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Systematic or Meta-analysis Studies



The COVID-19 pandemic: An opportunity to rethink and harmonise the frequency of follow-up visits for patients with early stage breast cancer

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ARTICLE INFO

Keywords:

COVID-19

Follow-up interval

Breast cancer

ABSTRACT

Purpose: While routine, in-person follow-up of early-stage breast cancer patients (EBC) after completion of initial treatment is common, the COVID-19 pandemic has resulted in unprecedented changes in clinical practice. A systematic review was performed to evaluate the evidence supporting different frequencies of routine follow-up. **Methods:** MEDLINE and the Cochrane Collaboration Library were searched from database inception to July 16, 2020 for randomized controlled trials (RCTs) and prospective cohort studies (PCS) evaluating different frequencies of routine follow-up. Citations were assessed by pairs of independent reviewers. Risk of Bias (RoB) was assessed using the Cochrane RoB tool for RCTs and the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. Findings were summarized narratively.

Results: The literature search identified 3316 studies, of which 7 (6 RCTs and 1 PCS) were eligible. Study endpoints included; quality of life (QoL; 5 RCTs and 1 PCS), disease free survival (DFS) (1 RCT), overall survival (OS) (1 RCT) and cost-effectiveness (1 RCT). The results showed reduction in follow-up frequency had no adverse effect on: QoL (6 studies, n = 920), DFS (1 trial, n = 472) or OS (1 trial, n = 472), but improved cost-effectiveness (1 trial, n = 472). Four RCTs specifically examined follow-up on-demand versus scheduled follow-up visits and found no statistically significant differences in QoL (n = 544).

Conclusion: While no evidence-based guidelines suggest that follow-up of EBC patients improves DFS or OS, routinely scheduled in-person assessment is common. RCT data suggests that reduced frequency of follow-up has no adverse effects.

Introduction

Routine, in-person, follow-up of early stage breast cancer patients (EBC) after completion of their acute phase of treatment (i.e. surgery/radiation and/or chemotherapy) is common. The goals of such follow-up vary, including early detection of recurrence, evaluation and treatment of therapy-related complications, motivation of patients to continue

therapy, and provision of on going support [1]. We are not aware of any evidence that routine follow-up of asymptomatic patients has any impact on either disease free survival (DFS) or overall survival (OS). This type of follow-up does, however, have significant resource implications for health care systems as the prevalence of breast cancer continues to rise [2,3].

The COVID-19 pandemic has placed unprecedented pressure on

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<https://doi.org/10.1016/j.ctrv.2021.102188>

Received 1 February 2021; Received in revised form 15 March 2021; Accepted 17 March 2021

Available online 23 March 2021

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health care systems around the world. It has been demonstrated through observational studies that patients with active or previous malignancy suffer high rates of mortality from COVID-19, irrespective of whether they are actively receiving anticancer therapy [4,5]. This necessitates harm reduction strategies that enable the safe provision of cancer care to continue, through such strategies as testing for SARS-CoV-2 prior to starting anticancer therapy, upon admission to oncology wards or palliative care units, and for ambulatory patients with certain high risk features [6–9].

The rapid introduction of physical distancing protocols has resulted in both patients and health care providers re-evaluating how clinics are run. This has led to a significant increase in the use of virtual visits as well as decrease in in-person evaluation and examination of patients [10,11]. The COVID-19 pandemic thus provides a unique motivation to re-evaluate the totality of evidence around the frequency and type of follow-up [12].

While the National Institute for Health and Care Excellence (NICE) recommends avoidance of routine follow-up in asymptomatic patients [13], other national and international practice guidelines recommend regular follow-up with health care providers, sometimes as often as every 3–6 months, for several years (Table 1) [1,14–18]. Given the importance of providing evidence-based follow-up care during the COVID-19 pandemic, this systematic review was performed to provide up-to-date evidence around optimal recommendations in terms of both frequency and duration of follow-up care. In addition, we hoped to identify areas where further studies are needed.

Methods

Search strategy and selection criteria

A protocol was prepared a priori and was registered with the Open Science Framework (OSF) (Registration DOI: <https://doi.org/10.17605/OSF.IO/R4AQ2>).

The research question of interest was as follows: “In EBC, what are the risks and benefits of reduced follow-up frequency in terms of quality of life (QoL), DFS, OS and cost-effectiveness?”. This systematic review report was prepared in consideration of guidance from the PRISMA statement [19–21]. Grey literature sources were not accessed. There were no protocol deviations.

Searching the literature

Data sources for the search were English language journal publications from MEDLINE and the Cochrane Collaboration Library published from database inception until July 16, 2020. The search included terms related to breast cancer and follow-up; the full search strategy is provided in Appendix A and was designed and implemented by an information specialist (RS).

Study eligibility criteria and selection process

The population of interest included women with breast cancer who had completed the initial intensive phase of adjuvant therapy (i.e. after completion of surgery, chemotherapy/anti-HER2 therapy, radiotherapy, and commencement of endocrine therapy, if hormone receptor positive). We included randomized controlled trials (RCTs) and prospective cohort studies (PCs) whose primary objective was assessing different intervals between follow-up appointments after an initial phase of adjuvant therapy. There were no restrictions in type of setting, the type of health care professional, duration of follow-up. Outcomes of a priori interest consisted of DFS, OS, QoL (broadly including validated scales or any other outcome pertaining to anxiety, depression and worry), cost-effectiveness, number of investigations ordered, treatment or investigation related harm as classified by each study’s authors including type of harm, frequency and grade (if applicable), and patient satisfaction. The reference lists of relevant clinical guidelines from ASCO, ESMO, and

Table 1
Summary of follow up guidelines from major advisory bodies [1,8–12].

