

DOUTORAMENTO

INVESTIGAÇÃO CLÍNICA E EM SERVIÇOS DE SAÚDE

**RISK PERCEPTION AND ATTITUDES TOWARDS
GASTROINTESTINAL CANCER ENDOSCOPY**

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Risk perception and attitudes towards gastrointestinal cancer endoscopy

DOUTORAMENTO EM INVESTIGAÇÃO CLÍNICA E EM SERVIÇOS DE SAÚDE

João Carlos Silva

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**DISSERTAÇÃO DE CANDIDATURA AO GRAU DE DOUTOR APRESENTADA À FACULDADE DE
MEDICINA DA UNIVERSIDADE DO PORTO**

Title: Risk perception and attitudes towards gastrointestinal cancer endoscopy

Título: Perceção do risco e atitudes face à endoscopia na deteção de cancro digestivo

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LIST OF ABBREVIATIONS AND ACRONYMS

AI, Artificial Intelligence.

ARSN, *Administração Regional de Saúde do Norte*.

ASR, Age-Standardized Rate.

CEU, Contracted Endoscopy Units.

CRC, Colorectal Cancer.

ESGE, European Society of Gastrointestinal Endoscopy.

EU, European Union.

FIT, Fecal Immunochemical Test.

FN, False Negative.

GC, Gastric Cancer.

GI, Gastrointestinal.

gFOBT, guaiac-based Fecal Occult Blood Test.

HBM, Health Belief Model.

HP, *Helicobacter pylori*.

HPSA, *Helicobacter pylori* stool antigen test.

ICER, Incremental Cost-Effectiveness Ratio.

OLGA, Operative Link of Gastritis Assessment.

OLGIM, Operative Link of Gastric Intestinal Metaplasia.

RON, *Registo Oncológico Nacional*.

SNS, *Serviço Nacional de Saúde*.

TOGAS, Towards Gastric Cancer Screening Implementation in the European Union project.

UGIE, Upper Gastrointestinal Endoscopy.

UGIS, Upper Gastrointestinal Series.

LIST OF FIGURES



Figure 1: Overview of the thesis structure.

Figure 2[‡]: Colorectal cancer screening programs across European countries.

Figure 3[‡]: European countries classified as intermediate risk for gastric cancer.

Figure 4: A model of risk perception and risk behavior.

Figure 5: Potential strategies for gastric cancer screening in European countries with intermediate risk.

[‡] Created with MapChart.



Outline of thesis and list of publications

OUTLINE OF THESIS

The **Summary** provides a concise overview of this Thesis.

The reasoning and motivation of the presented studies are outlined in **Chapter I (Rationale)**, emphasizing the assessment of colorectal cancer screening participation rates, the exploration of potential individualized screening strategies, and the evaluation of the feasibility of implementing gastric cancer screening in intermediate-risk regions.

The current status of implemented population-based screening programs, along with the challenges and opportunities in gastrointestinal cancer screening, is reviewed in **Chapter II (Introduction)**, with a particular focus on the impact of risk perception.

Unmet needs in gastrointestinal cancer screening are detailed throughout the research questions and aims in **Chapter III (Research Questions and Aims)**.

The systematic review with meta-analysis presented in **Chapter IV (Current Status of Gastric Cancer Screening)** evaluates the impact of gastric cancer screening on mortality and compares the diagnostic yield and adherence of three methods: upper gastrointestinal series, upper gastrointestinal endoscopy, and serological testing.

Four studies focusing on patients' risk perception are presented in **Chapter V (Risk Perception and Attitudes Toward Gastrointestinal Cancer Screening)**. These original articles assess intention to adhere to colorectal cancer screening, preference for the primary screening method, acceptance of upper gastrointestinal endoscopy combined with a screening colonoscopy for gastric cancer screening, and the perceived risk of complications

associated with endoscopic screening procedures. This section also includes a response to a letter concerning one of the aforementioned cross-sectional studies.

Finally, two retrospective cohort studies evaluating the real-world data on the impact of the population-based fecal immunochemical test screening program on early detection and survival, both for colorectal and gastric cancer, are presented in **Chapter VI (Real-World Data on the Impact of Digestive Cancer Screening)**.

In **Chapter VII (Discussion and Conclusions)**, an integrated discussion of all the studies is provided, focusing on the implications of the results in clinical practice.

In **Chapter VIII (Future Directions)**, potential areas for further investigation are explored.

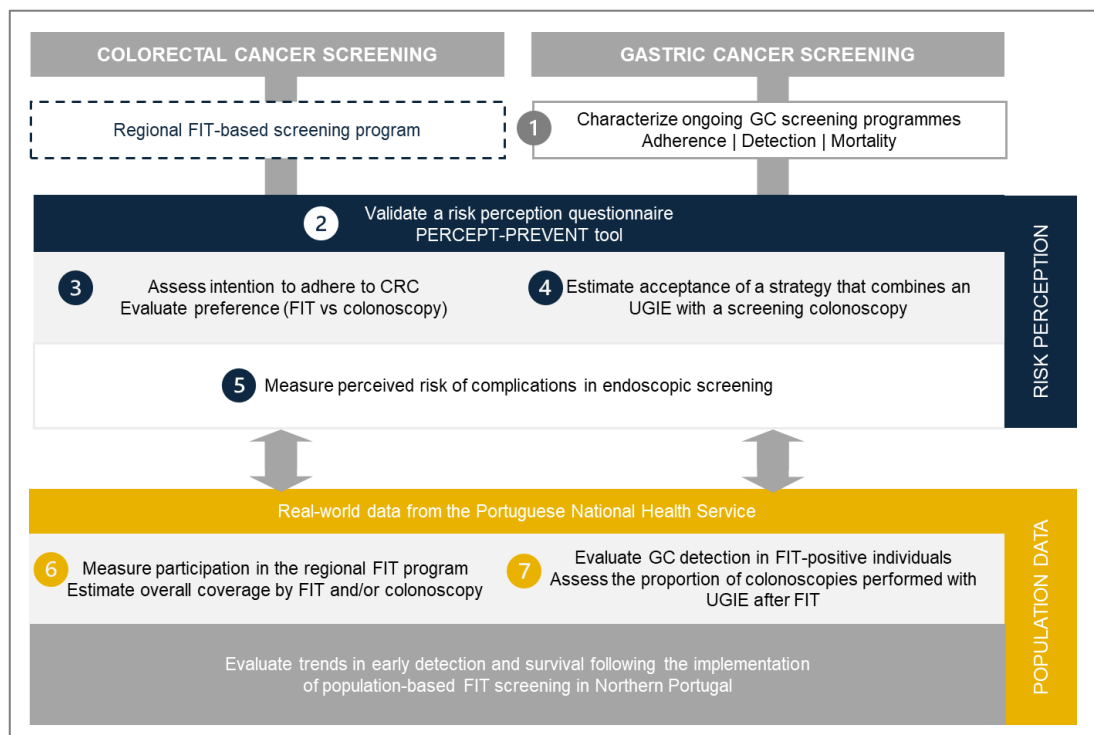


Figure 1: Overview of the thesis structure. CRC, Colorectal Cancer; FIT, Fecal Immunochemical Test; GC, Gastric Cancer; UGIE, Upper Gastrointestinal Endoscopy.

LIST OF PUBLICATIONS

This thesis is built upon a research project conducted in collaboration with the Portuguese National Health Service Executive Board and the Portuguese National Cancer Registry. The project received a three-year research grant from the Portuguese Society of Digestive Endoscopy in June 2021. Below is a complete list of the publications stemming from this research.

Chapter IV: Current status of gastric cancer screening

1. Gastric cancer screening: a systematic review and meta-analysis.

Lídia Faria*, João Carlos Silva*, Marta Rodríguez-Carrasco, Pedro Pimentel-Nunes, Mário Dinis-Ribeiro, Diogo Libânio.

*These authors contributed equally to the writing of this article.

- Scandinavian Journal of Gastroenterology. 2022 Oct; 57(10):1178-1188.
- Journal Impact Factor (2022): 1.9 (**Q2**).

Chapter V: Risk Perception and Attitudes Toward Gastrointestinal Cancer Screening

1. Development and validation of the PERCEPT-PREVENT tool to determine risk perception and attitudes towards digestive cancer screening.

João Carlos Silva, Cristina Santos, Mário Dinis-Ribeiro, Diogo Libânio.

- European Journal of Gastroenterology and Hepatology. 2024 Jan 1;36(1):45-51.
- Journal Impact Factor (2024): 1.8 (**Q2**).

2. Adherence, risk perception, and attitudes towards colorectal cancer screening: a road to individualized screening?

João Carlos Silva, Fernando Tavares, Mário Dinis-Ribeiro, Diogo Libânio.

- Digestive and Liver Disease. 2024. Dec 24:S1590-8658(24)01119-8.
- Journal Impact Factor (2024): 3.8 (**Q1**).

2.1 Author's Reply: "Improving screening participation: the need for socioeconomic considerations and psychological interventions in colorectal cancer programs."

João Carlos Silva, Mário Dinis-Ribeiro, Diogo Libânio.

- Digestive and Liver Disease. 2025 Jun;57(6):1333-1334.
- Journal Impact Factor (2024): 3.8 (**Q1**).

3. Gastric cancer screening: intention to adhere and patients' perspective?

João Carlos Silva, Fernando Tavares, Mário Dinis-Ribeiro, Diogo Libânio.

- Helicobacter. 2024 Sep-Oct;29(5):e13135.
- Journal Impact Factor (2024): 4.3 (**Q1**).

4. Exploring the perceived risk of complications in endoscopic screening procedures.

João Carlos Silva, Fernando Tavares, Mário Dinis-Ribeiro, Diogo Libânio.

- GE Port J Gastroenterol. 2024 Dec 14;32(6):404-413.
- Journal Impact Factor (2024): 0.6 (**Q3**).

Chapter VI: Real-world data on the impact of digestive cancer screening

1. An organized fecal immunochemical test-based screening program affects colorectal cancer early diagnosis and survival in the short term.

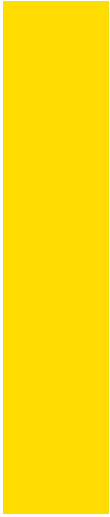
João Carlos Silva, Pedro Leite-Silva, Fernando Tavares, Maria José Bento, Diogo Libânio, Mário Dinis-Ribeiro.

- Am J Gastroenterol. 2025 Oct 13 (online ahead of print).
- Journal Impact Factor (2024): 7.6 (**Q1**).

2. Impact of a FIT-based colorectal cancer screening program on gastric cancer incidence, early diagnosis and patients' survival.

João Carlos Silva, Pedro Leite-Silva, Fernando Tavares, Maria José Bento, Diogo Libânio, Mário Dinis-Ribeiro.

- Helicobacter. 2025;30(5):e70071.
- Journal Impact Factor (2024): 4.3 (**Q1**).



Summary

SUMMARY

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide. While screening is expected to improve long-term outcomes, the most effective population-based strategy remains a topic of debate. Organized screening enables structured invitations, continuous quality assurance and centralized data management. In Europe, most countries have adopted organized, population-based programs using the fecal immunochemical test (FIT). When colonoscopy was used as the primary method within organized screening, participation rates did not exceed 20%. However, offering colonoscopy as an alternative to FIT led to an increase in population coverage in the context of opportunistic screening. Risk perception, including perceived susceptibility to cancer and perceived barriers to screening, may significantly influence adherence rates and, ultimately, the overall screening effectiveness.

While gastric cancer (GC) ranks as the fifth most common malignancy, population-based screening remains sparsely characterized. In Portugal, where incidence is moderate to high, screening may be cost-effective if an upper gastrointestinal endoscopy (UGIE) is combined with a screening colonoscopy. Same-day UGIE has been reported to detect up to 25% more malignancies than colonoscopy alone. To date, no population-based program has been implemented in intermediate-risk countries, despite the European Commission's commitment to advancing GC screening. The long-term impact of organized FIT screening on early detection and survival remains poorly defined for both CRC and GC.

This thesis aimed to assess adherence, compare preferences for FIT and colonoscopy, measure acceptance of combined UGIE and colonoscopy, and evaluate the impact of FIT-based screening on CRC and GC early detection and survival. More broadly, it focuses on the optimization of CRC screening strategies and the implementation of GC screening initiatives

through the assessment of individual risk perception and the analysis of real-world data from population-based screening.

To complement the substantial evidence on population-based CRC screening, we conducted a systematic review to synthesize data on GC screening. After a comprehensive assessment, only Japan and South Korea have implemented population-based screening, offering both Upper Gastrointestinal Series and UGIE. GC screening was associated with significantly lower GC mortality rates and UGIE reached the highest detection rates.

In order to measure risk perception a previously validated questionnaire on CRC risk perception, based on the Health Belief Model (HBM), underwent forward/backward translation and cultural adaptation and was further adapted to address GC screening and complication risk perception. Validation of the PERCEPT-PREVENT tool, in a test-retest study, was a necessary step to enable subsequent exploration of personalized screening and of synergistic screening approaches across three cross-sectional studies.

The first cross-sectional study was designed to evaluate the intention to adhere to CRC screening by examining preferences for fecal tests versus colonoscopy as the primary screening method and to assess the influence of risk perception on screening participation. Overall, the intention to adhere to CRC screening was reported in 95% of cases and was positively influenced by knowledge of the screening rationale. A clear preference for colonoscopy over fecal tests was evident, yet 25% of naïve participants preferred FIT.

Subsequently, a cross-sectional study was conducted to estimate patients' perspectives and adherence to GC screening using a strategy that combines UGIE with colonoscopy. Self-reported willingness to undergo UGIE combined with a screening colonoscopy reached 94%. Regular follow-up with the primary care physician, lower perceived negative health consequences of UGIE, and lower perceived financial burden were the only factors independently associated with a higher intention to undergo combined screening.

Previous data suggest that those naïve to CRC screening were more likely to overestimate colonoscopy complications. However, our third observational study found that 19% of never-screened and 45% of screened participants perceived a high risk of colonoscopy complications, while for UGIE, the figures were 14% and 41%, respectively. This is explained by greater awareness in screened individuals and limited knowledge in those without prior exposure to endoscopic procedures.

Taken together, the findings from the three cross-sectional studies on risk perception highlight limited health literacy regarding digestive cancer symptoms, risk factors, and the potential risks of endoscopic screening procedures. Our results highlight the pressing need for targeted initiatives aimed at improving health literacy.

Results from our population-based retrospective cohort study showed that FIT screening is effective at the population level. Despite the 20% false-negative rate, individuals who accepted FIT screening had significantly higher rates of early CRC detection (58% vs. 49%) and higher 3-year net survival (87.5% vs. 72%) compared to those who were not screened. Our findings also indicate that adherence to FIT is high (34%) and that coverage can be increased if alternatives to fecal tests are offered. In the cross-sectional assessment, most participants classified as non-adherent had previously undergone colonoscopy. This was further supported by real-world data showing a 10% increase in coverage by FIT and/or colonoscopy after including procedures performed alongside the organized screening program through referrals by primary care physicians. These findings support the potential of a more personalized approach to CRC screening, especially by offering primary colonoscopy to individuals who decline FIT as a strategy to maximize population coverage. Furthermore, fully utilizing the health system's comprehensive screening capacity has been essential in strengthening coverage.

In a real-world setting without a formal GC screening program in Northern Portugal, over 50% of individuals who accepted FIT and underwent colonoscopy also had UGIE. This

rate might reach the 94% acceptance observed in our previous cross-sectional study if population-based screening is implemented. Moreover, although the FIT program is not primarily designed to detect GC, it was associated with improved outcomes, including higher early detection rates and survival. Following the implementation of FIT-based screening, the proportion of early-stage diagnoses increased by 14% and the 3-year net survival improved from 42% to 49%.

This thesis highlights the pressing need to strengthen health literacy as a strategy to overcome barriers to cancer screening and, ultimately, to lessen the burden of both CRC and GC. Moreover, it provides robust evidence to inform screening strategies in Northern Portugal, supporting personalized approaches by offering colonoscopy as an alternative to FIT and by advocating for the pioneering implementation of GC screening through combined UGIE and colonoscopy.

RESUMO

Atualmente, o cancro colorretal (CCR) constitui a segunda principal causa de morte por doença oncológica a nível mundial. Apesar do impacto positivo associado ao rastreio, a escolha da estratégia mais adequada continua a suscitar debate na comunidade científica. O rastreio organizado permite o envio de convites automatizados, a monitorização contínua dos critérios de qualidade e o processamento centralizado da informação. A maioria dos países europeus implementou programas de rastreio organizado com recurso à pesquisa de sangue oculto nas fezes (PSOF) pelo método imunoquímico. Quando a colonoscopia foi utilizada como método primário no âmbito do rastreio organizado, as taxas de participação não excederam os 20%. No entanto, a disponibilização da colonoscopia em alternativa à PSOF, levou a um aumento da cobertura populacional, no contexto do rastreio oportunístico. A perceção do risco, incluindo a suscetibilidade individual e as barreiras ao rastreio, pode influenciar as taxas de adesão e, por consequência, a eficácia do rastreio.

Embora o cancro gástrico esteja classificado como a quinta neoplasia maligna mais comum, o rastreio populacional ainda está pouco caracterizado. Em Portugal, um país com incidência moderada a elevada, o rastreio poderá ser custo-efetivo se a endoscopia digestiva alta (EDA) for combinada com uma colonoscopia de rastreio. A realização de EDA concomitante poderá aumentar em até 25% a deteção de neoplasias. Ainda não foi implementado nenhum programa de base populacional em países de risco intermédio, apesar do compromisso da Comissão Europeia em promover o rastreio. O impacto a longo prazo do rastreio organizado por PSOF (método imunoquímico) na deteção precoce e na sobrevivência permanece mal definido tanto para o CCR como para o GC.

Os objetivos desta tese foram medir a adesão ao rastreio organizado, explorar a preferência individual pela PSOF ou pela colonoscopia, mensurar a aceitação da EDA combinada com a colonoscopia e avaliar o impacto do rastreio por PSOF (método

imunoquímico) na detecção precoce e sobrevivência por CCR e cancro gástrico. De forma mais abrangente, centra-se na otimização das estratégias de rastreio do CCR e na implementação do rastreio do cancro gástrico, através da avaliação da perceção individual do risco e da análise de dados populacionais.

Para complementar a evidência robusta existente acerca do rastreio do CCR, realizámos uma revisão sistemática com o objetivo de sintetizar os dados disponíveis sobre o rastreio do cancro gástrico. Após uma avaliação abrangente, verificou-se que apenas o Japão e a Coreia do Sul implementaram programas de rastreio de base populacional, oferecendo o trânsito gastroduodenal e a endoscopia digestiva alta (EDA). O rastreio do associou-se a uma redução significativa da mortalidade por cancro gástrico, tendo a EDA alcançado taxas de detecção superiores.

