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The value of routine physical examination in the follow up of women with a history of early breast cancer

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ABSTRACT

Purpose: Routine physical examination is recommended in follow up guidelines for women with a history of breast cancer. The objective of this paper is to assess the contribution of routine physical examination in addition to mammography in the early diagnosis of breast cancer recurrences.

Patients and methods: The medical follow-up documents of 669 patients were reviewed. 127 contra-lateral breast cancers (CBCs) and 58 loco-regional recurrences (LRRs) in 163 patients were included. The additional contribution of routine physical examination over mammography was evaluated with the proportions of CBCs or LRRs detected by physical examination alone. χ^2 tests were used to compare the difference of contribution of physical examination among subgroups.

Results: Seven (6%) out of 127 CBCs and 13 (22%) out of 58 LRRs were detected by routine physical examination alone. Six LRRs (17%; 6/35) were in patients after breast conserving surgery and seven LRRs (30%; 7/23) in patients after mastectomy. There was a trend that the contribution of physical examination is higher in women under 60 years of age in the detection of CBCs (9%; 5/57) and LRRs (28%, 8/29) than in women over 60 years of age (CBCs:3%; 2/70 and LRRs:17%, 5/29; $\chi^2 = 3.090$, $P = 0.079$).

Conclusions: Twenty-two percent of loco regional breast cancer recurrences would have been detected later without physical examination. Routine physical examination may be most valuable for women with a history of breast cancer younger than 60 years at follow-up visit.

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1. Introduction

A combination of high incidence and good survival makes breast cancer the most prevalent cancer in women.¹ This puts

an increasing burden on follow-up oncology clinics. It is predicted that there will be a 48% increased need for cancer services by 2020.² Specialists are facing an ever-increasing workload of providing long-term follow-up care for women

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with a history of early-stage breast cancer. This will call for guidelines and programmes to provide comprehensive, compassionate and cost-effective follow-up care.³

One of the main purposes of follow-up after breast cancer is early detection of isolated breast cancer recurrences such as loco-regional recurrence (LRR) and contra-lateral breast cancer (CBC), because these are the kind of recurrences that could be treated aiming at cure or long term disease free survival. A meta-analysis suggested that early detection of isolated breast cancer recurrences is associated with an increased chance of survival.⁴ Routine mammography and physical examination are recommended in the follow up guidelines for women with a history of breast cancer to detect these LRRs and CBCs early.^{5–7} The value of mammography for early detection of CBC has been confirmed in several studies.^{8–10} In addition, LRR in the conserved breast can often be detected early by mammography.^{11,12} However, the contribution of routine physical examination to the early detection of a recurrence is debatable and estimates for the proportion of recurrences detected by physical examination alone vary from 6% to 40%.¹³ It is known that the performance of physical examination is at least influenced by age and previous surgical treatment (breast conserving surgery versus mastectomy).^{14,15} In addition, a higher frequency physical examination in the first 5 year after primary treatment has been recommended.¹⁶ It was hypothesised that there might be more LRRs and CBCs detected by routine physical examination due to the intensive follow-up in the first 5 years after primary treatment. The aim of the current study is to evaluate the contribution of physical examination in addition to mammography during following up of women with a history of breast cancer, and to assess the influence of patient's age at follow-up visit, previous surgical treatment and the time since primary diagnosis on the diagnostic value of physical examination.

2. Patients and methods

2.1. Settings and subjects

Patients with breast cancer were selected from the files of the regional cancer registry of the former Comprehensive Cancer Centre North-Netherlands (CCCN, merged into the Comprehensive Cancer Centre Northeast-Netherlands in 2009). This cancer registry contains data on diagnosis, stage and treatment actively abstracted from the medical records of all hospitals within the CCCN catchment area using a national registration and coding manual of the Dutch Association of Comprehensive Cancer Centres.

For 5589 consecutive women, breast cancer was the first primary cancer diagnosed in four hospitals in the Northern part of the Netherlands (an academic hospital, a large teaching hospital and two non-teaching hospitals) from January 1989 to January 2003. A new primary tumour was defined as any new tumour that was not a recurrence or direct extension of the known tumour. All these women were without evidence of distant metastasis at the moment of primary diagnosis. Of these 5589 women a total of 139 patients developed CBC at least six months after the first tumour and those CBCs were registered in the database. Because the informa-

tion on follow-up and LRRs is not available in the cancer registry, this additional follow-up information was retrieved from the medical documents in the four participating hospitals. Follow-up information was collected for all 139 patients with a CBC and for a sample of the patients ($n = 597$) without a CBC. To minimise bias, patients without a CBC were stratified on hospital of diagnosis, age at first primary tumour and duration of follow-up before sampling.