Guideline	Physical exam	Self exam	Bloodwork	Mammography	Other Imaging	Pelvic exam
ASCO [10]	Px every 3–6 months in years 1–3, every 6–12 months in years 4–5, then annually	Monthly self exams (No RCT evidence)	Not recommended if asymptomatic	BCS: 1 year after initial mammogram, 6 months after rads. Otherwise: Yearly	Not recommended if asymptomatic	“Regular gynecologic follow up is recommended for all women”
NCCN Stage I-III [9]	Hx /Px every 4–6 months for 5 years then annually	Not mentioned	Not necessary Except: “Baseline and sequential” Estradiol, GnRH monitoring if amenorrheic and on AI.	Annually BCS: Wait 6–12 months after rads. Shorter if suspicious by mammography/Px Imaging of reconstructed breast is not indicated	Not recommended. But: “The use of breast MRI...is undefined.” Consider in greater than 20% lifetime risk of second primary.	Yearly gynecologic assessment if on tamoxifen and uterus is present
ESMO: Early breast cancer [1]	Hx/Px every 3–4 months in years 1–2 (or every 6 months for low risk and DCIS patients), then every 6–8 months in years 4–5. “...[adapt] to the risk of relapse and the patients’ needs”	Not mentioned	Not recommended if asymptomatic	Annually with US and breast MRI when needed	Not recommended except: Regular bone density if on AI or OFS	Yearly if on tamoxifen (no routine transvaginal US)
CCO (Separate guidelines for radiology and follow-up) [8,11]	Follow up by GP. No interval recommended, but mentions ASCO recommendations	No recommendation but mentions ASCO recommendations.	Not recommended if asymptomatic	Annually	Not recommended.	Not mentioned
ABIM - Choosing Wisely ABIM [12]	N/A	N/A	N/A	A maximum of one mammogram per year in women in neoadjuvant settings (ASTRO)	No routine PET or PET-CT for surveillance in asymptomatic patients (ASCO)	N/A

Abbreviations: Physical Exam: Px; ASCO: American Society of Clinical Oncology; RCT: randomized controlled trials; BCS: breast conserving surgery; NCCN: National Comprehensive Cancer Network; Hx: history; GnRH: gonadotropin-releasing hormone; AI: aromatase inhibitor; MRI: magnetic resonance imaging; ESMO: European Society for Medical Oncology; US: ultrasound; OFS: ovarian function suppression; CCO: Cancer Care Ontario; GP: general practitioner; ABIM: American Board of Internal Medicine; ASRO: American Society for Radiation Oncology; PET: positron emission tomography; CT: computed tomography.

NCCN were also reviewed for any relevant studies not found by our search [1,15,16]. Screening of titles and abstracts was performed independently by pairs of reviewers amongst a broad team (JS, HS, MA, AB, GL, SM, KC, MI, RF, AA, ML, MS, DS, LV, MC). Screening of the full text articles was performed independently by two reviewers (JS, HS). Conflicts over inclusion were resolved by consultation of a third reviewer (MC). The final process of study selection was documented by a flow diagram.

Data extraction and risk of bias appraisal

Primary outcomes of interest were OS and DFS. Relevant secondary outcomes were QoL, measures of cost effectiveness, number of investigations ordered, treatment or investigation related harm as classified by each study’s authors including type of harm, frequency and grade (if applicable), and patient satisfaction. Other extracted data items included study/publication characteristics (study title, authors, location, funding source, journal, publication date) study design details, study sample size, patients’ baseline demographics and disease characteristics, therapy received (adjuvant or neoadjuvant hormone therapy, chemotherapy/anti-HER-2/neu therapy, radiation, mastectomy vs lumpectomy) including specific agents used, sequence of therapy (if applicable), follow-up duration, setting, provider type and appointment schedule, and components of surveillance (History, physical exam, blood work, imaging, other investigations).

Risk of bias (RoB) was assessed using the Cochrane RoB 2 tool [22] for RCTs and the Newcastle-Ottawa Scale [23] for cohort studies. The completed review includes a descriptive summary of findings from these assessments (with detailed evaluations provided in Appendices D1 and

D2 respectively), which were considered in the context of drawing interpretations of the study data. Measures of central tendency and dispersion for continuous outcomes (including means, standard deviations, medians and ranges) and the numbers of patients experiencing events (and sample size) were collected when available. For time-to-event outcomes, hazard ratios with corresponding 95% confidence intervals were collected.

Data analysis

A descriptive summary of characteristics of the included studies was generated addressing the populations, comparators, outcomes and design features of the included studies. The research team discussed the homogeneity of the studies in terms of their study populations and methods. Presentation of data was appropriately grouped according to the treatment comparisons made within studies and according to the interval duration between follow-up visits. Descriptive summary and tables were used to present study-level findings. The appropriateness of meta-analysis was considered in light of the variability between studies in terms of clinical and methodologic characteristics, and the research team felt a descriptive approach to synthesis was most appropriate.

