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ORIGINAL ARTICLE

Unsolicited information letters to increase awareness of Lynch syndrome and familial colorectal cancer: reactions and attitudes

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Abstract
Dissemination of information on a genetically increased risk should according to guidelines primarily be family-mediated. Incomplete and incorrect information spread has, however, been documented and implies missed possibilities for prevention. In Denmark, the national HNPCC register has been granted an exception to send unsolicited letters with information on hereditary colorectal cancer and an invitation to genetic counseling to members of families with familial and hereditary colorectal cancer. To evaluate this approach, we investigated reactions and attitudes to unsolicited letters in 708 members of families with genetic predisposition and in 1600 individuals from the general population. Support for information letters was expressed by 78% of the family members and by 82% of the general population. Regarding route of information, 90% of family members preferred a letter to no information, 66% preferred information from the hospital rather than from family members and 40% preferred to obtain information from a close family member. Our results suggest that use of unsolicited information letters from the health care system may be a feasible and highly acceptable strategy to disseminate information to families at high risk of colorectal cancer.

Keywords Hereditary colorectal cancer · Dissemination of genetic information · Direct approach · Attitudes towards unsolicited risk information · Reactions to risk information

Introduction

Genetic factors are estimated to contribute to at least 20% of colorectal cancer with disease-predisposing germline variants, most commonly linked to Lynch syndrome, identified in 4% of the patients [1–3]. Suspicion of heredity is typically based on an individual or a family history of cancer with multiple affected family members, young age at onset and characteristic tumor features such as mismatch-repair (MMR) defects in Lynch syndrome-associated tumors. Despite guidelines aimed to improve the identification of familial and hereditary cancer and increasing implementation of reflex MMR tumor testing in colorectal cancer, only a minority of the individuals with familial colorectal cancer have been identified [1]. Suboptimal communication and incomplete dissemination of information in the family and lack of awareness of genetic counseling options are estimated to be the main causes hereof. This shortcoming implies missed possibilities to reduce morbidity and mortality from colorectal cancer through surveillance of individuals at increased risk [4].

In most countries, legislation and clinical guidelines call for family-mediated dissemination of information on familial and hereditary cancer [5]. Family members are considered to have a moral obligation to contribute to information spread but are left with a difficult task related to when information should be delivered, which family members should be informed, and how information on inheritance, risk, genetic diagnostics and surveillance should be expressed. Family structure and relations, personal preferences and perceptions, culture and context influence communication and affect uptake of genetic testing and participation in surveillance

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programs [6, 7]. The family-mediated approach has therefore been questioned in relation to efficacy and accuracy [8, 9]. Genetic counsellors may be considered to have an ethical duty to inform family members at potentially increased risk, but this approach needs to be balanced against legislation and requirements for patient confidentiality [10–12]. Studies that have evaluated direct contact from genetic services to individuals at risk have shown high levels of acceptability [13, 14]. An approach with cascade genetic testing, where family members are directly contacted by genetic field workers, has been demonstrated to increase uptake of genetic testing in other genetic diseases [15].

In Danish health care, genetic information is in principle family-mediated, but families at high risk of colorectal cancer have been granted an exception with unsolicited information letters sent from the national Hereditary Nonpolyposis Colorectal Cancer (HNPCC) register. The possibility for direct contact with family members applies to families classified as Lynch syndrome and Familial Colorectal Cancer Type X (FCCTX) [16]. This approach is motivated by the family members' "right to know" about a hereditary risk of a potentially deadly disease for which effective surveillance colonoscopy programs exist. However, this strategy has been ethically questioned with the argument that it may deprive family members of their "right not to know". The rapid developments in genetic technologies and application of next-generation sequencing in diagnostics and treatment prediction will lead to identification of an increasing numbers individuals and families with genetic variants linked to an increased risk. Members of families with hereditary or familial cancer as well as individuals in the general population thus represent target groups.

We investigated acceptance for a direct approach from health care to members of families with high risk of colorectal cancer. Psychological reactions and attitudes toward unsolicited information letters were investigated in the general population and in family members who had received such information letters.