For these 736 patients, follow-up information was retrieved from medical documents in the four participating hospitals (Fig. 1). Follow up documents were unavailable for 67 patients (9%) of whom 12 patients had CBCs. Of the remaining 669 women included in this cohort, 51 patients were found to have developed a total of 58 LRRs (recurrences in the conserved breast, chest wall, axilla or supraclavicular nodes at the same side of the primary tumour). Recurrences that were detected in the same patient within a six months period were considered as one recurrence.

Therefore, a total of 127 CBCs and 58 LRRs in 163 patients were reported in this cohort. In the other 506 patients there was no evidence of LRRs or CBCs. Patients who developed distant metastases before or at the time of CBC or LRR were not included.

2.2. Data abstraction

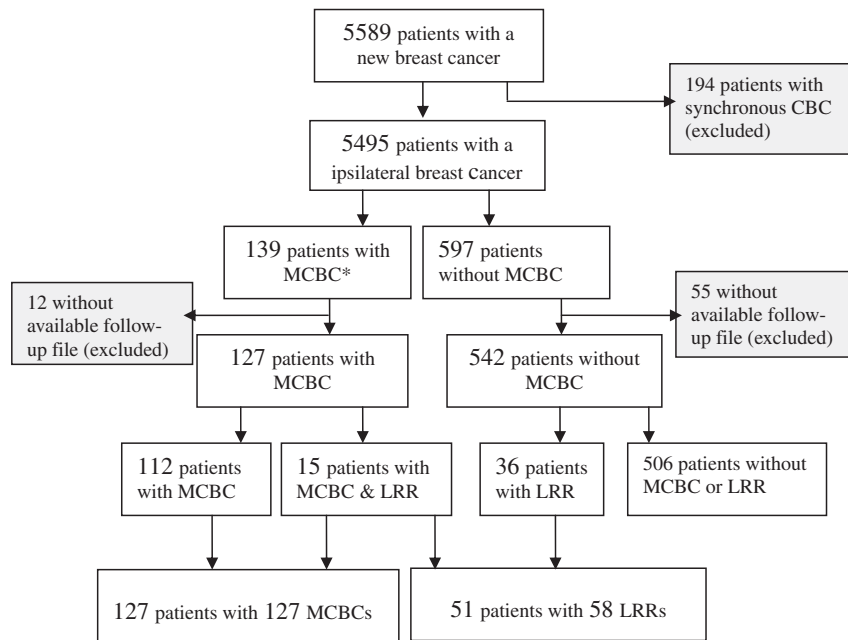
For all patients included in our study cohort, the information regarding appointments and tests were retrieved, including date of appointment, symptoms reported by the patients during or pending the appointment (yes or no; and kind of symptoms if applicable), findings of routine physical examination (mass, abnormality in scar, abnormality in axilla or supra-clavicular) and mammography. For these analyses, all follow-up visits were regrouped into episodes, which were defined as 45-d periods. It was assumed that follow-up appointments that happened within these episodes were related to each other, so the information was combined.

2.3. Definitions

Routine physical examination was defined as the physical examination undertaken by a physician during the routine follow-up visits with or without mammography. Routine mammography was defined as a mammography that was undertaken during routine follow-up visits with or without physical breast examination.

The mode of detection of CBCs and LRRs was classified as mammography alone (in case of normal findings on physical examination and abnormal mammograms in asymptomatic patients); physical examination alone (in case of abnormal findings on physical examination and normal mammograms in asymptomatic patients); both mammography and physical examination (in case of abnormal findings of physical examination and abnormal mammograms in asymptomatic patients) and symptoms (reported by patients at interval visits between two scheduled follow-up visits or presented at scheduled follow-up visits).

The contribution of routine physical examination was evaluated by assessing the proportion of recurrences detected by routine physical examination alone. The analysis of the



* MCBC : Metachronous contra-lateral breast cancer

Fig. 1 – Graphical illustration of the sampling of study cohort.

contribution of physical examination was based on the number of recurrences.

