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Genetic counselling for familial colorectal cancer. Predictors of efficacy and implications for practice

PhD Thesis Extended Summary

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CONTENTS

SUMMARY

This thesis focuses on genetic counselling for familial and hereditary colorectal cancer (CRC). Genetic counselling helps individuals understand and adapt to a genetic condition. Up to a third of CRC cases might have an underlying hereditary cause. In the past decades, technological advances and understanding of genetics has enabled health care professionals to accurately identify individuals at increased risk of developing CRC and to improve and personalize medical and psychosocial care.

The thesis explores and addresses important aspects regarding the psychosocial impact of familial and hereditary CRC. The thesis builds upon existing knowledge to design and implement 5 studies aimed at, ultimately, improving the psychosocial care and genetic counselling for familial and hereditary CRC. The first study is aimed at mapping the available psychosocial interventions for familial and hereditary CRC described in the literature. The second and third studies are aimed at analysing affective (i.e., emotional distress) and behavioural (i.e., screening uptake) aspects of CRC. The fourth study is aimed at exploring the needs and challenges in setting up a cancer genetic counselling service. The fifth and final study is aimed at investigating the efficacy of genetic counselling for familial and hereditary CRC in a randomized clinical trial. The research presented in this thesis contributes to the field at multiple levels: (1) theoretical, through a mapping systematic review, (2) methodological, by implementing the first randomized controlled trial of genetic counselling for familial CRC, and (3) practical, by setting up and delivering a state-of-the-art service to an underserved population – cancer genetic counselling.

The thesis includes an introductory chapter on genetic counselling for hereditary and familial CRC, an overview chapter presenting the methodological aspects of the thesis, a chapter detailing the original research, and a final chapter discussing the results and overall contributions of the research studies conducted.

CHAPTER I. INTRODUCTION

1. Overview of Genetic Counselling

Currently, genetic counselling is defined as a "process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: (1) interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; (2) education about inheritance, testing, management, prevention, resources and research; (3) counselling to promote informed choices and adaptation to the risk or condition" (Resta et al., 2006).

1.1. The genetic counselling process

Genetic counselling is a complex and personalised approach that usually follows a well-established process. There have been proposed several overarching elements of genetic counselling, common across all medical specialties: a clear diagnosis, a clear documentation of the family history, risk estimations, empathic rapport, emotional support (Harper, 2011; Biesecker, 2019; Resta, 2019).

1.2. Genetic counselling efficacy

The efficacy of genetic counselling has been demonstrated in several previous meta-analyses (Meiser & Halliday, 2002; Braithwaite, Emery, Walter, Prevost, & Sutton, 2006; Moldovan, Pintea & Austin, 2017; Bracke, Roberts, & McVeigh, 2020). Although the evidence base supporting the efficacy of genetic counselling is constantly growing, the literature could benefit from additional studies exploring the predictors of its efficacy as well as additional empirical data collected in randomised controlled trials.

2. Genetic counselling for familial CRC

Cancer genetic counselling is aimed at identifying and providing support for individuals affected by or at increased risk of developing a form of inherited cancer. Cancer genetic counselling is very much tailored to the needs and context of the individuals but the sessions usually include several common aspects (Riley et al., 2012). One of them is taking a detailed, comprehensive personal and familial medical history, whenever possible, for a minimum of 3 generations. The assessment of the genetic cancer risk is based on information gathered from personal and family medical history information and contributes to approximating the level of risk an individual has of developing cancer. If needed, genetic counselling can facilitate informed consent for genetic testing. Best practice guidelines

recommend discussing/offering genetic testing under certain circumstances: (1) clinical conditions (i.e., a suggestive family history for inherited cancer, and the test has an influence on the medical management for the individual and/or the family) and (2) ethical conditions (i.e., testing is voluntary and informed consent is given, benefits of the test outweigh the risks, and test results can be adequately interpreted) (Riley et al., 2012; Robson, Storm, Weitzel, Wollins, & Offit, 2010). Disclosure of genetic test results includes a tailored interpretation, adjusted cancer risk assessment according to the results, and identification of family members at risk (Riley et al., 2012). Another common aspect addressed is the psychosocial assessment and support. This includes but is not limited to reasons for seeking genetic counselling or testing, addressing misconceptions, evaluating psychological outcomes such as cancer worry or risk perceptions (Riley et al., 2012).

2.1. Epidemiology and Aetiology of CRC

CRC is the second most frequent cause of cancer related death (Global Cancer Observatory, 2020). The CRC mortality worldwide is 8.9 to 100.000 (Global Cancer Observatory, 2020). The lifetime probability to develop CRC is 1 in 23 for men and 1 in 25 for women (Siegel, Miller, & Jemal, 2020). Eastern Europe has the highest estimated rates of CRC mortality in both men and women, compared to other regions (Global Cancer Observatory, 2020). In Romania, CRC is the second most frequent cause of cancer death for both men and women (Global Cancer Observatory, 2020).

Depending on the origin and current understanding of mutations and genes, CRC can be classified in sporadic and inherited or familial (Mármol et al., 2017). Sporadic CRC accounts for approximately 70% of the total cases of CRC (Jasperson et al., 2010). Currently described inherited CRC syndromes account for approximately 5% of the total cases of CRC (Jasperson et al., 2010). The term “familial CRC” is commonly used to describe CRC cases that more frequently cluster in the same family. Familial CRC accounts for approximately 25% of the total cases of CRC (Jasperson et al., 2010).

2.2. Clinical particularities of CRC

2.2.1 Sporadic CRC

For comparison purposes we briefly describe the characteristics of sporadic CRC. The lifetime risk of developing CRC in the general population is approximately 1 in 23 (4.4%) for men and 1 in 25 (4.1%) for women. The average age at diagnosis is 68 years for men and 72

years for women. The majority of CRC guidelines recommend screening for average-risk individuals to start at age 50, using colonoscopy at 10 years intervals (Bénard et al., 2018). Recently, the American Cancer Society has lowered the threshold to 45 years of age (Wolf et al., 2018).

2.2.2. Hereditary CRC

Lynch syndrome

Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is one of the best documented cancer syndromes associated with CRC and it accounts for approximately 2-4% of CRC cases (Hampel et al., 2008) and approximately 1.4% of endometrial cancer cases (Chadwick et al., 2001). LS is characterised by increased lifetime risk of developing CRC (52%-82%), endometrial cancer (25%-60%), gastric cancer (6%-13%), ovarian cancer (4%-12%) and other associated cancers. Amsterdam criteria (I and II) were set up to better identify individuals and families affected by LS based on family history (Vasen, Watson, Mecklin, & Lynch, 1999).

Management of affected individuals and family members at risk requires a multidisciplinary approach focused on genetic counselling and testing, screening recommendations, prevention and treatment options. Prevention or early detection of LS associated cancers can increase survival and improve quality of life. With some variation regarding the starting age and screening intervals, the guidelines recommend screening of the colorectum, uterus, ovaries, stomach, urinary tract and central nervous system (Valle, Gruber, & Capellá, 2018).

APC-associated polyposis conditions

Familial Adenomatous Polyposis (FAP), also known as APC-associated polyposis condition, is characterised by an increased risk of CRC. FAP is associated with pathogenic mutations in the APC gene (Jasperson et al., 2017). Attenuated Familial Adenomatous Polyposis (aFAP) is a milder phenotype of the condition, as a result of a mutation in a different location of the APC gene (Valle, Gruber, & Capellá, 2018). FAP and aFAP account for approximately 1% of the CRC cases (Jarvinen, 1992). In FAP, the penetrance is close to 100% by the age of 40 (Bisgaard et al., 1994). In aFAP, the penetrance is less clearly defined but research suggests the risk of developing CRC by the age of 80 is approximately 70% (Burt et al., 2004). Surveillance guidelines in both FAP and aFAP recommend screening for

tumours for several high-risk cancer sites: colorectum, duodenum, thyroid, hepatoblastoma and desmoid (Valle, Gruber, & Capellá, 2018).

2.2.3. Familial CRC

Familial CRC encompasses CRC cases that develop in a familial context. The term has been proposed to define the group of CRC cases that occur in a familial higher-risk setting, such as a first-degree relative with a diagnosis of CRC under the age of 50-55 or multiple first-degree relatives with CRC (Jasperson et al., 2010; Kerber et al., 2005). Population studies show that approximately 20% of CRC cases are due to a familial risk (Kerber et al., 2005). A positive family history of CRC increases the risk to develop CRC to a 2–6-fold compared to the general population, depending on the age of at diagnosis and number of family members affected (Jasperson et al., 2010; Johns & Houlston, 2001).

Another distinct high-risk category of familial CRC has been proposed to describe the approximately 50-60% of CRC cases that meet the Amsterdam II criteria, but do not have a known genetic background (Zetner & Bisgaard, 2017). The term Familial Colorectal Cancer Type X (FCCTX) has been used to define the CRC-affected families which fulfil the Amsterdam II criteria for Lynch Syndrome, but test negative for the MMR genes associated with the syndrome (Lindor et al., 2005). FCCTX accounts for 1-2% of the total cases of CRC (Jasperson et al., 2010). The name is suggestive of a yet unknown gene or genes that are likely to be penetrant enough to produce an autosomal dominant inheritance pattern (Jasperson et al., 2010). Very recently, the BRIP1 gene known until now to be involved in hereditary ovarian cancer, has been found to be involved in FCCTX (Martin-Morales et al., 2020).

2.3. Psychosocial implications of inherited or familial CRC

Several psychosocial aspects related to genetic testing, screening, risk reduction behaviours, and quality of life have been associated with inherited or familial CRC.

2.3.1. Psychosocial aspects related to genetic testing

Identifying genes associated with an increased risk of cancer allowed setting up diagnostic testing for affected individuals and predictive testing for at risk family members. In 2015, the American College of Medical Genetics and Genomics issued standards and guidelines for the classification of mutation variants (Richards et al., 2015). This was particularly valuable for the interpretation of genetic test results in clinical practice. The

guidelines recommend the classification of variants in a 5-category system: (1) pathogenic, (2) likely pathogenic, (3) uncertain significance, (4) likely benign, or (5) benign.

Knowing the mutation status allows a better estimation of the risk to develop CRC, particularly in the context of a relatively early age of onset and with high penetrant cancers. Screening strategies are adjusted depending on mutation status and are aimed at detecting cancer in the early phases as well as improving therapeutic outcomes (Jasperson et al., 2010). A systematic review of the literature showed that approximately half (52%) of the first-degree relatives of LS probands received genetic testing (Sharaf, Myer, Stave, Diamond, & Ladabaum, 2013). More recently, a Finnish registry for LS reported that approximately 60% of the individuals with parents diagnosed with LS chose to undergo predictive testing (Seppälä, Pylvänäinen, & Mecklin, 2017). Given the medical, psychological and familial implications of genetic testing, the majority of professional societies and international guidelines recommend genetic testing to be done in parallel with genetic counselling (Riley et al., 2012; Hampel et al., 2015; PDQ Cancer Genetics Editorial Board, 2019).

The psychological impact of genetic testing for CRC depends on the test results; unaffected non-carriers have the most optimal psychological outcomes; that said, unaffected carriers do not show long-term increased distress (Meiser, 2005). Due to the possibility of childhood-onset of CRC associated with several syndromes, predictive genetic testing is available for children (Michie et al., 2001; Codori et al., 2003; Kattentidt-Mouravieva et al., 2014). Testing for an inherited condition has implications not only for the individual, but also for the family. As one of the motivations to test for inherited CRC is to understand the risk for future children, assessing reproductive options is a relevant implication of genetic testing (Galiatsatos et al., 2015).

