

Clinician-Reported Barriers to Implementing Breast Cancer Chemoprevention in the UK: A Qualitative Investigation

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Key Words

Consolidated Framework for Implementation Research · Chemoprevention · Breast cancer prevention · Preventive therapy · Qualitative investigation

Abstract

Aims: The use of tamoxifen and raloxifene as preventive therapy for women at increased risk of breast cancer was approved by the National Institute for Health and Care Excellence (NICE) in 2013. We undertook a qualitative investigation to investigate the factors affecting the implementation of preventive therapy within the UK. **Methods:** We recruited general practitioners (GPs) (n = 10) and clinicians working in family history or clinical genetics settings (FHCG clinicians) (n = 15) to participate in semi-structured interviews. Data were coded thematically within the Consolidated Framework for Implementation Research. **Results:** FHCG clinicians focussed on the perceived lack of benefit of preventive therapy and difficulties interpreting the NICE guidelines. FHCG clinicians felt poorly informed about preventive therapy, and this discouraged patient discussions on the topic. GPs were unfamiliar with the concept of preventive therapy, and were not aware that they may be asked to prescribe it for high-risk women. GPs were reluctant to initiate therapy because it is not licensed, but were willing to continue a pre-

scription if it had been started in secondary or tertiary care. **Conclusions:** Barriers to implementing preventive therapy within routine clinical practice are common and could be addressed by engaging all stakeholders during the development of policy documents.

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Background

Breast cancer is the most commonly diagnosed cancer in developed countries, and incidence is increasing worldwide [1]. Treatment advances have improved survival [2, 3], but primary prevention can play a role in reducing disease burden. Preventive therapy using Selective Oestrogen-Receptor Modulators (SERMs) such as tamoxifen and raloxifene can reduce incidence of breast cancer by 30% or more among higher-risk women [4]. SERMs also increase the risk of a thromboembolic event, endometrial cancer, and menopausal side effects. A meta-analysis reported that 16% of women accepted the offer of preventive therapy [5], but most were US studies and initiation in the UK may be lower [6]. Uptake to preventive therapy trials is higher than initiation rates observed in clinical settings [5].

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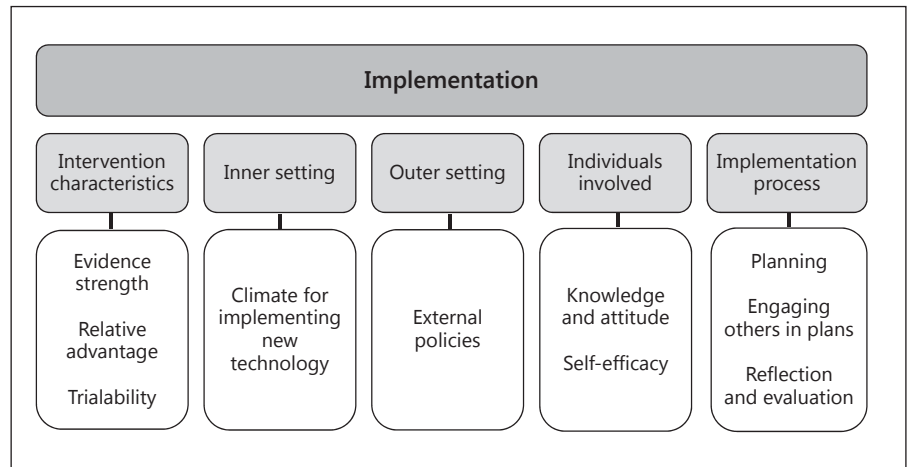


Fig. 1. Overview of CFIR as applied to preventive therapy. See table 1 for detailed descriptions of themes and sub-themes.

In 2013, the UK National Institute for Health and Care Excellence (NICE) approved the use of tamoxifen and raloxifene for women at increased risk due to their family history [7]. Several UK genetics and family history centres were involved in the IBIS-I trial that provided data to support this decision [8]. However, patient enrolment was between 1992 and 2001, meaning many clinicians are unfamiliar with tamoxifen and do not have experience discussing its use with patients. Furthermore, not all UK centres were involved in the IBIS-I trial, and the barriers to implementing the NICE guidelines experienced by these clinicians are largely unknown.

A national survey in the US reported that 27% of physicians had prescribed tamoxifen for breast cancer prevention in the last year [9]. However, an Australian study suggested opportunities to discuss preventive therapy may be being missed, with <60% of relevant consultations including a discussion about chemoprevention [10]. There have been few attempts to understand clinician attitudes. A focus group study in Australia in 2009 reported a degree of confusion over the eligibility of specific patient groups, with some clinicians expressing greater confidence in discussing preventive therapy with carriers of deleterious BRCA1 and BRCA2 mutations, despite poor evidence in this group [11]. Clinicians recognised their limitations in knowledge, and this affected their willingness to discuss it with patients. The status of tamoxifen as an unlicensed medication was also a barrier to implementing preventive therapy. Although UK general practitioners (GPs) prescribe ‘off-label’ medications in other contexts, their willingness to offer tamoxifen and raloxifene for the primary prevention of breast cancer is not known [12–14].