2.4. Statistical analysis

Comparisons of the contribution of physical examination were performed by χ^2 tests among subgroups with respect to the type of recurrences, the surgical treatment of the first tumour, age of the patient at the time of recurrence and the time from the first tumour. For all the patients included in this sample, the information on follow-up and LRR was collected from the documents in hospital including the follow-up appointments and the follow-up procedures. The number of mammographies and physical examinations performed during the follow-up of each patient was analysed aiming to give a profile of the burden of follow-up in case of a LRR. Because CBC events were oversampled, the burden of follow-up to detect CBCs early could not be assessed. The number of routine physical examinations undertaken for the early detection of one additional loco-regional recurrence in addition to routine mammography was calculated in subgroups with respect to surgical treatment modality, patients' age and the time from the first tumour.

3. Results

3.1. Characteristics of patients and the primary breast cancer

Of the 669 included patients, 56% ($n = 375$) were younger than 60 years of age when the primary breast cancer was diagnosed (Table 1). 32% ($n = 214$) of patients received breast conserving surgery as primary treatment, 57% ($n = 383$) of the

patients received radiotherapy, 15% ($n = 101$) chemotherapy and 21% ($n = 139$) hormonal therapy, respectively. The median follow-up time was 11.0 years (1.6–18.1).

3.2. Characteristics of CBCs and LRRs

Out of 127 CBCs, 45% ($n = 57$) were diagnosed in patients under the age of 60 (Table 1). Seventy-five percent ($n = 84$) out of 112 CBCs with specified pathological T stage were detected at stage T1 or Tis. Of all CBCs, 70% (80/114) were detected without lymph nodes involved. 31% ($n = 39$) of 127 patients with CBC received radiotherapy for the CBC, 13% ($n = 16$) received chemotherapy and 26% (33) received hormonal therapy. Thirty-four percent of CBCs ($n = 43$) were diagnosed more than 5 years after primary treatment.

Out of the 58 isolated LRRs, 50% (29) were diagnosed in patients under the age of 60 (Table 1). Forty-nine percent of the LRRs ($n = 25$) were treated with mastectomy, where 51% of LRRs ($n = 26$) were treated with local excision. Five LRRs were detected in women who had breast conserving surgery previously and 21 LRRs were detected in women who had mastectomy previously. For seven LRRs the type of surgical treatment was unknown.

For 34% of LRRs ($n = 20$), patients received radiotherapy, for 85% of LRRs ($n = 49$), patients received chemotherapy and for 33% of LRRs ($n = 19$) patients received hormonal therapy. Thirty-one (53%) out of 58 LRRs developed more than 5 years after the primary treatment.

3.3. Detection of contra-lateral breast cancers

Of 127 CBCs, seven (6%) were detected by routine physical examination alone, 42 (33%) were detected by mammography

Table 1 – Characteristics of patients and their tumours^a n (%).

| Characteristics | Primary tumour N = 669 | CBC N = 127 | LRR N = 58 |
|--|------------------------|-----------------|-----------------|
| <i>Age group at diagnosis</i> | | | |
| <60 | 375 (56) | 57 (45) | 29 (50) |
| 60+ | 294 (44) | 70 (55) | 29 (50) |
| <i>Pathologic T stage</i> | | | |
| pTis | 57 (9) | 14 (12) | – |
| pT1 | 321 (49) | 70 (63) | – |
| pT2/3/4 | 281 (42) | 28 (25) | – |
| Unknown | 10 | 15 | – |
| <i>Pathologic N stage</i> | | | |
| N0 | 439 (67) | 80 (70) | – |
| N+ | 215 (33) | 34 (30) | – |
| Unknown | 15 | 13 | – |
| <i>Surgery</i> | | | |
| Lumpectomy/local excision | 214 (33) | 35 (34) | 26 (51) |
| Mastectomy | 429 (67) | 68 (66) | 25 (49) |
| Unknown | 26 | 24 | 7 |
| <i>Radiation therapy</i> | | | |
| Yes | 383 (57) | 39 (31) | 20 (34) |
| No | 286 (43) | 88 (69) | 38 (66) |
| <i>Chemotherapy</i> | | | |
| Yes | 101 (15) | 16 (13) | 49 (85) |
| No | 568 (85) | 111 (87) | 9 (15) |
| <i>Hormonal therapy</i> | | | |
| Yes | 139 (21) | 33 (26) | 19 (33) |
| No | 530 (79) | 94 (74) | 39 (67) |
| Time of follow up (median (range) years) | 11.0 (1.6–18.1) | 10.0 (1.6–18.1) | 11.6 (2.2–17.5) |
| Time from first tumour (years) | – | 3.8 (0.6–11.9) | 5.0 (0.6–15.6) |
| <5 years | – | 84 (66) | 27 (47) |
| 5 years or more | – | 43 (34) | 31 (53) |