Findings

Extent of evidence identified

A total of 3316 citations were identified for review by the electronic literature search. A total of 3288 were excluded during screening of titles/abstracts due to ineligibility, leaving 28 citations for full text

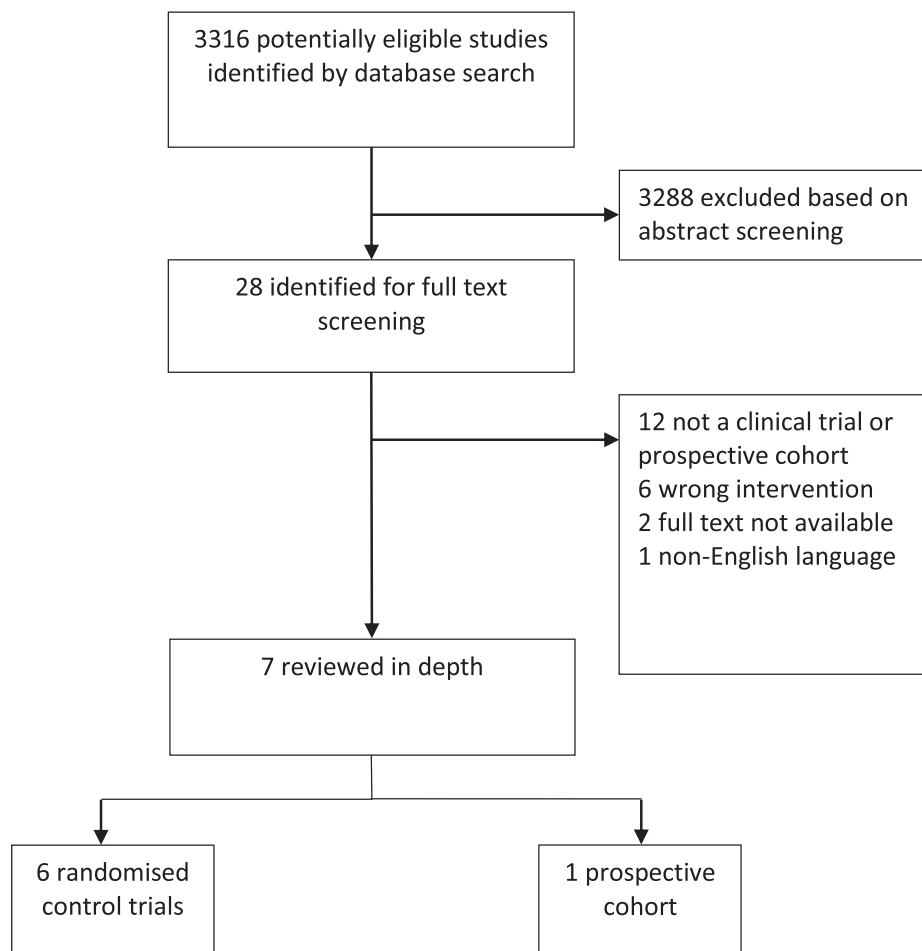


Fig. 1. Diagrammatic representation of literature search, study selection, and exclusions at each stage of review.

review. Of these, 21 studies were excluded because they were not clinical trials or PCS ($n = 12$), involved interventions not related to varying follow-up intervals ($n = 6$), were published in a non-English language (1), or the full text reports could not be accessed ($n = 2$). In total, 7 studies met the a priori eligibility criteria; Fig. 1 depicts the study selection process.

Study characteristics

Study characteristics are outlined in Table 2, while patients' baseline characteristics are detailed in Table 3. Of the 7 studies included, 6 studies were RCTs and 1 PCS. The studies were published between 1997 and 2020 (Table 2). Four studies examined follow-up on-demand [24–27], 1 study examined various predetermined follow-up schedules [28], 1 study tailored the follow-up frequency based on risk of recurrence [29], and 1 examined used follow-up only after mammography [30]. Three studies excluded patients who received chemotherapy [25,27,30], 1 of which included only patients on tamoxifen alone or no active therapy [30]. Two studies examined quality of life as a primary outcome [25,27] and 1 as a secondary outcome [24]. Similarly, 2 studies examined psychological impact as primary outcomes [27,29], 3 studies explored patient satisfaction as primary outcomes [24,29,30] and 1 as a secondary outcome [27]. One study examined survival as a primary outcome [28], and 1 study examined recurrences and method of detection as a secondary outcome [26]. One study examined cost effectiveness and healthcare utilization as a primary outcome [28] and 2 as a secondary outcomes [24,29].

Due to the differences outlined above in inclusion criteria, variations in experimental follow-up strategies, absence of standard follow-up schedules being specified, and differences in study outcomes, the evidence was judged by the study team to be too heterogeneous for meta-analysis. As of such, a descriptive approach to summarize findings was used.

Risk of bias assessment

Findings from risk of bias appraisals are provided in Appendix D. All RCTs were adequate in random sequence generation. While allocation concealment was not explicitly mentioned in any study, there was specific concern regarding Kokko et al. [28], where the patient population appeared to have been studied in several different trials. Minor protocol deviations were observed in Riis et al. [24] who excluded some patients for reasons that were logical but outside their prespecified exclusion criteria, Kokko et al. [28] who called a small number of patients outside of the study protocol but accounted for this in analysis, Brown et al. [27] who did not collect data on some patients enrolled, and Gulliford et al. [30] who saw three patients who decided to pursue an alternative follow-up schedule. None of these deviations were expected to significantly impact overall findings. By the nature of the intervention, blinding of studies was not possible. Within the limitations of assessment without access to the original study protocols, here were no concerns regarding significant losses to follow-up, or incomplete outcome data or selective reporting except for Kokko et al. [28] who reported no differences between arms in the prespecified outcome of DFS, without described data. This study also reports on OS which was not a pre-planned study outcome. Per-protocol analysis was used by Riis et al. [24], Brown et al. [27], and Gulliford et al. [30]. The remaining studies appear to have used intention to treat but were not explicit in their description. Risk of bias was deemed high for Kokko et al. [28], intermediate for Gulliford et al. [30] and low for all other RCTs.

One single-arm prospective trial, van Hezewijk, et al. [29], was assessed using the Newcastle-Ottawa Scale and was found to have high risk of bias, largely due to the nature of single-arm studies.