Only a small proportion of medical innovations and technologies result in changes to routine clinical practice [15], and there is wide variation in the rates of implementation between clinicians and healthcare organisations [16]. Barriers to implementation may exist at multiple levels, including at the patient, provider, organisation and policy stages [17]. Implementation science models have been developed to explain why medical innovations are not introduced into practice by incorporating factors across these levels [18]. These models could explain why preventive therapy is poorly accepted by both clinicians and patients in routine clinical practice.

The Consolidated Framework for Implementation Research (CFIR) is a meta-theoretical model comprised of common constructs from a range of implementation science theories [18]. The CFIR outlines five domains that affect the likelihood of a clinical guideline or medical innovation being incorporated into routine care, each of which is composed of sub-themes (fig. 1; table 1). Qualitative enquiry with key stakeholders is needed to identify which of these domains is important in the context of implementing preventive therapy. The CFIR is supported by findings from a meta-review of 12 systematic reviews, which found evidence for its major themes in the context of implementing clinical guidelines [19]. The model has also received support from a study investigating factors affecting the prescription of new medications among rheumatologists [20]. Identifying the most serious challenges to implementation using models such as the CFIR can help to inform future healthcare policy.

Ensuring preventive therapy is adequately prescribed in the NHS is a priority of the Independent Cancer Taskforce [21]. Incorporating the perspective of key stake-

holders can identify the precise levels and contexts in which barriers occur, allowing quality improvement measures to be put in place. We used semi-structured interviews to investigate the barriers to implementing breast cancer preventive therapy within a UK clinical setting among GPs and clinicians caring for women with increased risk of familial breast cancer.

Methods

Management of People at Risk of Breast Cancer

The management of women at increased risk of breast cancer in the UK National Health Service involves primary, secondary and tertiary care services and follows NICE guidance [7]. The most common management pathway is for patients to present to their GP because of concerns about their risk of breast cancer. Women meeting NICE referral criteria are seen in specialist family history clinics (FHCs), clinical genetics services or breast clinics, depending on local protocol. Moderate-risk women (17–30% lifetime risk) and high-risk women ($\geq 30\%$ lifetime risk) are offered annual mammography, and some clinical groups can access MRI surveillance [7]. There is no formal established pathway for the prescription of preventive therapy. For newly referred patients, preventive therapy is discussed during the initial appointment within secondary or tertiary care. For patients already registered with FHCs and genetics services, preventive therapy is discussed during follow-up appointments.

Sample of Clinicians

An overview of our research programme was presented at a national clinical genetics research meeting, a national breast physician meeting and two local multidisciplinary team meetings. A request was made for clinicians to take part in a 30- to 40-min interview on the topic of breast cancer preventive therapy. This approach was taken to purposively recruit clinicians with different levels of experience and with backgrounds in different disciplines. Inclusion criteria were having a patient caseload and working in a clinic where breast cancer preventive therapy could be discussed with patients, even if it was not current protocol. Family history and clinical genetics clinicians (herein referred to as FHCG clinicians) were either breast physicians or clinicians, family history nurses, nurse practitioners, clinical geneticists, genetic counsellors or surgeons. Those recruited were from the South-East of England, the Midlands and Yorkshire. GPs were paid £50 to participate and were asked to contact the lead investigator (S.G.S.) if they were interested in participating. Advertising for the study was sent through professional networks. GPs were eligible if they had a current patient caseload.

Procedure

Clinicians approaching the lead investigator were sent an information sheet and consent form. An interview was scheduled at a mutually convenient time and location. The majority of interviews ($n = 19$) were done by telephone. At the beginning of the interview, clinicians were asked structured questions about their clinical background and experience (see online suppl. appendix; see www.karger.com/doi/10.1159/000447552). This included information on their current patient caseload, the type of clinic they work in and their level of clinical experience. FHCG clinicians were asked for their typical appointment duration, patient volume

Table 1. Definitions of identified themes within the CFIR as applied to preventive therapy

| Construct | Definition |
|-------------------------------------|--|
| <i>Intervention characteristics</i> | |
| Evidence strength | Stakeholders' perceptions of the quality and validity of evidence supporting chemoprevention |
| Relative advantage | Stakeholders' perception of the advantage of implementing chemoprevention versus an alternative solution |
| Trialability | The ability to test chemoprevention on a small scale in the organization |
| Complexity | Perceived difficulty of implementing chemoprevention, reflected by disruptiveness and number of steps required |
| Costs | Financial costs associated with implementing chemoprevention |
| <i>Inner setting</i> | |
| Implementation climate | The capacity for change and extent to which use of chemoprevention will be rewarded, supported, and expected by the institution and colleagues |
| <i>Outer setting</i> | |
| External policies | External strategies to spread use of chemoprevention, including policy and regulations (e.g. NICE guidelines) |
| <i>Individual characteristics</i> | |
| Knowledge and attitudes | Individuals' attitudes toward chemoprevention as well as familiarity with factual information about chemoprevention |
| Self-efficacy | Individual belief in their own capabilities to execute courses of action to achieve chemoprevention goals |
| <i>Implementation process</i> | |
| Planning | The degree to which tasks for implementing chemoprevention are developed in advance, and the quality of that planning |
| Engaging others in plans | Attracting and involving appropriate individuals in the implementation of chemoprevention through various strategies |

Definitions adapted from the CFIR website: <http://cfirguide.org/constructs.html>; only constructs identified in the interviews are included here. Issues associated with the implementation process were incorporated within other themes (e.g. external policies).

per year and their personal and hospital's experience in recruiting to preventive therapy trials. GPs were asked about their experience referring patients to secondary or tertiary care due to a familial risk of breast cancer.

