Title: Genetic cancer risk assessment in general practice: systematic review of tools available, clinician attitudes and outcomes for patients.

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Abstract

Background The growing demand for cancer genetic services has led to suggestions for the involvement of general practitioners. How and in which conditions they can be involved need to be defined and there may be important barriers to implementation.

Aim To review the tools available, clinicians' attitudes and experiences, and the effects on patients of genetic cancer risk assessment in general practice.

Design and setting Systematic review

Method: Searching MEDLINE/Ovid, EMBASE, Cochrane Library, CINAHL and PsycInfo databases and grey literature from 1996 to December 2017. Study quality was assessed with relevant Critical Appraisal Skills Programme (CASP) tool checklists and a narrative synthesis of fiindings was conducted.

Results: 40 studies were included. There was a variety of tools available for genetic cancer risk assessment in general practice, both testing and screening, principally for breast, breast-ovarian and colorectal cancer risk. Practitioners often reported low knowledge and confidence to engage with genetic cancer risk assessment, and despite barriers of time pressure, and worries about confidentiality especially concerning impact of results for family members, some recognised potential importance relating to such a development of the GP's role. Studies found few reported benefits for patients. Concerns about negative impacts on patient anxiety and cancer worries were largely not borne out.

Conclusion General practitioners may have a potential role in identifying patients at risk of hereditary cancer that can be facilitated by family history tools. There is currently insufficient evidence to support implementation of population-wide screening for genetic cancer risk within the competing demands of general practice.

How this fits in

Cancer incidence is rising across the world and genetic risk is a significant contributor. Cancer risk screening and testing is a potential role for General practitioners (GPs). Several tools are available but none is superior. GPs identify needs for more education to improve their knowledge and confidence regarding cancer genetic risks before wider implementation.

INTRODUCTION

According to the World Health Organization, one in six deaths is due to cancer and number of new cases is expected to rise by 70% over the next two decades. In UK, 5% of patients with bowel cancer have a family history of bowel cancer, 3% of breast cancers are associated with inherited faulty genes and 10% of melanoma cases are also associated with a family history of the disease[1]. In those cases and other cancers in which genetic risks are involved, earlier detection and treatment could reduce cancer mortality.

There is an increasing demand for cancer genetic services and the potential importance of involving general practitioners is recognized[2]. Patients commonly seek out information regarding their risks and clinicians need to be able to respond to this demand. Direct-to-consumer testing is also increasingly available[3]. In addition to such 'testing', when presented or accessed by patients, there are also potential opportunities for systematically or opportunistically screening attendees in general practice, perhaps based on increased familial risk (see Box 1). However, the ways in which general practitioners might respond to such trends, particularly within the context of increasingly time- and resource-constrained everyday practice have not been effectively established[4].

Family medical history is commonly used in general practice and could be regarded as a genetic screening strategy[5,6]. This tool needs to be developed and standardized to optimize health outcomes in those at risk of inherited cancer. General practitioners are potentially well placed with access to longitudinal comprehensive health records and their focus on family to recognise individuals at risk[7,8]. In the UK (National Health Service), a patient is eligible for a genetic test if: an inherited faulty gene has already been identified in one of the patient's relatives or, there is a strong family history of cancer in his/her family. In these scenarios, patients are referred to specialist genetics services (33 across UK) for consideration of further genetics tests.

Carroll et al suggest GPs have a potential role as gatekeepers in genetic cancer risk assessment (testing and screening) [9]. However, general practitioners may face challenges regarding this expanding role due to a lack of clinical genetics knowledge, perceived lack of confidence in the domain, and time constraints[3,10–15]. There may be difficulties in considering genetic cancer risk in routine primary care visits, especially as acute illness is often the priority, and other (e.g. cardiovascular) preventive measures have greater prominence than genetic risk of cancer. Testing or screening, leading to preventive measures, will be more successful if cancer genetic

risk is assessed in large segments of society, not only those who are better informed and actively consult their general practitioner.

This study aims to examine and review the tools available, clinicians' attitudes and effects on patients of genetic cancer risk assessment in general practice. From this we aim also to discuss potential roles that general practitioners might play in genetic cancer risk assessment and whether systematic screening may be feasible and effective in general practice.

To meet these aims, the following research questions were addressed:

1) What tests (medical procedure to detect those at high risk) and tools (support or format for those procedures) are available for identifying increased genetic risk of cancer in general practice?
2) What are clinicians' attitudes towards screening or testing the population groups for genetic cancer risk?
3) What are the levels of patient knowledge, satisfaction and anxiety in relation to tests and communication by a general practitioner about cancer risk? What are patients' risk perceptions following screening or testing for genetic cancer risk in primary care?
4) What are the outcomes of referrals to secondary care following genetic cancer risk identification in general practice?