Efficacy endpoints

Studies evaluating QoL or patient satisfaction

Six studies examined QoL metrics. Riis et al. [24] conducted a pilot RCT which enrolled 134 postmenopausal women with hormone positive EBC after primary surgery and scheduled for at least five years of adjuvant endocrine therapy. Patients were randomized to either standard follow-up with prescheduled follow-up every 6 months ($n = 69$) or individualized follow-up with electronic patient reported outcomes (reports from the patient evaluating her health status) to screen for the need of consultations ($n = 65$). The primary outcome was satisfaction with the assigned follow-up care and unmet needs as measured by a Patient Experience Questionnaire (PEQ) administered every three months for two-years. Secondary outcomes were use of consultations, adherence to treatment (audit of electronic medical records) and QoL (EORTC QLQ-C30, EORTC QLQ-BR23). At the end of the study period, no statistically significant differences were reported in relation to satisfaction, unmet needs, treatment adherence or QoL. Findings were summarized graphically but numeric estimates were not provided for QoL endpoints.

Kirshbaum et al. [25] conducted an RCT that evaluated women newly diagnosed with stage 1 or 2 EBC, treated with curative intent and considered clinically to be at low risk of recurrence. The study excluded women who received adjuvant chemotherapy, those participating in other trials that required an alternate follow-up protocol or having a high risk for recurrence. There were 112 patients randomized to either standardized breast clinic aftercare ($n = 56$) versus follow-up on demand by open access aftercare by breast care nurses ($n = 56$). The exact follow-up schedule in the control group was not provided. The primary outcome was QoL (EORTC QLQ-C30, EORTC QLQ-BR23 and HADS) administered at 0, 6, 12, 18 and 24 months. EORTC QLQ-C30 had 15 sub-score domains and EORTC QLQ-BR23 had 7. Numeric sub-scores with standard deviations were provided for each domain at each time point, but no easily communicable summative qualitative score was provided. After the 24-month study period, they found no difference in QoL between the study arms.

Sheppard et al. [26] conducted a RCT which evaluated all patients two years after initial diagnosis, who were not undergoing current treatment (except endocrine therapy), with no clinical signs of recurrence. Two hundred and thirty-seven (237) patients were recruited and 214 completed the study. Patients were randomized to either 6-monthly review ($n = 107$) or point of need access to specialist care via a nurse specialist ($n = 107$). The primary outcomes were psychological morbidity (GHQ12 questionnaire), QoL (FACT-B), fear and isolation at baseline, 9 and 18 months. After 18-months there was no difference between groups in absolute difference in adjust mean scores for the primary endpoints of psychological morbidity (-0.1 points; 95% CI -1.4 to 1.0; $p = 0.767$) or QoL (-1.6 points; 95% CI -4.6 to 8.0; $p = 0.282$). Two secondary outcomes were fear of recurrence and feelings of isolation. Fear of recurrence was measured in all participants using a non-validated three-item questionnaire at 18 months. Fear scores were not significantly different between groups (0.5 points; 95% CI -0.3 to 1.0, $p = 0.066$). Isolation was measured by asking the patients in both groups to record at 9 and 18 months whether they had felt isolated since their last review. Of patients who responded, 9 of 99 participants in the standard group reported feeling isolated at some point versus 14 of 97 in the point of need access group ($p = 0.245$). Patients in the point of need access group were given the option of returning to 6-month clinical review or not. Of these patients, 5 of 107 chose to return to 6-monthly review.

Brown et al. [27] reported the results of a RCT of 61 women previously treated for stage I EBC randomized to standard clinic follow-up versus patient-initiated follow-up with written information on signs and symptoms being provided. The exact schedule followed in the control arm was not provided, though at the time of recruitment patients were being followed either every 4 months, 6 months or yearly. The

Table 2
Summary of studies identified from systematic review.

Study	Participants	Intervention	Comparator	Primary outcome	Secondary outcomes	Planned follow-up duration	Other components of surveillance	Result
RCT								
Riis, 2020	Single center in Denmark. Postmenopausal women with hormone positive early stage breast cancer in remission after primary surgery and scheduled for at least five years of adjuvant endocrine therapy. 134 patients randomized	Individualized follow-up with electronic patient reported outcomes to screen for the need of consultations (n = 65)	Standard follow up with prescheduled follow-up every 6 months (n = 69)	Satisfaction with the assigned follow-up care and unmet needs (Patient Experience Questionnaire)	Use of consultations, adherence to treatment (audit of electronic medical records) and quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	5 years	Mammogram, breast ultrasound	No statistically significant differences were reported in relation to satisfaction, unmet needs, adherence to treatment or quality of life. Women in standard care attended twice as many consultations during the two-year follow-up period as women in individualized care (4.3 [95% CI 3.9–4.7] vs 2.1 [1.6–2.6])
Kirshbaum, 2017	Single center in the UK. Women newly diagnosed with AJCC Stage 1 or Stage 2 breast cancer, treated with curative intent and considered to be clinically at low risk of recurrence. Excluded women with Stage 3 or 4 breast cancer, receiving or received adjuvant chemotherapy, participating in another trial that required an alternate follow-up protocol or identified as having high risk for recurrence. 112 patients enrolled	Follow-up on demand by open access aftercare by breast care nurses (not routinely followed up) (n = 56)	Standardized breast clinic aftercare (exact schedule not specified) (n = 56)	Quality of life as assessed by three questionnaires (EORTC QLQ-C30, EORTC QLQ-BR23 and HADS)	None	5 years	Mammogram	Women treated for early breast cancer were not disadvantaged by allocation to the open access supportive care model in terms of quality of life experienced
Sheppard, 2009	Single center in the UK. All patients diagnosed 2 years prior, who were not undergoing current treatment (except endocrine therapy), with no clinical signs of recurrence. 237 patients recruited, 214 patients completed the study	Point of need access to specialist care via a nurse specialist (n = 107)	6-monthly review (n = 107)	Psychological morbidity using the GHQ12 questionnaire, quality of life using the FACT-B plus endocrine subscale	Recurrences and methods of detection, fear and isolation	18 months	Mammogram	Patients were not exposed to risks of increased psychological morbidity (p = 0.767) or decline of quality of life (p = 0.282). Patients not receiving regular review did not feel isolated and did not wish to return to 6-month clinical reviews. The presentation of recurrences and