In the semi-structured interview, FHCG clinicians were asked about their attitudes towards preventive therapy, how it is imple-

| Genetics and family history interview | GP interview |
|---|---|
| <ul style="list-style-type: none"> • Thank you and introduction to the project • Structured questions (table 2) • In your own words, please tell me what you think about breast cancer chemoprevention <ul style="list-style-type: none"> – Is chemoprevention routinely offered in your current practice – Is there a standard protocol for offering chemoprevention? – What do you think of the evidence behind chemoprevention? – If a woman was interested, what would be the next steps? | <ul style="list-style-type: none"> • Thank you and introduction to the project • Structured questions (table 3) • In your own words, please tell me what you know about breast cancer chemoprevention <ul style="list-style-type: none"> – Were you familiar with the NICE guidelines before today? – Have you ever been asked to prescribe chemoprevention? – If a woman was interested, what would be the next steps? – What are your thoughts about tamoxifen and raloxifene being 'off-label' • Brief description of preventive therapy evidence^a |
| <p>^a Described evidence was from Cuzick et al. [4]. GPs were told that there was a ~40% reduction in breast cancer incidence among women taking preventive therapy for 5 years, which was accompanied by an increase in thromboembolic events, endometrial cancer and vasomotor symptoms. Twenty-two women need to take tamoxifen for 5 years to prevent one breast cancer case. There is no recorded mortality benefit among users.</p> | |

Fig. 2. Overview of interview schedule for FHCG clinicians and GPs.

mented within their clinic, their perception of the evidence, and the local processes for prescribing tamoxifen or raloxifene (fig. 2). Difficulties implementing preventive therapy within everyday clinical practice were pursued with additional questioning. GPs were asked about their familiarity with the topic of preventive therapy, their experience and willingness to prescribe tamoxifen and raloxifene for primary prevention, local processes for prescribing new medications, and issues associated with prescribing 'off-label' medication (fig. 2). After eliciting initial reactions to preventive therapy, the evidence for SERMs was described using data from the most up-to-date meta-analysis [4]. The topic guide was developed collaboratively within the research team (S.G.S., L.S., J.W.) and refined as the study progressed. The interviews were undertaken by a behavioural scientist with expertise in qualitative research methods (S.G.S.) between November, 2014 and July, 2015. Ethical approval was obtained from the Queen Mary University of London Research Ethics Committee.

Analysis

Interviews were digitally recorded and transcribed verbatim. Thematic analysis was used to identify patterns (described here as themes) within the interview data [22]. Each transcript was read several times by two independent researchers (S.G.S. and S.F.M.) and coding began when they were familiar with the data. Descriptive themes were produced inductively based on the data. Data from FHCG clinicians were initially analysed separately from the GPs in recognition of their different experience and understanding of preventive therapy. Following the independent generation of descriptive themes by two researchers (S.G.S. and S.F.M.), the process of grouping the independent datasets into higher level analytical themes was initiated. This process was informed by the existing CFIR model (table 1) [18], but disconfirming data were sought throughout [23]. Interview data from both FHCG clinicians and GPs were then combined to identify similar barriers to the implementation of preventive therapy. The quotes presented here are the richest examples of the finalised analytical themes. All analyses were performed in a Microsoft Office Excel database.

Results

Sample

Fifteen FHCG clinicians were recruited (table 2). Thirteen were women (87%) and were generally highly experienced, with 80% having at least 6 years' experience. The majority were recruited from clinical genetics services (40%) or family history clinics (47%), and there was a wide range in patient volume per year. Nine clinicians (60%) had a clinical caseload involving both moderate and high-risk groups, and 6 (40%) saw high-risk women only. Four (27%) of the FHCG clinicians had personally recruited for breast cancer-preventive therapy trials, although 53% worked in centres that were involved in trial recruitment. Two FHCG clinicians worked in centres that did not discuss preventive therapy with eligible patients.

Ten GPs were included (table 3). Most were women (90%) and worked in larger practices (>12,000 registered patients) (60%). The GPs had a range of experience levels, and most (80%) had experience of referring a patient to secondary or tertiary care because of her familial risk of breast cancer. Four of the GPs were familiar with the NICE guidelines for preventive therapy, and 2 were working in practices where preventive therapy had been discussed with a patient. However, no GP within this study had personally been asked to prescribe preventive therapy.

Summary of Qualitative Data

FHCG clinicians referred to all five domains of the CFIR, although the majority of discussion was focussed on the intervention characteristics (e.g. evidence and relative benefit) and the outer setting (e.g. NICE guidelines). Several quotes and topics covered multiple themes within the CFIR framework. As a result, no quotes were included for the 'process' theme. While processes such as planning and engaging were considered to be an important aspect of implementing preventive therapy, these issues were driven by factors within other themes (e.g. external policies). GPs also highlighted problems with external policies such as NICE guidelines, as well as concerns regarding their own lack of awareness.