METHOD

The following databases were electronically searched: MEDLINE/Ovid, EMBASE, The Cochrane Library, CINAHL and PsycInfo from 1996 to December 2017. The grey literature was also searched via OpenGrey and The Health Management Information Consortium (HMIC) database (also to December 2017). The search strategy was adapted to each database, with layers of terms around: general practice, cancer, genetics, testing and tools, attitudes, outcomes and effectiveness. Hand searching of key journals (Family Practice, Genetics in Medicine and British Journal of General Practice) and reference lists of relevant papers was also conducted. The search outputs were downloaded and merged into Zotero, where duplicates were removed.

Inclusion criteria:

- Study population:

Studies involving adults (age 18 and above), of either gender, considered to be at high risk of hereditary cancer were eligible for inclusion.
As advocated by Scheuner et al[16] high-risk family history characteristics include the presence of multiple affected first-degree relatives (FDR) or a FDR with age of onset of 50 years or less.

And

- Intervention:

Strategies used for cancer genetic risk testing or screening within general practice. As suggested by Olesen[17], general practice (known as family practice in some countries) was defined as: “the general practitioner is a specialist trained to work in the front line of a healthcare system and to take the initial steps to provide care for any health problem(s) that patients may have.”
Or

- Studies assessing outcome variables;

Clinician attitudes to tests for cancer genetic risk assessment, patient outcomes following such tests or the outcomes of referrals to secondary care after the intervention in primary care.

- Study design

A range of study designs was included to address the different questions within the review: qualitative, focus groups, semi structured interviews, observational / cross-sectional, cluster randomised controlled trial, implementation studies.

Exclusion criteria:

- Study not based primarily in general practice or separate data relating to GPs not presented
- Non-cancerous conditions only
- Cancers without a known familial component
- Test activity described only i.e. number of tests undertaken
- Population based screening application only (not involving primary care)
- Non-English language studies

We wanted to investigate scenarios involving either the identification of patients at high risk of hereditary cancer in opportunistic health visits with their general practitioner, or potential broad systematic or opportunistic screening of patient populations in general practice to identify those at a high genetic cancer risk.

Assessment of study inclusion

The selection criteria were initially applied independently to all titles and/or abstracts by BM or FL. Once narrowed down to references that were potentially relevant, full-copy papers were also assessed by a third reviewer (AE) to determine inclusion and exclusion. Disagreements were resolved through discussion.

Data extraction

BM or FL extracted all data onto an excel spreadsheet, recording the study title, aims, design, setting, participants, inclusion and exclusion criteria, nature of intervention (where applicable), methods, outcome measures, analysis, key findings and limitations.

Assessment of methodological quality

The quality of all eligible studies was assessed using the relevant Critical Appraisal Skills Programme (CASP) tool checklists[18], dependent on study design for qualitative studies or trials. As there is no CASP tool for observational cross-sectional studies, common points included within the checklists for observational cohort and case-control study designs were selected and combined.

Data Synthesis

Due to the heterogeneous nature of the studies included, a narrative synthesis was undertaken to collate the evidence relating to each of the research questions [19]. Specific sub-groups of studies were assessed and are presented regarding testing and screening for genetic cancer risk.

RESULTS

Description of studies

Study selection is summarised in Figure 1. A total of 40 articles was included. Sixteen of these were observational: cross-sectional studies[2,20–32] and two retrospective[15,33]. There were six qualitative[4,9,34–37], including four semi structured interviews[4,34,35,37]. There were 13 intervention studies[38–50]: three validation studies[38,47,50], one before-after[49], three hybrid implementation[42,45,48], one comparison against standard care[40], two comparative[41,44] and three observational studies[39,43,46]. Three studies were cluster randomised controlled trials[51–53] and two descriptive feasibility studies[54,55].

Populations studied

All studies involved both male and female patients or their general practitioners, except for one study with only female patients and female practitioners. Fourteen studies were carried out in the UK[2,4,20–22,25,34,41,44,49–51,54,55], 17 in North America[9,15,23,27–31,35,37,39,42,43,45,48,52,53], two in South America[38,47], two in Australia[33,36]. The remaining four were conducted in EU[40,26,46,32] (Netherlands, Belgium, Spain) and one study reported data from four countries across Europe[24], namely UK, France, Germany and the Netherlands.