(continued on next page)

Table 2 (continued)

Study	Participants	Intervention	Comparator	Primary outcome	Secondary outcomes	Planned follow-up duration	Other components of surveillance	Result
Kokko, 2005	Single center in Finland. Breast cancer patients without distant metastasis after primary treatment. 472 patients enrolled	Four schedules differing in frequency of follow-up visits and intensity of diagnostic examinations: Arm A – Every 3 months, routine investigations (n = 125) Arm B – Every 3 months, investigations as needed (n = 114) Arm C – Every 6 months, routine investigations (n = 118) Arm D – Every 6 months, investigations as needed (n = 115)	N/A	Estimated cost per arm and per patient, and per recurrence. DFS.	None	5 years or until first relapse (whichever earlier)	Routine investigation arms only: Labs (CBC, Ca, ESR, ALP, ALT, Ca 15-3), CXR q6mo Liver US and bone scan q2y	short symptom history demonstrate that the recurrences observed were unlikely to have been detected at a routine visit. Recurrences were identified in only 4% of both arms. Neither the frequency of visits nor the intensity of diagnostic examinations had any effect on DFS or OS (qualitative data not provided). The total costs of follow up per patient varied from 1050 to 2269€, and between 4166 and 9149€ per recurrence.
Brown, 2002	Five clinics in the UK Women previously treated for stage I breast cancer now in remission 61 women randomized	Patient initiated follow-up with written information on signs and symptoms of recurrence (n = 30)	Standard clinic follow-up (Exact schedule not specified) (n = 31)	Cancer and breast cancer specific quality of life (EORTC QLQ-C30, QLQ-BR23), psychological morbidity (HAD scale)	Satisfaction with follow-up	Not reported	Annual mammogram	No major differences in quality of life and psychological morbidity. More women in the standard clinic group reported reassurance and being checked as advantages whereas more women in the patient-initiated follow-up group reported convenience as an advantage.
Gulliford, 1997	Two centers in the UK Patients with personal history of breast cancer proved by biopsy, lack of known recurrence of cancer, current lack of symptoms consistent with recurrence, no active management apart from active	Clinic visits only after mammography (n = 97)	Conventional schedule of clinic visits: Every 3 months if < 1 year from diagnosis, every 4 months if 1–2 years, every 6 months if 2–5 years and yearly if more than 5 years. (n = 96)	Acceptability of randomization, interim use of telephone and general practitioner, satisfaction with allocation to follow up	Details of disease stage for patients who declined participation.	Not reported, median follow-up 16 months	Mammogram	Twice as many patients in both groups expressed a preference for reducing rather than increasing follow-up. No increased used of local practitioner services or telephone triage was apparent in the cohort randomized to less frequent follow-

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Table 2 (continued)

Study	Participants	Intervention	Comparator	Primary outcome	Secondary outcomes	Planned follow-up duration	Other components of surveillance	Result
	tamoxifen, home telephone, fluency in English, informed consent.							up by specialists.
	196 of 211 eligible patients randomized. 3 patients excluded.							Patients who did not participate were more likely to be under 50 years, to be two to five years after diagnosis, and to have had aggressive primary disease.
Single-arm prospective cohort								
van Hezewijk, 2014	Single center in The Netherlands Patients with pT1-2 NO-2 cM0 breast cancer. Stratified by risk category (low, intermediate, high) High risk group excluded (1 patient only) 180 patients enrolled	Tailored follow-up programme in which the number of planned follow-up visits after one year depending on the patient's risk of locoregional recurrence (n = 179)	None	Feasibility of tailored follow-up based on the number of follow up visits, patient satisfaction, anxiety and attitude towards follow-up	Reasons for visits, incidence, time to detection of local recurrences and the use of alternative care	2–5 years	Mammogram	In the second year of follow up, 22% reduction in visits per patient in the low-risk group compared to the intermediate-risk group (2.8 vs 3.6 visits). No significant differences were found in the attitude towards follow-up, patient satisfaction, anxiety and depression, alternative health care use or local recurrences between the risk groups.

primary outcome was cancer and breast cancer specific QoL (EORTC QLQ-C30, QLQ-BR23) and psychological morbidity (HAD scale). The secondary outcome was satisfaction with follow-up as assessed by a structured interview. Median scores with ranges were provided in table form for all categories and time points, but no easily communicable summative qualitative score was provided. The study reported no major differences in QoL (no p-values provided) apart from observing higher scores for arm (p = 0.028) and breast symptoms (p = 0.033) in the control group. There were no differences between groups in anxiety (p = 0.069) or depression (p = 0.232). More women in the standard clinic group reported reassurance of being assessed as advantages (p = 0.003) whereas more women in the patient-initiated follow-up group reported convenience as an advantage (p = 0.000).