Intervention Characteristics

Evidence Strength

The perceived benefits of preventive therapy varied. The recent release of trial data demonstrating a lack of effect on mortality reduction among women taking tamoxifen [8] affected clinicians' enthusiasm and led to the perception that the absolute benefit for women was small:

'I wouldn't be convinced about that [evidence for preventive therapy]. I don't think there's enough information to make a full decision, and the lack of long-term data is critical, really.' (J.N., GP, male)

Some FHCG clinicians and GPs were more positive and framed the decision to offer preventive therapy in terms of overall disease burden, rather than focussing on mortality outcomes:

'...even if you don't reduce mortality, you can reduce [the] burden of disease which is associated with a significant morbidity, anxiety of having diagnosed with cancer, and treatment costs and toxicities...If you can bring that entire burden down by 30%, then I think that is a sufficiently attractive proposition.' (R.P., FHCG clinician, male)

Some FHCG clinicians voiced enthusiasm for preventive therapy with particular clinical groups. However, this was not always consistent because of confusion regarding which risk group it should be offered to. The perception among some FHCG clinicians was that preventive therapy trials mainly recruited moderate-risk women, and therefore the evidence was most relevant for them:

'I deal mainly with high-risk women, it's not something that I was entirely comfortable with in the beginning because a lot of the studies are done in moderate-risk women who I don't see that many of. So I find it quite difficult to have those kind of conversations...' (T.D., FHCG clinician, female)

However, other FHCG clinicians felt that the moderate-risk group were not at a sufficiently high level of risk

Table 2. Characteristics of clinicians working in genetics and family history setting

| | |
|--|---------|
| Gender | |
| Male | 2 (13) |
| Female | 13 (87) |
| Patient group | |
| Moderate or high risk | 9 (60) |
| High risk only | 6 (40) |
| Clinic type | |
| Clinical genetics service | 6 (40) |
| Family history clinic | 7 (47) |
| Breast clinic | 2 (13) |
| Years since qualified | |
| 0–5 | 3 (20) |
| 6–10 | 6 (40) |
| >10 | 6 (40) |
| Appointment times | |
| ≤15 min | 3 (20) |
| 15–30 min | 4 (27) |
| 31–45 min | 6 (40) |
| 45 min+ | 1 (7) |
| Patient volume per year (clinic level) | |
| ≤100 | 5 (33) |
| 101–500 | 5 (33) |
| 500+ | 5 (33) |
| Personal participation in IBIS trials | |
| Yes | 4 (27) |
| No | 11 (73) |
| Centre participation in IBIS trials | |
| Yes | 8 (53) |
| No | 7 (47) |

Data are presented as n (%). Numbers may not compute to 15 as one clinician did not have a dedicated clinic for seeing high-risk patients.

Table 3. Characteristics of GPs

| | |
|---|---|
| Gender | |
| Male | 1 |
| Female | 9 |
| Years since qualified | |
| 0–10 | 3 |
| 11–20 | 6 |
| 20+ | 1 |
| Number of registered patients at current practice | |
| ≤12,000 | 3 |
| >12,000 | 6 |
| Experience of referring high-risk women | |
| Yes | 8 |
| No | 2 |

One GP was a locum and therefore could not respond to the item regarding practice size.

to warrant potential side effects, and therefore adopted a local policy to only discuss preventive therapy with high-risk women:

‘It was felt for the...moderate-risk group, the risk/benefit risk ratio wasn’t clear. You know, the side effect profile compared to the benefit that they would potentially get from chemoprevention, we didn’t feel was sufficient to offer them chemoprevention.’ (S.M., FHCG clinician, female)

Relative Advantage

Several factors led FHCG clinicians to believe the relative advantage of offering preventive therapy was minimal. The side effects experienced by healthy women using tamoxifen led clinicians to report they avoided conversations with some patients to prevent unnecessarily disturbing their general physical and mental health:

‘If someone is perfectly happy with their level of risk, their level of surveillance, and it’s all ticking over nicely, they’re breast aware, it’s not impacting on their life too much, I personally, maybe subjectively, maybe subconsciously don’t really want to mess that up.’ (L.O., FHCG clinician, female)

The ‘window of opportunity’ during which the advantages of preventive therapy outweighed the harms was considered to be small. Some women at high risk of breast cancer are eligible for surgical intervention regardless of age, but preventive therapy is only available from the age of 35 years. Tamoxifen and raloxifene are also not available to women planning pregnancy or those taking the contraceptive pill. As a result, FHCG clinicians questioned the advantages of preventive therapy for large proportions of this population:

‘Yes, they recommend salpingo-oophorectomy from the age of 40, so actually women having children in their 30s, then they get to 40 and then have an oophorectomy and then get put on HRT. There isn’t really, for the [BRCA 1 and BRCA 2] carriers, a big opportunity to take on tamoxifen.’ (S.M., FHCG clinician, female)

Despite recognising the increase in morbidity associated with risk-reducing mastectomy, surgical intervention was considered a more obvious choice for patients:

‘So for example [risk-reducing mastectomy] does add life years...so you know, obviously that’s a very much harsher choice, but it’s so much better and clearer cut in what it offers.’ (C.S., FHCG clinician, female)

There were also a number of examples of the ‘status quo’ effect, a phenomenon that occurs when two options are perceived to be comparable, but the most contemporary option is neglected in favour of existing practice. Several FHCG clinicians recognised the limitations associated with mammography, but still felt screening should be prioritised ahead of discussions about prevention:

