The relationship between fears of cancer recurrence and patient age: A systematic review and meta-analysis

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List of abbreviations:

AYA = adolescent and young adults

ES = effect size

FCR = fears of cancer recurrence

F0P = fears of progression

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT = randomized control trials

Words

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1 Abstract

Background: Fears of cancer recurrence (FCR) is one of the most prevalent concerns and a common unmet need reported by cancer patients. Patient age is a demographic variable which has been linked to FCR, among others. Although it is recognised by researchers that age and FCR may be negatively correlated, the strength of this correlation has yet to be established.

Aim: The aims of this study were to (i) conduct a meta-analysis to investigate the overall association of patient age in years with FCR across studies from 2009 to February 2019, and (ii) scrutinize for patterns of these effect sizes across studies.

Methods and Results: Peer-reviewed papers were gathered from the literature via online databases (PubMed, EMBASE, MEDLINE, PsycINFO). Systematic review guidelines including a quality assessment were applied to the 31 selected studies (pooled participant N size = 19,777). The meta-analysis demonstrated a significant negative association between age and FCR (ES=-0.12; 95%CI=-0.17, -0.07). Meta-regression revealed the association of patient age and FCR significantly reduced over the last decade. A significant effect (β = -0.17, p = 0.005) of breast cancer versus other cancers on this age by FCR association was also identified.

Conclusion: The reliable and readily accessible personal information of age of patient can be utilized as a weak indicator of FCR level especially in the breast cancer field where the majority of studies were drawn. The suggestion that age and FCR association may be attenuated in recent years requires confirmation.

Trial Registration: PROSPERO CRD42019135580; https://www.crd.york.ac.uk/PROSPERO/

2 Introduction

Fears of cancer recurrence (FCR) has attracted considerable research interest in the past decade or more. Simard [1] and more recently Yang [2] presented evidence of overall positive correlations between FCR and patient factors such as presence or severity of physical symptoms, psychological distress and female gender. Variables such as age and good social support, in contrast, were more often negatively associated with FCR. Social support has been observed to be beneficial to assist coping mechanisms against uncertainty and psychosocial distress [3-6].

To date, there are no reviews that have focused exclusively on the overall effect of age on FCR. An important reason to focus on this association was that a patient's age is a very reliable, accessible, and consistent measure obtained quickly in a clinical situation, either from records or directly on questioning the patient. A systematic review and meta-analysis was considered of interest to researchers and clinicians to understand the relationship more thoroughly.

The definition of FCR that is routinely accepted is "fear, worry, or concerns about cancer returning or progressing", as developed by a panel of researchers, policy makers, trainees, and patient advocated, via a rigorous consensus-based procedure, in 2016 [7]. FCR has been demonstrated as one of the most commonly reported concerns of cancer patients [8] while also being one of the main concerns overlooked by healthcare professionals [9]. Patients reporting high FCR levels can exhibit specific difficulties [10]. These include hypervigilance of internal bodily sensations that might indicate danger signals, excessive checking of body parts, health service utilisation and lack of future planning. [11 12].

A structured review of quantitative studies by Simard et al [1] identified various determinants of FCR. Age was a consistently significant factor linked to FCR. Notably, the review confirmed that there was no study with a positive correlation between age and FCR. Twenty-two studies showed a negative correlation whereas 18 gave a 'nil' association. However, a simple tally cannot easily calibrate the overall strength of the correlation from this important initial review.

Contradictory results from multiple studies will always present a conundrum for interpretation, therefore, the open statistical procedures of meta-analysis would assist identifying the reasons, bias or errors underlying the body of selected work. As outlined by Borenstein [13], the main aim of a meta-analysis is to demonstrate a relationship between two variables reported by various studies to establish its overall significance.

Hence the aims of this study were:

(i) to conduct a meta-analysis to investigate the overall effect size of patient age association with FCR across studies. In addition,

(ii) to scrutinize any systematic association of these effect sizes found between groups of studies categorised across various factors, notably: cancer type, measurement focus employed by researchers i.e. FCR or Fear of Progression (FoP), publication year and type of association statistic presented, controlling for mean age of sample.

3 Methods

3.1 Protocol

The present study is registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; ID: CRD42019135580).

3.2 Literature search

MEDLINE, PubMed, Embase and PsycINFO databases were systematically searched from 1st January 2009 to the 31st December 2018 to identify the relevant articles . The PRISMA systematic review and meta-analysis guidelines were adhered to [14]. The key search terms were ("fear" [MESH] or worry or concern or anxiety) AND ("neoplasm" [MESH] or cancer or carcinoma) AND ("recurrence" [MESH] or "neoplasm recurrence" [MESH] or progression or return or relapse or remit) AND (adult or adolescent or age*). See Supplementary File 1 for example detailed search strategy for MEDLINE database.

3.3 Inclusion and exclusion criteria

Studies found from the search were inspected for eligibility prior to inclusion. In accordance with the PICOS guideline, references had to adhere to the following criteria to be considered for this systemic review/meta-analysis: Participants (P): cancer survivors aged between 15-95 years at cancer diagnosis or at survey; Interventions (I): not applicable; Comparisons (C): not applicable; Outcomes (O): quantitative FCR results on prevalence, influencing factors, age and consequence; Study Design (S): longitudinal, cross-sectional, validation or randomized control trial (RCT) studies. Papers needed to be published in peer-reviewed journals, written in English and to report the relationship status between patient age (in years) and FCR. References were excluded if they were editorials, qualitative studies, conference abstracts, commentaries, dissertations, review articles, pilot studies, protocols or case studies. Studies that had no mention of "fear" or "fear of" or "fear of recurrence" or "fear of cancer recurrence" or any similar phrases like "fear of cancer progression/relapse/etc." from title or

abstract were excluded. In addition, studies that reported fear of recurrence of diseases of non-neoplastic/non-cancerous origin were excluded.

3.4 Assessment of FCR

The measurements of fears of cancer recurrence vary from single-item to multi-item scales. Multi-item scales tend to possess more evidence for their psychometric properties [15]. Therefore, it was decided that studies that utilized single-item scale measures of FCR will be excluded from this meta-analysis. In this study, the measures of FCR (with number of studies extracted utilising each measure) included the Fears of Cancer Recurrence Inventory (FCRI, n=6) [16], Fears of Cancer Recurrence Inventory-Short Form (FCRI-SF, n=1) [17], Cancer Worry Scale (CWS, n=4) [18, 19], Concerns about Recurrence Scale (CARS, n=7) [20], Assessment of Survivor Concerns (ASC, n=1) [21], Fears of Progression Questionnaire-Short Form (FoP-Q-SF, n=9) [22],FCR7 [23] (n=1) and Memorial Anxiety Scale for Prostate Cancer (MAX-PC, n=1) [24]. Evidence for validity of each FCR measurement has been reported (see Supplementary File 2 for summary details of these measures).