Setting, materials and methods

Study setting

Denmark has a population of 5.7 million. Health care is taxation-payed with genetic diagnostics and surveillance provided free of charge. The national Danish HNPCC register was established in 1991 with the aim to prevent cancer and improve survival in individuals with an increased risk of colorectal cancer based on familial aggregation. The register includes all subtypes of hereditary and familial colorectal cancer, except for familial adenomatous polyposis for which a separate register exists. At present, the HNPCC register contains information about 67,000 individuals of whom 41,400 are alive. Of the 4500 families classified to be at increased risk, 400 constitute Lynch syndrome based on disease-predisposing pathogenic germline MMR gene variants. Lynch syndrome is a multi-tumor syndrome with the highest lifetime risks for colorectal cancer (30–80%), endometrial cancer (40–60%), ovarian cancer (10–15%) and urothelial tract cancer (5–10%) [1, 3]. The Danish Lynch syndrome mutation spectrum is 40% MSH2, 35% MLH1, 20% MSH6 and 5% PMS2 [17]. Further, 550 families are classified as FCCTX based on fulfillment of the Amsterdam criteria and lack of pathogenic MMR gene variants [18]. The genetic basis of FCCTX is undefined and likely heterogeneous. Individuals at risk of Lynch syndrome and FCCTX are recommended colorectal cancer surveillance with colonoscopy every 2 years from age 25 in Lynch syndrome and every 5 years in FCCTX starting 10 years before the lowest age at onset in the family [19]. Additionally, women with Lynch syndrome are recommended surveillance for gynecologic cancer according to international guidelines.

Since 1997, the HNPCC register has sent unsolicited letters containing information on an increased risk of colorectal cancer and an invitation to genetic counselling to more than 2600 individuals in families classified as having Lynch syndrome (65% of the letters) or FCCTX (35%). During genetic counselling, probands were encouraged to inform relevant family members about a potentially increased risk of cancer and that they could expect to receive an information letter from the HNPCC register. The letters did not reveal the identity of the proband or other family members and contained information on a potentially increased risk of cancer, possibilities of surveillance for colorectal cancer and encouraged the recipients to contact their general practitioner for a referral to genetic counseling:

> We write you to ensure, that you are informed about hereditary cancer in your family, and to provide you with the opportunity to test whether you have inherited an alteration in one of your genes that implies an increased risk of cancer. (Letter to members of Lynch syndrome families)

The FCCTX family members were informed that:

> Your family has been investigated for hereditary cancer at the request of one of your relatives. From your pedigree, we can tell, that in your family there is likely an increased risk of cancer due to a hereditary predisposition. (Letter to members of FCCTX families)

The letters should as default be sent prior to genetic counseling, testing, and enrollment in a surveillance program. In some cases, the HNPCC register lacked information on genetic counseling, which meant that some patients who had

indeed participated in genetic counselling received letters. This was, however, also accounted for in the letters:

> You may already have learned about hereditary risk from a family member or genetic counseling. We contact you since we want to make sure that everyone, who may benefit from a surveillance program, is informed. (Letter to members of Lynch syndrome families)

In families with Lynch syndrome, information letters were sent to first-degree relatives of individuals with pathogenic germline variants, irrespective of a cancer diagnosis. If the relevant first-degree relative was deceased, letters were sent to their children. In FCCTX families the letter was sent to first-degree relatives of individuals affected with colorectal cancer.

Relevant family members were identified from the pedigrees register in the HNPCC register and from the Danish Central Population Registry (DCPR) [20]. With few exceptions, the letters were sent regardless of whether the proband agreed to the dissemination of information in the family and within 6–12 months after genetic counseling of the proband.

Family members' perspectives

Family members' perspectives on unsolicited information letters were investigated using a questionnaire. A study-specific questionnaire was developed based on telephone interviews with family members and input from clinical geneticists and genetic practitioners.