De forma a medir a perceção de risco, utilizou-se um questionário previamente validado sobre perceção de risco para o CCR, que foi sujeito a tradução, adaptação cultural e posterior adaptação para abranger o rastreio do cancro gástrico e a perceção do risco de complicações. A validação do questionário PERCEPT-PREVENT constituiu um passo necessário para viabilizar o estudo de abordagens de rastreio personalizado e estratégias sinérgicas no rastreio oncológico, desenvolvido posteriormente ao longo de três estudos transversais.

O primeiro estudo transversal foi desenvolvido para estimar a intenção de aderir ao rastreio, analisando a preferência pela PSOF ou pela colonoscopia, bem como para avaliar a influência da perceção de risco na adesão. Globalmente, 95% dos participantes reportaram a intenção de aderir, tendo este resultado sido positivamente influenciado pelo conhecimento do racional para o rastreio. Observou-se uma clara preferência pela colonoscopia em detrimento dos testes fecais, embora 25% dos participantes naïve para o rastreio tenham preferido a PSOF.

Realizámos subsequentemente um estudo transversal para avaliar as perspetivas dos doentes e a sua adesão a uma estratégia que combinasse a EDA à colonoscopia de rastreio.

No total, 94% aceitaram realizar a EDA em combinação com a colonoscopia de rastreio. O acompanhamento regular pelo médico de família, a menor percepção das consequências negativas da EDA e a percepção de um menor impacto financeiro foram os únicos fatores independentemente associados a uma maior intenção de aderir ao rastreio combinado.

Evidência prévia sugeriu que indivíduos naïve para o rastreio tendem a sobrestimar o risco de complicações da colonoscopia. No entanto, o nosso terceiro estudo observacional revelou que 19% destes indivíduos e 45% dos já rastreados apresentaram uma percepção elevada do risco de complicações da colonoscopia, enquanto para a EDA os valores foram de 14% e 41%, respetivamente. Tal explica-se por uma percepção mais adequada nos indivíduos previamente rastreados e por um conhecimento limitado entre os indivíduos sem experiência prévia.

Globalmente, os resultados dos três estudos transversais sobre a percepção de risco evidenciam uma limitada literacia em saúde, especificamente no que diz respeito ao conhecimento dos possíveis sintomas, fatores de risco e dos riscos associados ao rastreio endoscópico. Estes resultados denotam a necessidade premente de levar a cabo iniciativas dirigidas à melhoria da literacia em saúde.

Os resultados do nosso estudo de coorte retrospectivo de base populacional demonstraram que o rastreio por PSOF pelo método imunoquímico é eficaz. Apesar da taxa de falsos negativos de 20%, os indivíduos que aceitaram o rastreio por PSOF apresentaram taxas significativamente mais elevadas de deteção precoce (58% vs. 49%) e de sobrevivência a 3 anos (87,5% vs. 72%). Os nossos resultados indicam ainda que a adesão ao rastreio por PSOF é elevada (34%) e que a cobertura pode ser aumentada se forem oferecidas alternativas aos testes fecais. No estudo transversal, a maioria dos participantes que não aderiram ao rastreio por PSOF tinha sido submetida a colonoscopia previamente. Estes resultados foram reforçados pelos dados de base populacional, que demonstraram um aumento de 10% na cobertura por PSOF e/ou colonoscopia após a inclusão dos procedimentos realizados em

paralelo com o programa de rastreio organizado, mediante referência pelos cuidados de saúde primários. Estes resultados sustentam o potencial de uma abordagem mais individualizada ao rastreio do CCR, nomeadamente através da oferta da colonoscopia aos indivíduos que recusam a PSOF (método imunoquímico), como estratégia para maximizar a cobertura populacional. Além disso, a plena utilização da capacidade de rastreio disponível no sistema de saúde revelou-se crucial para o reforço da cobertura.

Em contexto de vida real e na ausência de um programa formal de rastreio de cancro gástrico no Norte de Portugal, mais de 50% dos indivíduos que aceitaram a PSOF (método imunoquímico) e realizaram colonoscopia efetuaram também uma EDA. Esta taxa poderá atingir os 94% de aceitação observados no nosso estudo transversal, caso venha a ser implementado um programa de rastreio de base populacional. Além disso, embora o programa de rastreio por PSOF não tenha como objetivo principal a deteção de cancro gástrico, esteve associado a maiores taxas de deteção precoce e de sobrevivência. Após a implementação do programa de rastreio, a deteção precoce aumentou 14% e a sobrevivência a 3 anos passou de 42% para 49%.

Esta tese realça a necessidade urgente de reforçar a literacia em saúde como forma de ultrapassar barreiras ao rastreio oncológico e, em última análise, reduzir o impacto do CCR e do cancro gástrico. Além disso, apresenta evidência robusta que pode orientar a tomada de decisões relativamente às estratégias de rastreio na região Norte de Portugal, sustentando uma abordagem personalizada que disponibiliza a colonoscopia como alternativa ao rastreio por PSOF e apoia a implementação pioneira do rastreio do cancro gástrico através da combinação da EDA com a colonoscopia de rastreio.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ✓ Population-based screening can reduce CRC incidence and mortality through early detection, although the optimal strategy remains under debate.
- ✓ Combining UGIE with a screening colonoscopy may be cost-effective in countries with intermediate incidence, yet no GC screening program has been implemented in Europe.

WHAT THIS STUDY ADDS

- ✓ In Northern Portugal, adherence to FIT screening was 34%, while overall coverage by any test for CRC detection, including colonoscopies performed outside the FIT program, was 45%. Early detection and survival were higher among FIT participants than non-participants.
- ✓ Willingness to undergo UGIE combined with a screening colonoscopy was reported in 94%. More than 50% of those who accepted FIT screening and underwent colonoscopy also had an UGIE. FIT screening was associated with earlier detection and improved survival in GC.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ✓ Underscores the urgent need to improve literacy in digestive health.
- ✓ Supports offering colonoscopy as an alternative to FIT, as personalized screening approaches may improve participation rates.
- ✓ Calls for the implementation of population-based GC screening in Northern Portugal through the combination of UGIE with colonoscopy.



Chapter I – Rationale

RATIONALE

Colorectal cancer (CRC) is the third most diagnosed cancer^{1,2}. The projected burden of CRC is expected to rise, with an estimated 3 million new cases anticipated by 2040 if the global incidence rates remain unchanged². Considerable debate exists regarding the most effective strategy for population-based CRC screening³. European recommendations advocate for population-based fecal immunochemical test (FIT) screening for individuals aged 50 to 75, while allowing primary colonoscopy or sigmoidoscopy based on local factors such as adherence rates and colonoscopy availability^{4,5}. To date, most European countries have implemented organized, invitational screening programs based on fecal tests. In contrast, Poland adopted a distinct approach by selecting colonoscopy as the primary modality for organized nationwide screening⁶⁻⁸.

In Northern Portugal, following a pilot program in early 2017, a regional FIT-based screening program was launched in 2018 to cover 1.1 million residents⁹. The rollout was phased by county, ensuring that all eligible age groups were invited by 2022⁹. The decision to implement biennial FIT screening was based on a previous cost-utility analysis comparing biennial FIT or colonoscopy every ten years versus non-screening in Portugal⁵. Biennial FIT was the most cost-effective strategy, maximizing population coverage and optimizing the use of endoscopic resources⁵. Nonetheless, the participation rates used in the cost-utility analysis were derived from European and North American estimates, as adherence to both FIT and colonoscopy remains largely unknown in the Portuguese population^{10,11}. In European countries and specifically in Portugal, the intention to adhere to CRC screening and patients' preferences (for fecal tests or colonoscopy as the primary screening method) has not yet been evaluated.

Risk perception, knowledge about cancer risk, and attitudes toward screening have seldom been addressed in the context of population-based screening programs, especially in

Western countries^{12,13}. Assessing risk perception is crucial for selecting the preferred screening method, identifying factors associated with non-adherence, and overcoming barriers to screening. Moreover, data on perceived risk of endoscopy-related complications in the screening setting remain limited¹⁴. Risk perception in digestive cancer screening involves two primary dimensions: first, the perceived risk of foregoing screening, early diagnosis, or timely treatment for serious conditions; and second, the perceived risk of complications associated with the endoscopic procedures themselves. Together, these dimensions shape individuals' willingness to participate in screening programs and highlight areas where tailored communication strategies may enhance engagement and improve health outcomes.

Besides CRC, gastric cancer (GC) poses as an emerging potential target for screening in Europe¹⁵. GC is the fifth most common cancer and the third cause of cancer mortality worldwide¹⁶. However, population-based screening has only been implemented in high-risk regions, characterized by an age-standardized incidence rate (ASR) of ≥ 20 per 100,000¹⁷⁻¹⁹. In late 2022, the Council of the European Union on Cancer Screening introduced an updated recommendation, which expands screening to include lung, prostate, and gastric neoplasms^{15,20}. Regarding GC screening, the revised directive emphasizes screen-and-treat strategies for *Helicobacter pylori* (Hp) infection, as well as the identification and surveillance of individuals with precancerous gastric lesions. From a policy perspective, this marks a pivotal opportunity for the implementation of GC screening across Europe. Moreover, the European Society of Gastrointestinal Endoscopy (ESGE) position statement on digestive cancer screening suggests that, in regions with an intermediate risk of gastric cancer (ASR 10–20 per 100,000), combining upper gastrointestinal endoscopy with screening colonoscopy may be considered if cost-effectiveness is demonstrated within the context of the national healthcare system⁴. This recommendation is based on a Portuguese cost-utility analysis that concluded that endoscopic screening for GC is cost-effective when combined with a screening

colonoscopy every 5 or 10 years, assuming full compliance^{21,22}. The Northern region of Portugal has a higher incidence of GC compared to the national average, with estimated ASR reaching 25 to 30 cases per 100,000^{18,23}. Combined screening constitutes a potentially effective approach for European countries with intermediate GC risk, especially those with well-established, organized, population-based CRC screening programs^{4,23}. However, the extent to which this screening strategy is accepted by the target populations remains largely unknown.

The implementation of CRC screening initiatives has markedly enhanced early detection rates and decreased cancer incidence, with the most substantial reductions observed in Northern European countries with longstanding programs and high participation rates²⁴⁻²⁷. However, the impact of Portugal's recently introduced FIT-based screening program on CRC early diagnosis and survival has not yet been determined. Furthermore, critical metrics, including participation rates, diagnostic accuracy, and overall population coverage for CRC screening, have yet to be systematically evaluated.

It has been proposed that performing same-day upper gastrointestinal endoscopy (UGIE) in individuals with positive fecal test results, including both FIT and guaiac-based fecal occult blood tests (gFOBT), who are undergoing colonoscopy, may improve the detection of upper GI cancers regardless of colonic findings²⁸. In the Dutch screening program, although FIT-positive individuals had a significantly higher risk of cancer proximal to the colon, the 3-year cumulative incidence remained below 1%, not supporting routine UGIE for all asymptomatic FIT-positive individuals²⁹. However, it is important to note that the Netherlands is considered a low-risk region for GC, with ASR below 10 per 100,000²³. The impact of a FIT-based population screening program on the early diagnosis and survival of GC in intermediate-risk regions, such as Northern Portugal, has yet to be fully elucidated.

Thus, the research conducted in this Thesis focuses on the optimization of CRC screening strategies and the implementation of GC screening initiatives, through the

assessment of individual risk perception and analysis of real-world data from population-based screening. The aims were to characterize ongoing GC screening programs and compare GC screening methods; to evaluate risk perception and attitudes towards screening, including intention to participate in CRC screening, preferred CRC screening method, and acceptance of UGIE combined with screening colonoscopy; to measure the perceived risk of complications associated with screening endoscopic procedures, and also to evaluate the impact of a population-based FIT screening program on early detection and survival not only for CRC but also for GC.

The research questions elaborated are clinically relevant, especially in Northern Portugal, where organized, population-based FIT screening has been implemented, despite the ongoing debate on the optimal screening modality for CRC. Moreover, in a country with a moderate to high incidence of GC, the assessment of potential initiatives for early detection is of paramount importance. Our results may provide valuable insights to inform and refine health policies, supporting evidence-based adjustments to screening protocols and strategies that ultimately enhance the effectiveness and reach of public health interventions.



Chapter II – Introduction

INTRODUCTION

1. Conceptual framework of digestive cancer screening

Cancer prevention can be achieved through primary prevention, which seeks to prevent the occurrence of the disease (e.g., addressing risk factors and promoting healthy behaviours), or through secondary prevention, which focuses on diagnosing cancer at an early stage to reduce morbidity and mortality³⁰. Screening and early detection are the principal instruments of secondary cancer prevention and a fundamental component of any cancer control strategy aimed at reducing cancer-related mortality⁴.

In Europe, GI cancer accounts for a substantial disease burden, largely due to population ageing and environmental risk factors, representing around one quarter of all diagnosed malignancies⁴. Screening can detect precancerous colorectal and gastric lesions, and their effective treatment can prevent malignant transformation^{31,32}. Indeed, it is now understood that most GI cancers are preceded by slow-growing precancerous conditions or early invasive stages, which create opportunities for effective intervention⁴. Beyond the classical adenoma–carcinoma and serrated pathways described in CRC, analogous metaplasia–dysplasia–carcinoma sequences have been established for upper GI neoplasms⁴. Not only the detection of incidental gastric neoplasms but also the identification of premalignant conditions is of critical relevance^{3,31}. Accordingly, surveillance is recommended for individuals with high-risk gastric intestinal metaplasia (GIM) phenotypes, including corpus-extended GIM, advanced Operative Link of GIM (OLGIM) stages III/IV and the incomplete GIM subtype as well as for those with persistent or refractory Hp infection, and a family history of GC in a first-degree relative^{4,33-36}.

Endoscopy is a key component of digestive cancer screening, enabling early cancer detection as well as the resection of precancerous and early lesions, which contributes to lower incidence rates and improved survival^{4,23,31,35}. When implementing a population-based

cancer screening program, it is essential to consider the effectiveness of the screening tests, the associated costs, and the sustained engagement required from both the public and health-care providers³⁰. In this setting, non-invasive tests (e.g., fecal and serologic tests) have emerged as less costly and more widely accepted methods, which complement endoscopic screening³⁷⁻³⁹.

2. The landscape of gastrointestinal cancer screening programs

2.1. Global perspectives on colorectal cancer screening

2.1.1. European population-based colorectal cancer screening programs

European recommendations on the role of GI endoscopy in digestive cancer screening advocate for the establishment of organized population-based screening programs for average-risk populations based mainly on FIT^{3,4}. However, it is stated that, pending on local conditions, upfront endoscopic screening may also be considered⁴ and there is still debate over the optimal strategy for population-based CRC screening, resulting in considerable heterogeneity across European screening initiatives^{4,6,7,40-43}.

A high screening participation is essential for cost-effective mortality reduction⁵. This priority underpins the Europe's Beating Cancer Plan, which sets a target of reaching at least a 65% participation rate across the eligible population^{44,45}. Organized screening provides significant benefits over opportunistic approaches by actively inviting all eligible individuals and ensuring quality control. It also allows for reminder systems to improve participation and addresses obstacles in the screening pathway. In contrast to opportunistic screening, organized programs are more efficient and equitable, leading to higher participation rates⁴⁶⁻⁵². However, organized screening programs demand extensive organizational efforts, incur significant costs, and place increased pressure on endoscopic capacity.

In 2010, the European Parliament adopted the Written Declaration on tackling CRC, which urged the European Union (EU) Commission and Member States to strengthen public awareness and enhance national policies to reduce high CRC mortality rates^{53,54}. Since the initiation of a comprehensive screening strategy, access to CRC screening has expanded, leading to improved CRC outcomes. This was achieved by the growing number of countries adopting screening programs, many of which use fecal testing methods such as FIT or gFOBT followed by colonoscopy when the test result is positive^{7,43,55}.

In Europe, CRC screening strategies vary significantly, encompassing fully implemented national invitational programs, regional and partially rolled out initiatives, as well as opportunistic screening (Figure 2). This variability can be attributed in part to the significant differences in healthcare infrastructure, resource availability, and system organization across European countries.

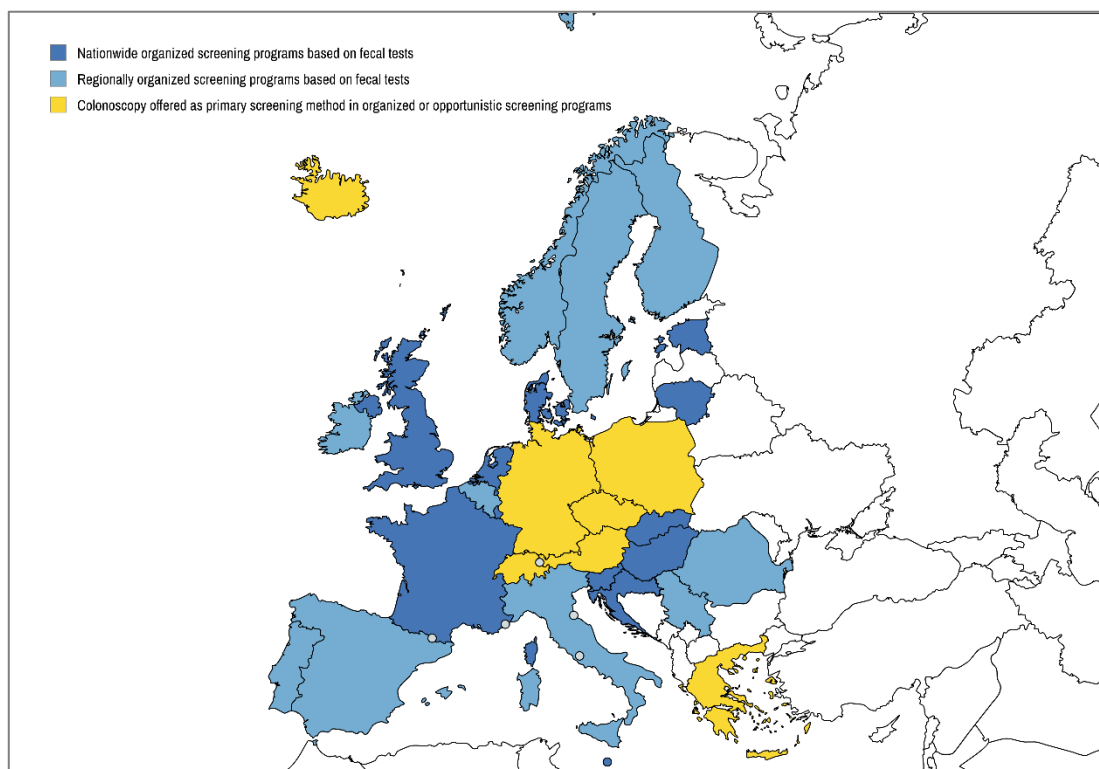


Figure 2: Colorectal cancer screening programs across European countries.

