Effectiveness of interventions to identify and manage patients with familial cancer risk in primary care: a systematic review

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Abstract

This systematic review evaluated the effectiveness of strategies to identify and manage patients with familial risk of breast, ovarian, colorectal and prostate cancer in primary care to improve clinical outcomes. MEDLINE, EMBASE, CINAHL and Cochrane library were searched from January 1980 to October 2017. We included randomised controlled trials (RCT) and non-randomised studies of interventions (NRSI). Primary outcomes were cancer incidence, cancer-related clinical outcomes or the identification of cancer predisposition; secondary outcomes were the appropriateness of referral, uptake of preventive strategies and cognitive and psychological effect. From 11,842 abstracts, 111 full texts were reviewed and three eligible studies (nine articles) identified. Two were cluster RCTs and one NRSI; all used risk assessment software. No studies identified our primary outcomes, with no consistent outcome across the three studies. In one RCT, intervention improved the proportion of genetic referrals meeting referral guidelines for breast cancer (OR 4.5, 95% CI 1.6 to 13.1). In the other RCT, there was no difference in screening adherence between the intervention and control group. However, there was borderline increased risk perception (OR 1.89, 95% CI 0.99 to 3.59) in the subgroup that under-estimated their colon cancer risk. In the NRSI, there was no change in psychological distress in patients at increased familial breast cancer risk, but population risk patients had reduced anxiety after intervention (state anxiety mean change – 3, 95% CI – 5 to – 2). Future studies should have better-defined comparator groups and longer follow-up and assess outcomes using validated tools.

Keywords Primary health care · Genetic predisposition to disease · Breast neoplasm · Ovarian neoplasms · Colorectal neoplasms · Prostatic neoplasms

Introduction

Familial cancer risk increases an individual's life time chance of developing cancer and at an earlier age of onset (Kerber and O'Brien 2005; Paluch-Shimon et al. 2016; Qureshi et al. 2009). A Swedish Cancer Registry study found that cancers with the highest familial proportions (proportion of cases with affected parents/siblings) were prostate, breast and colorectal cancer (Hemminki et al. 2008). As well as being the most

common cancers worldwide, they are associated with the commonest cancer-related gene mutations (Qureshi et al. 2007; World Cancer Research Fund). For instance, BRCA1 mutations increase the risk of breast, ovarian and prostate cancer, whilst DNA mismatch repair gene mutations are associated with Lynch Syndrome (Qureshi et al. 2007).

Familial cancers are usually divided into three categories. For example, the English National Institute for Health and Care Excellence (NICE) categorised breast cancer risk into at or near population (< 17% lifetime risk), moderate (17% to 29%) and high risk (> 30%) (NICE 2017). A 2005 California population survey reported the prevalence of strong and moderate familial cancer risk to be 5% and 7% for breast, 1% and 5% for colorectal and prostate cancer. This risk stratification was based on the proximity of affected relatives and age at cancer diagnosis (Scheuner et al. 2010).

As illustrated above, the definition of familial cancer risk varies in different countries and guidelines. Nevertheless, high risk generally indicates the probability of single gene disorder

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with Mendelian inheritance (Duffy et al. 2013; Qureshi et al. 2007; Scheuner et al. 2010). Conversely, moderate risk may be due to combinations of multiple low penetrance gene mutations with or without shared environmental or behavioural risk factors (Qureshi et al. 2007).

Preventive measures such as surveillance, prophylactic surgery or chemoprevention can reduce cancer incidence and mortality for patients with familial cancer risk (Carbine et al. 2018; Cuzick et al. 2013; Domchek et al. 2010; Duffy et al. 2013). A Cochrane review found that bilateral risk reducing mastectomy decreased breast cancer incidence and death, particularly in women with BRCA1/2 mutations (Carbine et al. 2018). The FH01 study estimated that annual mammogram for women aged 40–49 with moderate familial breast cancer risk (defined as at least 3% risk for this age group) reduced breast cancer mortality by 40% (Duffy et al. 2013). In a 15-year controlled trial, colonoscopy screening at three-year intervals reduced the colorectal cancer rate by 62% and overall mortality by 65% in families with Lynch Syndrome (Järvinen et al. 2000).