The telephone interviews were performed by the first author and included eight individuals aged 27–64 from Lynch syndrome families (two carriers of a pathogenic MMR gene variant, three non-carriers and three family members who had not undergone genetic diagnostics). All participants had received unsolicited letters within 2 years of the study. The interviews lasted around 30 min and were based on open-ended questions on experiences and attitudes to receiving an unsolicited information letter. The questionnaire contained three sections related to knowledge prior to the letter (8 items), reactions to and views on unsolicited information letters (15 items) and attitudes towards a direct approach in letter format (9 items) to a total of 32 questions. Information on age, sex, children, carrier status, recall of the unsolicited letter and participation in surveillance were collected and free-text comments were allowed. An English version of the questionnaire is available from the corresponding author upon request.

Individuals in families with Lynch syndrome or FCCTX, who had received unsolicited information letters between 2008 and 2015, were eligible for the study. This time period was chosen to ensure representativeness related to variable time since the information letters were received. Of 1278 eligible individuals, 708 individuals were invited and were selected to represent up to 50 individuals from each family type and year of the study period. Since there were not always 50 individuals per year in the FCCTX group, the letters were in total distributed to 318 individuals in FCCTX families and to 390 individuals in Lynch syndrome families. The study cohort included 48% women. Family type was Lynch syndrome in 55%. The letter of invitation and the questionnaire were sent by mail. The respondents were asked to return the questionnaire within 2 weeks, in written format or electronically via a personal QR code. One reminder was sent. The questionnaires were coded and kept separate from identifiable data during the data analysis.

General population's perspectives

Views and attitudes on unsolicited risk information among individuals in the general population were investigated using a questionnaire developed in collaboration with Statistics Denmark. This questionnaire contained five key questions that reflected the content of the information letter. In 2014, Statistics Denmark invited a stratified sample of 1600 individuals, aged 16–74 years, from the general population to a telephone interview. Data were collected as a part of a larger omnibus survey and weighted to represent the adult population in Denmark. Prior to the telephone interview the participants had received a letter with information about the survey, why they were chosen for participation and possibilities for further information.

Data analysis

The pilot interviews aimed to develop the family questionnaire were audio taped, transcribed verbatim and analyzed using content analysis [21]. Data from the family member questionnaire and from the general population survey were analyzed using descriptive statistics. Discrete data are presented as counts and percentages. Univariate analyses included sex, germline variant status, having received an unsolicited letter or not, and participating in a surveillance program or not. Associations were investigated using Chi square test or Fisher's exact test. Free text comments are provided as examples of reactions to the questions and subjects.

Ethical considerations

The study was carried out in accordance with the Helsinki Declaration. According to the Danish Act on Research, ethical approval for the study was not needed. The study has been registered with the Danish Data Protection Agency. All participants were informed about anonymity and confidentiality. Information about voluntariness and the possibility to withdraw from the study were provided in the invitation

letter. Written consent was provided by the participants in the pilot study. A returned questionnaire was considered as consent for participation in the study of family members' perspectives. In the population study, potential informants received a letter from Statistic Denmark prior to the telephone interview with contact information, information about the study and why they were chosen for participation. The practice of sending unsolicited risk information letters was approved by the Danish Ministry of Health and has been recommended by the Danish National Committee of Health Research Ethics.

Results

Pilot study in families with Lynch syndrome

The majority of the informants in the pilot study had been informed about an increased risk of cancer in the family prior to receiving the letter. Some family members expressed relief to obtain an explanation to the many cancer cases in the family. Information about hereditary risk was preferably obtained from family members, but if the information would come from a family member that the informant did not feel emotionally connected to, information from the health care system was preferred. Overall, the informants expressed positive attitudes towards a direct approach from the health care system and considered the information provided in the unsolicited letter to be important and relevant. All informants stated that they preferred to receive a letter to not receiving any information. Some informants reported feelings of surprise and shock when reading the letter, but despite this expressed that they were happy to receive the information. This can be exemplified with a quote from a woman with Lynch syndrome: "I went through a lot of emotions (when receiving the letter). But I am grateful that somebody is watching me, so I can concentrate on other things in life knowing that cancer around me is kept under control".