Overall, 25 countries have implemented organized screening programs across Europe^{4,7,43,46,54,56-59}. Table 1 provides an overview of CRC screening programs across European countries. While most countries have adopted call–recall systems to actively invite the target population at regular intervals, Lithuania and Hungary's screening programs rely on primary healthcare providers to send out invitations⁵⁹⁻⁶¹. Most countries regularly invite the target population for screening, offering biennial FIT, with colonoscopy as a follow-up for positive results⁴³. Twelve countries have fully implemented nationwide CRC screening programs based on fecal tests, including the Netherlands, Denmark, Slovenia, Croatia, Slovakia, Hungary, Lithuania, Estonia, the United Kingdom, France, Luxembourg and Malta^{7,43}. Several countries, including Italy, Spain, Portugal, Belgium, Czechia, Ireland, Sweden, Finland, Norway, Serbia, and Romania, have introduced regionally organized screening programs^{43,62,63}. Although biennial FIT is the prevailing method across Europe, certain exceptions still exist. The Croatian screening program still offers gFOBT⁵⁹. Poland is the only country that offers colonoscopy as the sole primary screening method⁴². In Italy, the Piemonte region offers a once-in-a-lifetime rectosigmoidoscopy as an alternative to biennial FIT^{39,40,64,65}. Since 2020, Czechia's organized screening program has offered primary colonoscopy as an alternative to FIT screening for individuals aged 50 or older⁶⁶. Similarly, canton-based screening programs in Switzerland offer both fecal tests and colonoscopy^{56,67}.

The Dutch screening program serves as a benchmark for organized CRC screening in Europe, achieving the highest participation rate (72%) and demonstrating satisfactory detection rates^{27,68}. After the implementation of the Dutch screening program, a decrease in overall and advanced-stage CRC incidence was observed^{27,37}. Similarly, Denmark and Slovenia have fully rolled out screening programs, inviting asymptomatic individuals to undergo biennial FIT screening, with reported adherence rates exceeding 50%^{43,69,70} (Table 1). In the opposite direction, the French national program, generalized to the entire national territory in 2008-2009 and currently offering biennial FIT screening, reported a participation rate of

34% for 2022–2023⁷¹. This is consistent with previous findings of participation rates below 50%^{6,72–74}. Therefore, participation rates vary considerably even among European screening programs that use fecal tests within fully implemented frameworks.

To address organizational challenges and better tailor cancer screening to target populations, several European countries have developed regional screening programs. Italy pioneered the introduction of regional screening programs and currently invites individuals aged 50 to 69 for biennial FIT testing in most regions⁶⁴. Participation rates vary widely, underscoring notable regional disparities in CRC screening^{43,64,75,76}. In Spain, population-based screening using fecal tests was integrated into the National Health System's services in 2014⁴⁴. Similar to Italy, Spain's program exhibits significant variation in participation rates, with disparities of up to six-fold between different regions^{44,77}. Identifying and overcoming barriers to participation remains a major challenge, especially in countries with regionally implemented programmes, where disparities in uptake persist^{43,64,75,76, 44,77}.

Poland is the only European country to implement a nationwide organized screening program that offers colonoscopy as the primary screening method⁴². The program invited individuals aged 50 to 66 for a once-in-a-lifetime colonoscopy. Despite colonoscopy's superior potential for detecting advanced adenomas and early-stage cancer, participation rates were disappointingly low⁵⁷. Although the average rate slightly increased to 17% between 2014 and 2018, it remains significantly lower than invitation-based programs using FIT, underscoring the challenges in achieving adequate coverage⁵⁷. Similarly, in Czechia and Switzerland, where regionally organized programmes offered colonoscopy as an alternative to FIT, participation rates did not exceed 50%^{66,78 56,67}.

Despite the well-established benefits of organized screening, several FIT-based programs still report suboptimal coverage^{7,43}. Additionally, in countries where screening is implemented regionally, considerable heterogeneity is evident^{43,44,64,77}. Low adherence rates were observed in primary colonoscopy screening⁵⁷. Despite considerable advances in

organized CRC screening across Europe, significant knowledge gaps persist regarding the determinants of participation, individual preferences for screening tests, and the barriers that hinder uptake.

2.1.2. Opportunistic Screening in Europe

In contexts where organized screening is not yet established, opportunistic, case-by-case screening remains a viable alternative. Opportunistic screening is reported in Germany, Austria, Latvia, Greece, and Iceland⁴³ (Figure 2; Table 1). No formally described screening is currently underway in Bulgaria, Belarus, Ukraine, Moldova, North Macedonia, Kosovo, Albania, Montenegro, or Bosnia and Herzegovina⁴³.

In the setting of opportunistic screening, four European countries (Germany, Austria, Greece and Iceland) offer colonoscopy at 10-year intervals as an alternative to annual/biennial fecal tests^{7,43,56,59}. Notably, a cross-sectional study based on data from the European Health Interview Survey (2018–2020) found that Germany and Austria surpassed the 65% up-to-date utilization threshold set by the European Commission⁷⁹. Despite encouraging coverage in Germany and Austria, participation rates in countries offering opportunistic screening, regardless of the strategy employed, remain generally low^{7,43}.

Even where relatively high coverage is achieved, as in some countries offering colonoscopy as an alternative to fecal testing, concerns persist regarding the consistency of quality control measures^{43,56,66,67,78,104}.

Table 1: CRC screening programs across European countries.

COUNTRY	PROGRAM STRUCTURE	YEAR OF IMPLEMENTATION	TEST TYPE	AGE GROUP	SCREENING INTERVAL	PARTICIPATION RATE
Croatia ⁸⁰	Organized - nationwide	2007	gFOBT	50-74	Every 2yrs	36%
United Kingdom ⁸¹⁻⁸⁴	Organized - nationwide ^a	2006-2010	FIT	54-74	Every 2yrs	58-70%
France ⁷¹	Organized - nationwide ^b	2009	FIT	54-74	Every 2yrs	34%
Slovenia ^{69,85}	Organized - nationwide	2009	FIT	50-69	Every 2yrs	58%
Malta ⁸⁶	Organized - nationwide	2012	FIT	60-74	Every 2 yrs	31%
The Netherlands ²⁷	Organized - nationwide	2014	FIT	55-75	Every 2yrs	72%
Denmark ^{70,87}	Organized - nationwide	2014	FIT	50-74	Every 2yrs	60%
Lithuania ⁸⁸	Organized - nationwide	2014	FIT	50-74	Every 2yrs	50%
Hungary ^{61,89}	Organized - nationwide	2018	FIT	50-70	Every 2 yrs	46%
Slovakia ⁹⁰	Organized - nationwide	2019	FIT	50-75	Every 2yrs	34%
Luxembourg ⁹¹	Organized - nationwide	2019	FIT	45-74	Every 2yrs	34%
Estonia ^{43,92,93}	Organized - nationwide ^c	2022	FIT	60-69	Every 2yrs	22%
Poland ^{42,57}	Organized - nationwide	2012	Colonoscopy	55–64	Once only	17%
Italy ^{94,95}	Organized - regional ^d	1982-2017	FIT FIT or rectosigmoidoscopy	50-69 50-69 58-60	Every 2yrs Every 2yrs Once only	34%
Spain ^{44,62,77}	Organized - regional ^e	2000-2010	FIT		Every 2yrs	35-76%
Belgium ⁹⁶	Organized - regional ^f	2009-2013	FIT	50-74	Every 2yrs	14-43%
Ireland ^{97,98}	Organized – regional	2013	FIT	60-69	Every 2yrs	47%
Serbia ^{99,100}	Organized - regional ^g	2013	FIT	50-74	Every 2yrs	52%
Switzerland ^{56,67}	Organized - regional ^h	2013-2019	FIT or colonoscopy	50-69	Every 2yrs Every 10yrs	11-49%
Czechia ^{66,78}	Organized – regional	2014	FIT or colonoscopy	50-54 55+	Every 1yr Every 2yrs Every 10yrs	39%
Sweden ^{95,101}	Organized - regional ⁱ	2015	FIT	60-69	Every 2yrs	66%
Portugal ⁹	Organized - regional ^j	2018	FIT	50-74	Every 2yrs	29%
Finland ^{95,102}	Organized - regional ^k	2019	FIT	60-74	Every 2yrs	79%
Norway ^{63,103}	Organized - regional ^l	2022	FIT	55+	Every 2yrs	59%
Romania ^{53,62}	Organized - regional ^m	2022	FIT	50-74	Every 2yrs	81-95%
Germany ¹⁰⁴	Opportunistic	2002	FIT FIT or colonoscopy	50-54 55+	Every 1yr Every 2yrs Every 10yrs	77%
Austria ^{105,106}	Opportunistic ^o	2003	FIT or colonoscopy		Every 2yrs Every 10yrs	29-39%
Latvia ^{43,95}	Opportunistic	2005	gFOBT	50-74	Every 1yr	30%
Greece ^{43,107}	Opportunistic	n/a	gFOBT or colonoscopy	50-74	Every 2yrs Every 10yrs	10%
Iceland ^{43,107}	Opportunistic	n/a	Colonoscopy	50+	Every 10yrs	30%

^a In England, organized screening started in 2006 through biennial gFOBT (transitioned to FIT in 2019) or once-only sigmoidoscopy (discontinued in 2020). In Scotland, Wales, and Northern Ireland, organized screening programs were launched in 2007, 2008, and 2010, respectively, with a transition to FIT in 2017 in Scotland and in 2019 in both Wales and Northern Ireland. ^b FIT replaced gFOBT in the French screening program in 2015. ^c In Estonia, an organized colorectal cancer screening program was piloted for insured individuals from 2016 to 2022, before being expanded to include all eligible individuals. ^d In Italy, the first organized CRC screening program was launched in Tuscany in 1982, while the southern regions of Calabria and Sicily were the last to implement organized screening, achieving full implementation in 2017. Transition from gFOBT to FIT was progressively implemented between 2013 and 2017. In Italy, biennial FIT serves as the primary screening method across all regions, except for the Piemonte region, where a one-time rectosigmoidoscopy is offered as an alternative. ^e In Spain, organized screening started in 2000 in Catalonia and was progressively implemented in the remaining autonomous communities by 2017. ^f In the French Community (Wallonia and Brussels), the screening program was initiated in 2009, with the transition to FIT occurring in 2016. In Flanders, FIT-based screening has been implemented since 2013. ^g The first round of screening within 2013-2014 encompassed 28 out of 160 municipalities in Serbia. ^h Early adopters of organized screening, such as Uri (2013), Vaud, and Geneva (2015), were followed by other cantons, with about half of Switzerland's 26 cantons having implemented programs by 2024. ⁱ In Sweden, organized screening started at the regional level in the Stockholm and Gotland counties. ^j In Portugal, organized screening began with a pilot phase in 2017, followed by a phased implementation across the Northern region starting in 2018. ^k The Finnish gFOBT program was suspended in 2016, and in 2019, organized screening was relaunched through a pilot phase using FIT, targeting nine municipalities. ^l In Norway organized screening started by a pilot study was conducted in Viken county, with subsequent expansion to a national level. ^m The pilot programs were initiated in four administrative regions of Romania: South-East, South-Muntenia, South-West Oltenia, and Bucharest-Ilfov. ^o The “Burgenland prevention trial of colorectal cancer disease with immunological testing (B-PREDICT)” was conducted between 2003 and 2014 in the Burgenland region using FIT. FIT, Fecal Immunochemical Test; gFOBT, guaiac-based Fecal Occult Blood Test; n/a, not applicable; yrs, years.

2.1.3. Colorectal cancer screening outside Europe

In North America, Canada provides CRC screening through population-based programmes using mainly fecal tests, reporting participation rates from 41-67%^{108,109}. In contrast, CRC screening in the US is primarily opportunistic, as there is no nationwide, government-organized program¹⁰⁸. Instead, screening is typically carried out through a combination of private healthcare providers (e.g., Kaiser Permanente Northern California organized screening program; Veterans Health Administration program)^{110,111}, insurance mandates, and local or regional initiatives led by healthcare systems^{30,112}. The US Preventive Services Task Force recommends several screening methods, including colonoscopy, flexible sigmoidoscopy, colon capsule endoscopy, computed tomography colonography, and stool-based tests such as FIT, gFOBT, and the multitarget stool DNA test combined with FIT^{88,89}. Endoscopic screening, including sigmoidoscopy and colonoscopy, has been historically reported as the most widely used approach, with coverage rates of up to 60%, compared with only 7% for noninvasive tests^{108,113,114}. Nevertheless, formally updated comparative analyses are lacking.

Among Asian countries, South Korea, Taiwan, Japan, Singapore and Thailand have implemented population-based organized screening programs based on FIT^{108,115}. Implemented in 2004, the Korean National Cancer Screening Programme has seen steady growth in participation, with adherence to diagnostic colonoscopy after a positive FIT increasing to around 32%¹¹⁶. The Taiwanese FIT-based screening program has reported a 34% reduction of advanced-stage CRCs and a 40% reduction in cancer-related mortality¹¹⁷. Japan runs a municipality-led screening programme, but despite the establishment of a national cancer registry in 2016, there is no unified call-and-recall system and invitations vary by municipality^{108,118}. Within the Asia-Pacific region, both Australia and New Zealand implemented FIT-based screening programs with participation rates reaching up to 57%¹⁰⁸. In the Middle East, Israel and Qatar offer organised screening using FIT, while in the United Arab

Emirates both FIT (every 2 years) and colonoscopy (every 10 years) are offered across the country¹⁰⁸. In South America, Argentina, Brazil, and Chile have conducted only regional pilot studies using FIT, whereas in Africa no population-based initiatives have been implemented^{108,119}.

2.2. Gastric Cancer Screening - Key Considerations and Strategic Approaches for Population-Based Programs

GC is the fifth most common cancer and the third cause of cancer mortality worldwide¹⁶. Detection at early stages is expected to positively impact survival rates¹²⁰. Incidence rates are highest in Eastern Asia and Eastern Europe, whereas rates in North America and Northern Europe are generally low¹²¹. When implementing a population-based screening program in a specific country or region, it is crucial to consider several key factors. Foremost among these is the ASR, which provides insight into the burden of disease across different age groups, allowing for effective targeting of screening efforts. Furthermore, assessing the potential impact on mortality rates is crucial for evaluating the overall benefit of screening. These considerations ensure that the screening strategy is not only efficient but also tailored to the local epidemiology, maximizing early detection and reducing cancer-related deaths.

For GC, global risk areas can be categorized into three distinct levels based on the ASR. These include: 1) High-risk areas, characterized by an ASR of ≥ 20 per 100,000, such as Japan, South Korea, and China; 2) Intermediate-risk areas, with an ASR between 10 and 20 per 100,000, including Portugal, Lithuania, Romania, and Slovenia (Figure 3); and 3) Low-risk areas, where the ASR is less than 10 per 100,000, such as the US, United Kingdom, the Netherlands and Germany¹²². This classification aids in tailoring screening efforts and preventive strategies according to regional risk profiles.

Screening initiatives have been introduced in countries with a high incidence of GC¹⁷. However, a formal characterization of the implemented programmes worldwide is lacking¹²³. Concerning screening tests, a variety of methods have been proposed, including endoscopy, radiologic imaging, and non-invasive serologic tests^{120,124,125}. Data from Asian countries suggests that endoscopic screening may reduce mortality¹²⁶. However, its invasive nature may limit adherence, and comparative evaluation against non-invasive alternatives is needed. Serum pepsinogen I and II levels, gastrin-17, serum anti-Hp IgG antibodies, and the Hp stool antigen test (HPSA) are among the proposed non-invasive methods for GC screening^{127,128}. A German prospective cohort study found that patients at high risk for GC [stages III and IV of the Operative Link of Gastritis Assessment (OLGA)] could be identified by a serum pepsinogen assessment¹²². A Slovenian study used serologic biomarkers in a population of FIT-positive patients to identify those with gastric preneoplastic conditions, eligible for further endoscopic screening and found a combined accuracy of up to 87%¹²⁹.

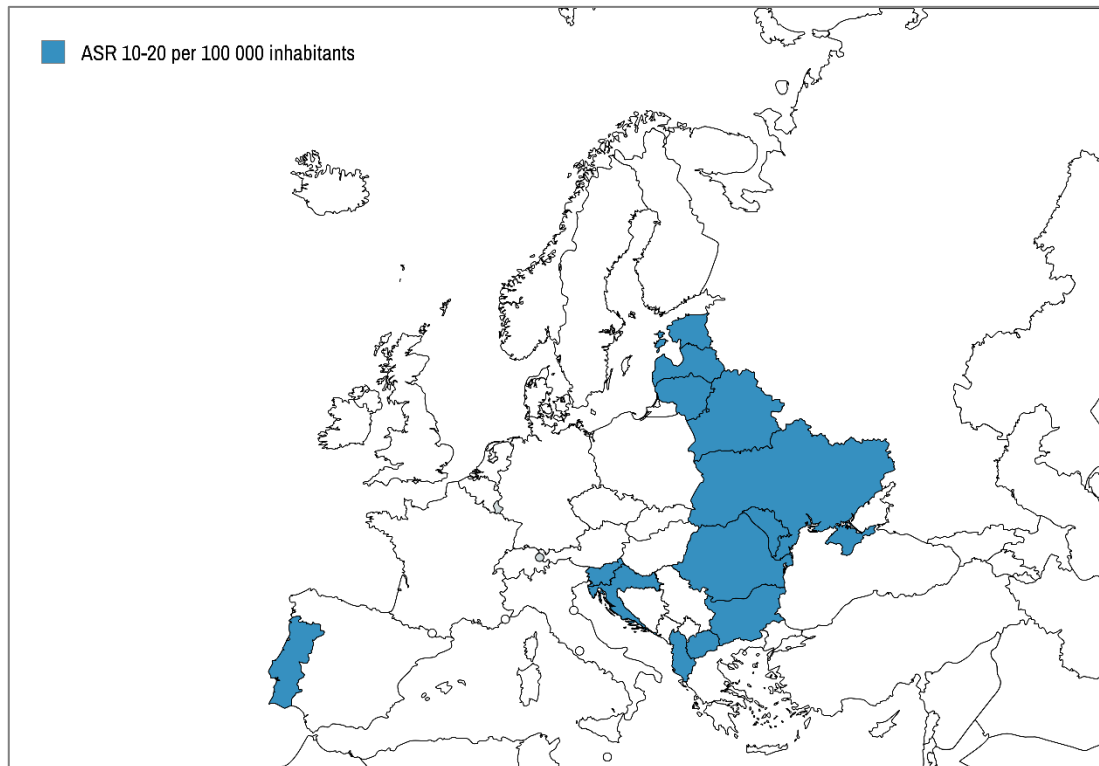


Figure 3: European countries classified as intermediate risk for gastric cancer. ASR, age-standardized incidence rate.