2.3.2. Screening and risk reduction behaviours

International guidelines recommend that average-risk individuals start their screening for CRC at 45-50 years old (Bénard et al., 2018; Wolf et al., 2018; Public Health England, 2018). For higher-risk categories, due to the highly penetrant nature of cancer and the relatively early age of onset, screening recommendations for inherited and familial CRC have been adjusted to allow timely detection of cancer. Previous research highlights the importance and benefits of screening programs in LS by achieving a 62% reduction in incidence of CRC and a 65-70% decrease in mortality in the families impacted by LS (de Vos tot Nederveen Cappel et al., 2013). For individuals at increased risk of developing CRC due to a family history of hereditary or familial CRC, guidelines tend to suggest when to start as

well as the type and frequency of screening. Adequate adherence to screening recommendations remains a worldwide concern. Even in countries where a national screening program is available, the compliance with screening recommendations remains suboptimal (Lowery et al., 2014; Brumbach et al., 2017). Genetic counselling and testing have been shown to facilitate a significant and relevant behavioural change regarding screening uptake in LS families, with carriers having an improved colonoscopy uptake and non-carriers reducing the colonoscopy attendance, in accordance to screening guidelines (Hadley et al., 2004; Halbert et al., 2004).

3. Objectives of the thesis

Although genetic counselling for familial CRC clearly addresses relevant aspects in relation to understanding and adaptation to the condition, several key gaps remain uncovered by the scientific literature and remain important to address.

The main aim of this thesis is to evaluate the impact of genetic counselling for hereditary and familial CRC. To achieve this aim, we outline several specific goals:

1. To map out and review the psychosocial interventions currently offered for familial and hereditary CRC.
2. To investigate affective correlates of CRC, specifically the emotional distress associated with a family history of CRC.
3. To investigate behavioural correlates of CRC, specifically the main predictors of colonoscopy uptake.
4. To explore the needs and challenges in setting up a cancer genetic counselling service
5. To investigate the efficacy of genetic counselling for familial and inherited CRC.

CHAPTER II. METHODS

This chapter details the particularities of each research method used throughout the five studies included in the thesis. First, we conducted a rapid mapping systematic review to understand the current state of the literature and identify potential research gaps (Study1). Next, we explored two key components of genetic counselling intervention, the adherence to screening recommendations (Study 2) and the impact of family history on the level of emotional distress (Study 3). Then, in order to successfully design and implement the intervention, we explored the needs and challenges stakeholders have in setting up a cancer genetic counselling service (Study 4). Finally, once we have integrated the findings from all

studies, we designed, implemented and investigated the efficacy of genetic counselling hereditary and familial CRC (Study 5).

1. Rapid mapping review

Systematic reviews are known to employ rigorous methods to include all relevant evidence in the analysis and usually require a significant amount of time to complete. Although undoubtedly valuable, there is an increase need for a timelier process to complete systematic reviews, especially in situations such as policy or healthcare decisions and rapid reviews methodologies emerged to address these issues. Rapid reviews optimise the traditional systematic review process to analyse the evidence in a shortened timeframe (Grant & Booth, 2009).

For this thesis, in order to understand the current state of the literature and research gaps related to psychosocial interventions in familial and hereditary CRC, we conducted a rapid mapping review. This enabled us to analyse and synthetise a rich and diverse body of literature and simultaneously focus and map out potential research gaps. Therefore, we performed a comprehensive and systematic search of the literature published until June 2020 without a specific starting point. We synthesised peer-reviewed quantitative studies investing the impact of clearly defined psychosocial interventions for familial CRC.

2. Receiver operating characteristic (ROC) analysis

Receiver Operating Characteristic (ROC) analysis is a procedure used to organise, select and visualise the diagnostic abilities of tests based on the discrimination performance between different categories of variables. More simply put, the performance of a diagnostic test is given by its ability to confirm the presence of a diagnosis (or characteristic) in an affected individual and to rule out the diagnosis in a healthy individual (Hajian-Tilaki, 2013). In the medical and psychosocial fields, ROC analysis is used mainly to establish the performance of a diagnosis test or a screening tool. ROC analysis and AUC coefficients can be used to determine the ability of a variable (e.g., sociodemographic variables, health and psychological variables or other healthcare related factors) to discriminate between two groups (i.e., screeners and non-screeners) (Pintea & Moldovan, 2009).

For the present thesis, in order to better understand screening behaviours related to CRC and their implications for genetic counselling, we designed and conducted a cross-sectional study to investigate the discriminative value of psychosocial variables to potentially distinguish between individuals attending vs. not attending colonoscopy screening for CRC.

ROC analysis was used to establish the discriminative value of psychosocial variables between the decision to attend or not attend colonoscopy screening.

3. Moderation analysis

In statistics, a moderation effect occurs when the relationship between independent (predictors) and dependent (outcomes) variables are influenced by a third variable, known as a moderator. Moderators can affect the relationship between two variables by modifying its direction and/or strength. The effect of a moderator is known as an interaction. Moderation analyses test for interaction that can influence the relationship between two variables when this relationship occurs (Blair, 2014). Moderation analysis addresses the questions "when" or "for whom" a variable predicts a cause or an outcome (Frazier, Tix, & Barron, 2004).

For this thesis, in order to better understand the emotional distress associated with a family history of cancer and its implications for genetic counselling, we conducted a cross-sectional study, which included individuals from the general population. We wanted to assess the main predictors of emotional distress, in the context of a familial history of cancer in general and CRC in particular. We also aimed to investigate potential moderators of this relationship, to better inform psychosocial interventions addressed to individuals with a family history of CRC.

4. Thematic analysis

Thematic analysis is one of the most common methods used in qualitative research for analysing data to answer research questions about people's experiences, perceptions, attitudes and representations of a given phenomenon. Thematic analysis is "a method for identifying, analysing, organizing, describing, and reporting patterns (themes) within data" (Braun & Clarke, 2006). It is theoretically flexible, it can draw upon concepts from a variety of fields, and it can be used to analyse most types of qualitative data (interviews, focus groups, discussion forums, diaries, qualitative surveys, vignettes, etc.) (Braun & Clarke, 2006).

In this thesis, we designed and conducted a qualitative research to explore the main needs and barriers in setting up a cancer genetic counselling service. We used a data source triangulation method and conducted 34 semi-structured interviews with 13 patients, 11 family members and 10 health care professionals. Purposive sampling was used to recruit participants based on their potential need to access or to recommend genetic counselling. Thematic analysis was used to explore and identify the main themes.

5. Randomised controlled trial (RCT)

A randomised controlled trial is a specific type of scientific experiment used to investigate the efficacy of treatments or interventions and is specifically designed to minimise sources of bias. RCTs are the golden standard for study designs aimed at investigating the efficacy of an intervention. In the hierarchy of medical evidence derived from original research studies with data that needs to be collected, analysed and interpreted for clinical implications, RCT studies occupy the highest position (Murad, Asi, Alsawas, & Alahdab, 2016). The main feature of an RCT is that the participants in the study are randomised into two groups. The experimental group is the group receiving the intervention that is being investigated, and the control group serves as comparison (Friedman, Furberg, & Demets, 2010).

In this thesis we designed and conducted an RCT to explore the efficacy of genetic counselling for CRC. To the best knowledge of the author, this is the first RCT aimed at investigating the efficacy of genetic counselling for CRC. Eligibility criteria to participate in the study were designed to include individuals affected or at risk for hereditary and familial CRC. To date, 53 individuals were included in the study. Participants were randomised to either the experimental arm (standard care + genetic counselling) or control arm (standard care). Our primary endpoint is empowerment, and secondary endpoints include knowledge, emotional distress, risk perception and screening behaviours.

CHAPTER III. ORIGINAL RESEARCH

1. Mapping psychosocial interventions in familial CRC: A rapid systematic review

Introduction

Psychosocial interventions address various psychological and social aspects of a condition and can be delivered in a counselling format, as health education or with a focus on social support. In familial CRC, psychosocial interventions are usually focused on (1) affective outcomes such as distress, anxiety and depression in relation to cancer or genetic testing, (2) cognitive outcomes such as knowledge about cancer and genetics, risk perception, or decision making, (3) behavioural outcomes related to screening, surveillance, and genetic testing.

In the absence of a systematic review, it is difficult to distil the vast amount of publications looking at rather diverse psychosocial interventions targeting various psychological, familial or social aspects. The present study aims to systematically map out the available psychosocial interventions for individuals with a family history of CRC and the current state of the research, in order to identify possible gaps and discuss the potential impact of the interventions.

Methods

An extensive electronic search was conducted to investigate the literature published until June 2020, without a starting point. PubMed, PsycInfo, and Cochrane databases were searched using the following keywords: colon cancer, CRC, bowel cancer, psychological intervention, psychosocial intervention, counselling, genetic counselling, psychoeducation, psychotherapy and first-degree relatives. Inclusion criteria consisted of (1) quantitative studies published in English that (2) explored the impact of psychosocial interventions for familial CRC, (3) clearly defined the psychosocial intervention offered, and (4) included participants with a family history of CRC. Studies were coded to identify: authors, year of publication, intervention type, study design, diagnosis, cancer history, outcome types, providers' background, intervention format, sample size and mean age of the participants.

Results

The literature search yielded 2702 articles. Based on the inclusion criteria, 59 publications were eligible for analysis. Of these, 7 were excluded due to multiple publications from the same cohort. The quantitative analysis included 52 articles. Figure 1 shows the literature search flow diagram. Table 1. presents the coding and characteristics of the articles included in the review.