Attitudes and reactions in families with hereditary cancer

Of the 708 family members invited to participate in the study, 396 (56%) responded to the questionnaire (Table 1). Age and family type were the only differences between respondents and non-respondents (Table 2). The same result was found in a mutually adjusted multiple logistic regression analysis (data not shown). Family type was Lynch syndrome in 52% and FCCTX in 48%. In the Lynch syndrome group, 41 individuals carried pathogenic MMR gene variants, 101 were non-carriers and 64 had not undergone genetic testing or did not know the result thereof. Indeed, only 20 of the 41 respondents with disease-predisposing genetic variants identified themselves as carriers, whereas 10 defined themselves as non-carriers and 11 were uncertain about their carrier status, though all but two participated in surveillance programs. Of the respondents, 91% recalled receiving an information letter, 44% reported being informed about an increased risk and 28% reported having undergone genetic counseling prior to receiving the information letter. Information about risk had been provided by family members in 92% and by physicians in 5%. The majority (94%) of all respondents had

Table 1 Univariate analysis of data from the respondents

	Non-repondents N (%)	Respondents N (%)	Total N (%)	P value*
Sex				
Female	144 (42.2)	197 (57.8)	341	0.4
Male	168 (45.8)	199 (54.2)	367	
Age				
Year Median, q1–q3	52 (41–63)	56 (45–67)	54 (43–65)	0.004
Individual type				
FCCTX	128 (40.3)	190 (59.7)	318	< 0.0001
Lynch, carrier	19 (31.7)	41 (68.3)	60	
Lynch, non-carrier	52 (34)	101 (66)	153	
Lynch, not tested	113 (63.8)	64 (36.2)	177	
Family type				
FCCTX	128 (40.3)	190 (59.7)	318	0.08
Lynch	184 (47.2)	206 (52.8)	390	
Time since letter				
Median, q1–q3	5 (2–6)	5 (2–7)	5 (2–6)	0.4
Mean	4.4	4.4	4.4	0.7

*Chi square and Wilcons' rank sum test was used

Table 2 Family members' reactions to receiving an unsolicited letter with risk information

Reported reaction	FCCTX family N (%)	Lynch syndrome family N (%)	Total N (%)	P value
Was glad to be notified				
Yes	78 (49)	95 (50)	173 (50)	0.33
No	40 (25)	58 (31)	98 (28)	
Don't know	40 (25)	37 (19)	77 (22)	
Missing[a]	32	16	48	
Was glad to get the information in writing				
Yes	117 (73)	127 (66)	244 (69)	0.30
No	14 (9)	26 (14)	40 (11)	
Don't know	29 (18)	39 (20)	68 (19)	
Missing	30	14	44	
Was surprised				
Yes	51 (32)	69 (36)	120 (34)	0.55
No	91 (57)	108 (56)	199 (57)	
Don't know	17 (11)	15 (8)	32 (9)	
Missing	31	14	45	
Felt relieved				
Yes	34 (21)	44 (23)	78 (22)	0.22
No	83 (52)	110 (58)	193 (55)	
Don't know	43 (27)	36 (19)	79 (23)	
Missing	33			
Felt angry				
Yes	4 (3)	14 (7)	18 (5)	0.11
No	143 (91)	166 (87)	309 (89)	
Don't know	10 (6)	10 (5)	20 (6)	
Missing	33	16	49	
Felt sad				
Yes	39 (25)	68 (36)	107 (31)	0.08
No	106 (67)	110 (59)	216 (62)	
Don't know	13 (8)	12 (6)	25 (7)	
Missing	32	16	48	
Was shocked				
Yes	20 (13)	46 (24)	66 (19)	0.015
No	127 (81)	136 (72)	263 (76)	
Don't know	10 (64)	7 (4)	17 (5)	
Missing	33	17	50	
Worried about children				
Yes	89 (59)	119 (65)	208 (62)	0.31
No	50 (33)	56 (30)	106 (32)	
Don't know	13 (9)	9 (5)	22 (7)	
Missing	38	22	60	
Was afraid of getting cancer				
Yes	77 (48)	109 (57)	186 (53)	0.40
No	65 (41)	35 (35)	133 (38)	
Don't know	17 (11)	15 (8)	32 (9)	
Missing	31	14	45	

[a]Missing data are presented but not included in the analysis

been informed about their potential risk after the age of 18. Data from the HNPCC register showed that nearly 80% of the respondents from Lynch syndrome families had undergone genetic testing median 111 (66–176) days after having received the letter.

