% CI
Screening history			
N0	0.8306		
N1–3	0.0751		
Clinical vs screened			
N0		0.920	(0.43–1.97)
N1–3		1.570	(0.96–2.58)
Histological grade			
N0	0.0080		
N1–3	0.0248		
Gr II–III vs Gr I			
N0		5.05	(1.52–16.73)
N1–3		2.88	(1.14– 7.27)
Tumour size			
N0	0.0040		
N1–3	0.1859		
>20 mm vs 1–20 mm			
N0		2.68	(1.37–5.26)
N1–3		1.39	(0.85–2.27)
Histological type			
N0	0.4464		
N1–3	0.5520		
Ductal and lobular vs specific types			
N0		1.745	(0.42–7.32)
N1–3		1.538	(0.37–6.36)

The key question in the present study is why breast cancers found among women who attended for screening behave differently from the cancers found among women who did not. Based on our results, the most important explanation for the beneficial effect of screening is the absence of axillary lymph node metastasis, good histological differentiation grade of breast cancer and small tumour size. Thus, our results are in line with earlier observations on the prognostic value of these variables.[23–25] When the cancer had spread into the axillary lymph nodes, the effect of screening was more pronounced than in the case of

women with small and localised cancers. This can be explained by the fact that for women with small and localised cancers survival is excellent however they are detected. Moreover, we made the new observation that screening had a beneficial effect even in women whose cancer had spread into the axillary lymph nodes.

Although unresolved questions about on the ultimate value of population-based screening mammography persist, it can be concluded that the breast cancer screening programme among women aged 40–74 in the city of Turku has been a successful health policy. The challenge for the forthcoming years will be to improve the facilities and equipment, with the goal of even better detection rates of cancer in its preclinical phase and of cancer that has metastasised,while it is at an even smaller stage. Another important target will be to characterise and identify the most aggressive breast cancers for intensive and individualised treatment. Finally, it is crucial to keep the compliance for screening high. This may be achieved by providing the screening free of charge to the screenee, a policy shown earlier to be effective.[11]

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References

1. Shapiro S. Evidence on screening for breast cancer from a randomised trial. Cancer 1977; 39: 2772–2782.
2. Hendrick R E, Smith R A, Rutledge III J H, Smart C R. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomised controlled trials. Monogr Natl Cancer Inst 1997; 22: 87–92.
3. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist L E. Long-term effect of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002; 359: 909–919.
4. Humphrey L L, Helfand M, Chan B K S, Woolf S H. Breast cancer screening: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2002; 137: 347–360.
5. Shapiro S, Coleman A, Broeders M et al. Breast cancer screening programmes in 22 countries: current policies, administration and guidelines. Int J Epidemiol 1998; 27: 735–742.
6. Jonsson H, Nystrom L, Tornberg S, Lenner P. Service screening with mammography of women aged 50–69 years in Sweden: effect on mortality from breast cancer. J Med Screen 2001; 8: 152–160.
7. Hakama M, Pukkala E, Heikkilä M, Kallio M. Effectiveness of the public health policy for breast cancer screening in Finland: population based cohort study. BMJ 1997; 314: 864–867.
8. van den Akker-van Marle E, de Koning H, Boer R, van der Maas P. Reduction in breast cancer mortality due to the introduction of mass screening in the Netherlands: comparison with the United Kingdom. J Med Screen 1999; 6: 30–34.
9. Klemi P J, Toikkanen S, Räsänen O, Parvinen I, Joensuu H. Mammography screening interval and the frequency of interval cancers in a population-based screening. Br J Cancer 1997; 75: 762–766.
10. Collett D. Modeling Survival Data in Medical Research. London: Chapman & Hall, 1994.
11. Immonen-Raiha P, Kauhava L, Parvinen I, Helenius H, Klemi P. Customer fee and participation in mammography screening. Lancet 2001; 358: 1425.
12. Feig S A. Ductal carcinoma in situ. Implications for screening mammography. Radiol Clin North Am 2000; 38: 653–668.
13. Joensuu H, Toikkanen S. Comparison of breast carcinomas diagnosed in the 1980s with those diagnosed in the 1940s to 1960s. BMJ 1991; 303: 155–158.
14. Verbeek A, Hendriks J, Holland R, Mravunac M, Strumans F, Day N E. Reduction of breast cancer screening mortality through mass screening with modern mammography: first results of the Nijmegen project. Lancet 1984; i: 1222–1224.
15. Tabar L, Vitak B, Chen H-H et al. The Swedish Two-County Trial twenty years later. Radiol Clin North Am 2000; 38: 625–651.
16. Duffy S W, Tabar L, Chen H-H et al. The impact of organized mammography service screening on breast carcinoma mortality in seven swedish counties. A collaborative evaluation. Cancer 2002; 95: 458–469. DOI: 10.1002/cncr.10765
17. Feig S A. Estimation of currently attainable benefit from mammographic screening of women aged 40–49 years. Cancer 1995; 75: 2412–2419.
18. Larsson L-G, Andersson I, Bjurstam N et al. Updated overview of the swedish randomised trials on breast cancer screening with mammography: age group 40–49 at randomization. Monogr Natl Cancer Inst 1997; 22: 57–61.
19. Smart C R, Byrne C, Smith R A et al. Twenty-year follow-up of the breast cancers diagnosed during the Breast Cancer Detection Demonstration project. CA Cancer J Clin 1997; 47: 134–149.
20. Kopans D B. The breast cancer screening controversy, the National Institute of Health Consensus Development Conference on Breast Cancer Screening for Women of Ages 40–49. Radiology 1999; 210: 4–9.
21. Andersson I. Mammographic screening under age 50: a review. Breast 2000; 9: 125–129.
22. Rosen P P, Groshen S, Saigo P E, Kinne O W, Hellman S. A long-term follow-up study of survival in Stage I (T1N0M0) and Stage II (T1N0M0) breast carcinoma. J Clin Oncol 1989; 7: 355–366.
23. Carter C L, Allen C, Henson D E. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989; 63: 181–187.
24. Duffy S W, Tabar L, Fagerberg G et al. Breast screening, prognostic factors and survival—results from the Swedish two county study. Br J Cancer 1991; 64: 1133–1138.
25. Lundin J, Lundin M, Holli K et al. Omission of histologic grading from clinical decision making may result in overuse of adjuvant therapies in breast cancer: results from a nation-wide study. J Clin Oncol 2001; 19: 28–36.