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High-risk individuals' perceptions of reproductive genetic testing for *CDH1* mutations

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Abstract

Reproductive genetic testing- PreNatal Diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD) - for *CDH1* mutations associated with Hereditary Diffuse Gastric Cancer is available in the UK. This qualitative interview study examined high-risk individuals' (n=35) views of *CDH1* reproductive genetic testing. Interviewees generally regarded reproductive genetic testing as an acceptable form of HDGC risk management. However, some were concerned that their genetic risks required them to plan reproduction and anticipated difficulties communicating this to reproductive partners. Individuals had a preference for PGD over PND because it avoided the need for a termination of pregnancy. However, those who had not yet had children expressed concerns about having to undergo IVF procedures and worries about their effectiveness and the need for embryo selection in PGD. It is suggested that high-risk individuals are provided with access to reproductive genetic counselling.

Keywords

Hereditary Diffuse Gastric Cancer (HDGC); e-Cadherin (*CDH1*); reproductive genetic testing; Preimplantation Genetic Diagnosis (PGD), Prenatal Diagnosis (PND); hereditary cancer

Introduction

Hereditary Diffuse Gastric Cancer (HDGC) is an autosomal dominantly inherited disorder, caused by mutations in the *E-cadherin* gene (*CDH1*)[1]. Mutation carriers have significantly increased risks of developing gastric cancer in early adulthood[2]. Because the prognosis of diffuse gastric cancer is poor, prophylactic total gastrectomy (PTG) during early adulthood is recommended[1]. PreNatal Diagnosis (PND) or Preimplantation Genetic Diagnosis (PGD)

for *CDHI* mutations is available in the UK, enabling at-risk couples to avoid the birth of a mutation positive child.

Little is known of high-risk individuals' perceptions of reproductive genetic testing for inherited cancers. Studies suggest a proportion of women are in favour of PGD to avoid the birth of a *BRCA1/2* positive child[3,4], and that *BRCA1/2* mutation carriers have more favourable views of PGD than PND plus termination of pregnancy (TOP), although they are wary of embryo selection and IVF procedures[4]. These studies note that few participants received information about reproductive testing[3–5]. Similarly, a study of family members at risk of Familial Adenomatous Polyposis (FAP) found that, although 30% had positive attitudes only 16% of those of childbearing age had previously received information about PGD and PND[6]. This paper reports high-risk individuals' perceptions of reproductive genetic testing for HDGC.

Methods

The study[7] included high-risk individuals from the Familial Gastric Cancer Study (FGCS) in the UK. Confirmed *CDHI* mutation carriers and/or those who had undergone PTG and were aged 18 years were sent a recruitment pack and an opt-out form to return to researchers.

Data collection and analysis

Data were collected in open-ended interviews which focussed upon: experiences of being at-risk, genetic testing, decision-making about risk management, experiences of undergoing surgery and the psychosocial impact of prophylactic gastrectomy (see Box 1).

Inductive methods using simultaneous data collection and analysis were employed. Early interviews indicated that conception when at-risk and reproductive genetic testing were important issues for interviewees and thus, subsequent interviewees were questioned about these topics. On four occasions the interviewee's partner was present. However, these were not joint interviews and in most cases partners commented infrequently, sometimes providing factual corrections to the interviewee's narrative, and occasionally describing their role in reproductive and surgical decisions. Audio-recorded interviews (length 60-210 minutes) were transcribed, anonymised and allocated pseudonyms. A framework for indexing and analysing the transcriptions was developed using the constant comparative method.[8]

Results

Participant characteristics

Forty-two FGCS participants were invited; two declined and five were unavailable for interview. Sixteen women and 19 men were interviewed (Table 1). Seventeen interviewees had children and one couple was awaiting the birth of their first child. This couple had one failed attempt at PGD and their current pregnancy involved no *CDHI* testing. Another couple scheduled PND in a previous pregnancy but, because Chorionic Villus Sampling was contraindicated, had proceeded without testing.