Gulliford et al. [30] reported the results of a pilot RCT which examined clinic visits only after mammography versus a conventional schedule of clinic visits. Frequency of follow-up in the control arm was every 3 months if <1 year from diagnosis, every 4 months if 1–2 years, every 6 months if 2–5 years and yearly if more than 5 years from diagnosis. Eligible patients with EBC, lack of known recurrence, no active management apart from active tamoxifen, home telephone and fluency in English, were randomized. Primary outcomes included the acceptability of randomization, interim use of telephone triage, general practitioner, and satisfaction with allocation to follow-up. The secondary outcome was details of disease stage for patients who declined participation. Out of 211 eligible patients, 196 were randomized and 193 were included in the analysis. Of the remaining 193 patients, 96 were randomized to the control arm and 97 to the follow-up with mammogram only arm. After a median follow-up of 16 months, twice as many patients in both groups expressed a preference for reducing (n = 17 control, n = 22 mammogram only) rather than increasing follow-up (n = 7 control, n = 10 mammogram only). No increased use of local

practitioner services or telephone triage was apparent in the cohort randomized to less frequent follow-up by specialists. Of eligible patients, 7.1% declined participation. Comparing patient satisfaction in the conventional versus mammogram-only visit groups, reassurance from specialist follow-up was reported in 94% versus 88% of patients respectively, preference for more frequent follow-up in 11% versus 16% respectively, and preference for less frequent follow-up in 25% versus 35% respectively (no p-value provided).

Finally, van Hezewijk et al. [29] presented a single-arm prospective cohort which evaluated feasibility of a follow-up program in which the number of planned follow-up visits varied depending on each patient's estimate risk of locoregional recurrence. The primary endpoints were the sum number of follow-up visits per patient (both planned and interval), patient satisfaction, anxiety and attitude towards follow-up. Risk was stratified using a point scale as follows: age <35 years (2 points), pN + status (1 point), breast conservative therapy (1 point) and no hormonal therapy (1 point). The low risk group was defined as 0–1 points, intermediate 4–5 points and high risk 4–5 points. The high-risk group was later dropped as only 1 patient was categorised as such. The intermediate group followed a guideline-based follow-up schedule of 4 times in the first year post-diagnosis, 2 times the second year, and yearly for the third, fourth and fifth year. The low risk group followed up 4 times in the first year, once in the second year, and once in the fourth year. Patients were discharged to their general practitioner or national screening program after the fifth and fourth years for the intermediate and low risk groups respectively. Primary outcomes included acceptability of randomization, interim use of telephone triage and general practitioner and satisfaction with allocation to follow-up. Patient satisfaction as per scored questionnaire was not significantly different between the low and intermediate group after the second year (median score 83 versus 75 points respectively, p = 0.72). There was no significant difference

Table 3
Baseline patient characteristics.

Study	Population size (Control, intervention)	Mean age, years (Control, intervention)	Surgery type, number (control, intervention)	Therapy received (Control, intervention)	TNM Stage, number (control, intervention)	Grade	Receptor status, number (control, intervention)	Tumor type (Control, intervention)	Percentage of male breast cancer
Riis, 2020	69,65	64.2,64.4	Breast conserving: 52, 48 Mastectomy: 15,14	RCT Chemotherapy: 32,24 HER-2 targeted: 5,3 Hormone therapy: 63,60 Radiation therapy: 60,55	T1:49,45 T2: 17,15 T3-4: 1,2 N0:40,44 N1: 24,17 N2:3,1	Not reported	ER positive: 67,62 HER-2 positive: 6,3	Not reported	0
Kirshbaum, 2017	56,56	60.5,60.7	Not reported	Chemotherapy excluded	“Stage 3 and 4 excluded”	Not reported	Not reported	Not reported	0
Sheppard, 2009	107,107	58,57	Wide excision:83,84 Mastectomy:31,27 Mastectomy + reconstruction:6,7	Hormone therapy:106,103 Chemotherapy: 26,37 Radiation: 80,87	Lymph node positive:27,25	DCIS:17,12 G1:50,43 G2:35,46 G3:17,17	Not reported	Not reported	Not reported
Kokko, 2005	472 patients total, 4 arms. A: 125 – q3mo, routine B: 114 – q3mo, indicated C: 118 – q6mo, routine D: 115 – q6mo, indicated	(A,B,C,D) 56.9, 56.8, 59.7, 60.5	Conservative (A,B, C,D): 63,49,54,48 Mastectomy(A,B, C,D): 61,61,61,62 None:1,4,3,5	Radiation (A,B,C,D): 91, 73, 79, 65 Chemotherapy/hormone therapy (A, B,C,D): 36,32,32,24	(A,B,C,D) T1: 80,78,77,76 T2: 41,32,38,35 T3-4: 4,4,3,4 N0: 89,92,92,95 N1: 36,22,26,20	Not reported	ER positive (A, B,C,D): 83,71,75,70 ER negative(A, B,C,D): 29,22,25,28 Unknown(A,B, C,D): 13,21,18,17	Not reported	0
Brown, 2002	31,30	63,68	Wide excision: 9,11 Wide excision + axillary clearance: 14,6 Mastectomy: 0,3 Mastectomy + axillary clearance: 8,10	Radiation: 10,5 Tamoxifen: 20,19 Chemotherapy excluded	All stage 1	G1: 6,9 G2: 25,21	Not reported	Invasive ductal: 25,22 Other: 6,8	0
Gulliford, 1997	96, 97	Only age groups are given	Lumpectomy: 61,58 Mastectomy: 24,32	Radiation: 56,52 Tamoxifen: 67,72 Chemotherapy excluded	T1: 36,33 T2: 22,26 T3/4: 5,5 Nx: 24,28 N0: 34,33 N1: 16,21	Not reported	Not reported	Not reported	Not reported
van Hezewijk, 2014	93,86	61.8,58.1	Breast conserving:40,80 Mastectomy:53,6	Hormone therapy:45,24 Chemotherapy:16,30 Herceptin:5,4	Tis: 32,0 pT1:41,69 pT2:20,17 pN0:56,48 pN1:10,32 pN2:0,3	G1:12,16 G2:48,44 G3:26,21 Missing:7,5	ER positive:58,65 ER negative :5,20 ER data missing:30,1 PR positive:45,47 PR negative:18,37 PR data missing:30,2	Ductal:74,71 Lobular:11,8 Other:7,5 Missing:1,2	0