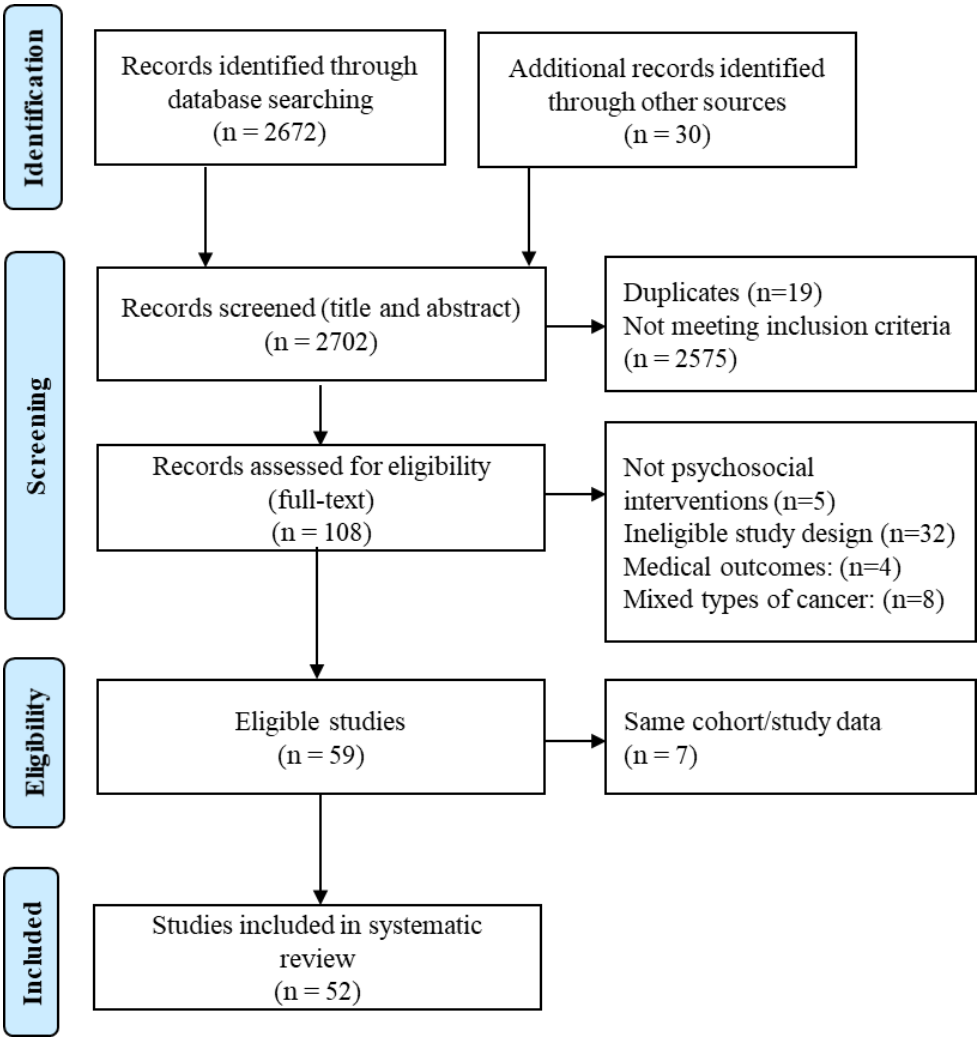

Fig. 1. Flow diagram of search procedure

Table 1. Studies characteristics

No.	Authors, Publication Year	Intervention Type	Study Design	Diagnosis	Cancer History	Outcome type	Provider's Background	Intervention Format	Mean Age	N
1	Aktan-Collan et al., 2007	GC	Prospective	LS	Familial	A, C, QOL	GB	FTF	51,6	72
2	Aktan-Collan et al., 2013	GC	Prospective	LS	Familial	A, C, QOL	GB	FTF	44,3	208
3	Anderson et al., 2014	EDU	Experimental	fCRC	Familial	A, C	CG	TEL	51,2	272
4	Armelao et al., 2010	EDU	Experimental	fCRC	Familial	B	NGB	FTF	57,57	796
5	Arver et al., 2004	GC	Prospective	LS	Familial	A, QOL	GB	FTF	42,7	20
6	Baghianimoghadam et al., 2012	EDU	Prospective	fCRC	Familial	C	NGB	FTF	39,05	99
7	Bastani et al., 2015	EDU	Experimental	fCRC	Familial	A, B	Print/NGB	WRT, TEL	51	1030
8	Bauer et al., 2018	EDU/EDU, PSI	Experimental	fCRC	Familial	B	Print/NGB	WRT, TEL	50.8	261
9	Brain et al., 2005	GC	Experimental	LS	Familial	A, C, QOL	GB	FTF	41	26
10	Burton-Chase et al., 2013	GC	Prospective	LS	Familial	B, C	GC, NBG	FTF	42	78
11	Claes et al., 2005	GC, PSI	Prospective	LS	Familial	A	GB, NGB	FTF	39,25	36
12	Codori et al., 2003	EDU	Prospective	FAP	Familial	A, B	GB	FTF	11,8	35
13	Codori et al., 2005	GC	Prospective	LS	Familial	A, C	GC, NGB	FTF	43,8	101
14	Collins et al., 2000 (a)	GC, EDU	Prospective	LS, fCRC	Mixt	C	GC, GB, NGB	FTF	46,7	126
15	Collins et al., 2000 (b)	GC, EDU	Prospective	LS, fCRC	Mixt	A	GC, GB, NGB	FTF	47	127
16	Collins et al., 2005	GC, EDU	Prospective	LS	Familial	B	NS	FTF	41,33	114
17	Collins et al., 2007	GC, EDU	Prospective	LS	Familial	A	NS	FTF	41	73
18	Dudok deWit et al., 1998	GC	Prospective	FAP	Familial	A	NGB	FTF	28,6	23
19	Esplen et al., 2019	EDU, PSI	Experimental	fCRC	Familial	B, C	GC/NBG	FTF/TEL	47.4	278
20	Glanz et al., 2007	EDU	Experimental	fCRC	Familial	A, B, C, QOL	NGB	FTF, TEL	54,4	176
21	Gritz et al., 1999	GC	Prospective	LS	Familial	A	GC, NGB	FTF	ns	11
22	Gritz et al., 2005	GC	Prospective	LS	Mixt	A, C, QOL	GC, NGB	FTF	ns	155
23	Hadley et al., 2004	GC	Prospective	LS	Familial	B	GC	FTF	38,1	56
24	Hadley et al., 2008	GC	Prospective	LS	Mixt	C, B	GC	FTF	37	65
25	Hadley et al., 2011	GC	Prospective	LS	Mixt	A, B	GC	FTF	41	129
26	Halbert et al., 2004	GC	Prospective	LS	Familial	B	NGB	FTF	49,3	71
27	Hasenbring et al., 2011	GC	Prospective	LS	Mixt	A	GB, NGB	FTF	40,86	122
28	Hawkes et al., 2012	PSI	Prospective	fCRC	Familial	A, B, QOL	NGB	TEL	47,3	22
29	Ho et al., 2012	PSI	Prospective	LS, FAP	Mixt	A, C	NGB	FTF	49,4	22
30	Ingrand et al., 2016	EDU	Experimental	fCRC	Mixt	B	Print/NGB	WRT, TEL	53,1	429

31	Johnson et al., 2002	GC	Prospective	LS, FAP	Familial	B	NS	FTF	55	65
32	Keller et al., 2002	GC, PSI, EDU	Prospective	LS	Mixt	A, C, QOL	GB, NGB	FTF	43,29	65
33	Keller et al., 2008	GC, PSI, EDU	Prospective	LS	Mixt	A, C	GB, NGB	FTF	44	372
34	Kinney et al., 2014	PSI	Experimental	fCRC	Familial	B	Print/GC	WRT, TEL	50,3	378
35	Loader et al., 2005	GC	Prospective	LS	Mixt	A, C, B	GC	FTF	59,9	38
36	Lowery et al., 2014	EDU/EDU, PSI	Experimental	LS, fCRC	Familial	B, C	Print/NGB	WRT, TEL	ns	632
37	Lynch et al., 1997	GC	Prospective	LS	Familial	C	GC	FTF	ns	20
38	Manne et al., 2009	EDU/EDU, PSI	Experimental	fCRC	Familial	B, C	Print/NGB	WRT, TEL	47,9	366
39	Manne et al., 2010	EDU	Experimental	fCRC	Mixt	A, C, B, QOL	NGB	FTF, WRT	46,3	213
40	McClish et al., 2014	EDU	Prospective	fCRC	Familial	B	Print, NS	WRT, TEL	46,8	70
41	McGowan et al., 2012	EDU	Experimental	fCRC	Familial	B, C	NGB	FTF	45,5	140
42	Meiser et al., 2004	GC	Prospective	LS	Familial	A	NS	FTF	41,3	114
43	Murakami et al., 2004	GC	Prospective	LS	Mixt	A	GB	FTF	47	42
44	Pieterse et al., 2005	GC	Prospective	fCRC	Mixt	A, C	GB	FTF	48,61	52
45	Rawl et al., 2008	EDU	Experimental	fCRC	Familial	B, C	Print	WRT	53	140
46	Rawl et al., 2015	EDU	Experimental	fCRC	Familial	B, C	Print/NGB	WRT, TEL	60	145
47	Rimes et al., 2006	GC	Prospective	fCRC	Familial	A, C	GB	FTF	44,2	37
48	Salimzadeh et al., 2018	PSI	Experimental	fCRC	Familial	B, C	NGB	TEL	47.2	240
49	Shiloh et al., 2008	GC	Prospective	LS	Mixt	A	GC	FTF	42,45	253
50	Stehpens & Moore, 2007	EDU	Experimental	fCRC	Mixt	B, C	Print	WRT	50,76	91
51	Voorwinden & Jaspers, 2015	GC	Prospective	LS	Familial	A, C	GC	FTF	41,87	28
52	Wakefield et al., 2008	GC, EDU	Experimental	LS	Mixt	B, C, QOL	Print/NS	FTF, WRT	50,5	109

Intervention: GC=Genetic counselling; EDU=Educational interventions; PSI=psychological interventions; **Diagnosis:** LS = Lynch Syndrome, FAP=Familial Adenomatous Polyposis, fCRC=familial Colorectal Cancer; **Cancer History:** Familial, Mixt=Personal + Familial; **Outcome type:** E=emotional; C=cognitive; B=behavioural, QOL=quality of life; **Provider's Background:** GC=genetic counsellor, GB=medical genetics background, NGB=non-genetics medical background; **Intervention format:** FTF=face to face, TEL=telephone, WRT=written, NS=not specified.

Overview of findings

Three main types of psychosocial interventions were identified: genetic counselling, educational interventions, psychological interventions; for the purpose of this review, we categorised the various combinations of genetic counselling, educational, and psychological interventions as multimodal interventions. Figure 2a. presents the scaled Venn diagram of the interventions and their intersection represents the multimodal interventions. In terms of explored outcomes, we identified a wide range of affective, cognitive and behavioural outcomes and quality of life. Figure 2b. shows the scaled Venn diagram of the explored outcomes and the intersections represent the different combinations found in the studies. In terms of diagnoses, LS was found in 25 studies, FAP in 2 studies, fCRC in 20 studies and combinations of the three were found in 5 studies. Figure 2c. presents the scaled Venn diagram of the diagnoses and the intersections represent different combinations found in the studies. Individuals with a family history of CRC were included in 35 studies and individuals with both personal and familial history of CRC were included in 17 studies. Figure 2d. presents the scaled Venn diagram of individuals included in the studies based on their familial and personal history of CRC.

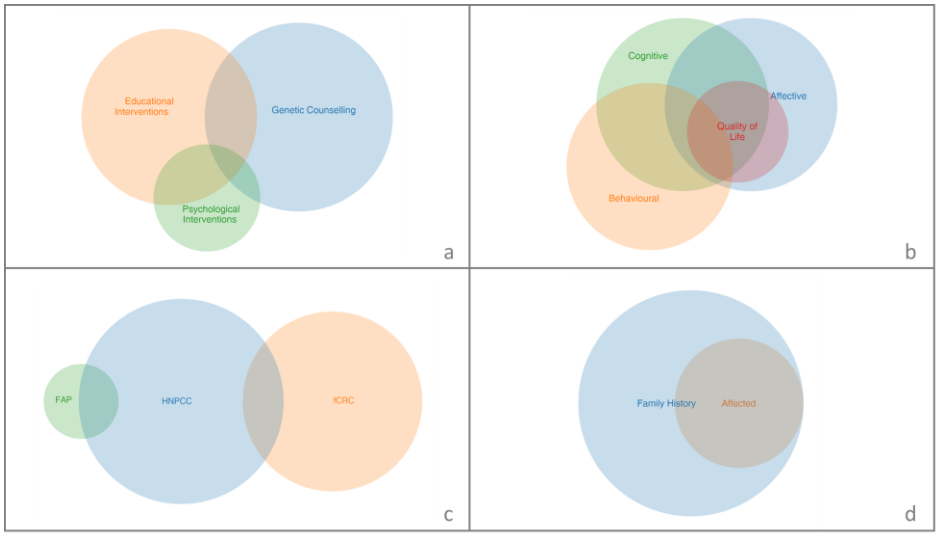

Fig. 2. a) Psychosocial interventions, b) Outcomes c) Diagnoses and d) Cancer history

Genetic counselling was investigated almost half of the articles included in this review. It was offered to unaffected family members at risk for CRC, as well as to individuals with a personal history of CRC. Affective outcomes (e.g., anxiety, depression, emotional distress, and specific fears) represent the most frequently explored outcome. Genetic counselling was mainly

provided genetic counsellors or medical professionals with background in genetics. All but one study measured the impact of genetic counselling with a prospective design.