3.5 Data extraction

After the removal of duplicate studies, the titles and abstracts of potential references were reviewed to remove any irrelevant articles. Full papers were subsequently acquired and assessed. Data extraction was independently conducted by EL and then identified papers shared with GH. Discrepancies of selection were discussed in detail between EL and GH with close inspection of those papers which indicated some disagreement. Hence, references were screened for eligibility and manually sorted by EL, and GH confirmed adherence to the inclusion and exclusion criteria. Only the papers which adhered to the full inclusion criteria were conserved. For each study, the following data were extracted: 1. Authors' names, 2. Year of publication, 3. Sample size of the study, 4. Gender (women) percentage, 5. Mean age when completed the FCR measure, 6. Age range, 7. Anatomical single site or mixed site studies, 8. Breast cancer or non-breast cancer, 9. Country of study, 10. FCR

measure, 11. Main findings of the study (FCR prevalence, levels of FCR in different age groups and outcomes), 12. Statistical data on age and FCR association (see Meta-analysis section).

3.6 Statistical analysis

3.6.1 Meta-analysis

A meta-analysis was conducted in adherence to PRISMA guidelines to assess the summary effect of age on FCR in the studies. The effect sizes were calculated using Comprehensive Meta-analysis routines (version 2.0). All articles were searched to obtain the raw correlation, regression coefficient (standardized or unstandardized), odds ratio or t test statistics for conversion to an effect size for inclusion in the analysis. Where papers reported more than one wave of data in a panel study, the association statistic presented at baseline was selected as this data collection point would have the largest sample size which was considered desirable from a descriptive power perspective. A lone study removed procedure was conducted to assess the sensitivity of the overall effect size of taking out a study. Publication bias was checked by calculating Begg and Egger statistics for completeness sake.

3.6.2 Heterogeneity

Heterogeneity in effect sizes refers to the difference, due to error, of the true effect size from the observed effect size [13]. To quantify the variance in true effect sizes of the studies, statistical measures of heterogeneity will be calculated: Q (random error), T^2 (variance of effect sizes), T (standard deviation of effect sizes) and I^2 (percentage heterogeneity) [13].

3.6.3 Random effects model

As agued previously, a random-effects model was used to ensure that no single study's effect size is overrepresented, and the mean effect size across all studies was properly demonstrated.

3.6.4 Meta-regression

A meta-regression was applied to evaluate a link between one or more independent variables to the dependent variable in a meta-analysis, namely: the effect sizes. It is comparable to a multiple regression as a similar statistical approach is applied [25], and can assess the relationship between a quality identified (sometimes referred to as a moderator variable) and the effect size of each study. A random-effects meta-regression model was applied.[25, 26]

An analysis to examine the moderating effects of factors *a priori* included: year of publication, breast cancer, type of measure (FCR or FoP), type of summary association statistic and overall central tendency statistic of age of patient (e.g. study average) was also performed. The graphs and diagrams of these statistical analyses were produced via STATA15 software (*metan, metareg, metabias*). Measures of heterogeneity such as T^2, I^2, adjusted R^2 and z values were also generated. Alpha level was set to conventional 0.05 (2 sided).

3.7 Quality Assessment

A modified version of the Joanna Briggs quality assessment tool for analytical cross-sectional studies was applied to the cross-sectional, longitudinal, validation and RCT studies used in this meta-analysis [27, 28]. The 6-item tool was manually applied to all 31 studies included in this review. The items in the modified checklist are presented in Box 1.

4 Results

4.1 Study Selection

Figure 1 summarises the results of the search. A total of 3819 references were identified with the presented search criteria in the four databases: EMBASE, MEDLINE, PubMed, PsycINFO. After removing duplicate references, 3242 title and abstracts were screened for relevance. Full text articles were obtained from the remaining 112 references to be assessed and relevant data regarding FCR and age was extracted if it was reported in an article. A final number of 31 papers were included (Table 1).

4.2 Overall effect

Apart from 6 studies [28-33] , twenty-five studies included in this analysis showed a negative correlation between FCR and age to some extent. However, on closer inspection of the confidence intervals the picture is less unanimous with 12 studies that show negative effect sizes and 19 with effect sizes that are inconclusive and could be considered 'nil' association. The forest plot (Figure 2) shows an overall negative effect size for FCR and patient age. The overall effect size was -0.12 with 95% confidence intervals of -0.17 to -0.07. A test of this effect size showed $Z = 4.71$, $p < 0.00001$). The range of values for the overall effect size with 'one study removed' was 0.015 (i.e. minimum -0.135 to maximum -0.120). Heterogeneity values for this analysis returned a chi-squared value of 429.41 (df = 30) equating to a $p = 0.005$, $I^2 = 93\%$ and Tau-squared value, $T^2 = 0.016$. Publication bias was inspected and Begg ($z = 0.56$, $p = 0.58$) and Eggers ($t = -2.54$, $p = 0.017$) statistics gave inconsistent results.

4.3 Quality assessment

To gain a satisfactory rating a paper needed to show positive assessments for half or more of the six criteria. For the purposes of this study, the quality of the papers included in the meta-analysis and systematic review were satisfactory (Figure 3). All studies matched the criterion of 50% or more

affirmative assignments of quality. Items 5 and 6 (basic psychometrics and appropriate statistical methods) were applied positively in all studies.

4.4 Meta-regression

A meta-regression was performed and five moderator variables were included simultaneously, namely: cancer type, publication date, type of association, measure of FCR or FoP and a central tendency measure of age of the study sample (Table 2). Gender was not entered as cancer type was confounded with this factor. Two studies did not present a central tendency aggregate statistic for age hence values were substituted (grand mean average for the 29 studies). Of note were the significant regression coefficients of cancer type and publication date. The scatterplots present the results (Figures 4a and b). The effect of breast cancer type versus other cancer on the age and FCR association was significant (p = 0.002). That is the relationship between age and FCR was reliably more negative in breast cancer samples compared to samples diagnosed with other cancer types.

Meta-regression showed that publication year has a statistically significant effect on the age and FCR correlation (p = 0.011) based upon the pooled overall sample size of 19,777 (N range: 46-6057). The scatterplot demonstrated that the effect size became less strong with the approach to the current year of publication when the search was conducted. The overall coefficient of the gradient is 0.027 with 95%CIs: 0.007, 0.048. Each circle on the scatterplots represents a study and the size portrays the weight as calculated by the meta-analysis procedure.

5 Discussion

This is the first systematic review and meta-analysis that has dedicated investigation primarily between patient age and FCR association. The focus on this relationship was considered important to establish a firmer overall estimate than has been previously possible. This analysis assists our understanding of this relationship more explicitly, and detects systematic patterns of FCR over many cancer centres. Overall, the meta-analysis of the associations of patient age and FCR reported in studies from 2009-2018 showed that there is a significant negative association. The effect size of -0.12 is considered small [34] although we argue that it is still of some significance as it reflects a reliable pattern across numerous patients (pooled sample of nearly 20,000 patients). The omission of any one of the 31 studies resulted in a stable overall value of the effect size. The analysis demonstrated a high level of heterogeneity which might be expected from such a broad selection of study designs and samples. In Hanprasertpong's [30] case, for example was the only article found to have investigated fears of cancer recurrence in cervical cancer.

