not confirm the initial findings. In 6 patients, no recurrence has developed from 6 to 8 years after the abnormal chest X-ray diagnosis. In the remaining 8 patients recurrence was detected, in 6 outside the chest and in 2 in the sternum or ribs. 2 of these 8 patients are still alive 3 and 6 years later. The remaining 6 died from 1 to 6 years (median 2.5 years) after the false positive diagnosis. No intrathoracic spread has developed in these 8 patients.

Malignant findings at X-ray within 12 months after scheduled X-ray

26 patients developed pulmonary symptoms including chest pain between scheduled clinical controls. In all these patients chest X-ray revealed malignant changes. 4 had pulmonary metastases, three carcinomatous lymphangitis, 10 pleural effusion, 1 pleural metastases and 8 skeletal metastases. 25 of the 26 patients have died; the median survival after recurrence was 11 months (range: 1–60+ months).

DISCUSSION

After performing a total of 1289 chest X-rays in 280 patients with primary operable breast cancer, DBCG stage II, unexpected malignant findings were revealed in only 17 patients. Almost twice as many (3 plus 26) had symptoms indicating thoracic spread at the time of diagnosis at chest X-ray, of which 90% were performed unscheduled (i.e. not fixed to the time of mastectomy). There was no significant survival difference after the diagnosis of thoracic spread between the 29 symptomatic and the 17 asymptomatic patients. According to Ojeda *et al.* [4], it is still uncertain whether chemotherapy and/or radiation may prolong the survival further if given to asymptomatic patients. This could, however, in part be due to the different symptomatology of the different types of spread. Pleural effusions and malignant lymphangitis rarely occur without symptoms, whereas pulmonary nodules usually cause no symptoms in the early stage [5].

In stage I breast cancer patients, it was necessary to perform 400 examinations to diagnose one case of asymptomatic thoracic spread [1]. The present study shows that in stage II breast cancer patients one case of malignancy was found when 76 scheduled chest X-rays were performed. This is of course a better cost/benefit ratio, but still low. As regards routinely performed bone scintigraphy in primary operable breast cancer patients who at the time of the scintigraphy are considered to be recurrence free, it has been stated that no more than 50 examinations should be done between the finding of one case of malignancy [6].

In our opinion the number of normal examinations between two abnormal examinations may not exceed 50 in a screening programme, where the examination dates are related to the day of surgery, especially when abnormal findings in asymptomatic patients do not seem to result in a significantly longer survival.

We conclude that due to an unsatisfactory cost/benefit ratio (number of malignant cases/total number of examinations, no difference in life time between asymptomatic and symptomatic patients) and a high frequency of false positive cases (causing expensive supplementary examinations), repeated routine chest X-rays in patients with stage II breast cancer are not warranted. Chest X-ray should therefore be reserved for patients with a suspicion of recurrence or with pulmonary symptoms; in this case the cost/benefit ratio is more satisfactory.

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Risk of Breast Cancer Subsequent to Proven Gross Cystic Disease

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3809 women in whom breast cysts were aspirated were followed up to evaluate the observed/expected ratio of subsequent breast cancer. Breast cancer at cyst aspiration was excluded by physical examination and mammography. The first year of follow-up was censored to avoid a prevalence screening effect. Subsequent breast cancers were found either directly or by means of a cancer registry which also provided the expected age and residence specific incidence rates. The number of expected cancers was assessed in person-years (15,915 in the total series). The observed/expected subsequent breast cancer ratio was 1.77 (34/19.15; 95% confidence interval 1.23–2.48, $P < 0.05$). The presence of gross cysts was associated with a moderately though significantly increased risk of subsequent breast cancer. Increased surveillance in such patients is not justified.
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INTRODUCTION

THE RELATIVE RISK of breast cancer associated with a history of benign breast cancer disease varies across studies, and different benign breast conditions carry different risks of subsequent cancer [1–3]. The frequency of breast carcinoma developing subsequent to gross cystic disease has been studied for at least four decades, which probably reflects the clinician's interest in knowing whether a frequent event such as gross cyst aspiration might suggest an increased risk of later cancer. Some of these studies have been criticized [4] for inadequate case definition or for the limited number of cases [5–7]. However, studies based on a large number of cases followed up for a long period report conflicting results, the relative risk of subsequent breast cancer ranging from 1.73 to 4.15 [4, 8].