‘There’s...no really good data to say that mammography in women aged 40–50 is really going to improve survival from breast cancer. [But]...it’s been around for so long, and it’s generally an accepted recommendation.’ (S.M., FHCG clinician, female)

Several FHCG clinicians felt that the relative advantage of tamoxifen was small, and instead were anticipating that alternative agents with less pronounced side effect profiles would be more acceptable:

‘...Although they [aromatase inhibitors, AIs] have their own side effects I suspect that a lot of these younger women will look at that profile in a less frightened way and I anticipate...that NICE will adopt AIs as well...and I think if they do, a lot more women may be interested.’ (R.I., FHCG clinician, female)

Trialability

Only one FHCG clinician discussed the option of taking tamoxifen for a short trial period. They also failed to mention the option of trying tamoxifen and switching to raloxifene, despite a generally more favourable side effect profile [24]. GPs were familiar with discussing medication cessation with patients, and were therefore more likely to consider short medication trial periods as an option for patients:

‘I think what some people don’t realise, and I had to spell out for one lady, was that they can stop it, because I think people think, ‘well how long do you have to take it for’ and I say ‘well in the studies people took it for 5 years, but if you’ve started to take it and you’ve hated it, you could stop’...For a lot of people that doesn’t really occur to them.’ (P.H., FHCG clinician, female)

Complexity

Incorporating preventive therapy within a busy clinic was considered challenging. Some had very limited time to achieve their goals for the consultation, and preventive therapy was often left until last and discussed if time remained. There was concern that initiating a conversation on preventive therapy without sufficient time to answer all questions might be harmful to patient care:

‘...There’s so much else to get through...that maybe you have 5 minutes left at the end and you just don’t have time for a really in depth discussion about it. You sort of just throw it out there and often it’s new information so they don’t really ask any questions because they haven’t really had a chance to process it.’ (P.H., FHCG clinician, female)

GPs were concerned about the complexity of managing patients experiencing side effects. They were sometimes willing to undertake this role, but felt that their options for supporting women were limited.

‘No. Not comfortable [managing side effects]. Apart from an option of stopping the medication, I wouldn’t really know how to

manage something. I wouldn't feel comfortable giving more drugs to treat a side effect in that case.' (Y.T., GP, female)

FHCG clinicians who were not qualified in medicine discussed that they were not trained to take on a management role. This highlights an important gap between GPs and FHCG clinicians in terms of responsibility for patient care:

'...my assumption would be the GP [would manage side effects], because we can't take that on, because I'm not a medically trained person, so I would have to ask the GP to manage them... and that's where I don't know if they'd be willing to take that on.' (T.D., FHCG clinician, female)

Costs

The financial implications of preventive therapy were rarely mentioned by FHCG clinicians. GPs were more aware of cost, and those with less experience or who were employed on a salary rather than as a practice partner were guided by their senior colleagues. Several mentioned that they would seek clinical commissioning group (CCG) approval, but there was little indication that cost would form an insurmountable barrier to prescribing.

'The funding, in terms of if we prescribe the medication, it comes out of our primary care budget. But that wouldn't concern me; I think my concern is to give the best possible care to the patient and evidence-based treatment which is as safe as possible.' (J.N., GP, Male)

Outer Setting

External Policies

The NICE guidelines for the management of familial breast cancer were a feature of most interviews with FHCG clinicians. They spoke of difficulties interpreting the guidelines' wording, making particular reference to the section describing which patient groups were eligible for preventive therapy. The use of the word 'consider' in reference to offering preventive therapy to women at moderate risk was thought to be particularly troublesome to implementing the guidelines in clinical practice:

'I think the difficulty has been in implementing this guidance, because of the use of this word 'consider'...having been to some national meetings the feeling was, if anything says 'consider', you're unlikely to have the resources, and [so] don't go there. Don't offer it.' (A.N., FHCG clinician, female)

The lack of guidance from NICE with regard to who should initiate prescriptions and offer subsequent patient care led to confusion. While preventive therapy was still being discussed with patients, FHCG clinicians were hesitant to go into too much detail because prescribing protocols were uncertain:

'...Everyone's caught a bit off guard by the recommendations... We [clinical genetics] are not willing to take [prescribing] on and we can't, the breast team don't want to take it on and I suspect the GPs don't want to either...so you're almost relieved when they say they're not interested.' (B.F., FHCG clinician, female)

Some FHCG clinicians were not medically trained, and so could not take on the role of prescribing. Furthermore, even medically trained FHCG clinicians were unfamiliar with prescribing medication and had little experience in the area. The lack of access to patient records led FHCG clinicians to suggest primary care may be the most suitable group to initiate prescribing:

'It's much better to have it started off with their GP, who can check it off with other medications that they might be on...[If] the patient doesn't turn up with that list [of medication]...then you can't really do that due diligence. So that's another reason for putting it back to the GP.' (C.S., FHCG clinician, female)

However, there was a clear reluctance from GPs to write the first prescription, and they preferred instead to continue it after initiation from secondary or tertiary care. One GP provides anecdotal evidence of this reluctance from GPs:

'One of their [clinical genetics] representatives had come to explain how the service was going to be set up and [they] started talking about [chemoprevention] as well because she'd suggested that GPs would initiate prescriptions. And the whole place was roaring with horror.' (O.C., GP, female)