According to the meta-analysis, there are 5 studies that reported an inconsistentpositive correlation between age and FCR [28, 29, 31-33] while one paper demonstrated no apparent correlation, i.e. virtually zero, between the 2 variables [30]. It is arguable that some of these results are based on various confounding variables, sample biases or even study designs which may have effected their results. For example, in Thewes' [28] and Cho's [31] papers, they investigated FCR in adolescent and young adults (AYA). In both studies, the age ranges of the cancer patients were approximately 15-35 years of age. This narrow age range effectively defines a censored sample. AYAs are also a group of patients that have been previously reported to have significantly higher levels of FCR when compared to other studies which utilised wider range of age groups [28]. It is therefore possible that the true relationship between age and FCR is underestimated.

In addition, in multivariate studies where it is common to present partial correlations or associations corrected for other independent variables, as reflected in regression tables, the effect sizes in this type of study presentation may also underestimate the effect size entered into the meta-

regression compared with inclusion of a simple raw correlation. Furthermore studies that present FCR levels across age groups and provide comparison tests (e.g. t values) may also give attenuated effect sizes. Another type of study such as those reported by Butow [29] and Dieng [32] were interested to show the effectiveness of psychological interventions to reduce FCR levels of cancer patients. They used RCT methodology and therefore the findings of a positive association between age and FCR would have been incidental to their main research question. In other words these associations tended to oppose the overall trend however these studies provide helpful additional material to this meta-analysis as there is no publication bias in their reporting of the age by FCR link.

The quality assessment gave reassurance that the studies were of a good methodological standard, however the assessment of publication bias gave equivocal results. The interpretation of these results (Begg and Eggers statistics) were not, on reflection, very meaningful as the authors of the large majority of studies did not have a focus specifically on the age by FCR association. It is therefore unlikely that studies will be purposively hidden by virtue of the age by FCR effect size level, therefore including a publication bias check may be considered redundant.

The discussion continues by focusing on explaining the two important moderating effects identified by the meta-regression analysis.

5.1 Breast cancer versus other cancers effect

The combination in patients, with breast cancer, of lower than average age level, compared with the majority of other cancers and virtually all female gender as predictors of FCR may explain the higher levels of FCR observed in breast cancer patients as opposed to other cancers. Consistent with this is the recent study conducted to determine the experiences of breast cancer patients regarding breast reconstruction surgery after mastectomy. The patients who opted for breast reconstruction surgery were found to rate their breasts as a crucial aspect for maintaining their femininity and attractiveness [35]. Age, gender and womanhood are three variables that would provide a satisfactory account as to why studies, which investigated factors linked to breast cancer, would report significantly higher levels of FCR in comparison to other studies which focused on other single-

site or mixed cancers. The report by Lebel and colleagues on younger women with breast cancer showed little evidence that looking after young children was a factor in exacerbating FCR. They found anxiety and intrusiveness as key variables and employed illness representations [10] to explain these interesting effects.

A further explanation of reduced FCR levels in younger patients is that health providers are delivering better treatments for rare and aggressive cancers. For example patients with breast cancer diagnosed with triple negative and HER2-positive classified tumours have a wider range of potential interventions to arrest the disease.

Attempts to extend comparison between patients with breast cancer versus other cancer types presents difficulties as the majority of reports focus on breast cancer. Furthermore, there are many other cancers that could be utilized for comparison but have received relatively less attention psychologically.

5.2 Publication year effect

Based on current literature, this investigation of publication year appears unique. Meta-regression analysis indicated a reliable effect; Figure 2a shows that as the publication year increases, that is the more recent the study, the strength of the effect size decreases. This indicates that there is smaller disparity between the FCR levels reported by older and younger patients more recently compared to studies published earlier in the past decade. Two possible explanations exist. First older patients may be reporting higher levels of FCR than previous. Second it may be that younger patients have been reporting lower levels of FCR recently. The finding appears not to be trivial because it was revealed even when a number of additional variables were entered into the regression. We believe that this publication data issue is intriguing and this conjecture invites speculative explanation.

The current literature appears not only to be lacking in studies to provide evidence to elucidate the FCR decrease in older patients but also the additional finding that the effect size of the age by FCR relationship reduces with recent publication. In the self-regulation model of Lee-Jones and colleagues, previously mentioned, a crucial component is the illness representation that patients hold about their diagnosis [10]. Illness representations are influenced primarily by experience of the patient, that in turn is a sum of all impacts of internal and external stimuli that can be divided into: the timeline of the disease, ability to control the disease, identity (labelling of the cancer itself), its consequences and causes. Explanations can be drawn from this model to assist with speculating on answering our conjecture. Three connected possibilities (presented in sections: 5.3 to 5.5) inform our speculation and are outlined below.

5.3 Life expectancy (Timeline representation)

When a patient reports high FCR, the patient may not be fearful of the cancer itself, but rather, the implications of re-contracting the disease. Patients may have family commitments that will be impeded by the consequences of a recurrence. Younger patients are more likely to have children to nurture as opposed to older patients whose children are likely to be independent. This would provide a viable explanation as to why a negative relationship between age and FCR is observed. At the other end of the age spectrum, older patients who believe they have a long life expectancy prior to cancer diagnosis may be more fearful of cancer returning a belief that would be consistent with the Lee-Jones and colleagues model [10] as follows. With increasing life expectancy it may be that recurrence fears are equalising between the age groups providing a clear rationale for a reduction in the association of patient age and FCR level with recent publication date.

5.4 Treatability of cancer (Control representation)

Advances in medicine have progressed. When a treatment emerges which has been trialled and demonstrated to be partially effective against an advanced condition, patients may be pre-occupied with the positive effects of such treatment e.g. increased survival. This issue has been discussed recently drawing attention to the concept of ‘curability’ of advanced cancer (Duberstein

2018). Patients' health beliefs of certainty of cure can be at odds with the overall clinician's explanation of potential increased survival but also the likely reduction in quality of life and experienced treatment-related toxicities that the medical therapy delivers (Loh 2019). The general public may have an altered perception of such treatment being a "panacea" that can solve most dilemmas associated with a particular disease. Hence the discordance of beliefs about treatment curability rated by patients versus the low perceived negative side-effects may be differentially held by various age groups and impact upon the age and FCR relationship. (Loh 2019).

5.5 Media and cancer (Identity and labelling representation)

Mainstream media (newspaper and magazines) contribute to a large portion of daily living as of 2019. Articles about cancer and cancer treatments may not be providing sufficient information for patients to develop a realistic and comprehensive perspective of cancer treatments. Studies in various countries have shown that the representation of cancer is often inaccurate, misleading or lacking in details regarding the implications of cancer diagnoses and treatment options and can have an influence on health behaviour [37]. This imprecise perspective of cancer treatments by the media can potentially raise over-optimistic patient expectations. These may become unmet by the reality of cancer treatments in healthcare settings. As the media have been shown to report on the more positive and hopeful aspects of cancer treatment such as aggressive treatment options [38], the more grim connotations regarding symptom management and palliative care should the cancer progress to a terminal stage have often been neglected. In a report about breast cancer screening in newspapers, it was discovered that citations and sources to information were often not declared and some of the articles were also found to have reported outdated information based on the literature from national organisations [39]. Age is another aspect of cancer found to be misrepresented in media; although older patients are at higher risks of developing cancer, articles of older patients with cancer have been marginalised in the media [39, 40]. This may potentially explain why younger patients

generally (although a notable exception is Lebel's study [36]) have a higher fear and awareness of cancer and its recurrence in comparison to the older generation of cancer patients.