Our aim was to assess the risk of breast cancer developing after proven gross cystic disease. 3809 women in whom a cyst was aspirated were retrospectively followed up by a breast cancer registry and the number of subsequent breast cancers was compared with the expected incidence.

PATIENTS AND METHODS

Women aged 15–69 in whom one or more cysts had been aspirated from January 1979 to December 1985 at the outpatient breast clinic were eligible. Women with previous histological evidence of invasive or *in situ* breast cancer or of atypical hyperplasia were excluded.

According to the diagnostic protocol adopted for self referring women in the study period, women aged below 40 and women with subjective symptoms other than sole pain at any age were physically examined, whereas mammography was routinely done in women aged 40 or over or in women with questionable clinical findings in women aged below 40. All palpable and/or mammographic abnormalities underwent fine needle aspiration. Cyst fluid cytology was routinely examined until 1983 and then such examination was limited to cases with bloody cyst content [9]. Pneumocystography was done only in cases of bloody cyst fluid [10]. No specific programme of periodic follow-up was advised after cyst aspiration.

Breast cancer in both breasts at the time of cyst aspiration was excluded by physical examination and/or mammography according to the above protocol. Infiltrating cancers before age 70 were considered, being either diagnosed at our clinic or recorded in a breast cancer histological registry that has been operating in the Florence district since 1973 [11]. Ten cases of breast cancer histologically proven within the first year since cyst aspiration were excluded from the study. In none of these cases was the cancer discovered as a result of investigations directly following the aspiration of the cyst. The first year of follow-up was not included in the calculation of person-years and observation of patients was stopped after age 70. Breast cancer occurrence and person-years for the study cohort were assessed at 31 December 1987.

The expected number of breast cancers was calculated by applying the age specific and residence specific (Florence vs other district municipalities) incidence rates assessed for the district of Florence in a previous study [11] to the respective age and residence specific person-years in the study cohort. The relative risk of breast cancer subsequent to proven gross cystic disease was estimated according to the standardized incidence ratio and its 95% confidence interval [12].

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Table 1. Age distribution of cases, person-years and observed/expected cancers

Age	No.	Person-years	Observed	Expected
15–19	28	59	0	0
20–24	49	100	0	0
25–29	120	344	0	0
30–34	241	691	0	0
35–39	533	1373	6	1.2
40–44	1060	2917	13	3.0
45–49	1123	4852	12	7.2
50–54	482	3783	3	5.1
55–59	93	1277	0	2.0
60–64	51	342	0	0.65
65–70	29	177	0	0
Total	3809	15,915	34	19.15

RESULTS

3809 women were eligible. Age ranged from 15 to 69 years; the average age was 43.3 (Table 1). Thirty-four infiltrating breast cancers were in the cancer registry. Thirteen cancers occurred in the same breast as a previously aspirated cyst, 11 in the contralateral breast and 10 in women with bilateral cysts. Time from cyst aspiration to cancer occurrence ranged from 2 to 7 years (mean 4.06). The follow-up ranged from 1 to 7 years (mean 4.18).

Table 2 shows the data for the observed/expected ratio of subsequent breast cancer incidence. Breast cancers expected in the study cohort according to age specific incidence rates were 19.15. The standardized incidence rate of the study cohort with respect to the normal population was 1.77 (95% confidence interval 1.23–2.48, $P < 0.05$). No time trend was observed for the standardized rate.