The optimal method for GC screening has not yet been clearly established^{4,126}. Initial large-scale initiatives relied on UGIS, which was later progressively replaced by UGIE^{130,131}. Non-invasive tests, including serologic and fecal assays, have been proposed as approaches that could potentially achieve higher acceptance among target populations and more favorable cost-effectiveness ratios^{127,128}. Nevertheless, a comparison of GC screening methods with respect to their impact on mortality, diagnostic yield, and adherence is still needed^{123,126,132}.

For GC screening, combining UGIE with a screening colonoscopy may be cost-effective in European regions with intermediate risk (Figure 3), based on two previously published cost-utility analyses^{4,21,22}. This emphasizes the need for localized evaluations of endoscopy's feasibility, considering the balance between benefits, costs, and healthcare infrastructure. The potential for combined screening is particularly important for European countries with an intermediate incidence of GC that have implemented population-based CRC screening programs^{4,23}.

Information on GC screening in Western countries remains limited¹³³. Although combined endoscopic screening has been suggested to be cost-effective, data on its acceptability among target populations are lacking. This gap limits a comprehensive assessment of its potential impact on early detection and survival, highlighting the critical need for additional research.

3. Challenges and barriers to gastrointestinal cancer screening

Few countries have achieved the minimum 65% participation rate set by the EU Commission (Table 1) and many nations still fail to reach adherence standards, undermining the overall screening effectiveness^{2,7,74,79}. Participation rates are highly variable and remain sparsely characterized especially in countries with recently implemented population-based programs, such as Portugal, Estonia, Norway or Czechia^{9,43,63,66,78,92,93,103}.

Suboptimal adherence rates remain a major challenge in CRC screening, making it essential to identify their determinants, with risk perception emerging as a key factor. Screening uptake is largely influenced by factors such as individual cancer risk perception, concerns about the potential risks of screening tests, access to testing, financial burden, and time constraints^{12,13}. Several factors contribute to non-participation, such as ambivalence, aversion to the screening process and its possible outcomes, and insufficient healthcare support^{70,134}. Additionally, social inequalities in health, including lower socioeconomic status, lower income, lower education and lower health literacy, can negatively affect participation rates^{72,103}. Moreover, organizational barriers can hinder the achievement of adequate participation rates. In this context, a thorough assessment of risk perception as a central determinant of screening uptake, together with the identification of predictive factors for non-adherence, is crucial for informing the development of more effective and equitable screening strategies.

The inherent limitations of screening tests must also be recognized. The effectiveness of fecal tests relies heavily on both the acceptance of follow-up colonoscopy for abnormal results and the consistent repetition of periodic screening if normal results are depicted. While FIT has progressively replaced the gFOBT, it is still not a highly accurate test^{37,135}. The reported sensitivity varies depending on the cut-off value for positivity, ranging between 72% and 80%, which corresponds to a non-negligible false negative (FN) rate^{38,39,136}. To address this limitation, the cut-off value for positivity can be lowered, resulting in enhanced sensitivity and a limited FN rate¹³⁶. Lowering the cutoff value inevitably increases the positivity rate, leading to more false positives and potentially placing considerable strain on colonoscopy capacity^{27,137}. Adjusting the sensitivity of FIT to match colonoscopy capacity is a feasible option as it ensures that the maximum public health benefit can be achieved within available resources⁹⁷. Notably, colonoscopy acceptance following a positive FIT result is a critical determinant of the effectiveness of CRC screening programs based on fecal tests. In European

countries with high baseline participation, such as the Netherlands and Denmark, adherence ranges from 75% to 90%^{47,48,50}, while studies from the US report rates under 80%^{46,49,138,139}.

Compared to fecal tests, colonoscopy offers a superior diagnostic yield, enabling a higher detection rate for advanced adenomas and early-stage cancer^{27,41,132,140}. However, adherence rates remain suboptimal, potentially due to factors such as financial burden and the invasive nature of the procedures^{42,57}. Direct costs encompass expenses related to bowel preparation, sedation, and the procedure itself¹⁴¹. Even in the context of full reimbursement, work-related absenteeism and access barriers may constrain colonoscopy utilization. Additionally, anticipated discomfort associated with bowel preparation and apprehension regarding the procedure itself ought to be considered. In this context, the perceived risk of complications associated with endoscopic procedures represents a major concern. Indeed, colonoscopy is a minimally invasive procedure that carries a risk of complications, which may be heightened by additional diagnostic or therapeutic interventions¹⁴². An observational US study concluded that never-screened individuals were more likely to overestimate the risk of complications from colonoscopy¹⁴. These findings highlight that endoscopic screening-related complications are a potential barrier to participation in digestive cancer screening programs. Nonetheless, the influence of perceived complication risk on adherence within the screening context remains poorly characterized, highlighting a critical area for further investigation.

Preference for a specific screening test can be a key factor in CRC screening uptake, as offering a more widely accepted method may significantly improve participation rates^{41,143,144,145}. Offering colonoscopy as an alternative to fecal testing in opportunistic screening has been reported to increase coverage by approximately 10%¹⁰⁴. Additionally, data from a randomized trial conducted in the US found that offering a blood-based screening test to individuals who declined FIT resulted in a 17.5% increase in screening uptake¹⁴⁶. These findings highlight the critical importance of evaluating preferences for each screening method at the local or national level.

Several barriers to the implementation of GC screening in Western countries have been identified, including financial constraints, limited endoscopic capacity, policy-related obstacles, and marked variation in incidence rates¹³⁰. Even in high-risk countries with established GC screening programs, such as Japan and South Korea, significant challenges persist, including insufficient endoscopy services, limited availability of qualified endoscopists and financial constraints^{122,130}.

The implementation of population-based GC screening has been considered for several intermediate-risk European countries^{4,21,147}. However, beyond policy constraints, there is still a lack of consensus regarding the optimal screening strategy, and ongoing debate opposes primary prevention and secondary prevention strategies^{147,148}.

For primary prevention, targeting individuals in their fourth decade of life for mass Hp eradication is anticipated to offer significant benefits, particularly by preventing the development of precancerous conditions and reducing transmission to offspring¹⁴⁹. However, implementation of the screen-and-treat strategy presents several challenges, including anticipated low participation rates in younger age groups, potential disturbances of the gut microbiome, costs associated with treatment reimbursement, and the risk of increased antibiotic resistance¹⁵⁰.

In the context of secondary prevention, three main strategies have been described: radiologic screening with UGIS, non-invasive tests to select high-risk patients for endoscopic evaluation and endoscopic screening, which not only detects incident GC but also identifies premalignant conditions warranting further endoscopic surveillance^{4,33-36}. European studies on non-invasive tests have failed to demonstrate an unequivocal benefit, despite the increasing interest in serological testing for serum pepsinogen I/II and Hp. Indeed, data from the GISTAR study indicated that the low sensitivity of the pepsinogen panel may limit its utility in a population-based screening setting¹²². Notably, pepsinogen testing alone would miss most GC cases, as only 32% of cancer patients had decreased levels¹⁴⁹.

The cost of endoscopic screening raises concerns about its implementation and feasibility in European intermediate-risk¹²⁶. To circumvent this barrier, GC screening may be combined with CRC screening. Assuming full compliance, combining UGIE with a screening colonoscopy following a positive FIT result was suggested as being cost-effective in Portugal^{21,22}. However, this strategy restricts UGIE to individuals with a positive FIT referred for colonoscopy, thereby limiting screening to a smaller segment of the eligible population and diverging from the traditional comprehensive model of an organized programme^{21,22,148}. Studies assessing adherence to combined screening and evaluating its impact on early detection and survival of gastric cancer are needed²⁹.

4. Risk perception and its impact on health behaviors

Health behaviours, particularly adherence to cancer screening, are strongly influenced by individuals' perceptions of their cancer risk and of the risks associated with screening procedures. Perceived risk is a complex construct integral to numerous health behavior theories and interventions¹⁵¹. Although many factors are known to influence health behaviors, risk perceptions are thought to play a key role in the behavioral process¹⁵². Individuals who underestimate their risks may be less likely to adopt recommended behaviours, whereas those who overestimate their risks may also avoid precautionary measures due to anxiety about potential results or the need for treatment¹⁵³⁻¹⁵⁵. Although behavioral processes are complex, wrong risk perceptions may prevent the adoption of self-care behaviors and, as a result, pose an additional risk for the occurrence of adverse health outcomes¹⁵².

Risk perception has been broadly assessed across various fields, including infectious diseases and cardiovascular sciences, highlighting its essential role in understanding health behaviors and informing preventive strategies¹⁵⁶⁻¹⁶⁰. Studies on patients with type 2 diabetes have shown perceptions on the risk of complications were generally biased, characterized by

low-risk awareness in most dimensions of the perceived risks measured and contaminated by optimistic bias¹⁵². Extensive research in individuals seeking genetic counseling also showed a common tendency to overestimate the risk of inheriting genetic disorders¹⁶¹. Personal factors (e.g., numeracy, socio-economic status, type of condition) and bounded rationality (e.g., tendency to overestimate the occurrence of low-probability events) are thought to bias the cognitive assessment process of risk estimates.

The relationship between personal risk perception and risk behavior can be explored through three primary hypotheses: the accuracy hypothesis, the behavior motivation hypothesis, and the risk reappraisal hypothesis (Figure 4)¹⁶²⁻¹⁶⁵. The accuracy hypothesis postulates that risk perceptions at a given point in time reflect an individual's current risk behaviors and associated factors, without suggesting causality. This hypothesis is generally tested using cross-sectional data, as it requires only a single time-point measurement. In contrast, the behavior motivation hypothesis explores how perceived risk drives behavior change, hypothesizing a causal link between an individual's perception of risk and subsequent actions aimed at mitigating that risk. Testing this hypothesis requires longitudinal data, with initial measurement of perceived risk followed by an assessment of behavioral changes over time. Lastly, the risk reappraisal hypothesis examines how behavioral actions influence perceived risk, suggesting that individuals who engage in preventive behaviors subsequently lower their risk perception. This hypothesis also necessitates a longitudinal approach, with baseline behavioral data and follow-up assessments of risk perception.

Building on these hypotheses, several theoretical models have been proposed to explain how perceived risk influences health-related decision-making. Among these are the theory of planned behavior, the protection motivation theory, the risk perception attitude framework and the Health Belief Model (HBM)¹⁵¹. According to HBM, health behaviours are determined by individuals' perceptions of their susceptibility to disease and the severity of its consequences. In the screening context, adherence is influenced by the balance between

perceived cancer risk and the anticipated benefits on one side (e.g., early detection and treatment), and perceived barriers on the other (e.g., financial barriers, time constraints).

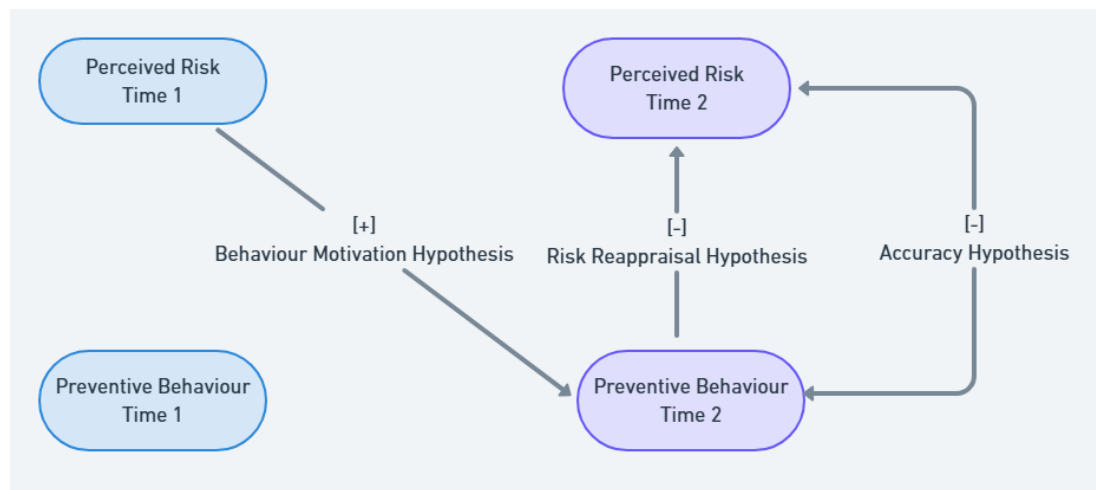


Figure 4: A model of risk perception and risk behavior. Straight lines represent causal relationships, while curved lines indicate non-causal associations. Adapted from [Brewer NT, *et al.* Ann Behav Med. 2004]

Two Eastern studies have previously used a structured survey based on the HBM to evaluate CRC risk perception^{12,13}. A structured survey based on the HBM was first validated in China to evaluate risk perception¹³. Knowledge of CRC symptoms and risk factors was low, while perceived health, psychological, and access barriers to CRC testing were high. Subsequently, the same tool was used in a multicentric study in the Asia-Pacific region to compare risk perception between countries with low- and high-CRC participation rates¹². While physician recommendation was the uniform predictor of screening behavior in all countries, respondents from low-participation countries had the least knowledge of symptoms, risk factors, and screening tests¹².

In Europe, research on risk perception assessment remains limited, and no structured questionnaire has been validated. Establishing such a tool is essential to better characterize barriers to screening, including concerns about potential harms of testing, and to identify factors underlying non-adherence. Furthermore, when considering the combination of UGIE

with colonoscopy for screening, it is essential to assess GC risk perceptions, as these may strongly influence adherence and the overall acceptability of combined strategies¹⁴. The absence of validated instruments in this field underscores the need to develop and validate questionnaires capable of reliably assessing risk perceptions, thereby providing a solid basis for future research and for improving participation in screening programmes

5. Evaluation of gastrointestinal cancer screening programs

5.1. From cost-effectiveness to real-world evidence in FIT-based screening

Biennial FIT screening, suggested to be cost-effective in Northern Portugal, has the potential to enhance population coverage, allowing more individuals to participate in screening while optimizing the allocation of endoscopic resources and minimizing the strain on healthcare infrastructure⁵.

Population-based cancer screening programmes provide a structured framework that enhances equity, quality, and overall effectiveness of cancer prevention strategies. Systematic quality assessment through key performance measures for colonoscopy, together with continuous monitoring, enables timely adjustments and targeted interventions^{46-52,69,166}. In addition, by actively inviting all eligible individuals, population coverage can be expanded^{46-52,166}. In instances of lower-than-expected screening uptake, supplementary measures may be implemented to address organizational challenges, such as reminder systems and patient navigation interventions specifically targeting non-adherent individuals^{72,167-172}. Moreover, personalized approaches (e.g., offering an alternative screening test) have been reported to increase screening coverage¹⁴⁶.

Despite the encouraging high participation rates reported in Northern European countries, adherence remains insufficiently characterized in many recently implemented screening programs^{9,27,70,87}. A low participation rate in FIT screening may undermine the

potential cost-effectiveness of these programmes, making a thorough assessment of adherence rates imperative for newly implemented initiatives, including the Northern Portuguese program.

Organized screening has indeed been shown to improve early detection and reduce mortality, with the most significant declines observed in countries with longstanding screening programs and high adherence rates²⁴⁻²⁶. A reduction in CRC incidence and a shift toward earlier-stage detection are anticipated benefits from FIT screening²⁷. Encouraging evidence supports the effectiveness of FIT-based population screening, but real-world data on its impact on early detection and survival are still needed^{75,117,173-175}.

5.2. The potential benefit of combined endoscopic screening

There is ongoing debate on the optimal pathway for the reduction of GC burden across European countries, especially those presenting intermediate to high incidence rates (ASR 10–20 per 100,000)^{21,31,147}. Proposed strategies include primary prevention through mass eradication of Hp and secondary prevention aimed at detecting premalignant gastric conditions and early-stage GC¹⁷⁶ (Figure 5). Recently published data indicate that up to 76% of GC cases may be attributable to Hp infection, underscoring the crucial role of population-based screen-and-treat strategies in reducing cancer burden¹⁷⁷.

Offering UGIE for GC screening to individuals referred for colonoscopy following a positive FIT result has been previously proposed^{21,22}. Supporting this approach, a Portuguese cost-utility analysis suggested that GC screening may be cost-effective when UGIE is combined with a screening colonoscopy, but not as a stand-alone strategy, whether through UGIE-alone or pepsinogen testing^{4,21}. More recently, an economic evaluation indicated that the use of artificial intelligence (AI) to assist UGIE may further increase the cost-effectiveness of combined gastric and CRC screening in European countries, depending on the accuracy and costs of the AI system²². The project Towards Gastric Cancer Screening Implementation in the

European Union (TOGAS) has launched three pilot studies across several European countries to advance knowledge on the feasibility, effectiveness, and implementation of GC prevention strategies¹⁴⁸. One of them will assess the prevalence of gastric precancerous lesions in individuals over 50 years undergoing screening colonoscopy within a CRC screening program, thereby evaluating the feasibility of a combined approach¹⁴⁸. Despite increasing interest in combined endoscopic screening, evidence on its acceptability remains limited, warranting further research into individuals' willingness to undergo both procedures and the factors shaping participation.