Both FHCG clinicians and GPs were concerned about prescribing a medication 'off-label'. Most GPs were unaware that tamoxifen and raloxifene were not licensed for a primary prevention indication. After being informed, GPs willingness to take on the prescribing role was reduced because of medico-legal concerns:

'I think particularly in this day and age, GPs, all doctors are so worried about getting sued, that people would be concerned if something adverse happened and it came back and it wasn't licensed, that that could be another thing levied at them.' (D.D., GP, female)

However, GPs discussed their experience of prescribing other off-label medications, such as for children and pregnant women. While they were cautious about prescribing in an off-label context, the status of the licence would not prevent them from doing so:

'I suppose the main issue is obviously with it being off-licence. But if it had come from secondary care and I had a letter, discussed it with her and discussed that it was off-licensed, I feel happy that the responsibility is kind of a, you know, they've taken the primary decision, and we are supporting it by prescribing.' (D.D., GP, female)

Inner Setting

Implementation Climate

Several FHCG clinicians reported that their clinic was not enthusiastic about implementing preventive therapy within their service. In clinics with affected and unaffected patients, the priority was on treating patients with cancer rather than prevention in high risk groups:

'They're [senior colleagues] so involved with dealing with cancer patients, and discharging patients who don't have cancer back to their GPs, this chemoprevention is not on their agenda.' (R.P., FHCG clinician, male)

In some centres, a lack of awareness about preventive therapy among senior clinicians was considered to inhibit implementation across the whole service. In other centres, senior clinicians were perceived to be making assumptions about the knowledge of less experienced staff members:

'I think there are people that have been involved in these studies, and they have a certain level of knowledge and just expect everybody else to know what they know, which is not possible if you haven't been involved.' (T.D., FHCG clinician, female)

Individuals Involved

Knowledge, Attitudes and Self-Efficacy

Some FHCG staff felt they were not sufficiently knowledgeable to be discussing preventive therapy with patients and lacked confidence in their own understanding. There was also uncertainty with regard to the evidence for SERMs among carriers of deleterious BRCA gene mutations. Some FHCG clinicians were unaware of the better cost/benefit ratio among BRCA 2 carriers relative to BRCA 1 carriers:

'It's difficult because of the actual lack of research, but what [are] the actual statistical benefits for different groups of patients. If they're BRCA 1, BRCA 2, are they the same?' (L.O., FHCG clinician, female)

GPs were broadly familiar with some side effects of tamoxifen, but rarely listed thromboembolic events or endometrial cancer. FHCG clinicians were more aware, although gaps in knowledge were apparent. For example, one FHCG clinician was unwilling to prescribe tamoxifen because they wanted all patients to undergo bone density scans prior to initiating therapy. This is despite bone density only decreasing in pre-menopausal women [25] and fracture rates improving overall among women using SERMs [4]:

'If I was the person prescribing it...I'd want to perhaps have a bone density scan and consideration of that person's bone health because we will cause the bone density to drop, and in a healthy person that's a risk that I don't think is fully worked out yet.' (C.S., FHCG clinician, female)

Throughout all discussions of preventive therapy, raloxifene was rarely mentioned. Clinicians reported knowing very little about this drug:

'I haven't come across using raloxifene at all... So basically chemoprevention for me is tamoxifen.' (T.T., FHCG clinician, female)

Discussion

In this qualitative investigation, GPs and clinicians working in a familial breast cancer setting reported multiple barriers to the implementation of preventive therapy within routine clinical practice. Difficulties across a range of CFIR domains were reported, with FHCG clinicians describing particular problems with interpreting NICE guidelines and agreeing protocols for prescribing. While most clinicians were interested in the concept of preventive therapy, the relative benefit for patients was considered to be small. Clinicians from both groups reported knowing relatively little about the topic, which discouraged discussions with patients, and this may be affecting uptake by women.

This study has implications for the care of women at higher risk of familial breast cancer. Some FHCG clinicians felt poorly informed about the evidence for preventive therapy, particularly with reference to specific clinical groups. Similar findings were observed among Australian clinicians who reported a preference for discussing preventive therapy with carriers of BRCA1 and BRCA2 deleterious mutations, despite a lack of evidence in these groups [11]. Encouraging dissemination of clinical trial findings through study days and local network meetings could improve clinician knowledge and enhance the quality of communication with patients. Such events should be carefully developed and informed by the barriers identified in the CFIR framework here.

For example, future research is needed to develop an evidence-based educational event addressing CFIR barriers such as knowledge of preventive medications, awareness of drug harms and benefits, and use of national guidelines. Such a strategy may reduce clinician's reluctance to initiate discussions about preventive therapy and enhance women's ability to make an informed decision [26, 27]. Knowledge deficits were noted with GPs, who were mostly unaware that tamoxifen and raloxifene could be used for primary prevention. GPs were reluctant to take on the role of managing women using preventive therapy because they felt their knowledge was insufficient. Several strategies for improving GP knowledge

were suggested, including using websites and publications to disseminate up-to-date scientific advice on the topic. They also suggested developing a brief pro forma on preventive therapy for secondary and tertiary care clinicians to include when asking GPs to prescribe. We plan to create template pro formas for FHCG clinicians to use and adapt. These will address many of the barriers identified from the CFIR framework, and the development process will involve GP stakeholders. A further benefit of providing these templates is that it will ensure the information provided to clinicians and patients is standardised across different regions.