Methodological quality

The details of studies are contained in Table 1. The included studies were generally well designed and reported. Recruitment of participants was suitable, and methods and analyses were described clearly. Studies varied in the generalizability of their findings to populations beyond those studied.

Screening

1) Method of screening

A variety of tools, which could be used in general practice for screening genetic cancer risk was described[15,29,30,38,39,42–45,47–50,52–55]. Examples of family history collection tools include Family Healthware[52,53], a self-administered web-based tool, and FHS-7[38] which comprises seven questions, both cover family history of breast, ovarian and colorectal cancer, MeTree[42,45,48] is a computerized tool stratifying risk of hereditary cancer syndromes, i.e. breast, ovarian and colorectal cancer, to be completed at routine visits and to support clinical decisions. Two studies examined an office screening form for familial breast cancer alone[29,30], whilst Walter et al[50]

developed a family history questionnaire assessing breast and colorectal cancer, to be completed at a planned data collection session in the general practice surgery. In 2013, The US Preventive Services Task Force updated their recommendations and recognised The Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool and FHS-7 as suitable for primary care providers to screen women and suggest testing for BRCA1 or 2 genes[56].

The Gail risk model provides the basis for a questionnaire implemented by Owens et al, and which identifies patients deemed high risk for breast cancer. Four studies described simple postal questionnaires[44,49,54,55], with Leggatt et al[49,54] screening for genetic risk assessment of breast and colorectal cancer, House et al[55] identifying those at risk of colorectal cancer alone and Qureshi[44] collecting non-specific cancer family history information. Biswas et al developed and tested a two-stage approach with three simplified versions of BRCAPRO to reduce the genetic counselling burden in general practice[15]. Flória-Santos[47] described a self-reported cancer family history as a tool to detect breast, prostate, and colon cancer, potentially also useful to screen other hereditary cancer syndromes.

2) Attitudes

Of the five studies examining GP attitudes, three addressed attitudes towards the process of screening patients for inherited cancer risk in general[27,28,37] and two studies reported attitudes towards specific screening tools[43,45]. Gramling et al[28] reported that 87% of 300 GPs surveyed agreed that screening patients for inherited cancer risk was important to their practice but only 62% were confident in their own screening effectiveness. Caroll et al[37] showed that primary care providers are prepared to discuss personalised medicine. Another study by Gramling et al[27], with a small sample of US family physicians, showed that the importance physicians placed on screening was positively related to their beliefs that a high-risk genetic test result would motivate behaviour change in patients. The methods for screening in question were not described[27,28].

In contrast, Owens et al[43] discussed that some providers were concerned with the accuracy of the Gail model formula in identifying high risk patients. Furthermore, there were worries over the time needed to counsel patients newly determined to be at high risk and about liability for not successfully providing risk counselling.

Wu et al[45] showed that physicians within two primary care clinics initially felt that they were already collecting high quality family histories and that MeTree would

negatively impact their workflow. They believed that patients would redirect discussions away from physician priorities to instead focus on MeTree recommendations. However post-MeTree integration, 86 % of physicians believed the tool improved the way they practiced medicine, making practice easier and none reported that it adversely affected their workflow[45].

3) Patient outcomes

Six studies assessed patient outcomes following the various methods of screening for genetic cancer risk[29,30,39,45,49,53]. There was some evidence that screening can lead to more accurate risk perceptions with risk feedback following an office screening form, with greater odds of a patient correctly rating their breast cancer risk as "high" in those who had a first degree relative with breast cancer[30]. Wang et al found that in comparison to control patients, those who underestimated their risk and who were screened using the Family Healthware tool, increased their perceptions of colon cancer risk, but not regarding breast or ovarian cancer[53]. However, Baer et al[39] found that a higher percentage of patients who had been screened via YHS (Your Health Snapshot) reported their perceived risk of colon cancer to be above average (possibly incorrectly) compared to the control group. Wu et al[45] found 85% of 1,184 patients believed MeTree generally raised their awareness of both their personal and family health risk, changing the way they think about health.

One study also showed that risk feedback following screening was associated with lower perceived severity of breast cancer but not with the perceived likelihood of developing breast cancer in the future[29]. Gramling et al[29] also found that patients who had had family medical history screened recently were less likely to be worried about developing breast cancer. This association was present even in those at high risk, although it was stronger for women with a lower risk family history. In contrast, Laggatt et al found that completing a screening questionnaire and receiving an assessment of high genetic risk had no significant impact on general anxiety and cancer worries[49].