For at-risk patients to benefit from these preventive measures, primary care providers play a crucial role. To assess familial cancer risk, primary care providers need to collect a family history; the English NICE guideline suggests using family history tools to collect comprehensive family histories (NICE 2017). Clinical decision support systems can then be used to translate this information into risk strata with evidence-based recommendation on appropriate management, e.g., referral to genetic services for those at high familial risk or reassurance of patients at near population risk (NICE 2017; Paluch-Shimon et al. 2016; U.S. Preventive Services Task Force 2015).

However, it is still unclear if familial cancer risk assessment and management in primary care improve clinically relevant outcome, such as cancer morbidity and mortality. Previous systematic reviews focused on the impact of multifactorial cancer risk assessment tools, the validity of family history tools, specialist risk assessment services and familial breast cancer only (Cleoplat et al. 2018; Hilgart et al. 2012; Qureshi et al. 2009; Walker et al. 2015).

The current systematic review focused on the effectiveness of primary care interventions to identify and manage patients at familial cancer risk, to improve clinical outcomes for breast, ovarian, prostate and colorectal cancers. This will help policy makers decide which familial cancer risk assessment interventions are worth adopting and help researchers identify the gaps in evidence.

Methods

The Cochrane Collaboration's guidance on review of interventions and the PRISMA-P checklist were followed (Higgins and Green 2011; Shamseer et al. 2015). The protocol was registered on PROSPERO in December 2017 (PROSPERO 2017).

Literature search

Databases searched were MEDLINE, EMBASE, CINAHL and Cochrane library. Aligned with the introduction of familial cancer clinics in the late 1980s, the search period was from 1 Jan 1980 to 4 October 2017 (Hilgart et al. 2012). We used controlled vocabulary and free text terms based on the concepts of 'cancer: breast, ovarian, colorectal and prostate', 'familial/hereditary cancer' and 'primary health care'.

With the Zetoc database, we also searched the table of contents within the last 5 years for Journal of Community Genetics, European Journal of Human Genetics, Genetics in Medicine and Public Health Genomics. Other searches included clinical trial registries (U.S. National Institutes of Health (www.clinicaltrials.gov), ISRCTN registry, WHO International Clinical Trials Registry Platform), The Networked Digital Library of Theses and Dissertations, the conference proceedings within the last 5 years for European Society of Human Genetics Conference and American College of Medical Genetics and Genomics annual meetings and the reference list of included studies (see supplementary material 1 for full details of the search strategy)

Study selection

Two authors screened the titles and abstracts (SL and MP/BD) and full texts (SL and MP) independently. Discrepancies were resolved with a third author (NQ). Authors of studies were contacted where clarification were required.

Studies were eligible if published in English and evaluated an intervention that identified and managed patients at risk of familial breast, ovarian, colorectal or prostate cancer. Data must have been presented separately for each cancer type, except breast and ovarian cancer, as BRCA1/2-associated breast and ovarian cancer is a recognised hereditary cancer syndrome (Petrucelli et al. 2010). Randomised controlled trials (RCT) and non-randomised studies for intervention (NRSI) were eligible. Reviews, genetic epidemiology studies with no clinical intervention, stand-alone guidelines, case reports, editorials, qualitative studies, abstracts and studies with no comparator arm were excluded.

Participants included were adults aged > 18 with no previous history of cancer or known cancer genetic mutation. The intervention must have been based in primary care or non-specialist community health service and care managed by primary care providers. We defined primary care providers as health professionals who delivered care to undifferentiated patients as the first contact point in the community. This could be a general practitioner (family doctor or family physician), internal medicine physician or obstetrician/gynaecologist practising in the community (Qureshi et al. 2007).

The primary outcomes were cancer incidence; cancer-related morbidity, mortality and survival; and identification

of cancer predisposition (increased familial risk) as defined by study authors. Secondary outcomes were appropriateness of specialist referrals (as defined by study authors), uptake of preventive strategies and cognitive and psychological effect measured with validated tools.

Data extraction and analysis

Data on study characteristics and pre-specified outcomes were extracted by two reviewers independently (SL and BD/JL) using standardised forms and discrepancies resolved with a third author (NQ). Where there were multiple publications from the same study, the data were grouped together and treated as a single study (Higgins and Green 2011).