Educational interventions were found in approximately a third of the articles analysed and were mostly focused on providing knowledge about the risk of developing CRC and prevention strategies. Behavioural outcomes were measured in 12 studies and represent the most frequently investigated outcome. The model of delivery was the most diverse across all psychosocial interventions, using written (i.e., booklets, leaflets, CDs), telephone, face to face, and mixed methods.

Psychological interventions were found in a small proportion of studies and targeted affective, behavioural and cognitive outcomes. Three studies included unaffected individuals at risk for fCRC and one study included individuals with a familial history of LS or FAP. The intervention was offered by health professionals with various professional backgrounds such as oncology nursing, clinical psychology, surgery in 3 studies and by a genetic counsellor in 1 study.

Multimodal interventions consist of different combinations of the 3 main psychosocial interventions. The outcomes investigated were varied from all categories of affective, cognitive, behavioural outcomes and quality of life. Multimodal interventions were provided face to face, by professionals with a wide variety of backgrounds.

Discussions

Our analysis provides an overview of the literature exploring the impact of psychosocial interventions for familial CRC. The analysis suggests that psychosocial interventions – genetic counselling, educational and psychological interventions - have an overall positive impact on emotional, cognitive, and behavioural outcomes. With an overview of the research available, we were also able to identify several research gaps and suggest potential strategies to address them.

Although psychosocial interventions generally reported a positive impact, it is essential for future research studies to rigorously assess their efficacy. Results from genetic counselling studies are undoubtedly positive. In order to provide unequivocal empirical evidence supporting the efficacy of genetic counselling, it is essential for future research to encourage randomised clinical trials. Educational interventions reported positive results on screening uptake. Yet, unsurprisingly, given the informative nature of the education interventions, their impact on

affective outcomes was less prominent. Undoubtedly, there is a clear need for more studies exploring the impact of psychological interventions for familial CRC. Psychological interventions have a strong empirical evidence base supporting their benefit in alleviating emotional distress for cancer in general (Li et al., 2021), and various medical conditions (Mikolasek et al., 2017), therefore only identifying 4 studies investigating psychological interventions was surprising. Given the heterogeneity of the multimodal interventions, the rather modest impact reported was perhaps not surprising.

2. Screeners vs. non-screeners for CRC among people over 50 years of age: factual and psychological discriminants

Introduction

Worldwide, CRC is the third most frequently diagnosed type of cancer. In Romania, it is the second most frequently diagnosed form of cancer (Global Cancer Observatory, 2020). Recent trends, particularly in Eastern Europe, have shown an increase in both incidence and mortality for CRC (Arnold et al., 2017; Vălean, Chira, & Dumitrașcu, 2018). This could be strongly connected with the absence of national screening programs for CRC cancer in many countries from this region.

According to a report of European Commission on cancer screening programs in European Union from 2017 (International Agency for Research on Cancer, 2017) Bulgaria, Greece, Slovakia, and Romania lack a screening program for CRC. In countries with a screening programme in place participation rates ranges between 4.5% and 71.3% (International Agency for Research on Cancer, 2017). In countries without a screening programme Eurostat surveys (Eurostat, 2014) shows high rates of individuals aged between 50 and 74 years that have never been screened for CRC: (Ionescu et al., 2015; United European Gastroenterology, 2020).

For the purpose of this study, and in line with previous literature (Simon et al., 2009; Kobayashi et al., 2014; Sohler et al., 2015; Symonds et al., 2018), we refer to cognitive dimensions (e.g., perceived benefits or barriers, self-efficacy, health-literacy) as *psychological* discriminants and we include healthcare dimensions and objective measures (e.g., presence or absence of screening recommendations, uptake of colonoscopy) under *factual* discriminants.

Our study aimed to explore and ranking factual and psychological discriminants between screeners and non-screeners for CRC in a convenience sample of people over 50 years of age. Having a clearer understanding of the contribution of relevant factors impacting on screening behaviours can better inform medical consultations and psychosocial interventions aimed at increasing colonoscopy uptake in specific populations.

Methods

Inclusion criteria consisted of individuals aged over 50 years old, without a personal history of CRC. The questionnaires were distributed in the morning and individuals who agreed to participate in the study returned the completed questionnaires the following day. Informed consent was obtained from all individual participants included in the study. A brief set of questions was included to assess cancer family history and different aspects related to healthcare including colonoscopy uptake. Health literacy was measured with the European Health Literacy Survey (HLS-EU) (Adams et al., 2019). Health belief model dimensions were measured using a 33-item questionnaire adapted for CRC screening (Murphy et al., 2013).

In order to explore the discriminative value of each variable between screeners and non-screeners, we used Receiver Operating Characteristic (ROC) analysis. For a more intuitive layout of the differences between groups we also calculated Cohen's d values. ROC analysis can be used to determine the ability of a variable (e.g., sociodemographic data, dimensions of the health belief model, health literacy or other healthcare related factors) to discriminate between two groups (i.e., screeners and non-screeners) (Pintea & Moldovan, 2009).

Results

***Participants Characteristics*.** We recruited a total number of 103 participants. Fifty-seven women and forty-six men participated in the study. The average age of participants was 63.47 years, SD= 8.27. Socio-demographic characteristics are presented in Table 1. The most frequent chronic illnesses declared by participants were cardiac conditions, diabetes, gastritis and osteoporosis. Twenty-five participants reported having had at least one colonoscopy in the past.

Table 1.
Participant Characteristics

		Non-Screeners	Screeners
		N=78	N=25
		Mean (SD)	Mean (SD)
Age	Years	62.75 (7.80)	65.72 (9.40)
		N (%)	N (%)
Gender	Male	36 (46.2)	10 (40.0)
	Female	42 (53.8)	15 (60.0)
Relationship	Married/relationship	56 (71.8)	17 (68.0)
	Not in a relationship	1 (1.3)	0 (0)
	Separated/Divorced	12 (15.4)	1 (4.0)
	Widowed	9 (11.5)	7 (28.0)
Last graduated school	Middle school	5 (6.4)	0 (0)
	High School	20 (25.6)	8 (32.0)
	College	22 (28.2)	3 (12.0)
	University degree	31 (39.7)	14 (56)
Living area	Urban	71 (91)	24 (96.0)
	Rural	7 (9.0)	1 (4.0)
Chronic illness	Yes	38 (48.7)	18 (72.0)
	No	40 (51.3)	7 (28.0)
Family History of cancer	Yes	15 (19.2)	10 (40.0)
	No	63 (80.8)	15 (60.0)
Employment	Employed	21 (26.9)	4 (16.0)
	Retired	57 (73.1)	21 (84.0)

***Health Belief Model Dimensions*.** In Table 2, we show the descriptive data for the Health Belief Model dimensions (benefits, barriers, self-efficacy, and outlook), and for the probability and confidence to discuss CRC. The percentage of participants who reported having received recommendations for prevention was 19.4%, and for screening recommendation the proportion was 17.3%. The percentage of participants who said they would consider preventive measures even in the in the absence of recommendations was 58.2% for prophylactic measures and 53.1% for screening measures.

Table 2.
Descriptive statistics of variables investigated

	Non-Screeners	Screeners
	N=78	N=25
Variable	M(SD)	M(SD)
Benefits	24.14 (4.21)	27.00 (13.66)
Barriers	29.31 (8.94)	27.08 (3.54)
Self-Efficacy	33.97 (8.20)	39.91 (8.63)
Outlook (optimism)	20.85 (2.95)	21.04 (4.40)
Discussion Probability	32.50 (30.85)	56.00 (33.97)
Discussion Confidence	63.25 (31.02)	79.58 (25.36)
	N (%) – "yes answers"	
Previous screening recommendation	6 (8.1)	11 (45.8)
Previous prevention recommendation	8 (10.8)	11(45.8)
Screening in absence of recommendation	38 (51.4)	19 (79.2)
Prevention in absence of recommendation	36 (48.6)	16 (66.7)

Barriers to screening. There was no significant difference in terms of perceived barriers for screeners (M=27.08 SD=3.54) and non-screeners (M=29.31 SD=8.94); t(96)=.958, p=.341. For the group of participants who had a screening colonoscopy in the past, the biggest barrier was the concern that the test might find something wrong (41.7%). The second reported barrier was the lack of symptoms (37.2%), and the third barrier was that the test was too expensive (33.4%) and the difficulty to return home after the procedure (33.4%). For the group of participants who did not undergo screening, the most frequent barrier was the lack of symptoms, with 62.2% of participants reporting high or very high agreement. The second reported barrier was that the screening was too expensive (32.4%), and the third barrier was the concern that the test might find something wrong (31.1%).

Benefits to screening. There was a significant difference in the benefits scores for screeners (M=27.00 SD=13.66) and non-screeners (M=24.14 SD=4.21); t(96)=-3.07, p<.003. For the group of participants who reported having done a screening colonoscopy, the greatest benefits were the increased chance of receiving a treatment (95.8%), and that screening is a self-care measure (95.8%). The next reported benefit was the possibility of finding cancer early (91.7%).

Health literacy index. The general health literacy index for all participants in the study was 32.98 (SD=5.55), [M=35.80, SD=6.85 for screeners, and M=32.06, SD=4.77 for non-

screeners], with a significant difference between screeners and non-screeners t(96)=-2.97, p<.004.

ROC Analysis. In order to explore the ability of the proposed variables to discriminate between two groups (i.e., screeners and non-screeners) a ROC analysis was performed on each variable. Table 5 shows the results of the ROC analysis for the discriminants investigated in this study. The most accurate discriminants are the perceived screening benefits of colonoscopy, the perceived probability to open up a discussion with health professionals about screening for CRC, and having received in the past a recommendation to do a colonoscopy. On the health literacy scale, the subscales that discriminated the best between participants who had and those who did not have a colonoscopy in the past, were the disease prevention subscale (DP-HL) and understanding health information subscale (DP-UHI).