The information letter was reported to be understandable by 90% and to be relevant by 77% of the respondents. Reactions to unsolicited letters are summarized in Table 2. Of the respondents, 50% reported they were glad to receive the information, among which 69% were glad to receive the information in writing and 15% were not. Other reactions included surprise (34%), sadness (31%), relief (22%), shock (19%) and anger (5%). A worry for children was expressed by 62% and worry about cancer by 53%. The only significant difference in reactions between families with Lynch syndrome and FCCTX related to feelings of shock that were common in individuals from Lynch syndrome families (24 vs. 13%, P = 0.015) (Table 2).

Attitudes to unsolicited information letters are summarized in Table 3 with no significant differences between individuals from FCCTX and Lynch syndrome families (Table 3). In total, 78% of the respondents found it acceptable to obtain information on hereditary cancer through a letter and 64% reported that it was acceptable to receive a letter without prior notification. Written information was preferred to no information by 90% and only 3% were negative to receiving a letter even if this would imply not being informed at all. The views on whether information should be provided by a close relative varied with 40% agreement and 40% disagreement. The preferred source of information was in 66% the healthcare system rather than a distant relative. Regarding information to children, 75% considered that this should be delivered from parents and 66% wanted children to receive a risk information letter at age 18. Moreover, informants in the pilot study as well as family members in the questionnaire study expressed needs for proactive initiatives and support from health care professionals during the information process.

Some respondents reported that the information could be difficult to take in. A woman from a family with Lynch syndrome described her reaction: *When the letter says "cancer in the close family" I thought of my siblings and children, but after having read the letter a couple of times I understood the context. I have more than 40 cousins and I do not know who has developed cancer*. Though the letters evoked emotions, the benefits were repeatedly reported to outweigh the risks. A wish for information earlier in life was expressed. A-64-year old woman from a family with Lynch syndrome was tested negative but wrote: *I can't believe I should turn 50 before I was told that my whole family had died from that gene. I could have used that information much earlier*. Only 3% of the respondents did not want any information at all. Comments suggest that such attitude towards the letter could

Table 3 Family members attitudes towards unsolicited risk information

	FCCTX family N (%)	Lynch syndrome family[a] N (%)	Total N (%)	P value
1. It is generally okay to be notified about risk of hereditary cancer by letter?				
Yes	147 (81)	153 (76)	300 (78)	0.33
No	21 (12)	33 (16)	54 (14)	
Don't know	14 (8)	15 (8)	29 (8)	
Missing[b]	8	5	13	
2. Is it important to be notified about the letter before receiving it?				
Yes	77 (42)	97 (49)	174 (45)	0.84
No	62 (34)	71 (34)	133 (35)	
Don't know	43 (24)	33 (16)	76 (20)	
Missing[b]	8	5	13	
3. Is it important that the first information on risk of hereditary cancer is coming from someone you are in close contact with?				
Yes	67 (37)	87 (43)	154 (40)	0.53
No	76 (42)	77 (38)	153 (40)	
Don't know	38 (21)	40 (20)	78 (20)	
Missing[b]	9	2	11	
4. Would you prefer to be notified of possible risk via letter from the hospital, if the person that would otherwise be informing you, was a distant relative?				
Yes	115 (63)	135 (68)	250 (66)	0.54
No	27 (15)	29 (15)	56 (14)	
Don't know	41 (22)	36 (18)	77 (20)	
Missing[b]	7	6	13	
5. Even if you are not informed that the letter is coming is it okay to be notified of possible risk of cancer by letter?				
Yes	123 (67)	124 (61)	247 (64)	0.50
No	38 (21)	52 (26)	90 (23)	
Don't know	23 (12)	26 (13)	49 (13)	
Missing[b]	6	4	10	
6. Would you prefer to be notified of possible risk of cancer by letter, if the alternative was that you got no information?				
Yes	167 (91)	180 (89)	347 (90)	0.86
No	4 (2)	6 (3)	10 (3)	
Don't know	13 (7)	16 (8)	29 (8)	
Missing[b]	6	4	10	
8. Is it important for you that it is you who tell your children about cancer risk and the possibility of prevention?				
Yes	128 (74)	151 (76)	279 (75)	0.34
No	26 (15)	20 (10)	46 (12)	
Don't know	20 (12)	27 (14)	47 (13	
Missing[b]	16	8	24	
9. Would you like your children to receive information about the risk of cancer and the possibility of prevention when they turn 18?				
Yes	110 (65)	128 (67)	238 (66)	0.73
No	27 (16)	32 (18)	59 (16)	
Don't know	33 (19)	31 (16)	64 (18)	
Missing[b]	20	15	35	