Quality assessment

Two authors reviewed the risk of bias for the included studies independently (SL and NQ/SW) with discrepancies resolved by a third author (SW/NQ). The Cochrane Collaboration Risk of Bias tool was used for RCT, and the ROBINS-I tool was used for NRSI (Higgins et al. 2011; Sterne et al. 2016). The GRADE approach was used to rate the certainty of evidence for the included outcomes (Schünemann et al. 2013).

Results

From the initial 11,842 titles and abstracts, we screened 111 full texts for eligibility (Fig. 1). Three studies comprising nine articles were included (Emery et al. 2007; Family Healthware Trial (O'Neil et al. 2009; Acheson et al. 2010; Rubinstein et al. 2011a, b; Ruffin et al. 2011; Wang et al. 2012, 2015); Van Erkelens et al. 2017). Only four outcomes were identified. No studies reported the same outcomes. Three further studies were identified that are ongoing or awaiting publication (ISRCTN 2014; Naicker et al. 2013; Voils 2017). Supplementary material 2 presents the table of excluded studies with reasons for exclusion.

Due to the limited number of included studies with varying study designs and study interventions, meta-analysis was not feasible. The outcomes were presented as a narrative summary. See supplementary material 3 for further details.

Included studies

Table 1 summarised the characteristics of the three included studies. Of these, two were cluster RCTs (Emery et al. 2007; Family Healthware Trial) and one NRSI (uncontrolled before and after study) (Van Erkelens et al. 2017). Two studies were based in Europe and one in the USA. Two studies evaluated interventions for breast, ovarian and colorectal cancer, and one study for breast cancer only. Follow-up duration ranged from

2 weeks to 12 months, with a median follow-up time of 6 months. The average age of patients ranged from 51 to 56. Patients were predominantly white, female and college educated.

All three studies used a bespoke software for familial cancer risk assessment: a clinician pedigree drawing tool based on patient completed family history questionnaire (Emery et al. 2007), a patient facing familial risk assessment tool online or via telephone interview (Family Healthware Trial) and a patient online self-test (Van Erkelens et al. 2017). All three subsequently generated a risk-based action plan: one informed general practitioners who needed genetic referral (Emery et al. 2007), another provided personalised familial risk assessment outcome and prevention plan for patients and all types of primary care providers (Family Healthware Trial), and the final study advised patients with increased risk to consult their primary care providers (unspecified health care professionals) (Van Erkelens et al. 2017).

Two studies used a proactive approach by screening all patients with an upcoming appointment with their primary care provider (Family Healthware Trial) or attending population-based breast cancer screening (Van Erkelens et al. 2017). One study employed a reactive approach and only conducted a familial risk assessment when approached by patients concerned about their cancer family history (Emery et al. 2007).

Primary outcome

No studies identified the review's primary outcome (cancer incidence, cancer-related morbidity, mortality, survival, or identification of cancer predisposition). Although the Family Healthware Impact Trial reported the characteristics of patients with interim cancer diagnosis during the 6-month follow-up period (five intervention and two control patients reported a new breast cancer diagnosis; 17 intervention and 10 control patients reported 'other' cancer; none reported colon or ovarian cancer diagnosis), the authors excluded these patients from the analyses of screening adherence as it was not clear whether the tests or consultations were performed for screening or diagnostic purposes during the intervention period (Rubinstein et al. 2011a).

Secondary outcome

None of the three studies reported the same outcomes. The four secondary outcomes reported were the appropriateness of specialist referrals, uptake of preventive strategies, patients' self-reported risk perception and patients' self-reported anxiety and depression. Details of each outcome were described below. Using the GRADE approach, these outcomes had *low* to *very low* certainty of evidence (Table 2). This is driven by weakness in the study design, leading to the risk of bias (see the *Risk of bias* section).