The accessibility of information through social media and the internet is another plausible explanation for the change in the age and FCR correlation over the years. Younger patients acquiring more information about various aspects of cancer and new treatments, through social networking sites as well as the internet. This may reduce FCR levels reported by younger patients. Social media has become increasingly relevant by the year. It is generally accepted that the older generation are generally less knowledgeable and competent in regard to digital skills and the internet. Younger patients are often more adept in identifying reliable sources of information compared to the older generation [41]. This disparity in social media influence would provide a viable explanation to the Lim-Humphris conjecture as the more accurate information patients obtain regarding cancer, the less fearful they are likely to be; in contrast, older patients who may have received inaccurate information may have had their views on cancer skewed and report higher FCR as they worry about the unknown. Although the benefits of the utilisation of social media in medicine have been acknowledged [42], caution is still advised as unwanted effects may still present. A comprehensive systematic review by Giustini mentioned that the phenomenon of 'virally' sharing information from poor quality sources of information on social networking platforms can affect the perceived reliability of the information [43]. False claims and inappropriate medical advice were also found to be spread within social media sites [44-46], which is misleading and could potentially cause harm to patients as they engage in avoidance behaviours.

5.6 Clinical implications

The results of this meta-analysis and systematic review can be significant in a few aspects of clinical practice. It has been commonly acknowledged by researchers that fears of cancer recurrence are often unmet in routine clinical practice [47]. As previously mentioned, doctors play a key role in healthcare communication as it is a vital component which can affect patient outcomes such as FCR [48]. Currently, there are recommendations for clinicians regarding fears of cancer recurrence in a

clinical setting [49]. Strategies include normalising FCR and the endorsement for patients to discuss any concerns they may have about cancer recurrence. However, patients with varying demographic characteristics are unlikely to react uniformly. A more personalised approach to managing patient FCR should be adopted to clinical settings. A recent review highlights the effects of interventions delivered by non-mental health specialists [76]. Initially, it might have been plausible for clinicians to be alerted of the potential FCR level by knowing the patient's age. This premise may need to be tempered with the finding that weaker correlations of age and FCR are found in recent studies.

5.7 Study limitations

There are inevitably limitations in this review and meta-analysis to be discussed. First, most of the studies in this review were breast cancer studies. Generalisability of this study's results to all types of cancer requires caution. Second, this study may not be representative of every single year from 2009-2018. Some years had a larger number of studies conducted while other years may have less or no FCR studies with an age by FCR association reported. Third, age of patient during administration of the survey instrument was prioritised over age at diagnosis, thereby introducing some error. Fourth, the FCR measurements in the papers were assessed using different measurement tools with varying number of scale items also introducing some additional unknown variance. Some attempt to control for this by comparing FCR to FoP measures demonstrated no systematic effect. Fifth, this review also excluded articles that were not written in English, reducing further generalisabilty. Sixth, only articles that included FCR terms in the title or abstract were gathered. It is possible that articles with FCR referred to only in the manuscript text might have contributed some relevant data, and have been unwittingly excluded. Seventh, no double screening of papers was conducted for entry. Finally, the raw correlations of age and FCR were prioritised over the adjusted correlation coefficients, which may have allowed some liberty for confounds to affect the data of this meta-analysis. However, the raw correlations were preferred to allow for a larger sample size as well as a more realistic relationship can be demonstrated. When covariates are controlled for, it may be more difficult to interpret and compare the results from various studies as

the number of covariates controlled for in each study may have varied. An additional analysis was performed to consider the factors which included values of raw correlation against adjusted correlations, however, this had no influence on the overall results of the meta-regression. Due to these limitations, the results of this study should be interpreted with care.

5.8 Future work

Prospective studies should attempt to focus on the various causes of the effect of publication year on the age and FCR association. In re-assessing FCR and its demographical predictors, more longitudinal studies should be conducted to determine changes in FCR patterns from time of diagnosis. Factors such as media exposure to cancer information in addition to other potential influences to FCR changes could also be examined when organising these studies.

6 Conclusion

The patient age and FCR association was significant when aggregated across studies over the past 10 years and supports the finding from a previous extensive FCR review [1]. However, the strength of this relationship may not be as stable as previously considered and warrants further investigation.

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8 Authors' Contributions:

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, G.H.; Methodology, E.L., G.H.; Investigation, E.L., G.H; Formal Analysis, E.L., G.H.; Resources, G.H.; Writing - Original Draft, E.L., G.H.; Writing - Review & Editing, G.H.; Visualization, E.L., G.H.; Supervision, G.H.; Funding Acquisition, G.H.
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9 Conflicts of Interest

Authors confirm there are no conflicts of interest

References

1. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv 2013;7(3):300-22.
2. Yang Y, Li W, Wen Y, et al. Fear of cancer recurrence in adolescent and young adult cancer survivors: A systematic review of the literature. Psycho-Oncology 2019.
3. Koch-gallenkamp L, Bertram H, Eberle A. Fear of Recurrence in Long-Term Cancer Survivors — Do Cancer Type , Sex , Time Since Diagnosis , and Social Support Matter ? Health Psychology 2016;35:1329-33.
4. Applebaum AJ, Stein, E. M., Lord-Bessen, J., Pessin, H., Rosenfeld, B., & Breitbart, W. Optimism, social support, and mental health outcomes in patients with advanced cancer. Psycho-Oncology 2014;23:299-306.
5. Sammarco A. Quality of life among older survivors of breast cancer. Cancer Nursing 2003;26:431-38.
6. Liu Y, Perez M, Schootman M, et al. Correlates of fear of cancer recurrence in women with ductal carcinoma in situ and early invasive breast cancer. Breast Cancer Res Treat 2011;130(1):165-73.
7. Lebel S, Ozakinci G, Humphris G, et al. From normal response to clinical problem : definition and clinical features of fear of cancer recurrence. Supportive Care in Cancer 2016:3265-68.
8. Baker F, Denniston M, Smith T, West MM. Adult cancer survivors: How are they faring? Cancer 2005;104(11):2565-76.
9. Armes J, Crowe M, Colbourne L, et al. Patients' supportive care needs beyond the end of cancer treatment: a prospective, longitudinal survey. J Clin Oncol 2009;27(36):6172-9.
10. Lee-Jones C, Humphris G, Dixon R, Bebbington-Hatcher M. Fear of cancer recurrence: a literature review and formulation to explain exacerbation of recurrence fears. Psycho-Oncology 1997;6:95-105.
11. Yang Y, Wen Y, Bedi C, Humphris G. The relationship between cancer patient's fear of recurrence and chemotherapy: A systematic review and meta-analysis. J Psychosom Res 2017;98:55-63.
12. Yang Y, Cameron J, Humphris G. The relationship between cancer patient's fear of recurrence and radiotherapy: a systematic review and meta-analysis. Psychooncology 2016.
13. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta‐Analysis. 2009.
14. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj 2015;350:g7647.
15. Streiner DL, Norman GR, J C. Health Measurement Scales - A Practical Guide to their Development and Use. 5th ed. Oxford: Oxford University Press; 2014.
16. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer 2009;17(3):241-51.
17. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. J Cancer Surviv 2015;9(3):481-91.
18. Custers AE, Bleiker EMA, Prins JB. The Cancer Worry Scale. Cancer Nursing 2014;37.
19. Custers JA, van den Berg SW, van Laarhoven HW, et al. The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. Cancer Nurs 2014;37(1):E44-50.
20. Vickberg SM. The Concerns About Recurrence Scale (CARS): a systematic measure of women's fears about the possibility of breast cancer recurrence. Ann Behav Med 2003;25(1):16-24.
21. Gotay CC, Pagano IS. Assessment of Survivor Concerns (ASC): a newly proposed brief questionnaire. Health Qual Life Outcomes 2007;5:15.
22. Herschbach P BP, Dankert A, et al. Fear of progression in chronic diseases: psychometric properties of the Fear of Progression Question- naire. J Psychosom Res. 2005;58:505-11.