FIT demonstrates higher specificity for lower GI bleeding, yet false-positive results may still arise from upper GI sources, including neoplasms^{28,178}. A systematic review evaluating opportunistic GC screening in subjects with a positive fecal test (including both FIT and gFOBT) undergoing colonoscopy found that same-day UGIE detects approximately 25% more malignancies than colonoscopy alone²⁸. Accordingly, data from the Dutch CRC screening program showed that significantly more cancers proximal to the colon, including those of the upper GI tract, oral cavity, nose, and throat, were detected among FIT-positives²⁹. However, the 3-year cumulative incidence remained below 1%, raising the question of whether UGIE is justified in all FIT-positive screenees in Western populations²⁹. Nevertheless, regional differences in GC incidence across European countries must be acknowledged (Figure 3). In a study designed to evaluate trends in GC incidence and mortality, incidence rates in Northern Portugal clearly exceeded those reported in both the Netherlands and Belgium²³. In the latter study, temporal trends revealed an increasing proportion of T1 GC alongside a decline in age-standardized mortality, thereby reinforcing the value of secondary prevention strategies²³. Several factors may account for these findings, including technological advances (e.g., high-definition endoscopes with integrated virtual chromoendoscopy), enhanced training in early neoplasia detection, and the implementation of quality improvement initiatives^{23,179}. The extent to which the observed trends are attributable to facilitated access to endoscopic

procedures and the impact of population-based FIT screening on GC outcomes remains largely unknown.

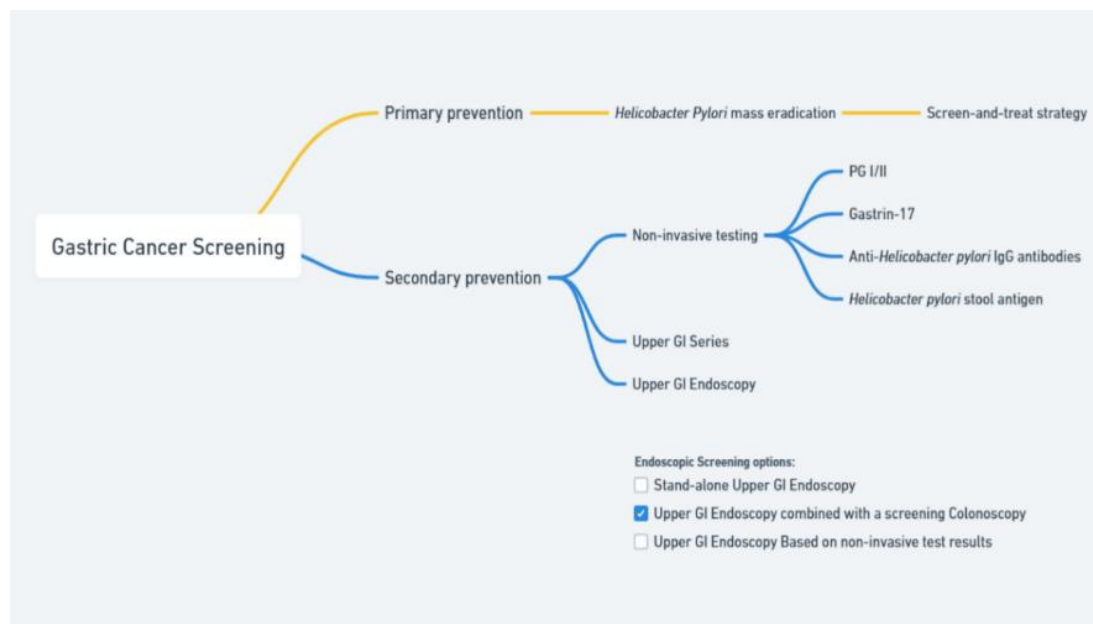


Figure 5: Potential strategies for gastric cancer screening in European countries with intermediate risk. PG, Serum Pepsinogen; GI, Gastrointestinal.



Chapter III – Research questions and aims

RESEARCH QUESTIONS AND AIMS

This project focused on the impact of individual risk perception on digestive cancer screening. The line of investigation was designed to explore the current status of GC screening and subsequently, to compare risk perception and attitudes towards screening—including both CRC and GC—with real-world data from population-based programmes.

In summary, the specific aims of this project were:

1. To identify and characterize ongoing GC screening programmes and compare screening tests regarding adherence, early detection, and mortality.
2. To evaluate individual risk perception and its influence on attitudes, decision-making, and participation in digestive cancer screening initiatives.
3. To evaluate the intention to adhere to CRC screening and the preference for the primary screening method (FIT vs colonoscopy).
4. To estimate acceptance of a strategy that combines an UGIE with a screening colonoscopy.
5. To assess the perceived risk of complications related to endoscopic screening procedures and evaluate its impact on adherence.
6. To analyze the impact of population-based FIT screening on early detection and survival of CRC and GC.



Chapter IV – Current status of gastric cancer screening



1. Gastric cancer screening: a systematic review and meta-analysis

Lídia Faria, João Carlos Silva, Marta Rodríguez-Carrasco,

Pedro Pimentel-Nunes, Mário Dinis-Ribeiro, Diogo Libânio

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REVIEW



Gastric cancer screening: a systematic review and meta-analysis

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ABSTRACT

Background and aims: Gastric cancer (GC) screening is recommended in high-risk populations, although screening methods and intervals vary. In intermediate-risk populations, screening through esophagogastroduodenoscopy (EGD) may be considered depending on local resources. The aim of this study was to compare GC screening methods regarding effect on mortality, diagnostic yield and adherence.

Methods: Systematic review and meta-analysis including studies evaluating population-based GC screening. Search was conducted in three online databases (MEDLINE, Scopus and clinicaltrials.gov), along with manual search.

Results: Forty-four studies were included. Studies in upper gastrointestinal series (UGIS) demonstrated that GC screening was associated with significantly lower GC mortality rates (OR 0.63, 95% CI 0.55–0.73). Benefits on mortality were also found in EGD and serum pepsinogen (PG) studies. EGD was associated with significantly higher GC (0.55%, 95% CI 0.39–0.75%) and early-GC (EGC) detection rates (0.48%, 95% CI 0.34–0.65%) when compared to UGIS (GC 0.19%, 95% CI 0.10–0.31%; EGC 0.08%, 95% CI 0.04–0.13%) and PG (GC 0.10%, 95% CI 0.05–0.16%; EGC 0.10%, 95% CI 0.04–0.19%). Non-invasive methods tended to higher adherence rates when compared to EGD. Regardless of the screening method, individualized recruitment performed better.

Discussion: Screening positively impacted GC mortality rates. EGD was associated with higher diagnostic yield, while UGIS and PG tended to higher adherence rates. Screening uptake was predominantly impacted by recruitment strategies independently of the adopted method.

Abbreviations: ASR: Age standardized incidence-rate; CI: Confidence interval; DOR: Diagnostic odds ratio; EGC: Early gastric cancer; EGD: Esophagogastroduodenoscopy; FDG-PET: F-Fluorodeoxyglucose-positron emission tomography; GC: Gastric cancer; IC: Invited cohort; LR: Likelihood ratio; NPV: Negative predictive value; OR: Odds ratio; PG: Serum pepsinogen; PPV: Positive predictive value; SF: Self-reporting; SROC: Summary receiver operating curve; RCT: Randomized controlled trial; UGIS: Upper gastrointestinal series

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Gastric cancer; cancer screening; preventive medicine; early detection of cancer; gastrointestinal endoscopy

Introduction

Gastric cancer (GC) is the fourth most common malignancy worldwide and ranks third on cancer-related death [1]. Detection of GC in early stages is associated with overall 5-year survival of 85–90% but populational GC screening programs are rare in Western countries mainly due to concerns of low adherence, efficacy and high costs and thus questionable cost-effectiveness [2]. The incidence and mortality of GC substantially vary across geographical areas, and Eastern Asia and Eastern Europe have the highest age-standardized incidence-rates (ASR) [1]. In countries with high incidence of GC, such as Japan and Korea, in which ASR exceeds 20 per 100,000 inhabitants, GC screening was started [2].

Implementation of GC screening in Asia led to an increase in the diagnosis of early gastric cancer (EGC), lower disease-specific mortality and higher 5-year survival [3,4]. However, even in Asia GC screening strategies vary across countries, and the outcomes of different screening methods were seldom compared. In countries with intermediate risk, GC screening is not established, yet the European Society of Gastrointestinal Endoscopy (ESGE) suggests that endoscopic screening may be considered depending on endoscopic resources [5]. Furthermore, the MAPS II Guideline suggests that GC screening might be cost-effective in European countries with a GC risk ≥ 10 per 100,000 inhabitants [6,7]. Evidence arises from a Markov cost-utility analysis from Areia et al., which concluded that endoscopic GC screening was cost-effective if combined with a screening colonoscopy in Portugal (ASR 13.1/100,000 inhabitants) [6].

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The comparison of different GC screening strategies and their outcomes in both Eastern and Western countries may provide evidence for further establishment of GC screening in intermediate and low-risk populations and optimize ongoing programs in high-risk populations. Pooled estimates of adherence and efficacy outcomes are also needed in order to perform adequate cost-effectiveness analysis. Therefore, the aim of this study was to compare GC screening methods regarding effect on mortality, diagnostic yield and adherence in both high and intermediate-risk populations.

Methods

Two studies were performed in order to assess GC screening: 1) a systematic review and meta-analysis of population-based GC screening programs; 2) a cross-sectional evaluation of existing GC screening programs, through a survey sent to 311 Endoscopy and Gastroenterology societies.

Systematic review of gastric cancer screening programs

Search strategy

This systematic review followed the PRISMA guidelines for systematic reviews [8]. Two online databases (MEDLINE, through PubMed and Scopus) and a clinical trial registry (clinicaltrials.gov) were used to identify relevant studies (date of last search: 23 October 2020). No language or temporal restrictions were applied. The search query was the following: (('stomach cancer') OR ('gastric cancer')) AND (('cancer early diagnosis') OR ('cancer screening') OR ('endoscopy screening') OR ('screening program')). The authors also manually searched abstracts from Gastroenterology and Endoscopy conferences proceedings. Clinical trial registries were also searched to identify ongoing studies. In addition, reference lists of included articles were reviewed to capture additional studies.

Eligibility criteria

All studies evaluating mass/populational GC screening programs, in asymptomatic individuals, at a national or regional level, reporting at least one of the outcomes of interest (see below) were included. Randomized-controlled trials (RCT), retrospective or prospective cohort and case-control studies, and cross-sectional studies were considered. Exclusion criteria were: 1) studies including symptomatic patients; 2) studies focusing on surveillance of patients with known premalignant conditions/lesions (e.g. chronic atrophic gastritis, intestinal metaplasia and dysplasia); 3) studies including patients with history of GC or EGC; 4) studies focusing on hereditary GC; 5) case-series, reviews, letters and guidelines. If there was patient population overlap, the study with highest number of participants was included.

Outcomes and definitions

The main outcomes were GC mortality, GC detection rate, EGC detection rate and adherence. GC mortality was defined as GC deaths for total screened individuals, as opposed to

GC deaths for unscreened individuals. GC and EGC detection rates were defined as GC or EGC cases for total screened individuals. Accuracy measures were extracted from each study using 2×2 contingency tables, for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) calculation. Positive likelihood ratio (LR) and diagnostic odds ratio (DOR) were additionally computed. Adherence was defined as screening participants for total number of invited individuals. For adherence evaluation, we classified the studies according to the method of participation ascertaining in: a) studies in which effective participation in screening was confirmed by the performance of the screening method (invited cohorts); b) studies in which participation was assessed through questionnaires/self-reporting.

Study selection

Two reviewers, Faria L and Silva JC, independently screened title and abstracts according to a prespecified protocol using Covidence online platform [9]. In case of disagreement, a third reviewer (Rodríguez-Carrasco M) made the final decision. Further full-article reading was performed independently by the abovementioned reviewers. Authors of unpublished studies or published studies in which data was missing were contacted to confirm eligibility. In the presence of articles with challenging translation, the authors were also contacted.

Data extraction and quality evaluation

Two reviewers (Faria L and Silva JC) independently retrieved data from full articles using a standardized predefined form, based on Cochrane data sheets. A third reviewer (Libânio D) checked the accuracy of extracted data. Data was obtained according to the target variables: 1) author; 2) year of publication; 3) baseline characteristics of target population [age and sex]; 4) country/region of screening program; 5) mechanisms for systematic invitation; 6) screening method used and setting – regional or national; 7) GC mortality rate; 8) GC detection rate; 9) EGC detection rate; 10) adherence rate.

Quality evaluation was also performed by Silva JC and Faria L. RCTs quality assessment was performed using Cochrane Collaboration risk of bias tool [10]. For each key domain, the studies were classified as 'low risk', 'high risk' or 'unclear risk'. Studies were classified as 'low risk' if bias that could seriously alter the results were considered unlikely for all key domains and 'high risk' if at least one domain had bias that potentially weakens confidence in the results. Observational studies were evaluated according to the Newcastle–Ottawa scale for observational studies [11].

Statistical analysis

Where adequate (at least three studies per outcome), pooled prevalences and pooled OR along with 95% CIs were calculated for GC mortality, GC detection, EGC detection and adherence, using random-effects model, through OpenMeta Analyst (for pooled prevalences through arcsine transformed proportions) [12] and RevMan version 5.3 (for pooled ORs)

[13]. Heterogeneity was evaluated with the I^2 and Cochran's Q test. Significant heterogeneity was defined as $I^2 > 40\%$ and $p < .05$. Subgroup analysis was planned according to screening method, region/country and method for ascertaining adherence (invited cohorts vs. self-reporting).

Pooled accuracy measures (sensitivity, specificity, positive LR and DOR) with 95% confidence intervals (CIs) and summary receiver operating curve (SROC) were calculated, when possible, using random-effects model through Meta-DiSc version 1.4 (Madrid, Spain) [14].

Cross-sectional assessment of ongoing gastric cancer screening programs

National and International Gastroenterology and Endoscopy societies were comprehensively searched and invited to participate in an online survey (Supplementary Appendix 1) on digestive cancer screening. The survey was sent by email in three different rounds, to the presidents of 311 Scientific Societies, between January and March 2020, to maximize adherence. Answers were then recorded and grouped by the authors. The following domains were evaluated: 1) target population [age, sex and risk factors for GC]; 2) country/region of screening program; 3) gastroenterology or endoscopy society; 4) screening setting [national or regional]; 5) screening method; 6) adherence rates.

Results

Systematic review and meta-analysis of gastric cancer screening programs

A total of 1359 articles were identified through systematic search, of which 37 were selected for inclusion. Seven additional studies were included from manual search, and thus, a total of 44 studies were included in this systematic review (Figure 1) – 17 from Japan, 13 from Korea, 7 from China, 2 from Taiwan, 1 from Finland, 1 from Turkey, 1 from Costa Rica, 1 from Iran and 1 from Portugal.

Four RCTs were included – two in which individuals were randomized to different invitation strategies [15,16], one in which individuals were randomized to different screening methods [17] and one in which individuals with positive PG test and/or first degree relatives with GC underwent EGD and individuals with negative PG test were randomly selected for EGD [18]. Most of the included studies were observational ($n = 40$; 91%), of which 30 (75%) cohort studies (prospective $n = 18$; retrospective $n = 12$) and 10 (25%) cross-sectional.

The main characteristics of included studies are presented in Table 1. There were seven double-arm studies comparing EGD and upper gastrointestinal series (UGIS), while 25 were single-arm studies evaluating outcomes of a given screening method [nine serum pepsinogen (PG), 10 EGD, 5 UGIS and 1 f-fluorodeoxyglucose-positron emission tomography

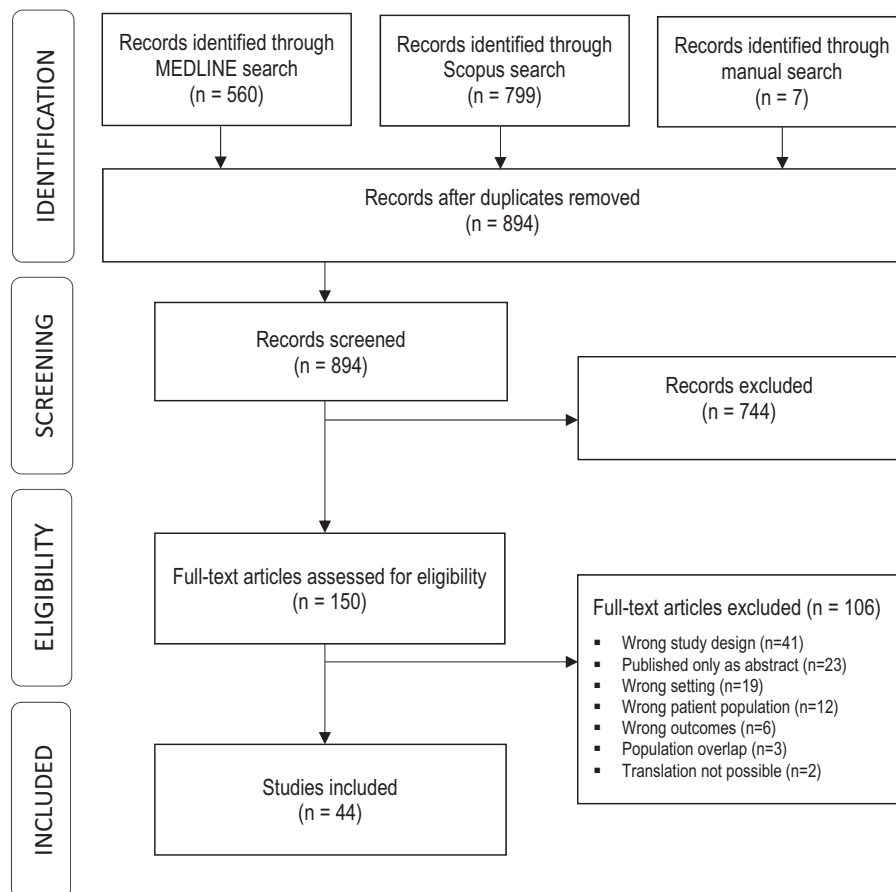


Figure 1. Flowchart of study selection.

Table 1. Characteristics of included studies and description of the outcomes according to the screening method.