Only 23 interviewees discussed reproductive testing at length during the interviews, their views and experiences are collated in Table 2. Eight interviewees had discussed reproductive genetic testing with healthcare professionals, most in passing, but a few during a dedicated consultation, the others had discussed this topic with family members or obtained information from websites.

Conceiving when at-risk

Those who had children before they knew of their risks expressed relief that they had not needed to consider HDGC when deciding whether and when to start a family. A couple of these interviewees said they would not have used reproductive genetic technologies had they known of their risks, and therefore, might not have proceeded with a pregnancy. Kay commented she would have had her children without undergoing reproductive testing, even if it had been offered, because she felt that screening out *CDH1* carriers was tantamount to saying their lives were worthless.

Kay: ... if you say that you're not prepared to have children, are you saying that OUR lives are worthless? Because that's almost what you're saying ...no more people should be born of people who have our gene, or you should get into the whole embryo selection. (Parent, partnered)

Others, in contrast, saw reproductive genetic testing as offering the chance to "stop the whole thing...all these genetically carried life or death things could stop overnight with IVF or abortion" (Boyd, Parent, partnered)

Some interviewees who had not yet had a child expressed a desire for spontaneity when conceiving.

Allannah: when I'm ready for a baby in the future I just kind want to stop using contraception and just let it happen, I don't really want to plan for a baby and I don't know whether I'd want to go through that, but then I think is that's selfish because that's then maybe putting my child at risk. (single)

These interviewees neither wanted to plan their pregnancy (Allannah) nor use reproductive genetic technologies (Ella); although they acknowledged that such attitudes are unrealistic and irresponsible.

Ella: I *don't* want to terminate a child. I don't even really like the idea of IVF, PGD or whatever. Just sifting through the [embryos] but, I mean that is like a gut feeling ... I think I'm probably going to have to just override that, perhaps do something a bit more sensible. (partnered)

The majority of those without children suggested they were prepared to consider reproductive testing, but acknowledged that this raised the difficult issue of telling (potential) partners about their risks and the impact on conception.

Phoebe: I think the fact that it would be unnatural is really upsetting for me ... and I think having to do that's quite a big deal for a partner as well and having to explain that you have to have that. (single)

While female carriers acknowledged they would bear the brunt of reproductive testing procedures, male carriers also talked about the difficulties of talking to potential partners about risk and reproductive testing.

Josh: ...it's a difficult one, you'd have to know [partner] quite a while before you even broached the subject of it, because I think otherwise if I was the girl I'd probably just say, 'Well it's not really worth sort of investing any more in you.' (partnered)

Using reproductive technologies

Most interviewees accepted the idea of reproductive genetic testing to prevent passing on mutations. However, they differed in the extent to which they supported PND and PGD. With the exception of the couple that had attempted PND, the majority expressed scepticism about PND, arguing that they would not be in favour of terminating a carrier fetus:

Keira: would you go on with the pregnancy if you knew that the [fetus was a carrier] that's a really tough question but I think I probably would. Because you could have five pregnancies and all of them, you know, where do you stop? At the tenth one do you think, well actually it's the tenth time, I'll just carry on with this pregnancy when actually you've discarded the first one? (single)

In contrast most interviewees were positive about PGD and the ability to screen embryos, but many worried about whether they would be able to cope with associated IVF procedures.

Rose: It is nice to know there is an option, a way of getting rid of the gene as such, but I can see there's a lot of heartache in that as well. I know you have to have hormone injections and that kind of thing, and my cousin's wife, she went through hell with it. So it is, it is a hard decision. (single)

It was clear that many interviewees regarded IVF as an unreliable method of conceiving a child "I want children, but then looking into that IVF, the genetic thing that is a total nightmare by the looks of it." (Ella). The stress of undergoing IVF was frequently commented upon, indeed, the couple who had undergone PGD reported they gave up after their first failed attempt "...because it was, it was just actually so stressful. We were doing IVF to try and do it without the gene, but it failed" (Joel's partner pregnant). Some said they felt these decisions might be unnecessary by the time they are ready for children as there might be other options available for *CDH1* carriers. Finally, a couple of younger interviewees said that they were prepared to avoid an at-risk pregnancy by adopting a child.