(continued on next page)

Table 3 (continued)

Study	Population size (Control, intervention)	Mean age, years (Control, intervention)	Surgery type, number (control, intervention)	Therapy received (Control, intervention)	TNM Stage, number (control, intervention)	Grade	Receptor status, number (control, intervention)	Tumor type (Control, intervention)	Percentage of male breast cancer
							HER-2 not reported		

between the low and intermediate groups in the number of healthcare professionals contacted in the second and third year after treatment (2.4 [SD 1.4] vs 2.8 [SD 1.1]; $p = 0.20$), mean perceived fear of recurrence score (39.5 [SD 23.1] vs 40.2 [SD 17.4]; $p = 0.88$), or mean scores on the HADS questionnaire for anxiety (3.7 [SD 3.6] vs 4.7 [SD 4.6]; $p = 0.15$) and depression (2.8 [SD 3.2] vs 2.7 [SD 3.4]; $p = 0.52$).

Studies examining disease free survival and overall survival

One study had a primary endpoint of DFS. Kokko et al. [28] was a four-arm RCT investigating different follow-up strategies. The 472 patients were randomized to either follow-up every 3 months with routine investigations ($n = 125$), every 6 months with routine investigations ($n = 118$), every 3 months with investigations only when indicated ($n = 114$), or every 6 months with investigations only when indicated ($n = 115$). Routine investigations included complete blood count, calcium, sedimentation rate, alkaline phosphatase, alanine aminotransferase and Ca 15-3 at every visit, chest X-ray every sixth month, and liver ultrasound and bone scan every second year. One primary outcome was DFS. Patients were followed for 5 years or until relapse, whichever came first. The investigators reported that neither frequency of visit nor intensity of investigations had any effect on DFS or OS, but did not report any quantitative effect size. Reference was made to a previous study by this group in which the utility of x-rays in detecting recurrence was examined in the same 472 patients in which no differences to DFS or OS were found.

Studies examining cost effectiveness and healthcare utilization

Kokko et al. [28] investigated cost per arm, per patient and per recurrence as primary outcomes. The study was performed at a single center in Finland. The cost per patient and recurrence was calculated by dividing the total cost in that study arm by the number of patients with recurrences in that arm, respectively. The authors reported that mean cost per patient and per recurrence for those receiving follow-up every 3 months with investigations as indicated was 1050€ and 4864€ respectively, as compared to 2269€ and 4166€ for those receiving follow-up every 6 months with investigations as indicated.

Riis et al. (2020) also examined use of consultations. Women in standard care attended twice as many consultations during the two-year follow-up period as women in individualized care (4.3 [95% CI 3.9–4.7] vs 2.1 [1.6–2.6]) (Table 2).

Gulliford et al. [30] examined interim use of telephone triage and visits to the general practitioner as primary outcomes. They reported receiving 21 phone calls from patients without symptoms in the 24-month follow-up period, 11 from the conventional follow-up group and 8 from the group with follow-up after mammogram only. They noted that 8 of the 11 calls from the conventional group pertained to appointment scheduling, as compared to only 1 such call from the mammogram-only visit group, although the subject of phone calls was not a prespecified secondary outcome. The actual number of individual patients who called or the number of phone calls per patient were not reported. They recorded 46 visits to general practitioners in the conventional group with 15% of these pertaining to cancer-related issues as compared to 53 in the mammogram-only visit group with 7.5% for cancer-related issues. Percentage of cancer related issues was not a prespecified secondary outcome and measures of uncertainty were not provided.

van Hezewijk et al. [29] examined feasibility of tailored follow-up in part based on the number of follow-up visits as primary outcomes. They also examined the reasons for visits as a secondary outcome. In the second and third years, patients in the low-risk group had significantly fewer follow-up contacts than those in the intermediate group (4.2 versus 5.0, $p = 0.02$). The authors corrected these values to exclude telephone calls and visits for test results, which while not prespecified, showed a 22% reduction in number of total visits per patient for the low versus intermediate group (2.8 versus 3.6, $p = 0.003$). It was noted that the low risk group had a higher percentage of interval visits compared to the intermediate group (65% versus 40% respectively, $p < 0.001$) and a higher percentage of interval visits being initiated by healthcare professionals in the low versus intermediate group (82% versus 65% respectively, $p = 0.001$). The ratio of planned versus interval visits did not differ significantly between the types of professionals, with the nurse practitioner being contacted most often followed by the radiation oncologist, medical oncologist and surgeon.

Studies examining how recurrent disease was detected

The secondary outcome of Sheppard et al. [26] was the number of recurrences and methods of detection. Nine (9) recurrences were detected during the study period, 5 of 112 patients in the experimental group and 4 of 112 in the control group. The presentation of recurrences and short symptom history demonstrate that the recurrences observed were unlikely to have been detected at a routine visit. Interestingly, one patient in the control group identified a local chest wall recurrence but waited two months until her next scheduled review.

van Hezewijk et al. [29] examined incidence and time to detection of local recurrences as secondary outcomes. A total of 12 recurrences were found with 6 each in the low and intermediate risk groups. In the low risk group two recurrences were local, 3 were contralateral breast cancer and 1 patient had distant metastases. Two recurrences were found by the patient, 1 by physical examination and 3 were asymptomatic and found on imaging. In the intermediate risk group, 1 recurrence was local, 1 was in a supraclavicular node and 5 were contralateral breast cancer. Two recurrences were found by the patient and 4 were asymptomatic and found on imaging. The median time to detection of recurrence was 18 months in the low risk group and 32 months in the intermediate group. While there was no control group to compare to standard follow-up, it is notable that the time to detection of recurrence was longer in the group with more frequent follow-up visits.