^a Recurrences-based analysis.**Table 2 – Contribution of physical examination to mammography in follow-up of patients with breast cancer^a n(%).**

| Method of detection | CBC (n = 127) | LRR_BCS ^b (n = 35) | LRR_Mastectomy ^c (n = 23) |
|------------------------------------|---------------|-------------------------------|--------------------------------------|
| Routine physical examination alone | 7 (6) | 6 (17) | 7 (30) |
| Routine mammography alone | 42 (33) | 7 (20) | – |
| Both | 26 (20) | 11 (31) | – |
| Symptoms reported by patients | 52 (41) | 11 (31) | 16(70) |

^a Recurrences-based analysis.^b LRR_BCS: Loco regional recurrence in patients after breast conserving surgery.^c LRR_Mastectomy: LRR in patients after mastectomy.

alone and 26 (21%) were detected by both follow-up modalities (Table 2). Of the 75 asymptomatic patients with CBCs, 33 (44%; 95%CI: 32–56%) were palpable by the physician at routine follow-up visits. Out of 52 patients (41%) who reported symptoms leading to the diagnosis of a CBC, 11 (9%) presented at scheduled follow-up visits and 41 (32%) presented as interval cases.

In total, 86 patients (67.7%) with CBCs were detected during routine follow-up visits and 41 (33.3%) presented as interval cases. Out of 86 patients detected during routine follow-up visits, 33 patients (38.4%) with CBCs were palpable in routine physical examinations.

3.4. Detection of loco-regional recurrences

In 214 patients who received breast conserving surgery for the primary tumour, 16% (n = 35) of LRRs were diagnosed. Eleven LRRs after BCS were diagnosed because of symptoms reported by the patient (31%) between two scheduled follow-up visits and none at the moment of a scheduled visit. Of the 24 asymptomatic LRRs, 17 (71%; 95%CI: 51–91%) were palpable by the physician at routine follow-up visits. Six of the LRRs (17%) were diagnosed by routine physical examination alone, 20% (n = 7) by routine mammography alone and 31% (n = 11) by both (Table 2).

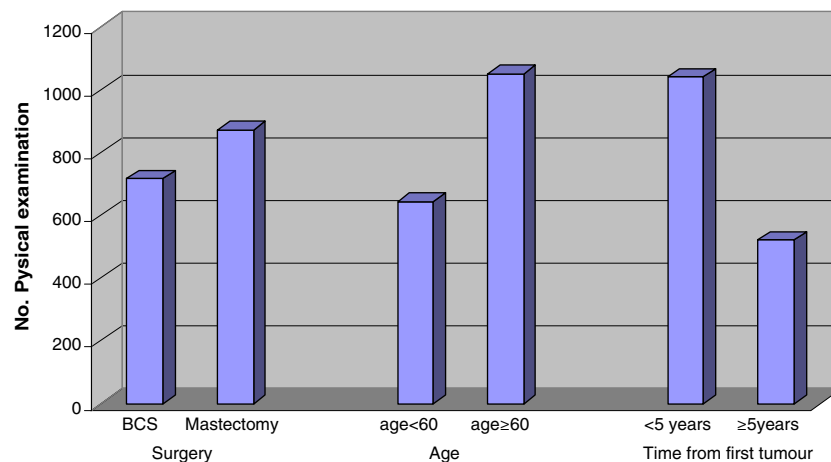


Fig. 2 – Number of routine physical examinations performed to detect one additional LRR.

Of the 429 patients treated with mastectomy, 5% ($n = 23$) LRRs were diagnosed. Of these, 30% ($n = 7$) were detected by routine physical examination alone (Table 2). Seventy percent ($n = 16$) presented with symptoms in which 40% ($n = 9$) presented at scheduled follow-up visits and 30% ($n = 7$) presented as interval cases.