Fig. 1 PRISMA flow diagram of study selection

Table 1 Summary description of included studies

Author, year	Study design	Country, setting	Participants	Intervention	Comparator	Outcomes
Emery et al. 2007	Cluster RCT	UK, primary care	Patients expressing concern about cancer family history	Lead clinician attended educational session and given access to software that conducts familial risk assessment to inform genetic referrals.	Lead clinician attended educational session and mailed familial cancer guidelines.	1. Proportion of GP referrals consistent with guidelines 2. Proportion of GP referrals assessed to be at increased risk by genetic clinic
Family Healthcare Trial 1. O'Neill et al. 2009 2. Acheson et al. 2010 3. Rubinstein et al. 2011a 4. Rubinstein et al. 2011b 5. Ruffin et al. 2011 6. Wang et al. 2012 7. Wang et al. 2015	Cluster RCT	USA, primary care	Existing patient list or patients with upcoming appointments	Patient received personalised familial risk assessment and prevention messages generated by software.	Patient received standard prevention messages about screening and healthy lifestyle choices.	1. Adherence to cancer screening 2. Cognitive: Patient risk perception
Van Erkelens et al. 2017	NRSI: uncontrolled before after study	The Netherlands, population BC screening programme	Women attending population BC screening	Patient completed FBC risk assessment and received risk status and advice online.	Same patients 2 weeks after initial FBC risk assessment.	Psychological: Patient anxiety and depression (STAI and HADS)

BC, breast cancer; FBC, familial breast cancer; GP, general practitioner; HADS, Hospital Anxiety Depression Scale; NRSI, non-randomised study of intervention; RCT, randomised controlled trial; STAI, State-Trait Anxiety Inventory

Table 2 GRADE evidence profile

Outcome/ cancer	Effect	Number of participants (studies)	GRADE criteria					Certainty in evidence
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
I. Appropriateness of specialist referral: general practitioners' referral letter (Emery et al. 2007)*								
Breast	Proportions meeting referral guidelines OR 4.5 (1.6 to 13.1)	45 practices, 167 patients (1 cluster RCT)	Present	Not applicable	Not serious	Absent	Not applicable	⊕⊕⊕ ^a Low
	Proportions confirmed at increased risk at genetic clinic OR 1.4 (0.6 to 3.5)	45 practices, 111 patients (1 cluster RCT)	Present	Not applicable	Not serious	Present	Not applicable	⊕○○○ ^b Very low
Colorectal	Proportions meeting referral guidelines OR 6.5 (0.5 to 83.7)	45 practices, 101 patients (1 cluster RCT)	Present	Not applicable	Not serious	Present	Not applicable	⊕○○○ ^c Very low
	Proportions confirmed at increased risk at genetic clinic OR 0.2 (0.1 to 0.8)	45 practices, 74 patients (1 cluster RCT)	Present	Not applicable	Not serious	Absent	Not applicable	⊕○○○ ^d Very low
II. Uptake of preventive strategies: improvement in proportion of patients adherent to risk-based screening (Rubinstein et al. 2011a)**								
Breast	Mammography 9% (intervention) vs 7% (control) improvement, <i>p</i> = 0.82	41 practices, 2063 patients (1 cluster RCT)	Present	Not applicable	Absent	Present	Not applicable	⊕○○○ ^e Very low
Colorectal	Colon cancer screening 8% vs 7% improvement, <i>p</i> = 0.95	41 practices, 2016 patients (1 cluster RCT)	Present	Not applicable	Absent	Present	Not applicable	⊕○○○ ^f Very low
III. Psychological: patients' anxiety and distress (Van Erkelens et al. 2017)***								
Breast	State anxiety (STAI) immediately after self-test Increased risk − 2 (− 6 to 2) Population risk − 2 (− 2 to − 1)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕○○○ ^g Very low
Breast	State anxiety (STAI) 2 weeks after self-test Increased risk 3 (− 5 to 10) Population risk − 3 (− 5 to − 2)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕○○○ ^h Very low
Breast	Trait anxiety (STAI) 2 weeks after self-test Increased risk 0 (− 3 to 4) Population risk − 1 (− 2 to − 1)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕○○○ ⁱ Very low
Breast	Hospital anxiety and depression score (HADS) 2 weeks after self-test Increased risk 1 (− 3 to 6) Population risk − 0 (− 1 to 0)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕○○○ ^j Very low

*Effects are adjusted odds ratio (95% confidence intervals) unless otherwise specified