[a]Numbers include individual with and without mutation and unknown mutation status

[b]Missing data are presented but not included in the analysis

relate to difficult circumstances in the respondents' lives. A woman with Lynch syndrome was upset because her son, who had been diagnosed with brain cancer, had received a letter with risk information: *I would have informed him myself when the time was right*.

Population survey

Of the 1600 individuals invited, 1002 (63%) responded to the population survey. Among the responders, the mean age was 46 (16–74) years, the median age was 47 (32–60) and 51% were women. We did not have access to data on the non-respondents since these data were collected as a part of a larger omnibus survey performed by Statistic Denmark. Among the respondents, 82% reported a wish to obtain information about their own risk of cancer (Table 4) with a higher frequency in respondents from households with children (87%) *versus* respondents without children 78% (P = 0.01). Information was preferred to come from healthcare professionals (59%), family members (29%) or other sources (10%) with the majority stating that they would like to be informed by healthcare professionals if their family member was unable to provide the information. Risk information through a letter was favored by 94% of the respondents and among those who did not want information, 60% thought that the health services should send a risk information letter to family members (Table 4).

Discussion

In Denmark, unsolicited letters containing information about a potentially increased risk of colorectal cancer and an invitation to genetic counseling have for 20 years been sent to individuals in families with Lynch syndrome and FCCTX. Since there is limited data on the acceptance for this intervention in the general population as well as among family members, we investigated reactions and attitudes in these groups. Acceptability was high, 86% in family members and 83% of the general population (Tables 3 and 4) and information provided by the health care system was preferred to information provided by distant family members. This support results from studies that suggest that health care professionals could have a more active role in informing family members at a potentially increased risk of disease [21–24].

Family-mediated dissemination of genetic information is recommended and is considered to represent standard of care. Our results, however, demonstrate that only 40% of the family members and 29% of the general population prefer to obtain the first information about a potential increased risk from a family member. Incomplete dissemination of risk-related information has been documented in with different genetic predispositions [22, 25]. Risk information is

Table 4 Attitudes in the general population towards information about risk of hereditary cancer

Question	Response	N (%)
1. If a member of your family was diagnosed with hereditary cancer, would you prefer to be informed about your own risk for hereditary cancer and your possibilities for prevention through regular surveillance programs?	Yes	820 (82)
	No	167 (17)
	Don't know	15 (1)
	Total	1002 (100)
2. *If "Yes" to no. 1*: how would you prefer being informed about your potential risk and opportunities for cancer prevention?	Family member	241 (29)
	Letter from hospital	487 (59)
	Other	81 (10)
	Don't know	11 (1)
	Total	820 (100)
3. *If answer to no. 2 was "Family member" or "Other"*: if your family member could or would not inform you about hereditary cancer in your family, would you prefer getting the information in a letter from the hospital?	Yes	263 (82)
	No	56 (17)
	Don't know	3 (1)
	Total	322 (100)
4. *If "Yes" to no. 1*: do you think that the hospital should send out letters with risk information to all family members?	Yes	771 (94)
	No	45 (6)
	Don't know	4 (0.5)
	Total	820 (100)
5. *If "No" to no. 1*: even if you do not want risk information personally, would you like the hospital to send out letters with risk information to other family member?	Yes	98 (59)
	No	63 (38)
	Don't know	6 (4)
	Total	167 (100)

sensitive to how different individuals provide, understand and interpret the information [26]. Recall bias may to some degree explain diverse interpretations [9, 26] and the information may be modified to fit family "rules" and patterns [22]. Uncertainty applies to how and when to inform family members how to handle poor family relations and whether to protect family members from distress and anxiety [26]. A change in focus from the content of the information to supporting and addressing the challenges in communication between generations in a life-cycle perspective has been suggested to support the families [27]. The disparity in information and uncertainty about the test result represent weaknesses that could be improved using refined, complementary written information.