Table 5. Results of ROC analysis indicators

Discriminator	AUC	Cohen's d	p value	Sensitivity	Specificity	Criterion
Screening Benefits	**0.711**	**0.787**	**0.001**	**54.17**	**83.78**	**>28**
Discussion probability	**0.697**	**0.729**	**0.002**	**87.5**	**47.3**	**>20**
Previous screening recommendation	**0.689**	**0.697**	**0.007**	**45.83**	**91.89**	**>0**
Previous prevention recommendation	**0.675**	**0.642**	**0.011**	**45.83**	**89.19**	**>0**
Self-Efficacy	**0.659**	**0.58**	**0.019**	**45.83**	**89.19**	**>42**
Discussion confidence	**0.655**	**0.564**	**0.012**	**87.5**	**45.95**	**>60**
Screening in absence of recommendation	**0.639**	**0.503**	**0.026**	**79.17**	**48.65**	**>0**
Family history	0.593	0.333	0.183	37.5	81.08	>0
Prevention in absence of recommendation	0.59	0.322	0.173	66.67	51.35	>0
Barriers	0.575	0.268	0.344	33.33	97.3	>13
Outlook	0.515	0.053	0.845	29.17	91.89	>24
G-HL	0.639	0.503	0.057	45.83	87.84	>35.82
DP-HL	**0.672**	**0.63**	**0.01**	**37.5**	**90.54**	**>38.89**
DP-UHI	**0.66**	**0.583**	**0.012**	**41.67**	**83.78**	**>44.44**
AHI	**0.652**	**0.552**	**0.03**	**58.33**	**74.32**	**>33.33**
FHI	**0.648**	**0.537**	**0.04**	**50**	**83.78**	**>34.62**
UHI	**0.641**	**0.511**	**0.048**	**50**	**81.08**	**>37.88**
HC-UHI	**0.635**	**0.489**	**0.033**	**41.67**	**83.78**	**>41.67**
HP-AHI	0.634	0.484	0.051	25	95.95	>41.67
DP-JHI	**0.633**	**0.48**	**0.045**	**45.83**	**77.03**	**>36.67**
HP-FHI	0.629	0.465	0.053	70.83	48.65	>26.67
DP-FHI	0.628	0.462	0.06	37.5	87.84	>41.67

DP-AHI	0.626	0.454	0.06	33.33	87.84	>33.33
HC-FHI	0.618	0.425	0.096	37.5	86.49	>37.5
HC-AHI	0.606	0.38	0.145	50	72.97	>37.5
HC-HL	0.605	0.376	0.143	45.83	82.43	>37.5
HP-HL	0.596	0.344	0.217	41.67	85.14	>34.38
JHI	0.575	0.268	0.285	41.67	79.73	>36.11
HP-UHI	0.57	0.249	0.376	45.83	83.78	>33.33
HP-JHI	0.55	0.177	0.492	33.33	81.08	>38.89
HC-JHI	0.524	0.085	0.73	29.17	81.08	>33.33

GHL = General health literacy, HC-HL = Health care health literacy, DP-HL = Disease prevention health literacy, HP-HL = Health promotion health literacy, FHI = finding health information, UHI = understanding health information, JHI = judging health information, AHI = applying health information, HC-FHI = health care finding health, HC-UHI = health care understanding health information, HC-JHI = health care judging health information, HC-AHI = health care applying health information, DP-FHI = disease prevention finding health information DP-UHI = disease prevention understanding health information DP-JHI = disease prevention judging health information DP-AHI = disease prevention applying health information, HP-FHI = health promotion finding health information, HP-UHI = health promotion understanding health information, HP-JHI = health promotion judging health information, HP-AHI = health promotion applying health information

Discussions

Perceived benefits of screening, previous recommendations for screening and prevention, and self-efficacy were the best discriminators, with medium effect sizes, between individuals who attended or did not attend colonoscopy screening for CRC. Disease prevention is the most relevant aspect of health literacy to discriminate between screeners and non-screeners. Individuals who reported higher perceived benefits of screening also reported higher probability of colonoscopy uptake. The accuracy of discrimination reported through AUC and Cohen's d had a medium effect size. Furthermore, there was a significant difference between screeners and non-screeners in terms of perceived benefits, but not in terms of perceived barriers. These findings are in line with previous evidence suggesting that perceived benefits weight more than perceived barriers in the decision to attend colonoscopy screening for CRC (Janz & Becker, 1984; Mastrokostas et al., 2018).

Our study has some limitations. Although we were guided by a power analysis in recruiting the participants and our sample is comparable with other similar studies investigating psychosocial aspects of screening for cancer (Williams et al., 2018; Jerome-D'Emilia & Suplee, 2015; Adams et al., 2019), the relatively small sample size we analysed should be factored in when extrapolating results.

3. The impact of risk perception on emotional distress in individuals with a family history of cancer

Introduction

A family history of cancer can sometimes highlight an inherited form of cancer, even when a genetic factor is not yet clearly identified (Wells and Wise 2017). Having a family history of cancer can be associated with being at risk for developing cancer. At-risk status is associated with higher cancer worry and perceived personal risk for developing cancer (Lerman et al., 1993; Schwartz et al., 1999; Erblich et al., 2000; Montgomery et al., 2003). The experience of having family members diagnosed with cancer has been shown to be a major life stressor (Mosher & Danoff-Burg, 2005) and it significantly contributes to higher levels of emotional distress (Liu & Cao 2014; Rabin et al., 2007; Rini et al., 2008). It appears that low awareness of family health history (Kaphingst et al., 2016) is also associated with a higher emotional distress. Data has also shown that a higher risk perception is associated with cancer worry and seems to be influenced by individual coping mechanisms (Molina et al., 2015). An inaccurate risk perception of developing cancer is another factor that can lead to higher psychological distress for individuals with a family history of cancer (Schwartz et al., 1995; Rutherford et al., 2018). Higher emotional distress tends to be more frequent in individuals who provided care for a family member affected by cancer (Zakowski et al., 1997, Erblich et al., 2000), or lost a family member because of cancer (Erblich et al., 2000; McDowell 2013).

The empirical evidence available, mainly derived from breast and prostate familial cancer research, provides an insightful framework to investigate emotional distress associated with other types of familial cancer such as colorectal cancer (CRC), where research is rather scarce.

Method

Participants were recruited based on convenience sampling. We advertised our research amongst undergraduate and postgraduate students through email list and social media. Students who volunteered to participate were informed on the purpose and procedure of the research and completed the questionnaire. Socio-demographic variables were assessed with a short questionnaire. Family history of cancer and perceived risk for developing CRC were assessed

using a purposefully designed form. Impact of Event Scale-Revised (IES-R) (Weiss 2007) was used to measure event-specific distress.

Results

A total of 253 participants completed the questionnaires. Participants' socio-demographic characteristics, family history of cancer and emotional distress scores are presented in Table 1.

Table 1.
Participant Characteristics

		Total N=253	
		Mean	SD
Age		24.92	8.78
		N	%
Sex	Male	97	38.1
	Female	156	61.9
Relationship	Married/relationship	57	22.7
	Not in a relationship	194	77.3
Last graduated school	Middle school	2	0.8
	High School	180	71.5
	College	9	3.6
	University degree	61	24.1
Employment	Student	178	70.4
	Employed	65	25.7
	Unemployed	9	3.6
	Retired	1	0.4
Area	Urban	218	86.2
	Rural	35	13.8
Family history of cancer	1st degree relative	22	8.7
	2nd degree relative	72	28.4
	3rd degree relative	54	21.3
	Total	121	47.8
		M	SD
IES	Total	16.17	17.23
	Intrusion	5.18	6.13
	Avoidance	7.47	8.00
	Hyperarousal	3.52	4.47

Results indicate that 27.9% of participants reported a very low perceived probability to develop CRC, 38.3% reported a low probability, 31.3% reported a medium probability, 1.7% reported a high probability, and 0.8% reported a very high probability.

Emotional distress

We conducted an independent-samples t-test to compare emotional distress in individuals with or without a family history of cancer. We found significant differences both when looking at family history of cancer in general and at family history of CRC. Individuals with a family history of cancer reported significantly higher levels of emotional distress (M= 25.87, SD=15.61) compared to those without a family history of cancer (M=7.27, SD=13.47), t(251)=-10.16, p<.001. The same trend was found when looking more specifically at a family history of CRC; individuals with a family history of CRC reported significantly higher levels of emotional distress (M= 32.17, SD=17.760) than individuals without a family history of CRC (M=15.37, SD=16.854), t(251)=-3.36, p=.001.

Impact of risk perception on emotional distress

Two multiple regression analyses were conducted to explore the moderating effect of risk perception in the relationship between emotional distress and (1) family history of cancer, and (2) family history of CRC. Risk perception significantly moderates the relationship between cancer family history and emotional distress. (β=0.38, CI=(1.68, 5.92), r^2=0.24, p<.001, d=0.25). Figure 1. shows a visual representation of this moderation analysis. More simply put, in the figure the higher the slope, the higher it is the moderation effect.

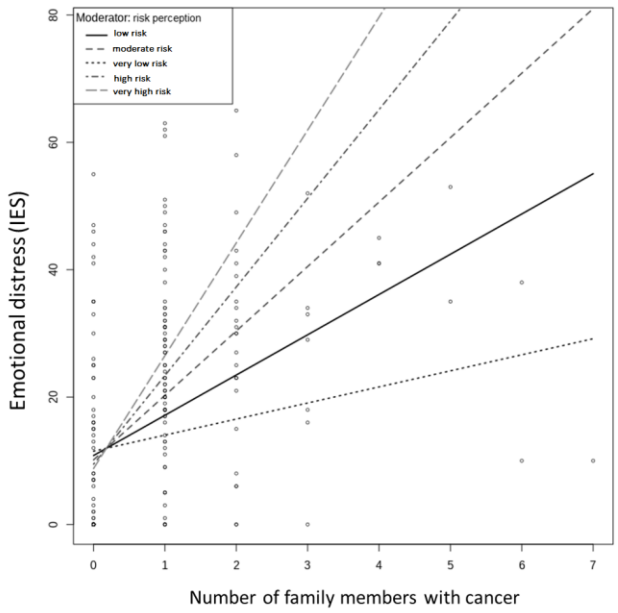

Figure 1.

Risk perception for CRC did not reach the statistical significance in the moderation analysis exploring the relationship between the family history of CRC and emotional distress. (β=4.8, CI=(-0.63, 10.22), r^2=0.06, p=0.08, d=0.29).

Discussion

Results showed a significant difference in emotional distress for individuals with a family history of cancer compared to those with no such history. Previous results in this area are mixed. When looking at the family history of cancer, overall, research suggests a higher emotional distress when associated with a family history of cancer (Rabin et al. 2007, Liu & Cao 2014). When looking specifically at various types of familial cancer, findings vary. Existing data show no difference when comparing individuals with or without history of prostate cancer (Dinkel et al. 2014, McDowell 2013), but differences are significant for breast cancer (Bradbury et al. 2016). Our results clearly show increased emotional distress in individuals with a family history of CRC, compared to individuals without a family history of CRC. This finding enables us to hypothesise that different types of cancer in the family history may have a different impact on emotional distress.

Moderation analysis showed a significant effect of perceived risk to develop CRC on the relationship between a family history of cancer and emotional distress, with small effect size. The moderating effect of perceived risk to develop CRC on the relationship between a family history of CRC and emotional distress did not reach the statistical significance. Our data showed that the higher the risk perception, the higher the emotional distress.

Our study is not without limitations. The study is based on general population data and due to recruitment strategy, it is more relevant for a younger population. Therefore, ecological validity needs to be considered and caution should be used when extrapolating the results to different populations. Further research is needed to draw more complex conclusions regarding the impact of various types of cancer on emotional distress.

4. Highlighting the needs, challenges and hopes of emergent cancer genetic counseling services

Introduction

Genetic counselling has become an established service in North America, Western Europe and Australia and we now have substantial empirical evidence supporting its efficacy (Braithwaite et al., 2006; Meiser & Halliday, 2002; Smerecnik et al., 2009). Although access to genetic counseling remains uneven globally, there are ongoing efforts and improvements across standards of practice, training, and regulation (Abacan et al., 2019).