23. Humphris G, Watson E, Sharpe M, Ozakinci G. Unidimensional scales for fears of cancer recurrence and their psychometric properties: The FCR4 and FCR7. Health and Quality of Life Outcomes 2018;16(1):30.
24. Roth A, Nelson, C. J., Rosenfeld, B., Warchowski, A., O'Shea, N., Scher, H., Holland, J. C., Slovin, S., Curley-Smart, T., Reynolds, T., Breitbart, W. Assessing Anxiety in Men With Prostate Cancer : Further Data on the Reliability and Validity of the Memorial Anxiety Scale for Prostate Cancer (MAX – PC). Psychomatics 2006;47:340-47.
25. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration 2011.
26. Thompson SG, Sharp, S. J. Explaining heterogeneity in meta-analysis: a comparison of methods. Statistics in Medicine 1999;18:2693-708.
27. Aromataris E, Fernandez R, Godfrey CM, et al. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015;13(3):132-40.
28. Thewes B, Kaal SEJ, Custers JAE, et al. Prevalence and correlates of high fear of cancer recurrence in late adolescents and young adults consulting a specialist adolescent and young adult (AYA) cancer service. 2018:1479-87.
29. Butow PN, Turner J, Gilchrist J, et al. Randomized Trial of ConquerFear : A Novel , Theoretically Based Psychosocial Intervention for Fear of Cancer Recurrence. Journal of Clinical Oncology 2017;35.
30. Hanprasertpong J, Geater A, Jiamset I, et al. Fear of cancer recurrence and its predictors among cervical cancer survivors. J Gynecol Oncol 2017;28.
31. Cho D, Park CL. Moderating effects of perceived growth on the association between fear of cancer recurrence and health-related quality of life among adolescent and young adult cancer survivors. J Psychosoc Oncol 2017;35(2):148-65.
32. Dieng M, Butow PN, Costa DS, et al. Psychoeducational Intervention to Reduce Fear of Cancer Recurrence in People at High Risk of Developing Another Primary Melanoma: Results of a Randomized Controlled Trial. J Clin Oncol 2016;34(36):4405-14.
33. Groß SE, Nitzsche A, Gloede TD, et al. The initial clinical interview — can it reduce cancer patients ' fear ? Support Care Cancer 2015;23:977-84.
34. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 1988.
35. Schmidt JL, Wetzel CM, Lange KW, Heine N. Patients' experience of breast reconstruction after mastectomy and its influence on postoperative satisfaction. Archives of Gynecology and Obstetrics 2017;296:827-34.
36. Lebel S, Tomei C, Feldstain A, Beattie S, McCallum M. Does fear of cancer recurrence predict cancer survivors' health care use? Support Care Cancer 2013;21(3):901-6.
37. Lebel S, Beattie S, Arès I, Bielajew C. Young and Worried : Age and Fear of Recurrence in Breast Cancer Survivors. 2013;32:695-705.
38. Duberstein PR, Chen M, Chapman BP, et al. Fatalism and educational disparities in beliefs about the curability of advanced cancer. Patient Educ Couns 2018;101(1):113-18.
39. Loh KP, Mohile SG, Epstein RM, et al. Willingness to bear adversity and beliefs about the curability of advanced cancer in older adults. Cancer 2019;125(14):2506-13.
40. Yanovitzky I, Blitz CL. Effect of media coverage and physician advice on utilization of breast cancer screening by women 40 years and older. J Health Commun 2000;5(2):117-34.
41. Fishman J, Have, T. T., Casarett, D. Cancer and the Media: How Does the News Report on Treatment and Outcomes? Arch Intern Med 2010;170:515-18.
42. Wells J, Marshall, P. M., Crawley, B., Dickersin, K. Newspaper Reporting of Screening Mammography. Annals of Internal Medicine 2001.
43. Macdonald S, Cunningham Y, Patterson C, et al. Mass media and risk factors for cancer : the under-representation of age. BMC Public Health 2018;18.
44. Deursen AV, Dijk JV. Internet skills and the digital divide. New Media & Society 2010;13:893-911.

45. George DR, Rovniak, L. S., Krashnewski, J. L. Dangers and opportunities for social media in medicine. Clin Obstet Gynecol 2013;56.
46. Giustini D, Ali SM, Fraser M, Boulos MNK. Effective uses of social media in public health and medicine : a systematic review of systematic reviews. Online Journal of Public Health Informatics * 2018;10.
47. Moorhead SA, Hazlett DE, Harrison L, et al. A New Dimension of Health Care : Systematic Review of the Uses , Benefits , and Limitations of Social Media for Health Communication. J Med Internet Res 2013;15.
48. Hamm MP, Shulhan J, Williams G, et al. A systematic review of the use and effectiveness of social media in child health. BMC Pediatrics 2014;14.
49. Koskan A KL, Davis SN, Gwede CK, Wells KJ, et al. Use and taxonomy of social media in cancer-related research: a systematic review. Am J Public Health. 2014;104:e20-37.
50. Armes J CM, Colbourne L, et al. Patients' supportive care needs beyond the end of cancer treatment: a prospective, longitudinal survey. J Clin Oncol 2009;27:6172-9.
51. Humphris G. Emotional talk of patients with breast cancer during review appointments with therapeutic radiographers : effects on fears of cancer recurrence. Supportive Care in Cancer 2018.
52. Butow P, Sharpe L, Thewes B, et al. Fear of Cancer Recurrence: A Practical Guide for Clinicians. Oncology 2018;32.
53. Liu JJ, Butow P, Beith J. Systematic review of interventions by non-mental health specialists for managing fear of cancer recurrence in adult cancer survivors. Support Care Cancer 2019.
54. Chien C-h, Chuang C-k, Liu K-l, Wu C-t, Pang S-t. Positive and negative affect and prostate cancer-specific anxiety in Taiwanese patients and their partners. European Journal of Oncology Nursing 2018;37:1-11.
55. Soriano EC, Pasipanodya EC, Losavio ST, et al. Social Constraints and Fear of Recurrence in Couples Coping With Early Stage Breast Cancer. Health Psychology 2018;37:874-84.
56. Wagner T, Augustin M, Blome C, et al. Fear of cancer progression in patients with stage IA malignant melanoma. Eur J Cancer Care 2018;27.
57. Yang Y, Sun H, Liu T, et al. Factors associated with fear of progression in chinese cancer patients : sociodemographic , clinical and psychological variables. Journal of Psychosomatic Research 2018;114:18-24.
58. Starreveld DEJ, Peters ML, Markovitz SE. The course of fear of cancer recurrence : Different patterns by age in breast cancer survivors. Psycho-Oncology 2018;27:295-301.
59. Dumalaon-Canaria JA, Prichard, I., Hutchinson, A. D., Wilson, C. Fear of cancer recurrence and psychological well- - being in women with breast cancer : The role of causal cancer attributions and optimism. Eur J Cancer Care 2018;27.
60. Maguire R, Hanly P, Drummond FJ, Gavin A, Sharp L. Regret and fear in prostate cancer : The relationship between treatment appraisals and fear of recurrence in prostate cancer survivors. Psycho-Oncology 2017;26:1825-31.
61. Hefner J, Berberich S, Lanvers E, Sanning M, Steimer A-k. New insights into frequency and contents of fear of cancer progression / recurrence (FOP / FCR) in outpatients with colorectal carcinoma (CRC) receiving oral capecitabine : a pilot study at a comprehensive cancer center. Patient Preference and Adherence 2017;11:1907-14.
62. Cohee AA, Adams RN, Johns SA, et al. Long-term fear of recurrence in young breast cancer survivors and partners. Psycho-Oncology 2017;28:22-28.
63. Cho D, Park CL. Moderating effects of perceived growth on the association between fear of cancer recurrence and health-related quality of life among adolescent and young adult cancer survivors. Journal of Psychosocial Oncology 2017;35:148-65.
64. Mcginty HL, Small BJ, Laronga C, Jacobsen PB. Predictors and Patterns of Fear of Cancer Recurrence in Breast Cancer Survivors. Health Psychology 2016;35:1-9.
65. Dieng M, Butow PN, Costa DSJ, et al. Psychoeducational Intervention to Reduce Fear of Cancer Recurrence in People at High Risk of Developing Another Primary Melanoma : Results of a Randomized Controlled Trial. Journal of Clinical Oncology 2016;34.

66. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. J Cancer Surviv 2015;9:481-91.
67. Hinz A, Mehnert A, Ernst J. Fear of progression in patients 6 months after cancer rehabilitation — a validation study of the fear of progression questionnaire FoP-Q-12. Support Care Cancer 2015;23:1579-87.
68. Sarkar S. Fear of recurrence and its impact on quality of life in patients with hematological cancers in the course of allogeneic hematopoietic SCT. Bone Marrow Transplantation 2014;49:1217-22.
69. Arès I, Lebel S, Bielajew C. The impact of motherhood on perceived stress , illness intrusiveness and fear of cancer recurrence in young breast cancer survivors over time. Psychology & Health 2014;29:651-70.
70. Thewes B, Bell ML, Butow P, et al. Psychological morbidity and stress but not social factors in fl uence level of fear of cancer recurrence in young women with early breast cancer : results of a cross-sectional study. Psycho-Oncology 2013;22:2797-806.
71. Melchior H, Büscher C, Thorenz A, et al. Self-ef fi cacy and fear of cancer progression during the year following diagnosis of breast cancer. Psycho-Oncology 2013;22:39-45.
72. Ziner KW, Jr GWS, Bell CJ, et al. Predicting Fear of Breast Cancer Recurrence and Self-Efficacy in Survivors by Age at Diagnosis. Oncology Nursing Forum 2012;39:287-96.
73. Petzel MQB, Parker NH, Valentine AD, et al. Fear of Cancer Recurrence after Curative Pancreatectomy : A Cross-sectional Study in Survivors of Pancreatic and Periampullary Tumors. Ann Surg Oncol 2012;19:4078-84.
74. Liu Y, Schootman, Mario, Jeffe DB. Correlates of fear of cancer recurrence in women with ductal carcinoma in situ and early invasive breast cancer. Breast Cancer Res Treat 2011;130:165-73.
75. Simard S, Savard J. Fear of Cancer Recurrence Inventory : development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer 2009;17:241-51.
76. Liu JJ, Butow P, Beith J. Systematic review of interventions by non-mental health specialists for managing fear of cancer recurrence in adult cancer survivors. Support Care Cancer 2019;27(11):4055-67.

Table 1: Characteristics of studies involved in statistical analyses

Author	Year of publica-tion	N size	Age at diagnosis, age at survey, mean(SD)/median	FCR measure-ment[1]	Cancer site	Raw correlation	Female %	Country	Association	Study design
Thewes [28]	2018	73	Mean=27.4 (4.6), NA	CWS	Mixed	Mean age (SD) = 26.3 (4.9) low FCR; 28 (4.4) high FCR	51%	Netherlands	Positive	Cross-sectional
Humphris [51]	2018	60	NA, mean=57.92 (11.26), range from35-85	FCR7	Breast cancer (single site	Pearson coefficient = -0.134	100%	Scotland	Negative	Mixed methods observational study
Chien [54]	2018	48	NA, mean=67 (6.8)	MAX-PC	Prostate cancer (single site)	Unstandardized beta value= -0.009, SE=0.007	0%	Taiwan	Negative	Prospective repeated methods design
Soriano[55]	2018	46	NA, mean=52.19 (10.98)	FCRI	Breast cancer (single site)	Unstandardized beta value= -0.025, SE=0.013	100%	USA	Negative	Cross-sectional
Wagner [56]	2018	136	NA, mean=54.3 (12.6), range from 25-88	FoP-Q-SF	Melanoma	Pearson coefficient = -0.198	46.3%	Germany	Negative	Cross-sectional
Yang [57]	2018	636	NA, mean=47.79 (11.59), range from 22-88	FoP-Q-SF	Mixed	Standardized beta value = -0.034	89.6%	China	Negative	Cross-sectional
Starreveld	2018	266	NA, mean=54.31 (10.09)	CARS	Breast cancer (single site)	Unstandardized beta value = -0.05, SE = 0.04	100%	Belgium	Negative	Longitudinal

Dumalaon-Canaria [59]	2018	314	NA, mean=55.22 (9.32)	CARS	Breast cancer (single site)	Standardized beta value = -0.217	100%	Australia	Negative	Cross-sectional
Butow [29]	2017	187	NA, mean=52.82 (10.07)	FCRI	Mixed	Pearson coefficient = 0.2	95%	Australia	Positive	RCT
Maguire [60]	2017	817	NA, mean=68.48 (7.87), range from 47-91	Self-designed items[2]	Prostate cancer (single site)	Standardized beta value = -0.02	0%	Republic of Ireland	Negative	Cross-sectional
Hefner [61]	2017	53	NA, mean=66 (12), range from 28-89	FoP-Q-SF	Colorectal cancer (single site)	Spearman coefficient = -0.022	24%	Germany	Negative	Cross-sectional
Hanprasertpong [30]	2017	699	NA, mean=52.78 (9.32), range from 21-70)	FoP-Q-SF (Thai version)	Cervical cancer (single site)	Mean FCR (SD) = 267 (38.2) young age group; 432 (61.8) old age group	100%	Thailand	Positive	Cross-sectional
Cohee [62]	2017	222	NA, mean=45.35 (4.7), range from 30-54	CARS	Breast cancer (single site)	Pearson coefficient = -0.239	100%	USA	Negative	Cross-sectional
Cho [63]	2017	292	NA, mean=33.32 (7.14), range from 18-47	ASC	Mixed	Pearson coefficient= 0.07	81%	USA	Positive	Cross-sectional
McGinty [64]	2016	160	NA, mean=61.48(9.6)	CWS	Breast cancer (single site)	Mean age (SD) = 63.22 (9.01) low FCR; 60.91 (9.79) high FCR	100%	USA	Negative	Prospective longitudinal study
Koch-Gallenkamp [3]	2016	6057	NA, mean=69	FoP-Q-SF	Mixed	Mean FCR (SD) = 31.2 (10.8) <54 years; 25.4 (8.9) 75+ years	NA	Germany	Negative	Cross-sectional
Dieng [65]	2016	151	NA, mean=58.5 (11.9)	FCRI	Melanoma (single site)	Mean FCR (SD) = 16.4 (7.9) low age group; 18.6 (6.8) high age group	45%	Australia	Positive	RCT