Discussion

Routine, in-person follow-up of EBC after completion of their acute phase of treatment is common. Despite differences in patient and health care provider perceptions around the role of routine follow-up [12] and the recommendations from guideline groups for what this follow-up should entail [1,15,16], there is no evidence that routine follow-up of asymptomatic patients has any impact on either DFS or OS [1,14–17]. This type of follow-up has significant resource implications for health care systems [31–33]. Data from our own institution, that sees approximately 1000 new breast cancer patients a year, has around 50,000 breast cancer follow-up visits each year (Kate Duke, personal communication 2020). The COVID-19 pandemic has suddenly made this issue critical, and health care providers have been forced to change the way in

which they assess their patients and thus presents an opportunity to rethink and harmonise clinical practice with the available evidence base. The purpose of this systematic review was to provide evidence as to how we can change the nature of our follow-up practices safely.

The data provided from these studies demonstrate that once the initial intense phase of treatment is complete, reducing the frequency of follow-up visits had no detrimental effects on either patient QoL or caused anxiety [24–27,29,30]. Of interest, many patients did not wish to return to the conventional schedule after the trial period [26]. Only one study evaluated DFS and OS, and while they reported no difference between different follow-up intervals, quantitative data was not provided [28]. The same study also demonstrated that less frequent follow-up is more cost-effective [28]. Also of interest was that in all 5 studies that compared routine prescheduled follow-up with follow-up triggered by symptoms/surveillance investigations there was no significant difference in clinically important outcomes [24–30].

Our findings are consistent with the growing body of evidence that deintensification of breast cancer follow-up is safe and effective. It has been shown that nurse or general practitioner led follow-up is no better than specialist follow-up, a message that has been reinforced by some institutions and regulatory bodies [34–38]. Several studies have also demonstrated that additional use of radiographic imaging, tumor markers and other serologic testing in the absence of concerning symptoms is of no benefit [39,40]. Perhaps most notably, there is evidence that early detection of breast cancer does not necessarily lead to better outcomes [13]. This information must be considered when recommending a follow-up protocol. While some groups and regulatory bodies have reflected this in their recommendations (Table 1), the suggested frequency of follow-up in these guidelines is either higher than that suggested by evidence or not specified at all. In light of our data, we believe it would be appropriate for groups such as Choosing Wisely and regulatory bodies to consider recommending risk-adapted follow-up plans in the absence of evidence that symptom-oriented strategies are inferior to intensive schedules.

There are several limitations in interpreting this data. Given the high prevalence of EBC, it was surprising that many of the trials were so small and that so little prospective data on DFS or OS were reported. Second, many studies did not state what schedule was followed in the control arm and thus require us to assume that evidence-based guidelines recommendations were followed. Third, while these studies selected for early stage and overall lower-risk disease, the risk of recurrence in breast cancer is nuanced and is impacted by more than pathologic staging with factors such as hormone expression, HER-2/Neu expression, gene expression profile, type of treatment are important and none of the studies stratified patients based on these factors. Fourth, for studies examining on-demand follow-up, it is not clear based on this data what information effectively educates patients when to trigger visits. Fifth, there was significant variability in study designs and endpoints that precluded the ability to pursue quantitative syntheses. Similarly, outcome data was often not reported in detail with relevant, meaningful numeric data frequently being absent. There is the issue of selection bias as patients who consent to studies in which they would be randomized to less frequent follow-up may be more likely to accept this change than the general population. Lastly, the data presented does not address the role of virtual visits. In all studies identified, every physician visit was accompanied by a physical exam, which is naturally absent from virtual follow-up. The role of telemedicine for example in this setting remains unclear.

Many of these issues should be addressed in future trials. These could evaluate not just impact of different follow-up strategies on quality of life and whether groups with different risk of recurrence benefit from different follow-up strategies but also the Health Economic aspects of different strategies. Additionally, it is important to examine what follow-up frequency is required to maintain adherence to long-term therapy and to manage treatment toxicity. In addition, it is likely that virtual visits will remain even after the COVID-19 pandemic, so studies

will need to address the issue of missing physical examinations at the time of follow-up, especially as the fraction of recurrences detected by clinical examination is falling [41]. Similarly, there is the issue of over examination as some guidelines even recommend yearly gynecologic assessment for women on tamoxifen based on expert consensus [1,15].

Conclusion

While no evidence-based guidelines suggest that follow-up of EBC patients improves either DFS or OS, routinely scheduled in-person assessment is common. The totality of the randomized data suggests that reduced frequency of follow-up has no adverse effects and more specifically, on-demand follow-up is associated with lower cost-per-recurrence detected than scheduled follow-up. Furthermore, it does not appear that follow-up must be specifically with a physician. While more trials are clearly required most evidence would suggest that moving to a model based upon follow-up to be triggered by patient demand or to review results of mammography is likely the most effective for implementing immediately. While the pandemic will pass, we need to ensure effective strategies are put in place.

Ethics approval

Ethics approval was not required for this systematic review.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Surujballi J, Hutton B, Larocque G, McGee S, Cole K and Clemons M drafted the protocol, developed the study selection criteria, the risk of bias assessment strategy and data extraction criteria. RS developed the search strategy. BH provided statistical expertise. Clinical expertise was provided by AA, GL, SM and MC. The review team included all authors.

Funding

This systematic review was internally funded from the REthinking Clinical Trials (REaCT) program.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2021.102188>.

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