**Effects are difference in screening adherence pre- and post-intervention period, p value for comparison between study arms, adjusting for practice clustering, risk, and baseline adherence

***Effects are mean change from baseline (95% confidence intervals) unless otherwise specified

^a Downgraded by 1 for high risk of bias (allocation concealment, blinding, responder bias), downgraded by 1 as unable to assess inconsistency and publication bias

^b Downgraded by 2 for high risk of bias (allocation concealment, blinding, incomplete outcome (participant non-attendance), responder bias) and imprecision (confidence interval crossing one), downgraded by 1 as unable to assess inconsistency and publication bias

^c Downgraded by 2 for high risk of bias (allocation concealment, blinding, responder bias) and imprecision (wide confidence interval), downgraded by 1 as unable to assess inconsistency and publication bias

^d Downgraded by 2 for high risk of bias (allocation concealment, blinding, incomplete outcome (participant non-attendance), responder bias), downgraded by 1 as unable to assess inconsistency and publication bias

^{e, f} Downgraded by 2 for high risk of bias (randomisation, allocation concealment, blinding, incomplete outcome, selective reporting) and imprecision (no sample size and confidence interval crosses zero); downgraded by 1 as unable to assess inconsistency and publication bias

^{g, h, i, j} Downgraded by 2 for critical risk of bias (non-randomised studies of intervention, confounding, missing data) and imprecision (no sample size calculation), downgraded by 1 as unable to assess inconsistency and publication bias

I. Appropriateness of specialist referrals

Emery et al.'s cluster RCT showed that the use of a risk assessment and decision support software resulted in significantly higher proportion of general practitioners' referral letters meeting the referral guidelines for breast cancer (93% intervention vs 73% control, OR 4.5, 95% CI 1.6 to 13.1) but not for colorectal cancer (99% vs 92%, OR 6.5, 95% CI 0.5 to 83.7) (2007).

After specialist review at the genetic clinic, the proportion of general practitioners' referrals that were confirmed as increased risk was similar for intervention and control for breast cancer (77% vs 70%, OR 1.4, 95% CI 0.6 to 3.5). In contrast, for colorectal cancer, the proportion assessed to be at increased risk by the specialist was lower in the intervention arm (56% vs 85%, OR 0.2, 95% CI 0.1 to 0.8) (Emery et al. 2007).

II. Uptake of preventive strategies

The Family Healthware cluster RCT found that 6 months post-intervention, there was no significant difference in improved adherence between the intervention and control arm for risk-based mammography (improvement in adherence, 9% intervention vs 7% control, $p = 0.82$) and colorectal cancer screening (8% vs 7%, $p = 0.95$). This was also the case for the subgroup of patients who were not adherent at baseline. During the intervention period, there was no difference between study arm in the number of women receiving CA-125 blood test and transvaginal ultrasound for ovarian cancer risk (supplementary material 3) (Rubinstein et al. 2011a).

III. Cognitive effect: patients' risk perception

The Family Healthware Trial did not report this outcome for all patients. However, in the subgroup of patients who underestimated their risk, more of the intervention patients' risk perception became consistent with their risk status at 6 months for colorectal cancer, although this was of borderline significance (17% vs 10%, OR 1.89, 95% CI 0.99 to 3.59). This was not observed for breast or ovarian cancer (Rubinstein et al. 2011a).

IV. Psychological effect: patients' anxiety and depression

Van Erkelens et al.'s NRSI used the State-Trait Anxiety Inventory (STAI) and Hospital Anxiety and Depression Scale (HADS). The analysis of the total study population was not presented. Subgroup analysis by risk status was provided: women told to be at *population risk* for breast cancer had reduced anxiety immediately after self-risk assessment (mean change of state anxiety -2 , 95% CI -2 to -1) and at 2 weeks (-3 , 95% CI -5 to -2). The HADS score remained

unchanged at 2 weeks. For women at *increased breast cancer risk*, there was no consistent change in anxiety and depression (Table 2). The mean score for STAI and HADS were below the levels of clinical significance and similar to those of the general population (supplementary material 3) (2017).