Custers [18]	2016	76	NA, median=67.3, range from 41-88	CWS	Colorectal cancer (single site)	T value = 1.58, p = 0.12	47%	Netherlands	Negative	Cross-sectional
Simard [66]	2015	60	NA, mean=60.3 (8.1), range from 39.1-74.8)	FCRI-SF	Mixed	Mean age (SD) = 59.7 (8.8) clinical FCR; 60.7 (7.6) non-clinical FCR	43.3%	Canada	Negative	Cross-sectional
Hinz [67]	2015	2059	NA, mean=62.4 (14.2)	FoP-Q-SF	Mixed	D value = 0.17, p = 0.033	41.2%	Germany	Negative	Validation study
Gross [33]	2015	152	NA, mean=65	FoP-Q-SF	Mixed	Standardized beta value = 0.047	43.4%	Germany	Positive	Longitudinal
Custers [19]	2014	194	NA, mean=57 (10.2), range from 30-88	CWS	Breast cancer (single site)	Pearson coefficient = -0.198	100%	Netherlands	Negative	Cross-sectional
Sarkar [68]	2014	239	NA, mean=50.4 (12.6), range from 18-71	FoP-Q-SF	Haematological cancer (single site)	Standardized beta value = -0.009	38%	Germany	Negative	Cohort/Panel study (Longitudinal)
Ares [69]	2014	742	NA, mean (children)=42 (4.2); mean (no children)=41 (4.7)	CARS	Breast cancer (single site)	Standardized beta value = -0.232	100%	USA & Canada	Negative	Cross-sectional
Lebel [37]	2013	3239	NA, NA	CARS	Breast cancer (single site)	F value = 45.89	100%	Canada	Negative	Cross-sectional
Thewes [70]	2013	218	mean=39 (4.6), NA, range from 28-45	FCRI	Breast cancer (single site)	Mean FCR (SD) = 68 (25.6) present sample mean; 60.6 (24.6) normative mean	100%	Australia	Negative	Cross-sectional

Melchior [71]	2013	107	NA, mean=54.2 (9.9), range from 26-85	FoP-Q-SF	Breast cancer (single site)	Unstandardized beta value = -0.127, SE = 0.089	100%	Germany	Negative	Cross-sectional
Ziner [72]	2012	1128	NA, NA, range <45; 55-70	CARS	Breast cancer (single site)	Mean FCR (SD) = 12.2 (5.2) younger group; 8.8 (4.5) older group	100%	USA	Negative	Cross-sectional
Petzel [73]	2012	240	NA, median=67, range from 34-92	FCRI	Pancreatic cancer	Odds Ratio = 0.96, p = 0.043	48%	USA	Negative	Cross-sectional
Liu [74]	2011	506	mean=58.3, NA, range from 40-89	CARS	Breast cancer (single site)	Pearson coefficient = -0.31	100%	USA	Negative	Longitudinal study
Simard [75]	2009	600	Mean=59 (0.6) breast; 69.1 (0.5) prostate; 61.6 (1.3) colorectal; 62 (1.5) NA	FCRI	Mixed	Pearson coefficient = -0.31	NA	Canada	Negative	Validation study

Notes: 1 See supplementary file for reference details of FCR measures
2 Refer to Maguire reference for details of measure

Table 2 Meta-regression of effect sizes (ES) by Year of publication and four other covariates

Factor	*B* Coef	SE	*t*	*p*	95%CI	
Year of publication [1]	0.02	0.01	2.19	**0.038**	0.001	0.042
Breast cancer vs other [2]	-0.17	0.05	-3.1	**0.005**	-0.276	-0.056
Pearson's vs other [3]	-0.02	0.05	-0.47	0.641	-0.118	0.074
FCR vs FCP [4]	-0.06	0.06	-0.97	0.341	-0.176	0.063
Age in years[5]	-0.06	0.14	-0.44	0.664	-0.341	0.221

Notes:

1. Year of publication: origin was set to 2009
2. Breast cancer diagnosis = 0, other cancer = 1
3. ES calculation based on: raw correlation =0, other = 1
4. Measure based upon: FC Recurrence = 0, FC Progression = 1
5. Central tendency value extracted and grand mean centred