In total, 40 patients (69.0%) with LRRs were detected during routine follow-up visits and 18 (31.0%) presented as interval cases. Out of 40 patients detected during routine follow-up visits, 24 patients (60.0%) with LRRs were palpable in routine physical examinations.

When considering only the first recurrence in each patient, it was found that seven (6%) out of 120 CBCs and six (14.0%) out of 43 LRRs (four LRRs after breast conserving surgery and two LRRs after mastectomy) were detected by routine physical examination alone.

3.5. Contribution of physical examination

Seven (6%) out of 127 CBCs and 13 (22%) out of 58 LRRs in which six LRRs (17%; 6/35) in patients after breast conserving surgery and seven LRRs (30%; 7/23) in patients after mastectomy were detected by routine physical examination alone. The incremental contribution of physical examination was higher in detecting LRRs than in detecting CBCs ($\chi^2 = 11.797$, $P = 0.001$).

Seventeen percent ($n = 6$) of 35 LRRs after breast conserving surgery and 30% ($n = 7$) of 23 LRRs after mastectomy would have been detected later, if there was no routine physical examination. The difference in the contribution of physical examination in the detection of LRRs after BCT or after mastectomy was not statistically significant ($\chi^2 = 1.410$, $P = 0.235$).

There was a trend that the proportion of recurrences detected by physical examination alone was higher in women under 60 years of age at follow-up visit than in those over 60 years ($\chi^2 = 3.090$, $P = 0.079$). In women under 60 years of age at follow-up visit, 9% ($n = 5$) of 57 CBCs and 28% ($n = 8$) of 29 LRRs would have been missed, if there was no routine physical examination. For women over 60, 3% ($n = 2$) of 70 CBCs and 17% ($n = 5$) of 29 LRRs would have been detected later if there was no routine physical examination, respectively.

Of the recurrences occurring within 5 years after the primary tumour, 4% ($n = 3$) of 84 CBCs and 26% ($n = 7$) of 27 LRRs were detected with routine physical examination alone. For recurrences occurring after 5 years from the first tumour, 9% ($n = 4$) of 43 CBCs and 19% ($n = 6$) of 31 LRRs were detected with routine physical examination. There is no significant association between the proportions of recurrences detected by physical examination alone and time from the first tumour ($\chi^2 = 0.934$, $P = 0.334$).

Eight hundred and one (10,411/13) physical examinations were done to detect one additional LRR. In patients after breast conserving surgery, 716 (4298/6) physical examinations were done to detect one additional LRR. In patients after mastectomy, 873 (6113/7) physical examinations were done to detect one additional LRR. For patients younger than 60 years, 644 (5152/8) physical examinations were done to detect one additional LRR, whereas the number was 1052 (5259/5) for patients older than 60. In the first 5 years, 1041 (7286/7) physical examinations were done to detect one additional LRR, whereas this number was 521 (3125/6) more than 5 years after primary treatment (Fig. 2).

4. Discussion

If there was no routine physical examination, 22% of 58 LRRs and 6% of 127 CBCs would have been detected later. There was a trend towards a higher contribution of physical examination in detecting LRR in younger (<60) patients than in older (≥ 60) patients. For patients younger than 60 years at follow-up visit, 644 physical examinations were performed to detect one additional LRR, whereas, for patients older than 60 years at follow-up visit, the number was 1052.

Regular mammography has proven its benefit in the early detection of CBC.^{8,17} There are only a few studies to evaluate the contribution of physical examination in early detection of CBC. In this study the number of CBCs was enriched to evaluate the contribution of physical examination on detecting CBCs by including all available patients with CBCs of 5589 patients with a history of breast cancer. The overall detection rate of CBC by routine physical examination alone is low in this study, which is consistent with results from a recent

study (6%).^{13,18} This result is also in line with one study adding routine physical examination to mammography for the screening for breast cancer, which reported an additional 5% of tumours detected by physical examination alone.¹⁹

There is a trend that the contribution of physical examination is higher in detecting LRRs in patients after mastectomy, however, the difference was not statistically significant, probably due to the small number of LRRs in both groups. Seven asymptomatic LRRs (30%) in patients after mastectomy were detected by physical examination alone during routine follow up. In patients treated with breast conserving surgery, mammography is available and useful for the detection of a LRR although the sensitivity of mammography will be decreased in the conserved breast due to the scar and changes in density of the breast after surgery.²⁰ After mastectomy, the detection of LRRs was therefore expected to depend more on physical examination. However, this did not translate into a lower number of physical examinations performed to detect one additional LRR after mastectomy due to the lower incidence of LRR in this group and because these patients often perceived their own recurrences. Overall, the absolute number of physical examinations to be performed to detect one additional LRR is therefore still higher after mastectomy than after breast conserving surgery.