4) Outcomes of referrals

Only one study[52] assessed the effectiveness of referrals following screening for genetic cancer risk. Rubinstein et al[52] found that in those at high risk, consultation rates with genetic specialists did not differ between the group that completed Family Healthware and the control group. Furthermore, both groups equally increased their adherence to risk-based colon cancer screening and mammography schedules.

Testing

1) Available tests and tools

Eight tools were described that could be used in general practice for assessing a genetic risk of cancer. These tools all incorporated family history into their assessment and some included further decision support and recommendations. The Gail model[43], MeTree[42,42,45,48] and FHS-7[38] were also used for testing. The GRAIDS[20,51] (Genetic Risk Assessment in Genetics) software provides risk estimates of breast, ovarian and colorectal cancer. RAGS[34,41] (Risk Assessment in Genetics) also addresses familial breast and ovarian cancer and YHS[39] (Your Health Snapshot) calculates inherited susceptibility to colon, lung, breast and prostate cancer. The set of GP guidelines by de Bock and al[40] assesses breast cancer risk and Qureshi et al's FHQ[44] (family history questionnaire), identifies the presence of relatives with cancer in general.

In relation to genomic tests, four studies reported testing for inherited susceptibility to breast cancer[23,24,26,31], and one study included ovarian cancer[31]. Another study related to predictive testing more broadly[9]. The remaining studies referred to the use of a standard family history for identifying individuals at risk of hereditary breast cancer[21,22,25,29,43] and non-specific cancer[2,4,23].

2) Clinician attitudes

A range of views of general practitioners to the genetic cancer risk assessment and testing was evident. Overall, GPs considered genetic risk assessment to be a potentially important role for them[2,9,24–26,37], but the extent to which they believed they should be involved with genetics varied. Genetic counselling of patients in regard to their risk and making management decisions was thought to be less appropriate for GPs, whilst providing emotional support following testing was acknowledged to be part of their job[2,21,23,25,26].

General practitioners admitted that they found assessing genetic risk difficult[34,37] and felt uncomfortable when doing so because of their lack of knowledge[2,4,22]. For instance, Hapgood et al[22] showed 89.5% of GPs included in their study incorrectly categorized a low-risk breast cancer family history as either moderate (52.9%) or high (36.6%) risk. General practitioners also lacked confidence in their ability to interpret genetic test results and explain them to patients[2,4,21,22,34]. Furthermore, inadequate skills in taking an appropriate family history were highlighted, with GPs often failing to get sufficient information from patients to appropriately assess their

risk[4,23,24]. Significant proportions of GPs were unfamiliar with their local cancer genetics guidelines and knew little of the services that were available to them[25,34].

From the studies included, it appeared that clinicians were commonly also not confident in discussing the benefits, risks and limitation of genetic testing with patients[2,21,37]. They were concerned by the unnecessary anxiety caused by the process of genetic testing itself, in addition to an increased risk result being received by patients[4,9,20,25,32]. The belief that decreased-risk results would create a false sense of security was also expressed by some GPs. Another further theme that arose was about ethical implications and fears of legal repercussions after genetic tests[9,44]. This particularly derived from concerns that when a positive result from testing had implications for patients' families, this generates concerns over patient confidentiality and how best to inform other family members of their risk[9].

Overall, GPs expressed concern regarding the validity of genomic testing and its clinical utility. Time constraints were a further reason that practitioners gave for not being able to sufficiently counsel patients regarding the benefits and risks of genomic testing or being able to interpret test results sufficiently[2,20,34,43,45]. Some GPs believed that they needed education[37] before exploring an expanded role, but studies conflicted for the intentions of GPs in seeking further education[4,21,31]. For example, Walter et al[25] reported that only a third of practitioners had attended education about risk management for breast cancer in the last three years.

Table 2 summarises main findings regarding clinicians' attitudes towards screening and testing.

3) Patient outcomes

Data about patient knowledge, satisfaction and anxiety in relation to tests and risk communication were limited. For the GRAIDS software, there were no significant differences in knowledge scores, but patients referred from intervention practices had significantly lower cancer worry scores[51]. There was also no difference in mean risk perception, although there was a non-significant trend towards more accurate risk perception, with fewer intervention patients overestimating their risk at the point of referral[51].

4) Outcomes of referrals

There were few data evaluating the effectiveness of referrals to secondary care, following the identification of high genetic risk of cancer in general practice. One

study[43] reported that of the patients referred to the breast centre after a high-risk consultation, only half actually attended for their visits. A retrospective audit in Australia found that GPs referred the majority of patients to the genetics service and were also the most likely to refer inappropriately[33].