Time was a barrier to discussing preventive therapy within clinics. FHCG clinicians were understandably reluctant to introduce a new topic to a consultation that was already short and complex. Decision aids have been evaluated in trial and clinical settings [28–33], and can improve patient decision-making in the absence of a clinician [34]. However, FHCG clinicians would be needed to follow-up with patients to ensure women have been able to make an informed decision. The financial implications of this need to be carefully monitored, and it may not be possible for all centres. Identifying cost-effective solutions to inform patients about preventive therapy in a simple format should be a priority for research and clinical practice.

Side effects are a major deterrent to initiating preventive therapy [35, 36], but few FHCG clinicians raised the topic of offering patients a short trial to assess their tolerance. GPs were more likely to suggest this possibility. FHCG clinicians should be encouraged to explain to patients that they are not expected to persist with therapy if they are unable to tolerate side effects. Short medication trials have the potential to improve informed decision-making by allowing their initial response to be taken into consideration when choosing whether to persist with preventive therapy.

This study also has implications for policy, particularly with regard to the NICE guidelines for the management of familial breast cancer, which uses the term ‘consider’ when describing which patient groups should be offered preventive therapy [7]. Our findings showed ‘consider’ was being interpreted by FHCG clinicians as something that should not be done in clinic, and should therefore be revised or clarified in the next version of the guideline. The lack of guidance for prescribing also appears to be hampering efforts to implement preventive therapy. A ‘one size fits all’ approach is unlikely to be possible, and our data highlight several issues that warrant consideration when developing local protocols. Opening commu-

nication channels between the two groups and involving all stakeholders will be key to resolving these problems. Future NICE guidance could offer several prescribing scenarios to facilitate the development of local protocols.

The majority of comments were accommodated within the five domains of the CFIR model. However, discussion regarding process was more closely aligned with other domains, such as the influence of policy in the outer setting. This adaptation was in keeping with the original framework, which was not intended to be a finalised model for implementation research [18]. Our data are also similar to a study using the CFIR to investigate barriers to prescribing biologic medication to treat rheumatoid arthritis [20]. Further investigations are needed in other contexts, but convincing clinicians of the effectiveness of the medication and ensuring there is clear guidance for prescribing appears to be important when introducing new medical therapies in clinical practice. Future trials to promote the implementation of guidelines are needed, and our data suggest that the CFIR model is a useful model on which to base these strategies.

This study had limitations. Our qualitative approach prohibited us from reporting the proportion of clinicians who experienced the barriers or the magnitude of their importance. The majority of the clinicians involved were female, and it is possible that gender influenced attitudes towards preventive therapy. We also relied on opportunistic recruitment, and it is not clear whether our findings generalise to centres not involved in this research. It is possible that clinicians interested in participating in this study were more likely to have experienced barriers to implementing preventive therapy. Alternatively, they could have been more positive about the topic than other FHCG clinicians, and our report could be underestimating the number of implementation barriers.

Conclusions

In conclusion, our qualitative investigation with GPs and FHCG clinicians identified multiple barriers to implementing preventive therapy within clinical practice. Clinicians reported particular difficulties with interpreting NICE guidelines and establishing local protocols for prescribing therapy. Self-reported knowledge of tamoxifen and raloxifene was often low, and clinicians felt this detracted from their willingness to discuss preventive therapy with patients. The barriers identified in our research can be addressed by engaging all of the key stakeholders during the development of local and national policy documents.