First Author (Publication year)	Country, region	Study design	Participants	Target population	Method invitation	Adherence rate, % (screened/invited)	EGC detection rate Positive, % (cases/screened)	GC detection rate Positive, % (cases/screened)	Sens,%	Spe,%	PPV,%	GC mortality rate, % (GC deaths/ screened) vs. % (GC deaths/ no screening)	Quality analysis ^{a,b}
GC screening (irrespective of screening method)													
Self-reported Choi KS et al. [19]	Korea	Cross-sectional	1625	Age ≥ 40 years; every 2 years	Personal letter	41.3 (701/1625)							6 ^a
Hahm MI et al. [20]	Korea	Retrospective cohort	1512	Age 40–69 years		54.9 (833/1517)							6 ^a
Kang JM et al. [21]	Korea	Cross-sectional	3557	Age ≥ 40 years; every 2 years		31.5 (894/2842)							6 ^a
Chang Y et al. [22]	Korea	Retrospective cohort	10658	Age ≥ 40 years; every 2 years		43.9 (4684/10658)							6 ^a
Invited cohort Lee MH et al. [15]	Korea	RCT	2065	Males 40–65 years	Phone call; personal letter	23.7 (23/97)							Low risk ^b
Hong NS and Kam [16]	Korea	RCT	923	Males 50–59 years	Phone call; personal letter	31.4 (220/700)							Low risk ^b
Korea National database analysis													
Park B et al. [23]	Korea	Cross-sectional	4082	Age ≥ 40years; every 2 years									6 ^a
Lee S et al. [24]	Korea	Cross-sectional	5,895,113	Age ≥ 40years; every 2 years	Personal letter								7 ^a
Suh M et al. [25]	Korea	Cross-sectional	30,105	Age ≥ 40years; every 2 years									6 ^a
Suh M et al. [26]	Korea	Cross-sectional	37,608,375	Age ≥ 40years; every 2 years									7 ^a
Lee EY et al. [27]	Korea	Cross-sectional	28,913	Age 40–74 years									6 ^a
GC screening through UGIS													
Nakamura Y et al. [28]	Japan	Prospective cohort	1115	Age ≥ 40years; every 1 year	Community campaign	71.8 (1115/1553)		0.52 (24/4609)				1.79 (20/1115); 3.42 (15/438)	5 ^a
Inaba S et al. [29]	Japan	Prospective cohort	24,134	Age ≥ 40years; every 1 year	Community campaign	61.0 (9142/14992)						0.13 (12/9142); 0.19 (28/14992)	5 ^a
GC screening through UGIS													
Mizoue T et al. [30]	Japan	Prospective cohort	87,312	Age ≥ 40years; every 1 year	Community campaign	35.2 (30771/87312)						0.40 (123/30771); 0.63 (357/56541)	6 ^a
Lee KI [31]	Japan	Prospective cohort	42,150	Age 40–60 years; every 1 year		36.0 (15189/42150)						0.32 (49/15189); 0.48 (130/26961)	6 ^a
Tashiro A et al. [32]	Japan	Cross-sectional	19,011	Age ≥ 40 years; every 2 years.			0.13 (24/19048)	0.22 (42/19048)					5 ^a
Matsumoto S et al. [33]	Japan	Retrospective cohort	7178	Age ≥ 40 years; every 2 years	Public notices; community activities.	26.6 (4261/16019)	0.02 (1/4261)	0.05 (2/4261)				0.02 (1/4261) ^c	4 ^a
Miyamoto A et al. [34]	Japan	Retrospective cohort	41,394	Age 40–60 years; every 1 year		58.0 (24014/41394)						0.29 (70/24014); 0.47 (82/17380)	6 ^a
Rosero-Bixby Land Sierra [35]	Costa Rica	Prospective cohort	6828	Age 50–75 years	Personal letter	78.4 (6828/8705)	0.47 (32/6828)	0.86 (59/6828)	90.8	66.6	2.5	0.38 (26/6828) ^c	5 ^a
Nakashima H et al. [36]	Japan	Retrospective cohort	5160	Age ≥ 40 years; every 2 years			0.07 (29/38971)	0.09 (37/38971)					5 ^a
Choi KS et al. [37]	Korea	Retrospective cohort	2,250,392	Age ≥ 40 years; every 2 years				0.07 (1196/1765909)	36.7	96.1	1.7		6 ^a
Hamashima C et al. [38]	Japan	Retrospective cohort	50,988	Age 40–79 years				0.46 (25/5410)	89.3	85.6	3.1		6 ^a
Gotoda T et al. [17]	Japan	RCT	1206	Age 30–74 years			0 (0/604)	0 (0/604)					Low risk ^b
Hamashima C et al. [39]	Japan	Retrospective cohort	50,521	Age 40–79 years	Community campaign			0.26 (90/34148)				0.24 (81/34148) ^c	5 ^a
GC screening through EGD													
Riecken B et al. [40]	China	Prospective cohort	4394	Age 35–44 years			1.32 (58/4394)					0.84 (37/4394)	4 ^a
Tashiro A et al. [32]	Japan	Cross-sectional	11,679	Age ≥ 40years; every 2 years			0.64 (126/19797)	0.85 (168/19797)					5 ^a

(continued)

Table 1. Continued.

First Author (Publication year)	Country, region	Study design	Participants	Target population	Method invitation	Adherence rate, % (screened/invited)	EGC detection rate Positive, % (cases/screened)	GC detection rate Positive, % (cases/screened)	Sens,%	Spe,%	PPV,%	GC mortality rate, % (GC deaths/ screened) vs. % (GC deaths/ no screening)	Quality analysis ^{a,b}
Matsumoto S et al. [33]	Japan	Prospective cohort	7178	Age ≥ 40years; every 2 years	Public notices; community activities	28.2 (7178/25454)	0.35 (25/7178)	0.39 (28/7178)				0.01 (1/7178) ^c	4 ^a
Hosokawa et al. [41]	Japan	Retrospective cohort	2192	Age 40–75 years			1.45 (32/2192)	1.87 (41/2192)				0.23 (5/2192)	5 ^a
Nakashima H et al. [36]	Japan	Retrospective cohort	5160	Age ≥ 40years; every 2 years			0.43 (22/5160)	0.45 (23/5160)					5 ^a
Choi KS et al. [37]	Korea	Retrospective cohort	2,250,392	Age ≥ 40years; every 2 years				0.26 (2415/924822)	69.0	96.0	6.2		6 ^a
Mansour GF et al. [42]	Iran	Prospective cohort	1382	Age ≥ 45years	Public media; house- to-house direct contact			0.51 (7/1382)					5 ^a
Kim BJ et al. [43]	Korea	Retrospective cohort	34,416	Age ≥ 40years; every 2 years			0.22 (74/34416)	0.29 (100/34416)					6 ^a
Hamashima C et al. [38]	Japan	Retrospective cohort	50,988	Age 40–79 years				0.87 (64/7388)	95.5	85.1	5.5		6 ^a
Lu YF et al. [44]	China	Prospective cohort	36,154	Age 40–69 years			0.67 (243/36154)	0.85 (307/36154)				0.15 (24/16373) ^c	5 ^a
Hamashima C et al. [39]	Japan	Retrospective cohort	50,521	Age 40–79 years	Community campaign			0.63 (103/16373)					5 ^a
GC screening through EGD													
Zheng X et al. [45]	China	Prospective cohort	12,453	Age 40–69 years			0.48 (60/12453)	0.48 (60/12453)				0.07 (9/12453) ^c	7 ^a
Gotoda T et al. [17]	Japan	RCT	1206	Age 30–74 years			0.50 (3/602)	0.50 (3/602)					Low risk ^b
Zhang M et al. [46]	China	Prospective cohort	88,263	Age 40–69 years			0.64 (565/88263)	0.85 (748/88263)					5 ^a
Akgul H et al. [47]	Turkey	Prospective cohort	7316	Age ≥ 40years			0.06 (4/7136)	0.29 (21/7316)					4 ^a
Guo L et al. [48]	China	Cross-sectional	7996	Age 40–69 years	Phone call, personal contact	18.4 (7996/43423)		0.09 (7/7996)					8 ^a
Ge X et al. [49]	China	Prospective cohort	8257	Age ≥ 40years			0.54 (45/8257)	0.67 (55/8257)					7 ^a
GC screening through PG													
Miki K et al. [50]	Japan	Cross-sectional	4647	Age ≥ 20years	Workplace screening		0.06 (3/4647)	0.09 (4/4647)					3 ^a
Hattori Y et al. [51]	Japan	Prospective cohort	4876	Age 40–61 years	Workplace screening.		0.16 (8/4876)	0.23 (11/4876)	66.7	81.5	1.3		3 ^a
Yoshihara M et al. [52]	Japan	Prospective cohort	10,996	Age ≥ 40years	Free health checkups.		0.17 (19/10996)	0.19 (21/10996)					6 ^a
Kitahara F et al. [53]	Japan	Prospective cohort	5133		Free health checkups.		0.14 (7/5113)	0.22 (11/5113)	84.6	73.5	0.8		5 ^a
Lomba-Viana R et al. [54]	Portugal	Prospective cohort	13,118	Age 40–79 years	Advertisement lectures; newspapers		0.02 (3/13118)	0.05 (6/13118)	66.7	46.90	2.1		6 ^a
Vohlonen I et al. [55]	Finland	Prospective cohort	12,175	Males 51–65 years	Personal letter	72.2 (12175/16872)		0.02 (2/12175)				0.25 (31/12175); 0.51 (24/4697)	5 ^a
Chiang TH et al. [56]	Taiwan	Retrospective cohort	1682	Age ≥ 30years		47.5 (1682/3541)		0.12 (2/1682)				0.83 (14/1682) ^c	6 ^a
Chiang TH et al. [57]	Taiwan	Prospective cohort	3895	Age ≥ 30years	Phone call or email; Advertisement in social media/ newspapers	59.8 (3895/6512)		0.10 (4/3895)	44.4	96.8	3.1		5 ^a
Ji L et al. [18]	China	RCT	7773	Age 40–69 years		39.1 (7773/19881)		0.04 (3/7773)	21.4	98.0	1.9		Low risk ^b
GC screening through FDG-PET													
Minamimoto R et al. [58]	Japan	Retrospective cohort	153,775	Age 30–80 years				0.08 (124/153775)					4 ^a

^aNewcastle–Ottawa scale for observational studies. ^bCochrane Collaboration guidelines for RCTs. ^cData on GC mortality rate in unscreened individuals unavailable. EGC: early gastric cancer; EGD: esophagogastroduodenoscopy; GC: gastric cancer; FDG-PET: F-fluorodeoxyglucose-positron emission tomography; PG: serum pepsinogen; PPV: positive predictive value; RCT: randomized controlled trial; Sens: sensitivity; Spe: specificity; UGIS: upper gastrointestinal series.

(FDG-PET)]. Eleven studies focused only on adherence to GC screening programs, regardless of the screening method used (UGIS or EGD or PG). Regarding quality evaluation, in all of the included RCTs low risk of bias was considered [10] (Table 1; Supplementary Figure 1). Observational studies were classified through a numerical scale according to the Newcastle–Ottawa scale for observational studies [11] (Table 1). Publication biases were evaluated for the primary end-points (Supplementary Figure 2).

In brief, GC screening is offered to healthy asymptomatic individuals in three Eastern countries. In Japan, UGIS or EGD are both first-line options for asymptomatic individuals ≥ 40 years old. The National Cancer Screening Program for GC in Korea offers biennial UGIS or EGD to individuals ≥ 40 years old. In China screening through EGD is available in high-risk areas, for individuals aged 40–69 years old. In contrast, in Western countries there are no population-based GC screening programs ongoing, yet some pilot programs were initiated. Regarding PG, although the validity of serum PGI and PGII for the diagnosis was previously evaluated [53,59,60] no GC screening program based on this method was yet implemented at a national level.

Effect of screening on GC mortality

GC mortality rate was evaluated in 13 studies (follow-up range 3–15 years) [28–31,33–35,39–41,45,55,56]. Five studies (median follow-up of 8 years) compared GC mortality between screening through UGIS and no screening, and pooled results showed that screening is associated with significantly lower GC mortality rates (OR 0.63, 95% CI 0.55–0.73, $I^2 = 0\%$) (Figure 2). Additionally, Rosero-Bixbi L and Sierra, reported a GC mortality rate of 0.38%, yet no comparison to unscreened individuals was established [35]. Only two studies directly compared GC mortality between populations submitted to screening through UGIS and EGD, precluding meta-analysis [33,39]. Matsumoto S et al. in a large cohort with 5 years of follow-up, found that screening through EGD significantly lowered GC mortality (OR 0.62, 95% CI 0.39–0.97), while Hamashima C et al. reported a trend to lower GC mortality in the EGD arm but without statistical significance (OR 0.59, 95% CI 0.04–9.49) [33,39]. One study compared GC mortality between screening through EGD and no screening, with results favoring EGD (OR 0.35, 95% CI 0.14–0.86) [41]. Two studies assessing PG also found a

significant benefit in GC mortality although data was not pooled in meta-analysis [55,56].

Diagnostic yield and diagnostic accuracy of the different screening methods

Overall, 28 of the included studies reported GC detection rates [17,18,28,32,33,35–39,41–58]. EGD was associated with significantly higher GC and EGC detection rate in double-arm studies directly comparing detection rates with UGIS (OR 3.29, 95% CI 2.49–4.35, $I^2 = 76\%$ and OR 5.50, 95% CI 3.93–7.70, $I^2 = 0\%$, respectively) (Figure 3). Several single-arm studies of the different screening methods also reported pooled GC detection rates, that were significantly higher for EGD (0.55%, 95% CI 0.39–0.75%) than for UGIS (0.19%, 95% CI 0.10–0.31%) and serum PG test (0.10%, 95% CI 0.05–0.16%) (Figure 4). EGC detection rate was also significantly higher with EGD than with UGIS or PG testing (EGD 0.48%, 95% CI 0.34–0.65%; UGIS 0.08%, 95% CI 0.04–0.13%; PG 0.10%, 95% CI 0.04–0.19%) (Figure 4). Two studies were excluded from meta-analysis once a different methodology was adopted (two or more screening rounds instead of one) [35,40]. Significant heterogeneity for both outcomes (pooled GC and EGC detection) was noted, but subgroup analysis (by study design or region of origin) did not decrease heterogeneity and did not significantly alter pooled prevalence in each subgroup. Further sensitivity analysis was performed excluding potential outliers [41], however, heterogeneity remained high and pooled prevalence in each subgroup was not significantly different. A retrospective study also assessed the diagnostic yield of FGD-PEG for GC screening, and a low GC detection rate was found (0.08%) [58].

Eight studies reported data on diagnostic properties of the screening method applied [18,35,37,38,51,53,54,57]. Two double-arm studies directly compared UGIS and EGD and both reported an overall higher diagnostic accuracy for EGD [37,38]. Comparison of pooled diagnostic properties between screening methods was not performed due to the limited number of data available for UGIS and EGD. Nonetheless, PG tended to lower specificity and DOR (Table 2; Supplementary Figure 3).

Adherence rate and factors that influence adherence

Twenty studies assessed GC screening adherence [15,16,18–30,35,48,55–57]. The majority of the studies

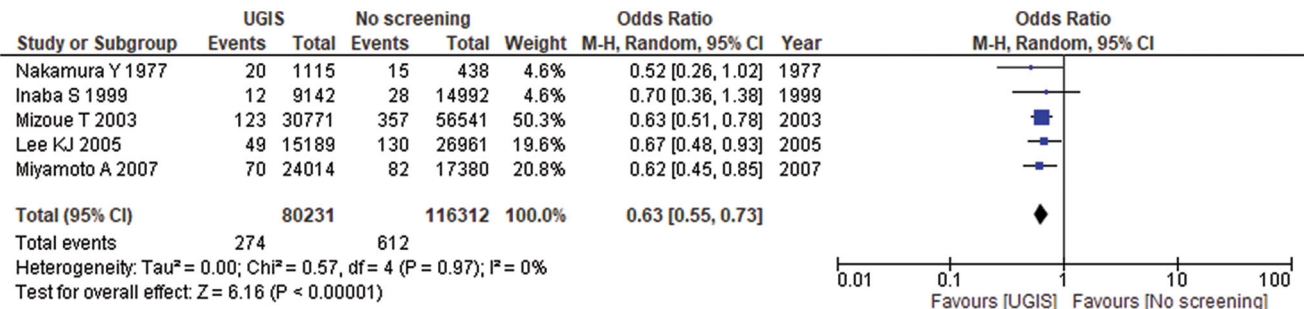


Figure 2. GC mortality with screening through UGIS and no screening. Heterogeneity between studies was assessed through p statistic and I^2 . $p < .05$ meaning statistical significance. CI: confidence interval; GC: gastric cancer; UGIS: upper gastrointestinal series.

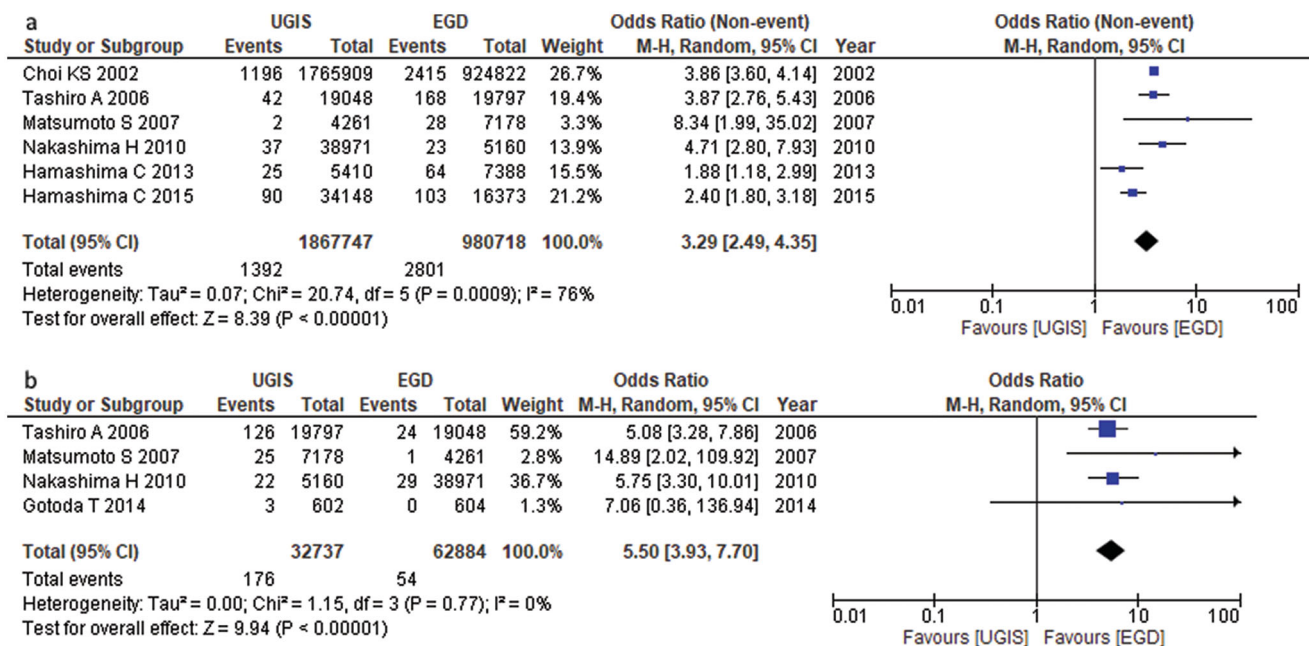


Figure 3. GC and EGC detection through UGIS and EGD in double-arm studies. a) GC detection rate; b) EGC detection rate. Heterogeneity between studies was assessed through p statistic and I^2 . $p < .05$ meaning statistical significance. CI: confidence interval; EGC: early gastric cancer; EGD esophagogastroduodenoscopy; GC: gastric cancer; UGIS: upper gastrointestinal series.

evaluated adherence to GC screening programs, independently of the method used, while some single-arm studies evaluated adherence to a specific screening method (Table 3).