Risk of bias

All three included studies were at high risk of bias (Table 3). For Emery et al.'s cluster RCT, allocation concealment and blinding of participants and clinicians were not possible. The patient's non-attendance at the genetic clinic was 28% (45/162) for intervention and 38% (32/84) for control, contributing to attrition bias. Responder bias was evident from the 74% (125/170) practices that declined to participate. The author commented that this recruitment rate is consistent with similar primary care trials and that practices that were interested in genetic medicine were more likely to participate (2007).

The Family Healthware Trial had no description of the random sequence generation or allocation concealment. From the published study design, there appeared to be no blinding. The participant recruitment rate was low (18%) with high attrition: 20% intervention (542/2650) and 20% control (324/1598) participants withdrew from consent to follow-up. Results for the change in risk perception were only reported for the subgroup who underestimated their risk. The selection of participants who were free of comorbidities led to healthy volunteer bias. The lengthy baseline questionnaire may have altered the behaviour in the control group, reducing the intervention effect.

In Van Erkelens's NRSI, there was no control of the confounders such as age and sociodemographic factors. Finally, 35% (101/287) of patients at baseline were lost to follow-up (2017).

Excluded studies: patients with a personal history of cancer

Two studies were excluded for having participants with a personal history of cancer but met other eligibility criteria: one cluster RCT and one before-after study (supplementary material 4) (Wilson et al. 2005; Wilson et al. 2006; Orlando et al. 2011; Orlando et al. 2013; Wu et al. 2013; Orlando et al. 2014; Orlando et al. 2016). Overall, there were 4 (22/588) to 8% (23/282) of participants with a personal history of cancer. Similar to the main review, the secondary outcomes reported were the appropriateness of referrals and uptake of preventive strategies. However, the findings were different from the main review: intervention had no impact on the appropriateness of genetic referrals (Wilson et al. 2005; Wilson et al. 2006), but there was improved preventive uptake of surveillance (breast magnetic resonance imaging) and gynaecology assessment for

Table 3 Risk of bias table

RCT (Cochrane risk of bias tool)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall bias
Emery et al. 2007	+	–	–	+	–	+	?	–
Family Healthcare Trial	?	?	–	–	–	?	–	–
NRSI (ROBINS-I risk of bias tool)	Confounding	Participants selection	Classification of intervention	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall bias
Van Erkelens et al. 2017	Critical	Serious	Moderate	Low	Serious	Moderate	Moderate	Critical

+, low risk; ?, unclear risk; –, high risk

ovarian cancer screening (supplementary material 3) (Orlando et al. 2016).

Discussion

Main findings

This is a comprehensive systematic review on the long-term clinical impact of primary care assessment and management of patients with familial breast, ovarian, prostate and colorectal cancer risk. Our review spanned the past 37 years and identified three studies. None of these studies assessed the review's primary outcome: cancer incidence, morbidity, mortality, survival or identification of cancer predisposition. The follow-up period (2 weeks to 12 months) would have been too short to identify the primary outcomes. For instance, a large community cohort study estimated that a period of 5 years is required for 1000 colorectal cancer cases to be identified from a sample size of 500,000 recruits (UK Biobank 2007).

The secondary outcomes predominantly evaluated short-term outcomes of process and psychological measures; these evidences were of limited quality due to weakness in the study design. The strongest evidence emerged from a cluster RCT, demonstrating improved appropriateness of general practitioners' genetic referral letters for patients at familial breast cancer risk. However, this still had a low GRADE level of certainty (Emery et al. 2007).

Comparison with previous systematic review

To our knowledge, no systematic review has evaluated the clinical impact of familial cancer risk assessment and management by non-specialist primary care providers in primary care settings. The previous four reviews covered broader areas of multifactorial cancer risk assessment tools, the validity and nature of cancer family history tools and familial breast cancer risk assessment by genetic services (Cleophas et al. 2018; Hilgart et al. 2012; Qureshi et al. 2009; Walker et al. 2015). All of these reviews shared some similar findings to the current review.

Walker et al. reviewed RCTs that evaluated the impact of cancer risk assessment tools in primary care. They identified 11 trials compared with three trials in our review, as we focused on familial cancer risk assessment, limited the types of cancer to those known to have a genetic component, grouped papers from the same study as a single trial and included only outcomes measured with validated tools. Despite focusing on familial cancer, our review findings were consistent with Walker et al.'s, specifically, there is limited evidence available on the effectiveness of cancer risk assessment on the uptake of screening and risk assessment does not increase psychological distress (2015).