Patients in Romania, as in many other countries, have limited access to integrated healthcare services and there is a disconnection between highly specialized care and primary or community care (Vlădescu et al., 2016). There is an increasing trend to provide integrated and personalized healthcare services however there are several challenges that need to be addressed. In cancer settings, limited funds are available for reimbursement of specialized services such as genetic testing, and the National Health Insurance is planning to improve access to genetic testing in oncology setting (National Health Insurance House, 2019). National screening programs for cancer are starting to develop, with ongoing or pilot programs, but there are no national screening programs for several types of cancer, including CRC (Cancer screening in the European Union, 2017). Furthermore, national guidelines and professional recommendations for psychosocial care in cancer settings are essentially lacking (Dégi, 2016).

Our main objective was to gain an in-depth perspective of the needs, barriers, and opportunities in the development of cancer genetic counselling services with input from patients, family members, and professionals working in cancer settings. We were also interested to see whether and to what extent there is awareness regarding genetic counselling.

Method

We conducted 34 semi-structured interviews using data source triangulation method (Carter, Bryant-Lukosius, DiCenso, Blythe, & Neville, 2014) to collect a comprehensive set of diverse experiences and to ensure data saturation, therefore we interviewed 13 patients, 11 family members and 10 health care professionals. Purposive sampling was used to recruit participants based on their potential need to access (i.e., patients and family members) or to

recommend genetic counseling (i.e., professionals with diverse backgrounds such as genetic counselling, genetics, oncology, surgery, psychology or social work).

The semi-structured interviews were focused on 3 main areas: (1) psychological and emotional needs; (2) medical and health care issues; and (3) individual and familial aspects; professionals had an additional set of questions explicitly related to genetic counseling. Most interviews were conducted face-to-face at the hospital or workplace, with some interviews conducted on the telephone due to convenience

Thematic analysis was used to explore and identify main themes in the interviews. Data analysis followed the procedure described by Brown and Clarke, 2006. Thematic map is available in figure 1.

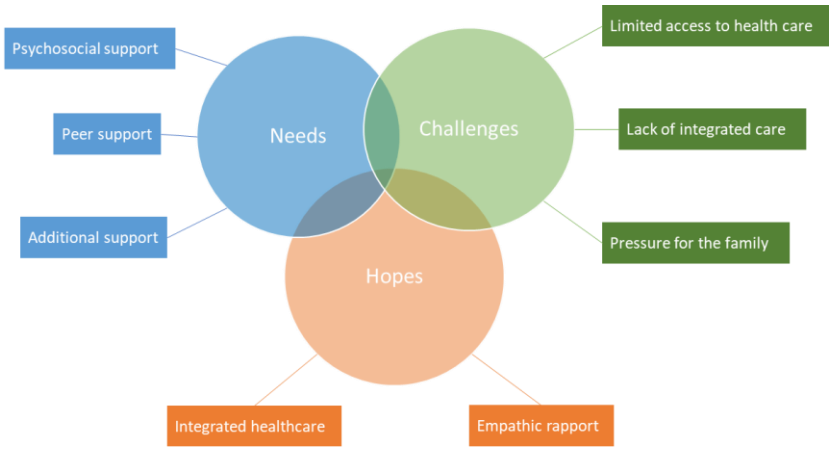

Figure 1. Thematic map

Results

In total, 34 semi-structured interviews were conducted and analyzed. Following the thematic analysis, three major themes emerged: (1) Needs; (2) Challenges; (3) Hopes. Due to significant overlap and convergent ideas across all three categories of participants, the themes and subthemes are discussed together.

(1) Needs

The most salient theme across all interviews and categories of participants was the strong need for support, for both patients and families. Understanding the type of support patients and families need in cancer setting is essential for a functional and meaningful integration of genetic

counseling services. Three sub-themes emerged here, each one describing different types of support needed. *Psychosocial support* was consistently mentioned by the participants. Support is needed when coping with a cancer diagnosis and managing subsequent life changes, dealing with anxiety related to surgery and response to treatment, understanding implications for family members, dealing with intense negative emotions as well as the fear of being pitied. *Peer support* was consistently as a valuable source of support. Patients' associations were described as "rescue lifelines" and several patients said they benefited from attending different meetings and conferences. Additional support was a sub-theme we identified as a distinct need for additional sources of support, in order to cope with long-term consequences and lifestyle changes following a cancer diagnosis.

(2) Challenges

Early in the course of the interviews it became clear that the overarching context of the health care system will be essential in understanding the needs and challenges of the stakeholders involved. The three sub-themes that emerged here are detailed below. *Limited access to health care* sub-theme highlights the difficulties some cancer families and professionals face with the national health care system. Whilst this may not be a challenge for individuals living in urban areas or with straightforward access to public or private hospitals, a number of individuals continue to struggle with access to adequate care. *Lack of integrated care* sub-theme highlighted the fact that integrated care for cancer patients is essentially lacking and there is a strong need to access (i.e., patients, family members) and provide (i.e., professionals) comprehensive, personalized care. *Pressure for the family* sub-theme describes the challenges family members are facing. They act as advocates and information facilitators for the patient and, when the health care pathways are not straightforward, they often initiate the contact with various professionals and take initiative in 'organizing' the care for their loved ones.

(3) Hopes

The third theme encompasses the transformational impact of health communication and personalized approach. Across most interviews, participants shared their experience with health information in general and genetics in particular. Participants touched upon hope, mainly as a result of health communication; patients discussed feeling hopeless after getting information from unreliable sources and in a few instances, professionals discussed how health communication can instill hope. Two sub-themes are included here. *Integrated healthcare* was

mentioned as an idea of a more personalized approach to their care, particularly in complex situations where a cancer family history is present. The need to better understand symptoms, causes, treatment options, risk factors for themselves or others, and screening options were mentioned repeatedly. Most of patients and family members mentioned the low awareness of genetic counseling. Whilst most professionals stressed the need for genetic counseling, they also discussed several barriers in setting up this service, such as trained specialists, willingness to incorporate the logistics of a new service, insufficient funding of genetics and genetic testing, and the lack of a systemic interdisciplinary mindset. *Empathic rapport* sub-theme is mainly focused on patients' wish for a more 'humane' interaction with the professionals and a more personalized communication throughout their care journey. The majority of participants described a great need for simple, plain language when discussing medical information.

I think it would be important to have at least one genetic counsellor in every genetics department. At least one… if not an army of them! To have them talk to patients because they need someone who speaks their language, who empathizes with them, to really feel that empathy. And be a little bit more… more available than doctors. Not that doctors are not available but I think they would also really need a genetic counsellor. (Professional)

"I'd like to see changes in terms of communication, but I also understand that the doctors don't have time to communicate, you know? I mean, they do their job in a very professional way. But there is no professional that has in the job description only this task, to communicate to the patient and the family how things are. And then you get this feeling of insecurity because you feel somehow misinformed, but it is not out of bad will, but out of the stiffness of the health care system. It is very difficult and inefficient. But if there was a way around this… I am talking about another kind of professional here… like in other areas, you have some kind of a spokesperson or something, you know?" (Family member)

Discussion

Our study was aimed at exploring the needs and challenges of patients, family members, and professionals working in cancer settings, in a health care system where genetic counseling is not typically offered. The most prominent theme across all interviews and categories of

participants was the need for support, for both patients and families. Patients and families were generally aware of a family history of cancer and often expressed concerns over adequately understanding the implications it had for their own diagnosis or the risks of other family members. The main challenges identified by most participants were limited access to health care and low availability of integrated care in cancer clinical settings. Patients and families mentioned having to access fragmented health care services which they have to navigate without much support. One particularly interesting finding was that most participants either clearly indicated or tentatively described the need to access genetic counseling services. Often, patients and family members described specific aspects of the genetic counseling process, without necessarily articulating how the service would look like or who the professional delivering that service should be.

Our approach had a bottom-up perspective, aiming to identify the needs and perceived barriers of service users and providers, with a view to set up cancer genetic counseling services. Clearly, policy and decision makers may have a different perspective; also, their input would likely have a broader perspective and that would undoubtedly bring a valuable input. The context of this study enables us to learn how genetic counselling services could be best tailored in order to address the challenges of a developing healthcare system. Locally, our study provides groundwork research for a more systematic approach aimed at integrating genetic counselling in clinical cancer settings.

5. The efficacy of genetic counselling for familial CRC. A pilot randomised controlled trial

Introduction

Research shows genetic counselling is an effective intervention for hereditary breast cancer (Meiser & Halliday, 2002) and has a positive impact on knowledge (Braithwaite et al., 2006), risk perception accuracy (Braithwaite et al., 2006; Smerecnik et al., 2009, Madlensky et al., 2017), anxiety, cancer-related worry, and decisional conflict (Madlenskyet al., 2017).

Our understanding of genetic factors associated with CRC is rapidly increasing (Wells & Wise, 2017). Familial CRC accounts for approximately 20% to 30% of the total cases of CRC (Jasperson et al., 2010; Lichtenstein et al., 2000). Approximately 5% of CRC cases have a well-defined genetic basis (Jasperson et al., 2010). Genetic counselling is recommended when testing

for cancer genetic susceptibility or for individuals at risk due to family history. Genetic counselling has been shown to improve several patient outcomes (Aktan-Collan et al., 2013; Keller et al., 2008; Hadley et al., 2011; Collins et al., 2007; Yuen et al., 2019; Voorwinden et al., 2020). although the overall effectiveness has not been clearly investigated.

The present trial aims to assess the efficacy of genetic counselling for familial CRC in terms of empowerment, cognitive, affective and behavioural outcomes for individual affected or at increased risk to develop CRC. The protocol and implementation of the trial were anchored on state-of-the-art guidelines for clinical trials (Friedman et al., 2010), followed recommendations for randomised clinical trials in genetic counselling (Athens et al., 2017), and included frequently used measures in genetic counselling research (Kasparian et al., 2007).

Methods

We designed a parallel 2-arm randomised controlled trial with 1:1 allocation ratio. The control arm consisted of treatment as usual and the experimental arm consisted of treatment as usual plus genetic counselling.

The trial is aimed to include individuals at risk or affected by familial CRC. Therefore, the study includes (1) individuals (at risk or diagnosed) with hereditary CRC and (2) individuals (at risk or diagnosed) with familial CRC (Jasperson et al., 2010). We used the following inclusion criteria: (1) Individuals from a family with confirmed hereditary CRC syndrome; (2) Individuals from a family with one first degree relative diagnosed with colorectal or endometrial cancer before the age of 50; (3) Individuals from a family with two or more first degree or second-degree relatives diagnosed with colorectal or endometrial cancer, regardless of age. Participants were randomised into two groups. The experimental group received the treatment as usual form their clinical oncologist, which does not include genetic counselling. In the experimental arm, participants received the treatment as usual and were offered a genetic counselling session.

The *primary endpoint* of the trial was empowerment. Genetic Counselling Outcome Scale (GCOS) is a validated 24-item questionnaire designed to measure empowerment in individuals impacted by a genetic condition (McAllister et al., 2011).

Secondary endpoints are grouped into four domains designed to support the primary outcome. Participants were assessed in terms of cognitive, emotional, behavioural aspects related to genetic counselling and their quality of life, which is an exploratory outcome.

Affective outcomes. Anxiety and Depression were measured with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983).

Cognitive outcomes. Distress symptoms were measured with the Impact of Event Scale (IES) (Horowitz et al., 1979). Knowledge was evaluated with self-reported purpose-designed items aimed to measure the level of knowledge about CRC and genetics, the trust in the knowledge, and the perceived utility of the knowledge. Risk perception was measured with two items; first, the perceived risk to develop/redevelop CRC and second, the perceived risk co carry a mutation associated with CRC. The decisional conflict was measured with Decisional Conflict Scale (DCS) (O'Connor, 1995).