Perran: I feel at the minute it would be better just to get the chop and never have children, then like adopt (single)

Discussion

This study suggests that high-risk individuals regard reproductive genetic testing as an acceptable form of risk management for HDGC and support planning reproduction (reproductive testing/adoption/intentional infertility) to avoid passing on *CDH1* mutations to future generations[3,5]. The perceived acceptability of reproductive genetic testing may be due to the fact that, in contrast to other inherited cancers[4,5], HDGC has an early onset, surveillance is less effective, prophylactic surgery is associated with long-term morbidity and cancer is often asymptomatic until advanced.

Like earlier research [4–6] the majority of interviewees voiced a preference for PGD over PND [4–6], because they were against TOP, however, those who had not yet had children expressed some anxiety about undergoing IVF and scepticism about the effectiveness of IVF procedures[4]. As in an earlier study of *BRCA1/2* carriers[3], younger interviewees expressed optimism about future developments in surveillance/prophylaxis arguing that the need for planned reproduction might become redundant.

In contrast to earlier studies [3–6] of *BRCA1/2* and *FAP* carriers, our interviewees appeared to have some awareness of reproductive genetic testing options, although the amount of information they had received from HCPs varied, which may account for observed differences in opinion. Mirroring earlier studies [3–6] our data suggest high-risk individuals of childbearing age would benefit from dedicated reproductive genetic counselling for HDGC. Indeed, since we undertook these interviews, international guidelines have been published which recommend at-risk patients are routinely offered reproductive counselling [1].

Finally, because of the relatively small sample size it is difficult to know the extent to which having a (completed) family, as was the case in 50% of interviewees, influenced interviewees' views about reproductive testing. Despite this, our data suggest high-risk individuals are interested in reproductive issues, and emphasise the need for a prospective study of reproductive decision-making for HDGC.

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Box 1**Interview topic guide****Demographic details**

Narrative about Cancer in family and self, - Can tell me your story about the cancers in your family – what happened, when where- (how did you find out about risk what have you done about it and why)?

Family and personal history

- Experiences of cancer in family
- Views of own and others' risk
- Genetic testing – why/why not
- Screening why/why not

Surgery

- Influences on surgical decisions - who involved, when, why, what
- Surgery and convalescence
- Feelings and experiences - Pre/post-surgery
- Impacts: health, eating, sociality, risk perception, work, identity, relationships

Information needs

- Information provided – good/bad
- What more information would you have liked
- What would you tell others considering these procedures

Family

- Experiences, views
- Communication about results and decisions
- Risk perceptions

Reproduction

- Views about reproduction – reproductive testing/pregnancy etc
- Discussions about reproduction (who/when/why)
- Views about Prenatal Testing or Preimplantation Genetic Diagnosis
- Information/support needs

Participant characteristics**Table 1**

	n	%
Age (years) at interview		
Range	19-17	
Mean	40	
Children		
Yes	17	49
Pregnant	1	2
No	17	49
Partnership status		
Married/de facto partnership	25	71
Divorced	2	5
Single	8	23
Education		
School only	12	34
Further Education	10	29
University	13	37
DNA Testing		
Confirmed mutation	32	91
No testing	3	9
PGD	1	2
PND	1	2
Risk management		
Current endoscopic surveillance	8	29
PTG	27	77
Age at surgery (n=27)		
35 years	13	37
36 Years	14	39

Table 2
Interviewees' attitudes and experiences of reproductive genetic testing

<i>Parents/currently pregnant</i>	
Would not (have) consider(ed) reproductive testing	4
Would (have) consider(ed) reproductive testing	1
Uncertain / don't know	3
Have undergone PGD	1
Scheduled to have PND	1
<i>Currently childless</i>	
Would not consider reproductive testing	2
Would consider reproductive testing	2
Unsure whether to pursue reproductive testing	7
Do not want children for other reasons	2