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References

- 1 Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJL, Naghavi M: Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* 2011;378:1461–1484.
- 2 Autier P, Boniol M, LaVecchia C, Vatten L, Gavin A, Héry C, Heanue M: Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. *BMJ* 2010; 341:c3620.
- 3 Youlden DR, Cramb SM, Dunn NAM, Muller JM, Pyke CM, Baade PD: The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. *Cancer Epidemiol* 2012;36:237–248.
- 4 Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, Dowsett M, Forbes JF, Ford L, LaCroix AZ, Mershon J, Mitlak BH, Powles T, Veronesi U, Vogel V, Wickerham DL, SERM Chemoprevention of Breast Cancer Overview Group: Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. *Lancet* 2013;381:1827–1834.
- 5 Smith SG, Sestak I, Forster A, Partridge A, Side L, Wolf MS, Horne R, Wardle J, Cuzick J: Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Ann Oncol* 2016; 27:575–590.
- 6 Donnelly LS, Evans DG, Wiseman J, Fox J, Greenhalgh R, Affen J, Juraskova I, Stavrinou P, Dawe S, Cuzick J, Howell A: Uptake of tamoxifen in consecutive premenopausal women under surveillance in a high-risk breast cancer clinic. *Br J Cancer* 2014;110: 1681–1687.
- 7 National Institute for Health and Care Excellence: Familial Breast Cancer. 2013. <https://www.nice.org.uk/guidance/cg164>.
- 8 Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, Forbes JF: Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol* 2015;16:67–75.
- 9 Armstrong K, Quistberg DA, Micco E, Domchek S, Guerra C: Prescription of tamoxifen for breast cancer prevention by primary care physicians. *Arch Intern Med* 2006;166:2260–2265.
- 10 Butow PN, Lobb EA: Analyzing the process and content of genetic counseling in familial breast cancer consultations. *J Genet Couns* 2004;13:403–424.
- 11 Keogh LA, Hopper JL, Rosenthal D, Phillips K-A: Australian clinicians and chemoprevention for women at high familial risk for breast cancer. *Hered Cancer Clin Pract* 2009;7:9.
- 12 Ekins-Daukes S, Helms PJ, Taylor MW, McLay JS: Off-label prescribing to children: attitudes and experience of general practitioners. *Br J Clin Pharmacol* 2005;60:145–149.
- 13 Mukattash T, Hawwa AF, Trew K, McElnay JC: Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. *Eur J Clin Pharmacol* 2011;67:449–461.
- 14 Stewart D, Rouf A, Snaith A, Elliott K, Helms PJ, McLay JS: Attitudes and experiences of community pharmacists towards paediatric off-label prescribing: a prospective survey. *Br J Clin Pharmacol* 2007;64:90–95.
- 15 Haines A, Kuruvilla S, Borchert M: Bridging the implementation gap between knowledge and action for health. *Bull World Health Organ* 2004;82:724–731.
- 16 Grol R: Successes and failures in the implementation of evidence-based guidelines for clinical practice. *Med Care* 2001;39(suppl 2):46–54.
- 17 Ferlie EB, Shortell SM: Improving the quality of health care in the United Kingdom and the United States: a framework for change. *Milbank Q* 2001;79:281–315.
- 18 Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC: Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci* 2009;4:50.
- 19 Francke AL, Smit MC, Veer AJ de, Mistiaen P: Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Med Inform Decis Mak* 2008;8:38.
- 20 Kalkan A, Roback K, Hallert E, Carlsson P: Factors influencing rheumatologists' prescription of biological treatment in rheumatoid arthritis: an interview study. *Implement Sci* 2014;9:153.
- 21 The Independent Cancer Taskforce: Achieving World-Class Cancer Outcomes: A Strategy for England (2015–2020). http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf
- 22 Braun V, Clarke V: Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
- 23 Barbour RS: Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? *BMJ* 2001;322:1115–1117.
- 24 Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER, Wade JL, Robidoux A, Margolese RG, James J, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N, for the National Surgical Adjuvant Breast and Bowel Project: Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev Res* 2010;3:696–706.
- 25 Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S: Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol* 1996; 14:78–84.
- 26 Rondanina G, Puntoni M, Severi G, Varrichio C, Zunino A, Feroce I, Bonanni B, Decensi A: Psychological and clinical factors implicated in decision making about a trial of low-dose tamoxifen in hormone replacement therapy users. *J Clin Oncol* 2008;26:1537–1543.
- 27 Cyrus-David MS, Strom SS: Chemoprevention of breast cancer with selective estrogen receptor modulators: views from broadly diverse focus groups of women with elevated risk for breast cancer. *Psychooncology* 2001; 10:521–533.

- 28 Banegas MP, McClure JB, Barlow WE, Ubel PA, Smith DM, Zikmund-Fisher BJ, et al: Results from a randomized trial of a web-based, tailored decision aid for women at high risk for breast cancer. *Patient Educ Couns* 2013; 91:364–371.
- 29 Fagerlin A, Zikmund-Fisher BJ, Smith DM, Nair V, Derry HA, McClure JB, et al: Women's decisions regarding tamoxifen for breast cancer prevention: responses to a tailored decision aid. *Breast Cancer Res Treat* 2010;119: 613–620.
- 30 Korfae IJ, Fuhrel-Forbis A, Ubel PA, Zikmund-Fisher BJ, Greene SM, McClure JB, Smith DM, Hensly Alford S, Fagerlin A: Informed choice about breast cancer prevention: randomized controlled trial of an online decision aid intervention. *Breast Cancer Res* 2013;15:R74.
- 31 Juraskova I, Butow P, Bonner C, Bell ML, Smith AB, Seccombe M, Boyle F, Reaby L, Cuzick J, Forbes JF: Improving decision making about clinical trial participation – a randomised controlled trial of a decision aid for women considering participation in the IBIS-II breast cancer prevention trial. *Br J Cancer* 2014;111:1–7.
- 32 Ubel PA, Smith DM, Zikmund-Fisher BJ, Derry HA, McClure J, Stark A, Wiese C, Greene S, Jankovic A, Fagerlin A: Testing whether decision aids introduce cognitive biases: results of a randomized trial. *Patient Educ Couns* 2010;80:158–163.
- 33 Fagerlin A, Dillard AJ, Smith DM, Zikmund-Fisher BJ, Pitsch R, McClure JB, Greene S, Alford SH, Nair V, Hayes DF, Wiese C, Ubel PA: Women's interest in taking tamoxifen and raloxifene for breast cancer prevention: response to a tailored decision aid. *Breast Cancer Res Treat* 2011;127:681–688.
- 34 Fagerlin A, Zikmund-Fisher BJ, Ubel PA: Helping patients decide: ten steps to better risk communication. *J Natl Cancer Inst* 2011; 103:1436–1443.
- 35 Bober SL, Hoke LA, Duda RB, Regan MM, Tung NM: Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. *J Clin Oncol* 2004;22:4951–4957.
- 36 Yeomans-Kinney A, Vernon SW, Frankowski RF, Weber DM, Bitsura JM, Vogel VG: Factors related to enrollment in the breast cancer prevention trial at a comprehensive cancer center during the first year of recruitment. *Cancer* 1995;76:46–56.