The contribution of physical examination was larger in detecting CBCs and LRRs among women younger than 60 at follow-up visit. This finding was in line with that of another study which evaluated the incremental contribution of physical examination over mammography in a breast cancer screening programme.²¹ Age has been reported to have an important influence on the sensitivity of mammography and the value of physical examination. Tumour characteristics are different across ages that might influence the performance of routine physical examination.^{17,19,22} In addition, it is possible that physicians might pay more attention when they examine younger patients due to the debatable performance of mammography. To our knowledge, the age of the patient has not been taken into account specifically yet during the follow up of patients with breast cancer. Our results indicate that more LRRs would be missed in the younger patients than in older patients if there was no routine physical examination although the numbers are too small to draw a firm conclusion. If the routine physical examination for patients older than 60 years of age was no longer performed, there would be a reduction up to 50% of the number of physical examinations at follow-up visits and 3% CBCs and 17% LRRs would be later detected. Though there is evidence that early detection of breast cancer recurrence has beneficial effects on survival,⁴ there is no convincing evidence that delayed detection of a LRR or CBC leads to increased mortality. The randomised trial that would be necessary to prove such an effect on survival is unlikely to be performed so that these data will not become available. The possible impact of a reduction of the frequency of follow-up visits on survival or cost-effectiveness of follow-up remains unclear and may be the subject of future studies.

The purposes of follow-up of women with breast cancer are not only early detection of recurrences but also meeting the needs of patients with respect to psychosocial problems and side effects, especially in the initial years. Regarding side effects and psychosocial problems, patient initiated follow-up

is an alternative for patients with breast cancer.^{23,24} Younger patients with breast cancer are a vulnerable group in terms of more severe psychosocial effects than older patients.²⁵ It is unlikely that stopping routine physical examination after the age of 60 changes the management of side effect and psychosocial problems.

Although the frequency of physical examination was higher in the first 5 years after primary treatment, this did not result in a significant increase of the proportion of tumours detected by routine physical examination alone. In the first 5 years after primary treatment, follow-up visits were scheduled with a decreasing frequency from four times in the 5 year to once in the fifth year. After 5 years from primary treatment, follow-up visits were scheduled once a year. Thus more physical examinations ($n = 1041$) were done to detect one additional LRR in the first 5 years than after 5 years since the primary treatment ($n = 521$). This could be an argument to reduce the number of follow-up visits during the first years after primary treatment although the goal of these visits is also to counsel patient and to detect side-effects of the treatment besides the early detection of LRRs and CBCs. The feasibility of reducing frequency of physical examination in the initial years after primary treatment deserves further investigation.

The workloads of physical examination for the early detection of one additional LRR were higher in patients after mastectomy, older patients and in the first 5 years after primary treatment. The estimates of the number of routine physical examination undertaken for the early detection of one additional recurrence are not applicable in detection of CBCs. The cohort in this study is a CBCs enriched cohort in which the proportion of CBCs is far higher than that in general cohort of patients with a history of breast cancer. As the incidence of CBC was lower than that of LRRs and the contribution of physical examination was less in detecting CBC than loco-regional breast cancer as well, we presume, more physical examinations were needed for one additional CBC detected than LRRs as shown in this study. It should be noted that our findings are only a descriptive cost-effectiveness analysis and more analytical cost-effectiveness and cost-benefit studies are needed.

In conclusion, 22% of loco-regional recurrences of breast cancer and 6% of contra-lateral breast cancers would have been detected later without physical examination. Routine physical examination probably has the highest contribution in younger patients (<60). This needs to be confirmed by studies with larger sample size before an advice can be given on follow-up regimens. When formulating policy and new guidelines of follow-up for patients with breast cancer, patients' age at follow-up and previous treatment should be taken into account. The impact of (less frequent) physical examination on survival deserves further study.

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Conflict of interest statement

None declared.

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