DISCUSSION

Previous studies of the association with subsequent breast cancer usually evaluated cases of histologically assessed benign breast disease. The risk of later breast cancer has been reported to be higher for proliferative lesions, in particular those showing atypias. Nevertheless, a low proportion of breast cancers have a previous history of benign biopsies, few of which show

Table 2. Observed vs expected cancer ratios

Year of follow-up	Subsequent breast cancers		SIR	CI	*P*
	Observed	Expected			
2nd	8	4.24	1.9	0.81–3.72	0.28
3rd	6	3.82	1.6	0.58–3.42	0.50
4th	8	3.16	2.5	1.09–4.99	<0.05
>4th	12	7.93	1.5	0.78–2.64	0.60
Total	34	19.15	1.77	1.23–2.48	<0.05

SIR = standardized incidence rate; CI = 95% confidence interval.

Table 3. Frequency of some breast cancer risk factors (random sample of 100 cases) compared with that expected in age-adjusted distribution of normal population

Risk factor	Observed frequency (%)	Expected frequency (%)
First-degree familiarity	4	3
No. of births:		
0	20	25
1	34	10
2	34	37
>2	12	28
Age at first pregnancy:		
Nulliparous	20	25
<21	7	17
21–23	24	22
24–28	34	25
>28	15	11

proliferative lesions and even less show atypia [13]. Thus selecting women for increased surveillance according to a previous history of histologically proven, high-risk benign lesions has a limited role in preventive strategies.

Even without histological confirmation, the aspiration of a cyst may be taken as sufficient evidence of benign breast disease. In the case of a positive association, cyst aspiration would be a more common risk indicator than the histological evidence of a high-risk benign lesion.

There are four possible biases in our results: selection, diagnostic and detection bias, and selective follow-up.

Women aware of risk factors for breast cancer (e.g. familiarity, advanced age at first pregnancy, previous biopsy for high-risk lesions) are more likely to present spontaneously. This selection bias should be less evident in women presenting with a symptomatic cyst but it might still have a confounding effect on the association between cysts and subsequent breast cancer. We reviewed the distribution of some risk factors, namely first-degree familiarity, number of births and age at first pregnancy, in a random sample of 100 cases from our cohort and compared the results with those from the normal population in a previous case-control study [14] (Table 3). No major difference was observed.

The presence of breast cancer at the time of breast aspiration was excluded by physical examination in all and by mammography in a subset. To reduce the effect of prevalence screening [4] patients-year at risk and breast cancers in the first year of follow-up were censored. However, the expected/observed cancer ratio in the first year was 2.1, which was similar to that in the further follow-up. Also, no effect of prevalence screening on breast cancer incidence was evident from the second year onwards. The absence of a prevalence screening effect could be explained by small synchronous cancers being missed on physical examination in younger women (25% of subjects were under age 40) and on mammography in women aged 40–49 (57% of the total) because of radiologically dense breast. This could also partly explain the higher frequency of subsequent cancer observed in the fourth decade in older women.

The identification of subsequent breast cancers was based on an histological cancer registry. Incident cases may have been under-registered but the estimate of expected cases according to age-adjusted incidence rates was based on the same source. Thus, this possible detection bias should not affect the reliability of observed/expected ratios. Although no specific follow-up was advised after cyst aspiration, it is likely that these patients have been checked more intensively than the normal population. The age specific incidence rates for the study cohort do suggest diagnostic anticipation but the stage distribution observed for cancer cases was not different from that expected. Overall, diagnostic bias cannot be ruled out. The absence of a trend during follow-up reassures us about early detection bias.

The study cohort was not actively followed up and person-years at risk might have been overestimated because of unknown drop-outs due to death from other causes or migration, and the estimated relative risk would be biased towards the null value. Overall mortality (age 35, 0.5/1000 year; age 54, 3.3/1000 year) and migration (age 35, 2%; age 54, 1%) rates in the cohort were not high [15] and selective follow-up should not represent a major bias.

This study showed that women with breast cysts have a risk of subsequent breast cancer higher than expected. In accord with other reports [1, 8] the observed risk increase was moderate and does not justify increased surveillance in these patients. Several biases have been discussed for our retrospective review and conclusions should be confirmed prospectively. A subtype of cysts has been reported to be associated with increased risk of breast cancer [16], although this observation needs to be confirmed [17].

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