Behavioural outcomes. Screening or surveillance behaviours were assessed with self-reported purpose-designed items.

Exploratory variables. Quality of life was measured with Ferrans and Powers Quality of Life Index (Ferrans & Powers, 1985). Perceived social support was measured with the Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet, Dahlem, Zimet & Farley, 1988). The quality of therapeutic relationship was measured with Working Alliance Inventory (Horvath & Greenberg, 1989). All participants also completed a short sociodemographic questionnaire.

Results

To date, 53 individuals were refereed and invited to take part in the study. Figure 1. Presents the flow of participants throughout the study.

The mean age of the participants was 46.82 years (SD=11.43). In total, 17 males and 17 females participated so far in the trial. Table 1 presents the detailed sociodemographic characteristics of the individuals participating in the study. Outcomes scores (means and standard deviations) for genetic counselling and treatment as usual groups for baseline and post-intervention are presented in table 2.

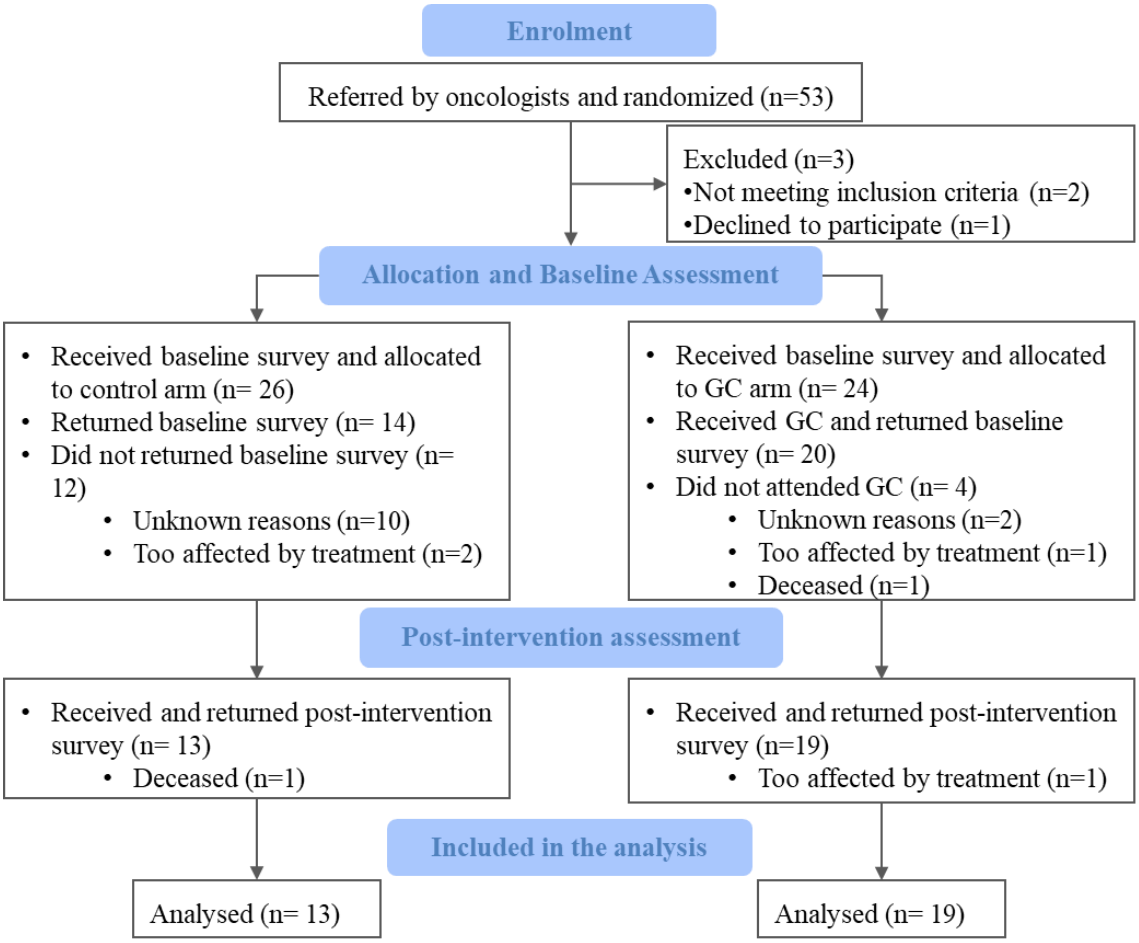

Figure 1. Flow of participants enrolment

Table 1. Participants Characteristics

Characteristic	Genetic Counselling Group (n= 20)		Treatment as Usual Group (n= 14)	
	Mean	SD	Mean	SD
Age of Participants	46.33	12.31	47.52	10.46
	%	N	%	N
Gender				
Male	50	10	50	7
Female	50	10	50	7
Diagnosis				
aFAP	10	2	7.1	1
CRC	55	11	64.3	9
Endometrial	0	0	14.3	2
Lynch	20	4	14.3	2
Breast (FH of CRC)	10	2	0	0
Genetic status				
Affected	70	14	85.7	12
At risk	10	2	14.3	2
Relationship status				
In a relationship	70	14	92.9	13
Divorced	15	3	0	0
Single	15	3	7.1	1
No. of children				
none	30	6	35.7	5
one	15	3	21.4	3
two	40	8	35.7	5
three or more	15	3	7.1	1
Education				
Middle school	5	1	0	0
High school	30	6	71.5	10
University	65	13	28.5	4
Occupation				
Student	5	1	0	0
Employed	80	16	57.1	8
Retired	3	15	42.9	6
Living area				
Urban	85	17	50	7
Rural	15	3	50	7
Religion				
Orthodox	75	15	78.6	11
Not religious	5	1	14.3	2
Other	20	4	7.1	1

Table 2. Means and standard deviations for all dependent measures by group at pre-intervention and post-intervention assessments

Measure	Genetic Counselling Group				Treatment as Usual Group			
	Pre-intervention (n=20)		Post-intervention (n=19)		Pre-intervention (n=14)		Post-intervention (n=13)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GCOS	121.55	14.43	130.84	12.97	108.07	16.90	106.15	18.92
Affective outcomes								
Anxiety (HADS)	6.15	3.98	5.37	3.35	8.86	3.90	8.31	4.05
Depression (HADS)	4.20	3.04	3.47	2.70	7.36	3.73	7.69	3.73
Cognitive Outcomes								
Impact of Event Scale	25.65	12.52	24.05	14.16	32.07	16.56	28.15	16.60
Knowledge Level	45.75	21.54	60.26	23.30	38.93	27.54	40.77	26.05
Knowledge Trust	53.75	26.45	69.74	26.69	42.86	27.01	41.54	29.40
Knowledge Utility	56.50	24.55	72.11	23.53	51.79	27.50	50.38	27.80
Risk perception CRC	35.90	30.09	40.11	25.05	40.71	29.99	44.62	31.85
Risk perception mut.	38.40	31.16	39.79	27.43	38.36	35.41	44.62	33.26
Decision conflict scale	26.72	15.84	22.94	22.23	28.57	16.68	28.73	15.18
Behavioural outcomes								
	n	%	n	%	n	%	n	%
Past screening (yes)	13	65	14	73.70	11	78.60	10	76.90
Past screening (no)	7	35	5	26.30	3	21.40	3	23.10
Screening intention (yes)	15	75	16	84.20	12	85.70	11	84.60
Screening intention (no)	5	25	3	15.80	2	14.30	2	15.40
Exploratory Outcomes								
Perceived Social Support	79.25	4.91	78.84	5.59	75.50	11.88	74.46	11.65
Quality of Life	23.46	4.21	23.80	3.87	20.22	4.94	20.61	5.44
Working alliance (coun.)			78.47	7.95				
Working alliance (patie.)			76.15	7.16				

Primary and secondary endpoints analysis

In order to have a robust understanding of the results, we conducted three statistical analyses. First, we ran independent sample t-tests to compare scores at baseline and post-intervention for all variables. Second, we conducted paired sample t-tests to investigate differences between baseline and post-intervention scores for the treatment groups. As several variables indicated significant differences between groups at baseline, we conducted covariance analyses to control for differences at baseline, for all variables. Table 3 presents all statistical coefficients for between groups, within groups and covariance analyses.

Table 3. Statistical analysis comparing timepoints, groups and ANCOVA with baseline scores as covariates

Statistical test	independent sample t-test (control vs counselling)						Paired sample t-test (pre vs post)						ANCOVA		
	Baseline			Post-intervention			Treatment as Usual Group			Genetic Counselling Group			baseline scores as covariates		
	t	p	d	t	p	d	t	p	d	t	p	d	F	p	d
GCOS	-2.498	0.018	0.857	-4.389	**0.000**	1.522	1.070	0.306	0.294	-4.472	**0.000**	1.028	18.030	**0.0002**	0.750
Affective outcomes															
Anxiety - HADS	1.969	0.058	0.686	2.239	**0.033**	0.792	1.996	0.069	0.561	1.997	0.061	0.459	1.45	0.23	0.204
Depression - HADS	2.715	0.011	0.926	3.722	**0.001**	1.300	-0.674	0.513	0.187	2.800	**0.012**	0.759	10.47	**0.03**	0.436
Cognitive Outcomes															
Impact of Event Scale	1.289	0.207	0.437	0.751	0.459	0.271	1.688	0.117	0.467	1.729	0.101	0.396	0.003	0.9	0.019
Knowledge Level	-0.810	0.424	0.275	-2.216	**0.034**	0.788	-0.889	0.391	0.247	-3.965	**0.001**	0.910	7.09	**0.01**	0.542
Knowledge Trust	-1.172	0.250	0.407	-2.818	**0.008**	1.004	0.433	0.673	0.120	-2.555	**0.020**	0.586	7.26	**0.01**	0.708
Knowledge Utility	-0.525	0.604	0.180	-2.383	**0.024**	0.843	1.298	0.219	0.361	-3.298	**0.004**	0.757	11.54	**0.02**	0.809
Risk perception CRC	0.460	0.649	0.160	0.448	0.657	0.157	-0.187	0.855	0.052	-0.509	0.617	0.117	0.22	0.63	0.006
Risk perception mutation	-0.004	0.997	0.001	0.448	0.657	0.158	-1.403	0.186	0.387	-0.091	0.928	0.021	0.19	0.65	0.108
Decision conflict scale	0.328	0.745	0.114	0.815	0.422	0.303	-0.704	0.495	0.196	0.693	0.497	0.159	0.65	0.42	0.286
Behavioural outcomes															
Past screening	0.838	0.408	0.310	0.201	0.842	0.068	constant	/	/	-1.000	0.331	0.265	0.482	0.493	0.090
Screening intention	0.744	0.462	0.273	0.030	0.976	0.027	constant	/	/	-1.455	0.163	0.319	0.901	0.350	0.216
Exploratory Outcomes															
Perceived Social Support	-1.272	0.213	0.412	-1.424	0.165	0.479	0.672	0.514	0.187	0.170	0.867	0.040	0.914	0.663	0.060
Quality of Life	-2.057	0.048	0.707	-1.943	0.062	0.676	-1.538	0.150	0.425	-0.996	0.332	0.230	0.076	0.785	0.038

Primary endpoint

A one-way ANCOVA was conducted in order to investigate the difference in post-intervention GCOS scores between groups, when controlling for pre-intervention GCOS scores. There is a significant effect in the genetic counselling group on post-intervention GCOS scores after controlling for pre-intervention GCOS scores ($F(1, 29) = 18.03$, $p=0.0002$).