Overall GC screening uptake (independently of the screening method used) was heterogeneous, and higher adherence rates were reported in studies based on interviews/self-report screening uptake than in studies in which the performance of the screening exam was confirmed by the investigators (invited cohorts) (Table 3). Two Korean RCTs assessed the effectiveness of interventions to increase adherence and showed that a combination of phone call and invitation reminder performed better than mail invitation alone [15,16]. Five studies also evaluated time-trends of screening uptake and screening method in Korea, based on the analysis of the National Cancer Screening Program databases [23–27]. These studies (all based on questionnaires/self-reporting) found that GC screening rates steadily increased from 7.4% in 2002 [24] to 74.8% in 2015 [27]. Participation rates were higher for females and in the age of 60–69 years. The proportion of individuals that were screened by EGD also increased over time, from 31.1% in 2002 to 72.5% in 2011. Male sex, younger age and higher socioeconomic status were associated with preference for EGD [24].

Given the significant between-studies heterogeneity (due to different methodology), pooled comparison of adherence rates between the different screening methods was not deemed adequate. In brief, only one study from China [48] evaluated adherence to EGD screening and a low adherence rate was found (~18%), while adherence rates with non-invasive methods (PG and UGIS) were higher (Table 3) [18,28–30,35,55–57]. Nonetheless, three Korean cross-sectional studies reported a trend toward EGD preference over time [19,23,24].

Individual factors seem also to impact intention to adhere to GC screening programs. Higher household income and education level were associated with higher adherence rates [19,22,61]. Similarly, family history of GC and past medical history of gastric ulcer, led to higher adherence rates [19,21]. Also, non-smokers are more likely to undergo GC screening [19,22].

Table 3 summarizes the pooled rates (GC detection, EGC detection and adherence) according to the screening method.

Cross-sectional assessment of ongoing gastric cancer screening programs

Among the surveys sent to 311 Endoscopy and Gastroenterology societies, a response rate of 22.0% was obtained (Supplementary Table 1). Data from five continents and 24 countries were obtained: Europe ($n = 16$), America ($n = 5$), Africa ($n = 1$), Asia ($n = 1$) and Oceania ($n = 1$).

Two countries (Sweden and Serbia) reported the existence of GC screening programs. In Sweden, the GC screening program is available only for high-risk populations (e.g. genetic mutations) and is performed through EGD. In Serbia, GC screening is performed by combining EGD with a screening colonoscopy and is directed to high-risk individuals younger than 65-year-old. Twenty-two countries answered that no GC screening program was implemented. More detailed information is presented in Supplementary Table 1.

Discussion

GC is still the third malignancy with more cancer-related deaths, despite the decreases in incidence and mortality rate in the last decades [1]. Screening programs have been implemented in some high-risk populations in Eastern countries,

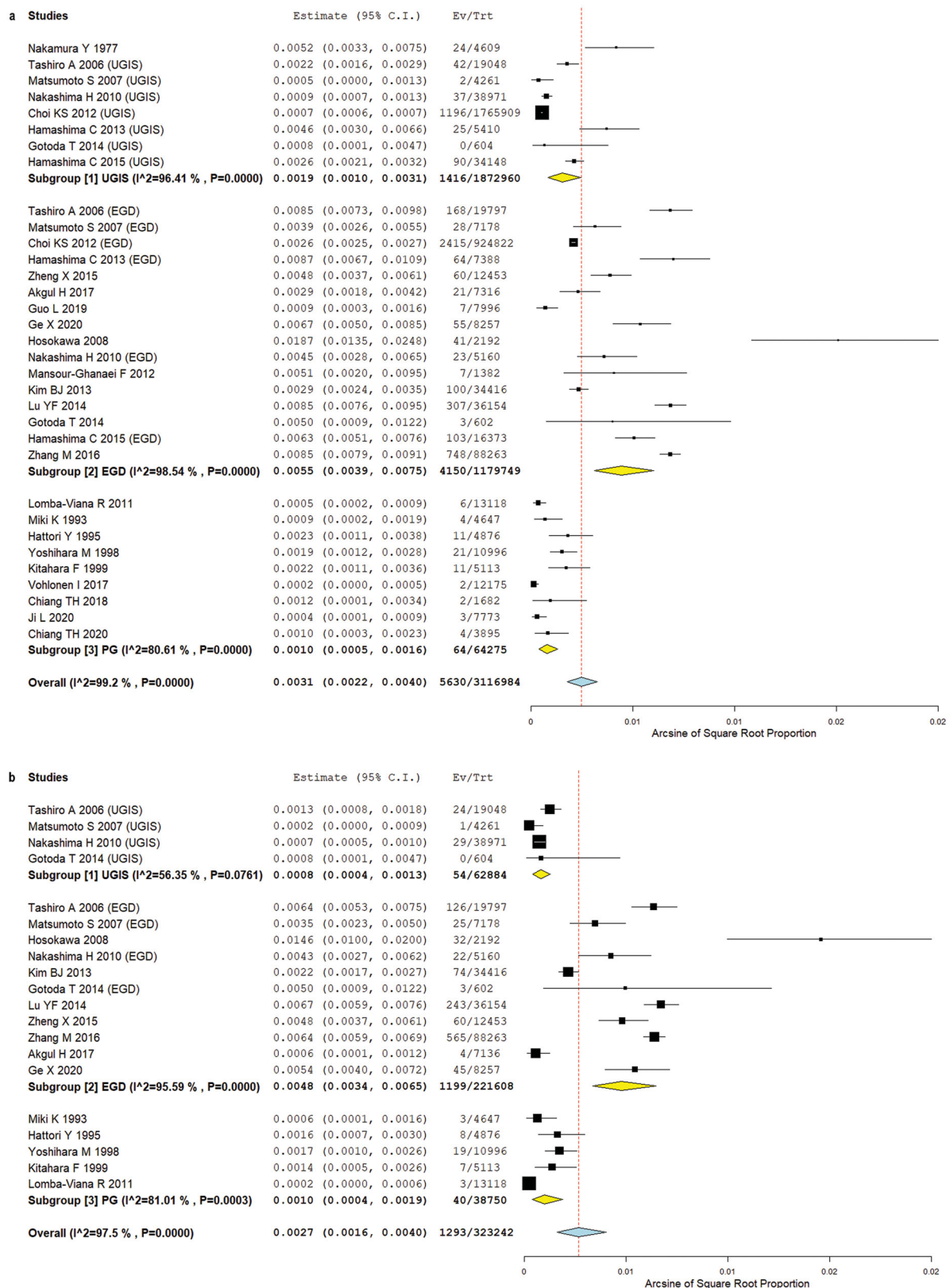


Figure 4. GC and EGC detection according to screening method, in single-arm studies. a) GC detection rate; b) EGC detection rate. Heterogeneity between studies was assessed through p statistic and I^2 . $p < .05$ meaning statistical significance. CI: confidence interval; EGC, early gastric cancer; EGD, esophagogastrroduodenoscopy; GC, gastric cancer; PG, serum pepsinogen; UGIS, upper gastrointestinal series.

Table 2. Sensitivity, specificity, positive LR and DOR for GC diagnosis according to the screening method.

Included studies		Sensitivity % (95% CI) ^a	Specificity % (95% CI) ^a	Positive LR (95% CI) ^a	DOR (95% CI) ^a
UGIS	Choi KS et al. [37]	36.7	96.1	9.4	14.2
	Hamashima et al. [38]	89.3	85.6	6.2	49.7
EGD	Choi KS et al. [37]	69.0	96.0	17.4	54.0
	Hamashima C et al. [38]	95.5	85.1	6.4	122.0
PG	Meta-analysis [18,51,53,54,57]	57.1 (44.0–69.5)	87.3 (86.9–87.8)	4.2 (2.3–7.6)	9.5 (4.1–22.1)

^aPooled sensitivity, specificity, positive LR and DOR with CI were computed only for PG (at least three studies per outcome).

CI: confidence interval; DOR: diagnostic odds ratio; EGD: esophagogastroduodenoscopy; GC: gastric cancer; LR: likelihood ratio; PG: serum pepsinogen; UGIS: upper gastrointestinal series.

Table 3. Summary table for GC detection, EGC detection and adherence.

			Adherence		
	GC detection Pooled GC detection rate % (95% CI)	EGC detection Pooled EGC detection rate % (95% CI)	Study design	Adherence rate % (95% CI)	
Overall ^a			SF	Meta-analysis ^b [19–22]	43.3 (35.2–51.5)
			IC	Lee MH et al. ^b [15]	23.7 (15.8–32.6)
UGIS	0.19% (0.10–0.31)	0.08% (0.04–0.13)		Hong NS and Kam ^b [16]	31.4 (28.0–34.9)
			SR	Meta-analysis ^b [28–30]	56.2 (34.7–76.5)
EGD	0.55% (0.39–0.75)	0.48% (0.34–0.65)	IC	Rosero L and Sierra ^b [35]	78.4 (77.6–79.3)
			IC	Guo L et al. ^b [48]	18.4 (18.0–18.8)
PG	0.10% (0.05–0.16)	0.10% (0.04–0.19)	IC	Meta-analysis ^b [56,57]	53.7 (41.6–65.5)
				Meta-analysis ^c [18,55]	56.0 (24.1–85.3)

^aIrrespective of the screening method adopted. ^bAdherence estimates from population-based screening programs. ^cAdherence estimates from research-based screening.

CI: confidence interval; EGC: early gastric cancer; EGD: esophagogastroduodenoscopy; GC: gastric cancer; IC: invited cohort; PG: serum pepsinogen; SF: self-reporting; UGIS: upper gastrointestinal series.

given the improvement in survival rates. Evidence regarding its application in other high-risk or intermediate-risk populations, namely in Western countries, is limited to a cost-utility analysis performed in Portugal [6,7].

This study comprehensively reviewed population-based GC screening programs in Eastern (Japan, Korea and China), as well as pilot programs in Western countries. Among Eastern countries, GC screening programs are well established in Japan and Korea through EGD or UGIS (chosen by screened individuals according to their preference). In contrast, in China GC screening is performed in high-risk areas solely through EGD. On the other hand, in Western countries GC screening pilot programs through UGIS, EGD and serologic testing were reported, but there was no data from implemented national GC screening programs.

Populational GC screening programs (mainly through UGIS) were found to have a significant impact on GC mortality and pilot studies with PG also showed a significant benefit on mortality. Two studies, one of them being a large cohort with 5 years of follow-up, also found that screening through EGD significantly lowered GC mortality when compared with UGIS screening, although data could not be pooled in meta-analysis. However, based on these two studies and the higher diagnostic yield of EGD, this screening method is likely to reach a higher benefit in GC mortality, at least for similar adherence rates. However, despite this benefit found on GC mortality from screening, it should be noted that these studies come from Eastern countries, and it is unclear if this benefit on mortality replicates if GC screening programs are implemented in the west.

EGD screening was associated with both significantly higher GC and EGC detection rates when compared to UGIS and PG. Additionally, EGD had higher detection rates in double-arm studies directly comparing screening through UGIS and EGD. Accordingly, high-definition EGD with

chromoendoscopy is the gold-standard for the diagnosis of gastric precancerous conditions and early neoplastic lesions [7]. In this setting, EGD also allows staging of gastric precancerous conditions (and selection of patients who benefit from surveillance) and adequate characterization of subtle early lesions hardly recognized through radiologic or serologic methods.

Significant heterogeneity, concerning study design (e.g. methods of screening; recruitment strategies) and screening uptake assessment (self-reported or confirmed by the investigators) made adherence measurement particularly challenging. UGIS and PG testing tended to higher adherence rates when compared to EGD, yet comparative data is scarce. This may be explained by the fact that less invasive screening procedures lead to better adherence rates. It is also relevant to note that studies that assessed preferences for different screening methods over time found a rising preference for EGD through the years. However, it should be highlighted that sociodemographic features (e.g. income, educational level and family history), procedure-related factors (e.g. previous experience with diagnostic exams and access to sedation) and invitation strategies may influence adherence rates, further than the screening method itself. Regardless of the chosen screening test, invitation strategies largely influenced the adherence rate, since individualized invitation (e.g. phone call and personal letter) performed better than workplace advertisements or community campaigns. Further studies comparing screening methods and invitation strategies may accurately measure adherence. Moreover, patient's risk perception evaluation may further explain variability in GC screening uptake.

An assessment of ongoing GC screening programs was performed through an online survey in order to complement the review process and obtain a real-live perspective, although only two Western countries reported the

implementation of GC screening at a national level in high-risk populations. Nonetheless, the response rate was only 22.0% and a higher participation could have been more informative in this setting.

This review highlights the favorable impact of screening on GC mortality and reinforces the higher diagnostic yield of EGD. Despite heterogenous data, less invasive methods tended to higher adherence rates, though screening uptake was mostly impacted by recruitment strategies.

Our review presents some limitations. Most included studies are observational and therefore more susceptible to selection bias. Significant heterogeneity was found for some outcomes, despite careful study selection, quality assessment and subgroup analysis. Also, most studies arise from high-risk populations of Eastern countries and data from intermediate risk regions is still scarce. As so, data from this review must be interpreted considering that the effectiveness of GC screening largely depends on regional GC rates. Additionally, UGIS and PG testing are currently sparsely used in clinical practice, despite the fact that the optimal screening method is not yet completely clarified. Yet, serologic testing combining serum PG and *Helicobacter pyloric* has also been proposed for mass screening [18,57]. Moreover, safety data was not defined as primary outcome. In fact, only one study recorded systematically the occurrence of adverse events [17] for UGIS and EGD screening.

Data from this meta-analysis (impact on GC mortality, estimates of diagnostic yield, diagnostic accuracy and adherence rates) should be used to assess the cost-effectiveness of GC screening methods across different Western countries. The MAPS II Guideline supports GC screening in high-risk populations as well as in intermediate-risk populations depending on specific economic studies for each local setting [7]. In fact, data from the present review may be considered in tailored economic studies. Additionally, data on available endoscopic resources and quality assessment in GC screening must be further considered.

Disclosure statement

The authors report no conflict of interest. Faria L and Silva JC contributed equally to the writing of this article. Dinis-Ribeiro M and Libânio D designed the study. Faria L, Silva JC, Rodriguez-Carrasco M and Libânio D performed the research and analysed the data. Rodriguez-Carrasco M, Pimentel-Nunes P, Dinis-Ribeiro M and Libânio D revised the paper for critically important intellectual content.

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Chapter V – Risk perception and attitudes toward gastrointestinal cancer screening

1. Development and validation of the PERCEPT-PREVENT tool to determine risk perception and attitudes towards digestive cancer screening

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Development and validation of the PERCEPT-PREVENT tool to determine risk perception and attitudes towards digestive cancer screening

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Background and aims Colorectal cancer (CRC) screening is recommended worldwide, while gastric cancer (GC) screening may also be defendable in some settings. However, adherence rates and factors influencing participation are not well characterized. This study aimed to validate a tool to determine risk perception of CRC and GC and also of endoscopy-related complications.

Methods A questionnaire in CRC risk perception based on the Health Belief Model was used. Forward/backward translation (English-Portuguese) and cultural adaptation were performed. After revision by a panel of experts, the questionnaire was adapted to target GC risk perception and perceptions towards endoscopy-related complications. The final version of the questionnaire (PERCEPT-PREVENT tool) was applied to 44 individuals, through telephonic interview, at enrolment and at intervals ≤ 3 weeks. Test-retest reliability and agreement were assessed.

Results Almost perfect reliability between test and retest was obtained for CRC symptom knowledge score (ICC = 0.88), risk factor knowledge score (ICC = 0.89), and perceived severity (ICC = 0.84). At least moderate agreement between test and retest was obtained for GC symptom knowledge score (ICC = 0.94), risk factor knowledge score (ICC = 0.92), and perceived severity (ICC = 0.58). Test-retest reliability was assessed for barrier domains [faecal occult blood test ICC = 0.63; colonoscopy ICC = 0.79; upper GI endoscopy (UGIE) ICC = 0.83]. A total of 91% and 98% of participants gave the same answer in the test and retest for preferred method of CRC screening and intention to undergo UGIE for GC screening combined with a screening colonoscopy, respectively.

Discussion PERCEPT-PREVENT is a valid and reliable tool for CRC and GC risk perception evaluation. Eur J Gastroenterol Hepatol XXX: XXXX-XXXX

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Introduction

Colorrectal cancer (CRC) is the most frequently diagnosed malignancy and the second leading cause of cancer mortality worldwide [1,2]. The estimated burden of CRC is expected to rise even if the global incidence rates decline by 2% per year [2]. The highest age-standardized incidence rate was registered in Southern (162/100 000) and Eastern Europe (158/100 000) for males aged between 50 and 74 years old [2].

Implementation of screening initiatives have positively impacted early detection and mortality rates, with the largest decreases in mortality rates seen in countries with longstanding programs [3,4]. In Europe, the highest proportion of screen-detected CRC (40–60%) was reported in regions and countries with well-established screening programs, while in most other regions and countries the proportions of screen-detected cancers were below 30% [5]. It is important to highlight that high adherence rates were reported in countries with the greatest proportions of screening-detected CRC [5]. Nonetheless, the effectiveness of organized screening at a nationwide level is directly related to the participation rate as lower adherence rates leads to a lower effect on mortality decrease and higher costs [6]. In fact, several countries with well-organized screening programs report suboptimal participation rates [2,6,7]. Adherence rates to CRC screening are sparsely characterized in European countries. Higher utilization rates of either faecal occult blood testing (FOBT) or colonoscopy are reported in countries with fully rolled out organized screening programs based on faecal tests (29.7% in Croatia to 66.7% in the UK) and countries offering both FOBT and colonoscopy (22.7% in Greece to 70.9% in Germany) in the setting of organized and/or opportunistic screening [7]. In Germany, the overall adherence to CRC screening increased after colonoscopy was added to the screening program as an alternative to FOBT, mainly due to an increase in screening colonoscopy

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Keywords: cancer screening, colorectal cancer screening, early detection of cancer, gastric cancer screening, gastrointestinal endoscopy, preventive medicine, risk perception

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uptake [8]. In Portugal, as in other European countries, the adherence rates to CRC screening are not well characterized. Moreover, the intention to adhere according to the screening method has not been previously evaluated.