Though some observations support a more active role for health professionals in the information process related to genetic predisposition, legislation do in most countries prevent geneticists and genetic counsellors to directly contact individuals at a potentially increased risk [5, 28]. Contact to patients' relatives is not permitted without consent from the patient, though health professionals have legal and ethical duties to make efforts to ensure that relatives are offered appropriate information about a potential genetic risk, e.g.by assisting the patients in providing the information [29]. The same principles for the dissemination of genetic information apply in Denmark, with the HNPCC register as a rare exception, which was granted more than 20 years ago due to the strong evidence for the benefit from surveillance in individuals at an increased risk of a life-threatening disease. Unsolicited risk information needs to respect autonomy and consider potential harm [10]. Our findings demonstrate that the majority of the respondents from families at risk of hereditary and familial cancer as well as from the general population support breach of confidentiality in relation to high risk of colorectal cancer. Studies from Norway and Sweden, with a cultural context similar to that in Denmark, have reached similar conclusions with general support for breach of confidentiality under selected circumstances [30, 31].

Our findings of high acceptability of information directly from the health care system also other preventable hereditary and familial diseases could be considered for such management.

An ethical concern related to a direct approach is potential adverse reactions evoked by the information provided [10]. About one-third of the respondents reported anger and shock when receiving the risk information letter (Table 2). Temporarily increased levels of distress have been documented after genetic diagnostics with a correlation to the pre-test psychological distress levels in the vast majority of patients [8, 32]. Only 3% of the respondents expressed that they did not want an information letter even if this would mean that they would not be informed at all. Comments from respondents suggest that this attitude towards information

could lay in experiences of a large burden of psychological distress and difficult circumstances in their lives. Although studies on direct approaches to individuals at increased risk are scarce, current data suggest that such management is possible without compromised privacy and autonomy and with the same psychological outcome as the family-mediated approach [31]. Data from the HNPCC register suggest a higher uptake of genetic testing (78%) compared to a recent study where almost two-thirds of the first generations had undergone genetic testing [33]. Limited data suggest a higher (46%) frequency of genetic testing the following information from a family cancer service compared to a family-mediated approach (24%) [14].

The majority of the respondents found risk information to family members relevant and important but also identified a need for support in this process. Information on heredity is predominantly disseminated to female first-degree relatives with less disclosure to distant relatives and young children, which suggest that support may be needed to reach these groups [34]. Decisions on how and when to disseminate information about potential risk for other family members are often based on anticipated reactions [22]. Concern for children as well as for other family members was frequently expressed. Family members that disclose risk information to e.g. children or siblings they are close to can be expected to have insight and understanding for the receiver's situation and potential reactions, which may explain that some respondents preferred to obtain information from close family members and to personally inform children.

Study limitations include response rates of 63% in the population survey and of 56% in individuals from genetically predisposed families. Further, we were not able to obtain data from non-respondents in the population survey. Item interpretation may also influence the results, though accordance between the three sub-studies argues for study credibility. Carriers of pathogenic variants were under-represented, which reflects probands in Lynch syndrome not receiving letters since they had undergone genetic counseling. Missing data were more common when respondents were asked to report reactions to the letter in the section on attitudes, which likely reflect recall difficulties. A potential effect from the information letters on genetic diagnostics could not be investigated due to lack of control group and data on adherence to surveillance. Finally, our data reflect the situation in the Danish public health care system with a strong tradition for registers and individual contacts from public institutions.

In summary, unsolicited information letters on a potentially increased risk of colorectal cancer were predominantly met with positive attitudes in family members as well as in the general population. In both groups, information from health care professionals was preferred to information from distant relatives. Shared responsibilities with proactivity and support from health care professionals could be considered to increase participation in surveillance programs. These results suggest that unsolicited information may be feasible and could in controlled formats be applied, although evaluation in other clinical and geographical settings would be valuable.

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