Secondary endpoints

Anxiety. Participants in the genetic counselling group had significantly lower post-intervention anxiety scores compared to the treatment as usual group ($t(30)=2.23$, $p=0.03$). The covariance analysis showed that the differences in post-intervention anxiety scores between groups when controlling for baseline scores is not reaching the statistical significance threshold. *Depression.* Participants in the genetic counselling group reported statistically significant lower scores at post-intervention, when compared to the treatment as usual group ($t(30)=3.722$, $p=0.001$). The covariance analysis showed that the observed differences in depression scores are statistically significant including after controlling for baseline scores ($F(1, 29) = 10.47$, $p=0.03$).

Distress symptoms. The covariance analysis showed no statistically significant differences at post-intervention between groups after controlling for baseline scores. ($F(1, 29) = 0.003$, $p= 0.9$). *Knowledge.* Statistically significant differences were identified when comparing the post-intervention scores for the genetic counselling and treatment as usual groups. (level of knowledge $t(30)= -2.216$, $p=0.034$; trust in knowledge $t(30)= -2.818$, $p=0.008$; utility of knowledge $t(30)= -2.383$, $p=0.024$) Further covariance analyses supported this finding, showing a statistically significant increase in knowledge (i.e. level, trust, utility) in the genetic counselling group after the intervention, when controlling for the baseline scores (level of knowledge $F(1, 29) = 7.09$, $p=0.01$; trust in knowledge $F(1, 29) = 7.26$, $p=0.01$; utility of knowledge $F(1, 29) = 11.54$, $p=0.02$).

Discussion

The aim of this trial was to investigate the efficacy of genetic counselling for individuals diagnosed with or at risk of familial and hereditary CRC.

Data analysis shows genetic counselling was effective in improving empowerment for both individuals at risk or affected by familial or hereditary CRC. This is in line with other prospective studies exploring empowerment following genetic counselling in cancer settings

(Aktan-Collan et al., 2013; Keller et al., 2008; Hadley et al., 2011; Collins et al., 2007; Yuen et al., 2019; Voorwinden et al., 2020).

When comparing the two groups and controlling for baseline depression scores, our data showed a significant decrease in depression after genetic counselling. This is in line with the previous research exploring depression as a genetic counselling outcome. Previous data has shown improvements in depression after genetic counselling and/or genetic testing, regardless of genetic test result (Collins et al., 2007; Gritz et al., 2005; Hadley et al., 2011; Keller et al., 2008; Meiser et al., 2004; Shiloh et al., 2008). Anxiety showed a significant decrease when compared with the treatment as usual group and a decreasing trend for the genetic counselling group when comparing pre-post scores; when controlling for baseline scores, the trend was maintained but did not reach the statistical significance. Studies investigating anxiety in genetic counselling settings, without genetic testing being offered or provided, have shown that gender and age have an impact on anxiety (Hasenbring, 2011).

Significant improvements were observed for the perceived level, trust and utility of knowledge about cancer genetics, when controlling for the equivalent baseline scores. This was an expected result, as previous research focusing on the efficacy of genetic counselling for CRC have shown similar results (Collins et al., 2000a; Pieterse et al., 2005; Loader et al., 2005). The novelty this study brings is that it also looked at the trust and utility of knowledge, which provides added value to the more standard assessment of knowledge from previous studies. Of note, our data show that not only knowledge improve but the knowledge acquired is trusted and seen as useful.

To conclude, the preliminary findings of our study support the efficacy of genetic counselling for familial and hereditary CRC. The primary outcome, empowerment, improved after genetic counselling when compared with the treatment as usual group and after controlling for baseline levels. The affective outcomes are in line with previous research showing improvement in depression and anxiety levels. The cognitive outcomes show significant improvements in terms of knowledge related to cancer and genetics.

CHAPTER IV. CONCLUSONS

1. General conclusions

Increasing understanding of cancer genetics and provision of psychosocial interventions such as genetic counselling has enabled health professionals to capitalise on empirical data available to improve and personalize care for CRC patients and individuals at risk. The present thesis was aimed at exploring and addressing aspects relevant for the psychosocial impact of familial and hereditary CRC. The thesis builds on existing knowledge related to psychosocial interventions and genetic counselling for familial and hereditary CRC by designing and implementing 5 interconnected studies.

The first study was aimed at mapping and reviewing the available psychosocial interventions for familial and hereditary CRC. The second and third studies were aimed at investigating affective (i.e., emotional distress) and behavioural (i.e., screening uptake) aspects of relevance in CRC. The fourth study was aimed at exploring the needs and challenges in setting up a cancer genetic counselling service. The fifth and final study was designed to investigate the efficacy of genetic counselling for familial and hereditary CRC in a randomized clinical trial.

The research presented in this thesis brings several important contributions to the field: (1) theoretical, through a systematic review, (2) methodological, by conducting the first randomized controlled trial to date investigating the efficacy of genetic counselling for familial CRC, and (3) practical, by setting up and delivering a state-of-the-art service to an underserved population.

2. Specific key conclusions

2.1. Systematic review of the psychosocial interventions

This systematic review included studies investigating the impact of psychosocial interventions for familial CRC. Our analysis provides a comprehensive review of available empirical original research. The psychosocial interventions currently available for familial CRC can be grouped in 4 categories: educational interventions, psychological interventions, genetic counselling, and multimodal interventions (which consist of combinations of the first 3

categories). Data suggests that psychosocial interventions have a positive impact on most emotional, cognitive, and behavioural patient related outcomes.

The quality of a review of secondary data is dependent on the quality of the primary data provided in the original studies. A large heterogeny across studies was noted, in terms of theoretical backgrounds of the interventions, outcomes, instruments and research designs. Given the substantial heterogeneity of the interventions, the systematic review was focused on a qualitative assessment, rather than a quantitative investigation. Future research could look into meta-analysis of primary empirical data to determinate the efficacy of the psychosocial interventions identified. Future research could also address several shortcomings identified in the literature. For example, aligning the objectives aimed by the interventions with the outcomes measured will allow a more reliable understanding of the impact and change brought by the intervention.

To the best of our knowledge, this is the first systematic review designed to map out the psychosocial interventions, their characteristics and their impact for individuals diagnosed with or at increased risk of developing familial CRC.

2.2. Factual and psychological discriminants in CRC screening

The results of our study provide an overview of the main factors associated with colonoscopy screening in people over 50 years of age. Both psychological and factual variables discriminated between screeners and non-screeners. Having a recommendation from a healthcare provider, with an emphasis on screening benefits, is very likely to be the most useful way to increase screening for CRC. This is a key finding, and particularly relevant for healthcare systems where, in the absence of national screening programmes, the main responsibility of screening uptake falls on individuals.

A very important limitation of the study is that the data was collected based on self-reported questionnaires. This might lead to inaccuracies such as potential errors in reporting family history or diagnoses, or the understanding of the purpose for the colonoscopy (i.e., screening or diagnosis). Future research should focus on documenting data regarding colonoscopy uptake from representative cohorts at the national level and investigating its direct impact on healthcare (e.g., incidence and early detection of CRC). This is particularly important

in the context of an absent national screening program for CRC and may be informative for other countries where national screening programs are still emerging.

Health care decisions are often complex and need to concomitantly factor in a multitude of aspects. The present study investigates, for the first time in the Romanian population, the medical and psychological factors contributing to the decision to undertake a colonoscopy with screening purposes. The study is especially relevant as there is currently no national screening program in place for CRC.

2.3. Emotional distress in individuals with a family history of cancer

This study contributes to a more comprehensive understanding of the emotional distress associated with familial CRC. There is increased variation in literature regarding the emotional distress associated with a family history of cancer. Our data have enabled us to hypothesise that different types of cancer may have a different impact on emotional distress; our results have additionally shown that risk perception plays an important role in the level of emotional distress.

An important limitation of our study is the relatively young population that participated in the research. Caution should be used when extrapolating the results to other populations. Future research might benefit from focusing on other types of cancer and their impact on the emotional distress, in the context of a family history of cancer. This would enable a better tailoring of psychosocial interventions, more mindful of public perception of inheritance risk in cancer.

Our study brings an important contribution to the existing literature by investigating the relationship between emotional distress and family history from a CRC perspective. Largely, the data available in the literature comes from studies investigating breast and prostate cancer, therefore exploring a frequent condition that equally affects both sexes, such as CRC, was aimed at bringing a wider reach of empirical data.

2.4. Establishing genetic counselling services

The study aimed to explore the needs and challenges of the stakeholders involved in integrating genetic counselling in the clinical practice. We aimed to gain an in-depth perspective from patients, family members and professionals in order to better understand current practice, unaddressed needs, and possible solutions. Three major themes were identified. The *Needs*

theme mainly focuses on various types of support that participants mentioned wanting: psychosocial, peer and additional support. The *Challenges* theme includes aspects related to limited access to healthcare, lack of integrated services and pressure on the families. The *Hopes* theme highlights the wish for integrated healthcare and an empathic rapport with healthcare providers. Setting up a genetic counselling service in a developing healthcare system combined with the rapid developments in genetics and precision medicine can provide the opportunity to design and implementation of well thought service delivery models for genetic counselling (Stoll et al., 2018).

Although patients and family members were more geographically diverse, the professionals interviewed were largely form the same region. This could potentially lead to more convergent opinions and attitudes; a more geographically diverse sample could bring other valuable perspectives. Further research should be designed to take into account data from other stakeholders (e.g., policy and decision makers) in order to better understand how a new healthcare service could be formally established. Future studies could also include additional quantitative data from within the healthcare system and potential service users.

The present research was the first study to explore cancer genetic counselling services in Romania. The study has brought valuable knowledge regarding the needs, opportunities and barriers when envisaging the integration of a state-of-the-art service in current practice. Our results can also be informative for other healthcare systems where cancer genetic counselling is not yet a traditional service.

2.5. Efficacy of genetic counselling for familial CRC

The present trial was designed to assess the efficacy of genetic counselling for familial CRC in terms of empowerment, cognitive, affective and behavioural outcomes. Data analysis shows genetic counselling to be effective in improving empowerment for both individuals diagnosed with or at risk of familial CRC. This is in line with other prospective studies measuring empowerment in cancer settings (Yuen et al., 2019; Voorwinden et al., 2020). Depression scores showed a significant decrease after genetic counselling. *Anxiety* also showed a significant decrease following genetic counselling. In line with previous studies (Collins et al., 2000a; Pieterse et al., 2005; Loader et al., 2005), a significant improvement was also observed in

the perceived level of knowledge as well as the trust and utility of knowledge related to the cancer genetics.

The present study is not without limitations. Heterogeneity of participants is relatively increased as individuals included in the study have very diverse diagnoses of CRC in terms of stage, treatment, time since diagnosis. Future research could benefit from a larger scale multi-site RCT, which would confer greater statistical power as well as the option to explore other variables with potential moderating role on the impact of genetic counselling. Future RCTs could also explore the efficacy of genetic counselling in tandem with genetic testing (e.g., diagnostic or predictive) and assess the outcomes longitudinally.

To the best of our knowledge, this is the first randomised clinical trial investigating the efficacy of genetic counselling for familial CRC. This addresses an important gap in the literature as most data available come from qualitative, cross-sectional and prospective studies.

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