Adjusted R^2 = 38.2% Model F(3,25) = 3.73; p = 0.012

Figure 1 PRISMA diagram

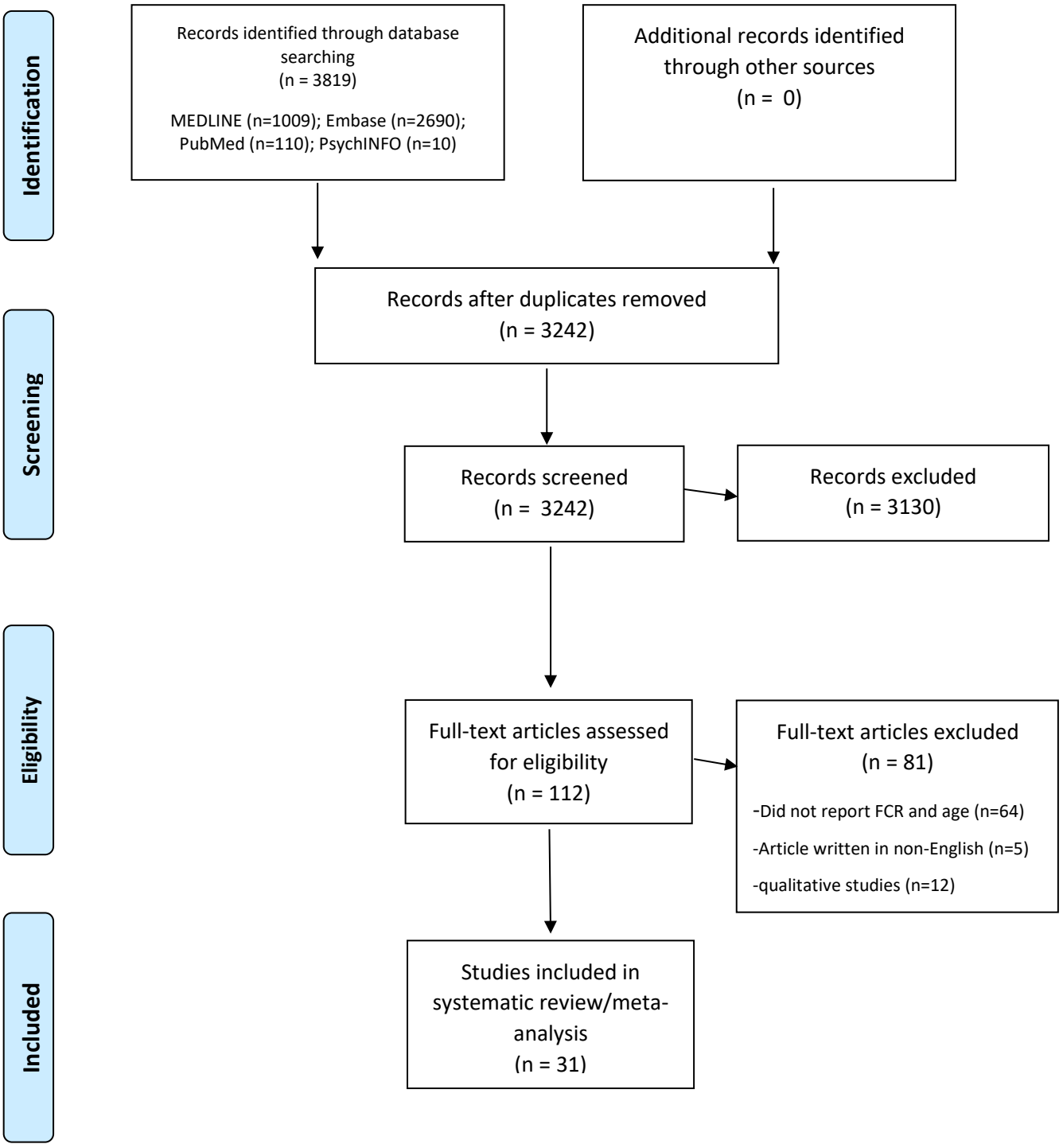

Figure 2 Forest plot of overall summary effect of FCR and age in a random effects model.

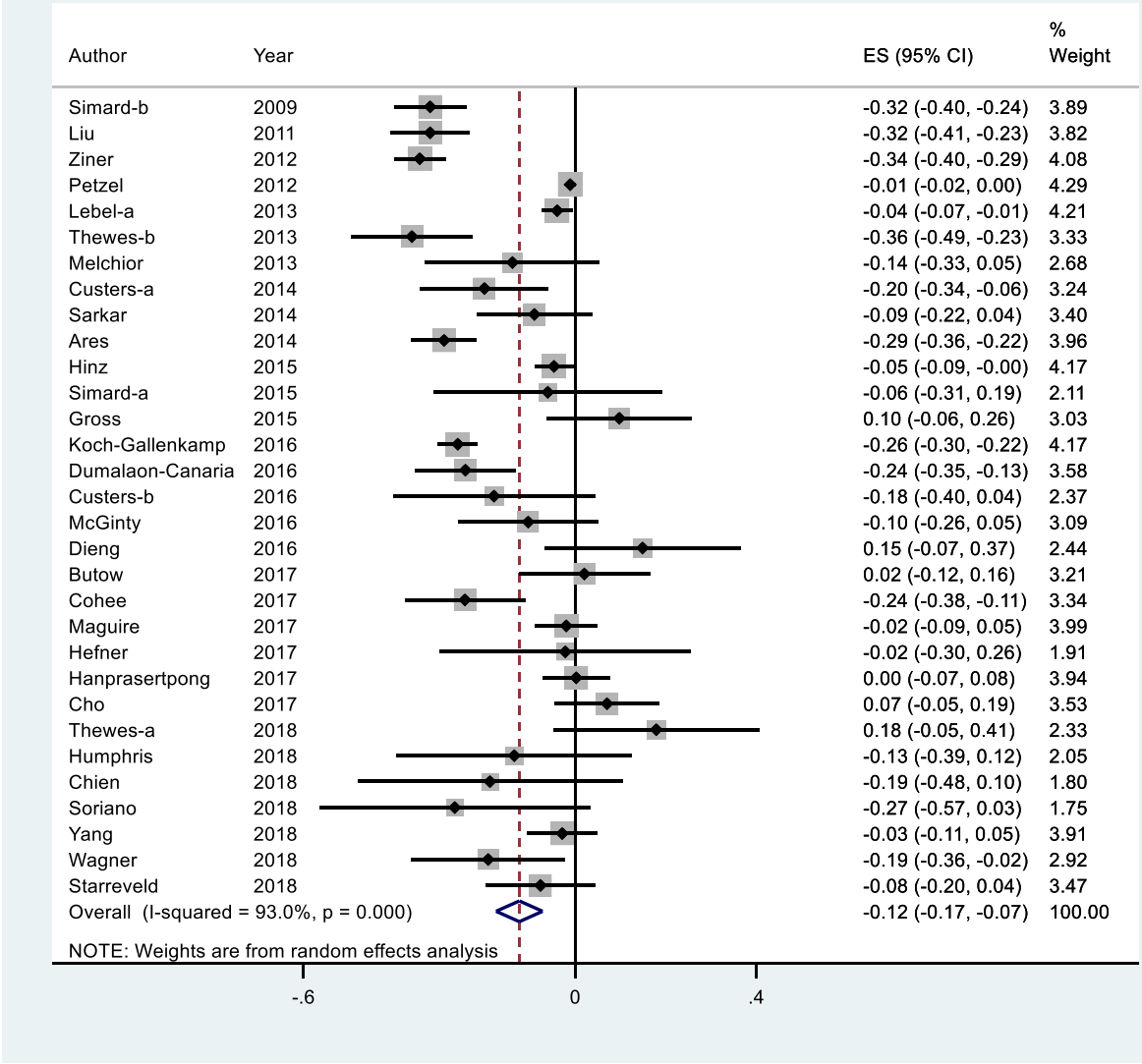

Figure 3 Quality assessment using Modified Joanna Briggs Tool

Author	Year	Item 1[§] Inclusion criteria	Item 2 Subject details	Item 3 Con-founds	Item 4 Strate-gies	Item 5 Measure-ment	Item 6 Statis-tics	Overall score (6 max)
Chien	2018							5
Dumalaon-Canaria	2018							6
Humphris	2018							4
Soriano	2018							5
Starraveld	2018							6
Thewes	2018							4
Wagner	2018							6
Yang	2018							6
Butow	2017							6
Cho	2017							6
Cohee	2017							4
Hansprasertpong	2017							5
Hefner	2017							3
Maguire	2017							4
Custers	2016							3
Dieng	2016							5
Koch-Gallenkamp	2016							6
McGinty	2016							6
Gross	2015							4
Hinz	2015							4
Simard	2015							4
Ares	2014							6
Custers	2014							3
Sarkar	2014							6
Lebel	2013							5
Melchior	2013							6
Thewes	2013							6
Petzel	2012							5
Ziner	2012							4
Liu	2011							6
Simard	2009							4

Score: Green = 'Yes'; Red = 'No'; Yellow = 'Unclear/Not applicable'

§ Full details of Modified items in Box 1

Figure 4 Scatterplots of (a, upper pane) publication year, and (b, lower pane) breast cancer versus other cancer type: on patient age by FCR association effect sizes (*z*)