Two reviews identified between 18 to 29 cancer family history tools used in primary care; a third of the tools provided risk stratification and action plan for patients or clinicians (Cleopha et al. 2018; Qureshi et al. 2009). Compared with structured genetic interviews, Qureshi et al. found that the tools demonstrated a 75–100% agreement of risk stratification (2009). In Cleopha et al.'s review, the validation methods and results were inconsistent. There was no formal evaluation of clinical utility but similar to our review, Cleopha et al. suggested potential benefits: improved quality of genetic referrals, increased compliance with cancer screening and no increase in psychological distress (2018).

Finally, both our review and Hilgart et al.'s Cochrane review suggested that familial cancer risk assessment may improve the accuracy of patients' risk perception and anxiety, even though the Cochrane review only included familial breast cancer services delivered by genetic specialists (2012).

Strength of the review and included studies

The strength of this systematic review is the robust search strategy and focused eligibility criteria. Restricting the evidence to the highest level of experimental study design but recognising the paucity of literature in this field, we expanded the inclusion criteria beyond RCT to NRSI. Two independent reviewers conducted the eligibility screen, data extraction and risk of bias assessment. To help interpret the results, we conducted a rigorous assessment of the evidence quality using established methods from Cochrane and GRADE (Higgins et al. 2011; Schünemann et al. 2013; Sterne et al. 2016).

Two of three included studies employed cluster RCT design, which is suitable for studies in primary care where cross-contamination of participants in the same primary care practice can dilute the effect of the intervention (Emery et al. 2007; Family Healthware Trial). Included studies also used validated measures for psychological outcomes: in Van Erkelen's study, the impact of familial cancer risk assessment on patient psychological outcomes was measured using STAI and HADS (2017).

Weakness of the review and included studies

Due to the low number of included studies with variable study designs and interventions, a quantitative synthesis was not feasible. The study design requirement of an intervention study and a comparator group increased the review's robustness but limited the number of included studies. Further, the risk of bias was high across all studies; hence, the results need to be interpreted with caution.

Studies that combined data for patients with and without previous cancer history were excluded. As the aim of the review was to identify the impact of intervention on cancer mortality and morbidity, it was decided that participants with

cancer history would not be included. Similarly, studies that combined outcome data for different cancers that could not be disentangled were excluded.

It was difficult to have a true comparator that reflected current usual care. In Emery et al.'s RCT, the lead clinician in both the intervention and control arm received an education session on cancer genetics, although continuing medical education could be considered as part of usual practice (2007). In the Family Healthware Trial, the control arm had a lengthy baseline survey, which may have had an intervention effect (Rubinstein et al. 2011a). Finally, studies predominantly included white educated females, limiting the findings' generalisability to the wider population.

Implication for future research

More studies are needed in primary care settings where the majority of health consultations take place (NHS England 2013). Current studies are not generalizable to the wider population; in particular, future studies need better representation from deprived and ethnic minority groups. Future studies should also incorporate robust comparator groups and use validated outcome measures. Current studies often do not state the participants' age range or personal history of cancer in the eligibility criteria, necessitating correspondence with the author. We suggest future studies should also make these inclusion criteria clearer.

Clinical trials with longer follow-up will allow for evaluation of clinical impact such as cancer-related outcome, but with relatively low prevalence of cancers with inherited predisposition, this would require studies with large sample sizes. Although classified as lower level of evidence, prospective cohort studies with robust design and longer follow-up may provide good quality clinical outcome data.

It has been 30 years since the introduction of familial cancer clinics, and since then there has been great advances in preventive management of familial cancer risk. We still need large well design studies to help us determine if systematic familial cancer risk assessment should be introduced as a routine case-finding approach in primary care.

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Compliance with ethical standards

Conflict of interest Nadeem Qureshi is a member of the NICE Guideline Development Group for Familial Breast Cancer and the

Advisory Board for Journal of Community Genetics. Siang Ing Lee, Mitesh Patel, Brittany Dutton, Stephen Weng and Jocelyn Luveta declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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