DISCUSSION

Summary

There are several tools available to GPs that can enable them to identify genetic risk of cancer. Most of these involve a family history component, as an effective way of determining a patient's risk of hereditary cancer. Regarding our review questions, there was most evidence about clinician attitudes to cancer genetics, whereby GPs consider the assessment of genetic risk to be a potentially important job for them. Lack of confidence and knowledge may be reasons for their reluctance to undertake an expanded role beyond that of a 'gatekeeper'. General practitioners were worried about the impact of genetic risk assessment on patient anxiety[32], particularly if discussions with whole families would then be required. Furthermore, their ability to adequately explain risk and its implications within short routine appointments was raised as a concern. The results regarding patient outcomes show that there may be a link between genetic risk assessment in primary care and lower cancer worry in patients, but there were not enough data to accurately describe the relationship in the general practice setting.

Strengths and limitations

A comprehensive search strategy was developed for high recall (sensitivity), with a range of databases, grey literature and hand searches of reference lists conducted. We included studies of various designs in order to gather evidence that addressed all of our questions. There was considerable heterogeneity in the results, making statistical analysis unfeasible and a narrative synthesis was conducted. Our inclusion criteria were applied strictly, with a particular effort made only to include studies that specified results from general practice. The main weakness of this literature review is the limited number of studies that were identified for our review. The heterogeneity of outcomes reported adds further to difficulties in drawing conclusions. We recognise that the nature of primary care is likely to vary across the many countries in which the included studies were conducted. This is particularly the case in North America (concerning "family medicine", which is the equivalent of general practice in Europe), from which almost half of the studies derived. Knowledge about genetic cancer risk and referrals have dramatically changed over the 20 years period[13] covered by those studies reviewed. We also recognize that the studied population is a sub-population in primary care. Nevertheless, this review still highlights where evidence is lacking.

Comparison with existing literature

Many studies have shown that GPs lack confidence in their skills involving cancer genetics[2,3,57]. Our results regarding clinician attitudes towards cancer genetics are similar to those of Mathers et al[12], who reported GPs' resistance to clinical genetics in general. They too showed that GPs believed genetic conditions required complex knowledge that should be covered by specialist services, as they were worried about the accuracy of their knowledge. A review by Emery and Hayflick[7] in 2001 identified family history as important and that GPs needed to gain generic knowledge and skills in the ascertainment of genetic cancer risk. Our review confirms the current evidence that clinicians' confidence in their knowledge is usually sub-optimal.

McClain et al[58] investigated six family history screening protocols for breast and/or ovarian cancer by applying them to family histories taken from four cohorts of women in a variety of settings. They showed that each of these protocols used alone gave too many screen-positive results, but when all six protocols agreed, there was a more acceptable screen-positive rate. Similarly, if some of the genetic cancer risk screening tools identified in this review were compared directly, a singular composite screening tool including key items, could potentially be identified.

Implications for practice and research

Advances in genetic medicine were expected to lead to a shift towards general practice being more involved with provision of genetic services. General practitioners are potentially important in identifying patients at increased risk of hereditary cancers to ensure suitable subsequent management. The value of taking a comprehensive family history should not be overlooked by clinicians, together with the many other tools identified in this review that could potentially be used in practice. None of the tools identified can be recommended for use over another at this stage, but improving clinician awareness of their existence could support future implementation. Being able to use one of these tools also implies being able to discuss advantages and disadvantages of such screening and testing and results with patients. This is a challenge also concerning test results that may be brought to GPs after direct-to-consumer tests (e.g. 23andme.com). There is little evidence that GPs have the combined knowledge, confidence, skills, experience or capacity to do this in usual practice.

Further studies are needed to evaluate patient outcomes, particularly psychological impact, of genetic cancer risk screening, particularly if it is to be offered routinely to patients in general practice. Moreover, it is important to consider acceptability of such screening to patients in primary care. Research with hard-to-reach groups who

may be less likely to take up screening when offered is also needed.

General practitioners have a potential role in identifying patients at risk of hereditary cancer, however family history-taking practices are often inadequate to assess risk. Consequently, several tools have been developed to help, facilitate and improve genetic risk assessment in general practice. But, at this current point in time, it is difficult to support the adoption of routinely available testing or population-wide screening practices within primary care. Before the implementation of such genetic risk assessment tools is recommended in practice, further well-conducted studies are needed to provide evidence of their benefits, particularly on patient outcomes. General practitioner knowledge and confidence regarding cancer genetics are barriers that must also be improved if they are to consider an expanded role.

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