Gastric cancer (GC) is the fifth most common cancer and the third cause of cancer mortality worldwide [9]. Currently, screening for GC is performed only in countries with a high risk of disease (defined as an age-standardized incidence rate ≥ 20 per 100 000) such as Japan and Korea (29.9 and 41.3, respectively) [10]. A cost-utility analysis found that combining an upper GI endoscopy (UGIE) with a screening colonoscopy is also cost-effective in countries with GC risk $\geq 10/100,000$ [11]. This means that in Europe if a CRC screening program is already in place (by means of FOBT or stand-alone colonoscopy) all countries with an intermediate incidence rate of GC such as Albania, Belarus, Macedonia, Russia, Latvia, Ukraine, Estonia, Lithuania, Portugal, Moldova, Romania, Slovenia, Bulgaria, and Croatia (age-standardized incidence rate from 10.3 to 20.1), might benefit by providing a screening UGIE in combination with colonoscopy for their populations [12]. The abovementioned cost-utility analysis assumed full compliance with endoscopic screening although it is known that in countries with well-established GC screening programs, the adherence rates are well below 100% [11,13]. Furthermore, the adherence rate to dual screening (CRC and GC) is not known in European intermediate-risk countries.

Risk perception and attitudes towards CRC/GC screening were rarely evaluated in Western countries, although two Eastern studies have previously used a structured survey based on the Health Belief Model (HBM) to evaluate CRC risk perception [14,15]. The questionnaire was first validated in a Chinese study to estimate predictors of CRC screening uptake [15]. Subsequently, the same tool was used in a multicentric study in the Asia-Pacific region to compare risk perception between countries with low- and high-CRC screening adherence rates [14]. Participation rates are largely influenced by patient's risk perception, namely the risk of developing CRC or GC, which is impacted by knowledge of symptoms, risk factors and screening procedures. Moreover, barriers to screening (complication risk perception, access to testing, financial burden, and time constraints), may also negatively impact adherence rates.

Using a previously developed questionnaire for CRC risk perception assessment [14,15], and further adapting it, this study aims to adapt and validate a risk perception questionnaire (PERCEPT-PREVENT tool) that targets both CRC and GC as well as endoscopy-related complications.

Methods

Study design and patient selection

The authors initially performed an adaptation of a previously developed questionnaire (detailed below). Then, a test-retest study was performed where asymptomatic men and women between the ages 50–74 years old eligible for the national CRC screening program were included. Participants from 4 counties (*Vila Nova de Gaia, Espinho, Santo Tirso* and *Trofa*) of the Northern region of Portugal

were randomly recruited from the regional CRC screening program database. Inclusion criteria: asymptomatic individuals who were not yet invited to CRC screening. Exclusion criteria: medical history of CRC or GC, known hereditary cancer risk, previous colectomy/gastrectomy, inflammatory bowel disease, dementia, inability and/or refusal to answer the questionnaire.

HBM based questionnaire

A questionnaire in CRC risk perception, based on the HBM, previously validated in two eastern population-based studies was used [14,15]. This tool measures the following components: 1) knowledge of symptoms, risk factors and screening methods; 2) perceived risk of cancer; 3) perceived severity of cancer; 4) perceived benefits of screening; 5) previous screening participation; 6) barriers to screening.

Knowledge of CRC symptoms and risk factors was evaluated through the following questions: 1) 'Do you know the possible symptoms of bowel cancer?' and 2) 'Do you know the risk factors for bowel cancer?'. Additionally, participants who responded positively were subsequently asked to enumerate possible CRC symptoms and risk factors. Adherence and attitudes towards CRC screening were also addressed. A question examining the need for regular screening in asymptomatic individuals aged 50 years and older was elaborated to determine whether respondents acknowledged the rationale for screening. To assess test knowledge score, participants were asked whether they had heard of each available screening tests. Perceived severity was evaluated by five items designed to assess the effect CRC would have on personal and family life (feeling anxious, causing anxiety to family members, negative economic impact in family members, developing passivity and creating a heavy burden for family members). Negative health consequences of screening, financial barriers, time constraints, and access barriers were evaluated.

Forward/backward translation and cultural adaptation

The original version of the questionnaire (English) was sent to an independent translator (Portuguese native speaker fluent in English), who performed a forward translation to the Portuguese language. An initial Portuguese version of the questionnaire was revised by the authors, compared with the original English version to confirm conceptual equivalence, and discussed with the translators. The cross-cultural adaptation procedure was conducted following international guidelines [16–18]. Thereafter, a Portuguese version of the questionnaire was accomplished and sent to backward translation into English. An expert committee (translator, physicians and nurses), reviewed and compared the backward translation with the original English version, reaching consensus and thus, confirming the consistency of the backward translation process.

Questionnaire adaptation

A panel of 3 physicians and 2 nurses with expertise in digestive cancer screening revised the Portuguese version of the questionnaire and added additional domains, in order to target GC screening. The main components of the

HBM were accordingly targeted: 1) knowledge of symptoms, risk factors and screening methods; 2) perceived risk of cancer; 3) perceived severity of cancer; 4) perceived benefits of screening; 5) barriers to screening. The sections of the questionnaire were adapted to the GC screening setting namely, possible symptoms, risk factors and screening methods. Additionally, perceived severity, negative consequences of screening and barriers were also approached.

To further explore barriers to CRC and GC screening a third section was added to evaluate perceptions towards endoscopy-related complications. To evaluate knowledge of possible complications during a UGIE and/or colonoscopy as well as factors that may increase the risk of complications, additional questions were formulated.

The panel of experts revised the adaptations proposed and after discussion, a final version of this section (Supplementary Appendix 1, Supplemental digital content 1, <http://links.lww.com/EJGH/A939> and 2, Supplemental digital content 2, <http://links.lww.com/EJGH/A940>) was unanimously approved.

Data collection

The study protocol was approved by the Ethical committees of the institutions involved in the study, namely, *Administração Regional De Saúde do Norte (ARSN)*, *Centro Hospitalar Vila Nova de Gaia Espinho (CHVNGE)* and *Instituto Português de Oncologia do Porto (IPO-Porto)*. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Since the national CRC screening program is performed and operationalized by *ARS Norte*, this organization provided random telephonic contacts of participants, after Data Protection Committee's approval.

Telephonic interviews were conducted by 2 dedicated Gastroenterology nurses. Prior to the recruitment, three formal training sessions were performed. The training included the following: rationale and aims of the study, overview of the survey, procedures in conducting the survey, recommendations for completing the questionnaire, quality control measures, and standard questions and answers. A fieldwork manual was used to guide the interviewers to conduct a qualified interview. Both interviewers were supervised by the project coordinator.

The final version of the questionnaire was applied, through telephonic interview, at enrolment and at intervals up to 3 weeks, from February to March 2023. Informed verbal consent was obtained from all participants after explanation of aims of the study. Individuals who refused to participate were not included in the study. A structured interview was conducted evaluating whether participants reported any difficulty answering the questions. The interviewers were instructed to evaluate if participants pointed any of the items as confusing, offensive and/or containing difficult vocabulary. Sociodemographic data including age, gender, educational level, and monthly income were registered. Data from patients who fulfilled eligibility criteria was collected in an electronic database, and each patient received a code number to secure anonymization.

Sample size calculation and statistical analysis

Sample size calculation was performed assuming an Intraclass Correlation Coefficient (ICC) of 0.41 (moderate

agreement) and a 95% confidence interval (CI) for a two-tailed test, an error of 0.05, and a power of 80%. Thus, a sample size of 43 participants was obtained.

Statistical Package for Social Sciences (SPSS) program version 27 (IBM Corporation, Armonk, NY) was used. Categorical variables are summarized as frequencies and percentages. Chi-square test or Fisher's exact test was used to compare categorical variables. Depending on the normality tests, continuous variables were expressed in means and SD or median and interquartile range (IQR). Means were compared using paired-samples t-test or related samples Wilcoxon signed-rank test, according to the normality tests.

Test-retest reliability was assessed, and data was examined by the ICC with a 95% CI. A 2-way random effects model, single measures, absolute agreement, and ICC were analyzed to express concordance between the test and retest. Values for ICC were interpreted according to the scale proposed by Landis and Koch (i.e. 0.41–0.60: moderate agreement; 0.61–0.80: substantial agreement; 0.81–1.00: almost perfect agreement) [19]. Bland and Altman graphs were obtained to assess agreement for key domains [20].

For dichotomous variables, reliability was accessed through Cohen's kappa (K) and interpreted according to the intervals defined by McHugh [21]: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. Overall and specific Proportions of Agreement (PA) were calculated to evaluate agreement for dichotomous variables.

Results

Patient demographics and screening uptake

During the recruitment period, 98 individuals were contacted. Thirty-three patients refused to participate and 13 met exclusion criteria. Finally, 52 completed the questionnaire at enrollment, yet 8 refused to complete the second questionnaire up to three weeks later (Fig. 1).

A total of 88 telephonic interviews were performed, concerning 44 patients. All patients completed the corresponding questionnaire in less than 45 min. There were no reports of items containing difficult vocabulary or upsetting/offensive content. The mean interval between interviews was 10 (3–25) days. The mean age was 54 (SD 5) years, and 61% ($n = 27$) were female. None of the included individuals had been yet recruited for the regional CRC screening program. Further characterization of sociodemographic features of our sample is displayed in Table 1.

Knowledge of symptoms, risk factors and screening methods

There was almost perfect agreement between test and retest in the symptom knowledge score for both CRC (ICC 0.88, 95% CI 0.77–0.93) and GC (ICC 0.94, 0.89–0.87). Similarly, there was at least substantial agreement for the risk factor knowledge score (CRC ICC 0.89, 95% CI 0.80–0.94; GC ICC 0.92, 95% CI 0.86–0.96), perceived risk score (CRC ICC 0.80, 95% CI 0.44–0.93; GC ICC 0.95, 95% CI 0.87–0.98) and risk factor awareness score

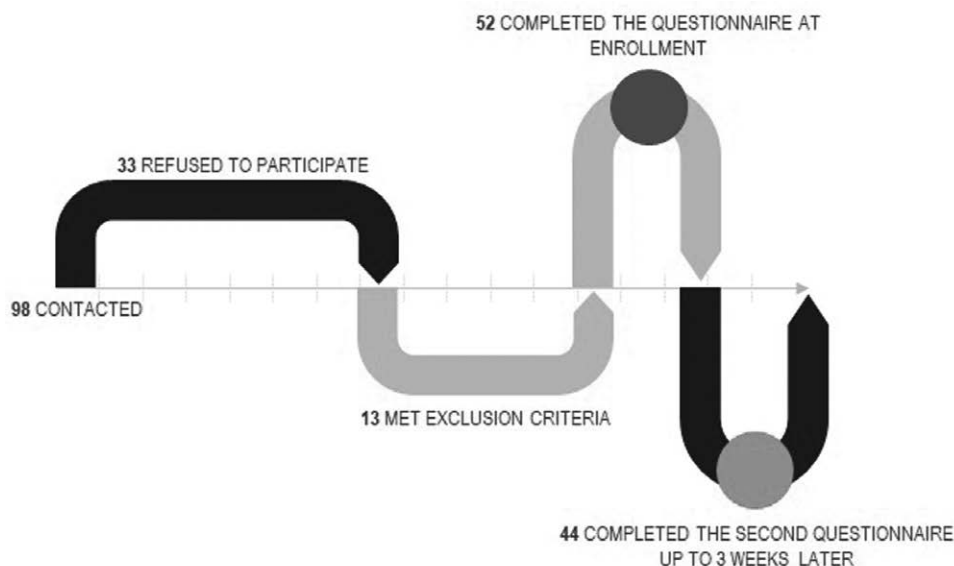


Fig. 1. Recruitment of individuals from the Portuguese regional CRC screening program database for PERCEPT-PREVENT tool validation study.

Table 1. Patient demographics

Baseline characteristics	Total (n = 44)
Female, n (%)	27 (61)
Age, years, mean (SD)	54 (5)
Married, n (%)	18 (42.9)
Basic educational level	22 (52.4)
Full time employment	26 (61.9)
Regular medical consultation	42 (95.5)
Health insurance	13 (29.5)

μ, mean.

(CRC ICC 0.96, 95% CI 0.93–0.98; GC ICC 0.92, 95% CI 0.86–0.96). Test–retest reliability results for all knowledge domains are shown in Table 2.

Perceived testing need scores were overall high for CRC and GC screening, and almost perfect agreement was obtained for both (ICC 1.0), in test and retest. Mean CRC test knowledge score was 4.3 (SD 0.9) at test and 4.1 (SD 0.8) at retest, with most patients reporting knowledge of colonoscopy (2 points) and FOBT (2 points). Substantial agreement was obtained (ICC 0.62, 95% CI 0.31–0.79). Bland and Altman plots for test knowledge score confirm agreement between test and retest as the differences between test and retest were acceptable (Table 2, supplementary figure 1, Supplemental digital content 3, <http://links.lww.com/EJGH/A941>).

Barriers to screening

Negative health consequences of testing included the perception of embarrassment, fear, physical discomfort, and possible corporal harm. Mean scores at both test and retest were overall higher for invasive procedures, namely colonoscopy and UGIE, in comparison with FOBT. Substantial agreement was obtained between test and retest for FOBT (ICC 0.73, 95% CI 0.51–0.85) while almost perfect agreement was obtained for both colonoscopy (ICC 0.87; 95% CI 0.76–0.93) and UGIE (ICC 0.89, 95% CI 0.80–0.94).

Overall barriers to screening scores included not only the perceived negative health consequences of testing but also financial barriers, time constraints, access barriers and perceived efficacy of testing. Substantial test–retest agreement was obtained for in the setting of CRC screening (FOBT ICC 0.63, 95% CI 0.33–0.80; colonoscopy ICC 0.79, 95% CI 0.61–0.88). Regarding UGIE for GC screening, almost perfect agreement was confirmed (ICC 0.83, 95% CI 0.70–0.91). Agreement between test and retest were confirmed for overall barriers to screening (FOBT, colonoscopy and UGIE) after analysis of the Bland and Altman plots as the differences between test and retest were acceptable (Table 3, supplementary figure 1, Supplemental digital content 3, <http://links.lww.com/EJGH/A941>).

To further explore the perceived complication risk, scores for awareness of possible endoscopy-related complications were calculated, with at least substantial agreement between test and retest (Table 3). In both interviews, all participants answered negatively when asked if they knew the possible risk factors for higher risk of complications in endoscopic procedures for screening purposes. Additionally, all reported not knowing the possible complications during a UGIE. Mean colonoscopy complication knowledge score was overall low, yet the test–retest agreement was almost perfect, ICC was 0.89 (95% CI 0.79–0.94).

Perceived cancer severity

Subjective perception of emotional and familiar distress in case of cancer diagnosis was accessed through the perceived cancer severity score. Higher agreement was obtained for CRC (ICC 0.84, 95% CI 0.70–0.91) in comparison with GC (ICC 0.58, 95% CI 0.22–0.77), although not statistically significant. Bland and Altman plots confirm agreement between test and retest for perceived severity of both CRC and GC as the differences between test and retest were acceptable (Table 3, supplementary figure

Table 2. Knowledge of symptoms, risk factors and screening methods

Knowledge	Test, mean (SD)	Retest, mean (SD)	ICC	95% CI	Mean difference	Bland-Altman limits
CRC symptom knowledge score (0–9)	0.9 (1.6)	1.2 (1.7)	0.88	0.77–0.93	-0.3	-2.4; 1.8
CRC risk factor knowledge score (0–12)	2.1 (2.5)	1.9 (2.3)	0.89	0.80–0.94	0.2	-2.8; 3.2
CRC Perceived risk score (0–2)	1.1 (1.0)	0.9 (1.0)	0.80	0.44–0.93	0.1	-1.6; 1.8
CRC risk factor awareness score (0–12)	2.7 (2.4)	2.5 (2.5)	0.96	0.93–0.98	0.2	-1.7; 2.0
CRC test knowledge score (0–10)	4.2 (0.9)	4.1 (0.8)	0.62	0.31–0.79	0.1	-1.6; 1.9
CRC Perceived testing need score (0–4)	3.9 (0.5)	3.9 (0.5)	1.00			
GC symptom knowledge score (0–10)	1.6 (2.2)	1.8 (2.3)	0.94	0.89–0.97	-0.2	-2.3; 1.9
GC risk factor knowledge score (0–13)	1.7 (1.8)	1.7 (1.9)	0.92	0.86–0.96	0.0	-1.9; 2.0
GC perceived risk score (0–2)	0.8 (1.0)	0.7 (1.0)	0.95	0.87–0.98	0.1	-0.8; 1.0
GC risk factor awareness score (0–10)	2.2 (1.7)	2.2 (1.7)	0.92	0.86–0.96	0.1	-1.6; 1.9
GC Perceived testing need score (0–4)	4.0 (0.1)	4.0 (0.1)	1.00			

CI, confidence interval; CRC, colorectal cancer; GC, gastric cancer; ICC, intraclass correlation coefficient.

Table 3. Barriers to screening and perceived cancer severity

Barriers to screening	Test mean (SD)	Retest mean (SD)	ICC	95% CI	Mean difference	Bland-Altman limits
Perceived negative health consequences of FOBT screening (0–16)	3.1 (1.7)	2.7 (1.8)	0.73	0.51–0.85	0.3	-2.8; 3.5
Overall perceived barriers to FOBT screening (0–32)	7.4 (2.6)	6.8 (2.8)	0.63	0.33–0.80	0.6	-4.9; 6.2
Perceived negative health consequences of colonoscopy screening (0–16)	5.6 (2.6)	5.3 (2.6)	0.87	0.76–0.93	0.3	-3.2; 3.8
Overall perceived barriers to colonoscopy screening (0–32)	10.3 (2.9)	9.6 (3.0)	0.79	0.61–0.88	0.7	-4.0; 5.4
Perceived negative health consequences of UGIE screening (0–16)	5.2 (2.8)	5.1 (2.8)	0.89	0.80–0.94	0.1	-3.4; 3.5
Overall perceived barriers to UGIE screening (0–32)	9.9 (3.7)	9.7 (3.1)	0.83	0.70–0.91	0.2	-4.8; 5.2
Complication knowledge	Test, n (%)	Retest, n (%)	ICC	95% CI	Mean difference	Bland-Altman limits
Did not know any risk factor for higher risk of complications during a colonoscopy	44 (100)	44 (100)				
Did not know any risk factor for higher risk of complications during an UGIE	44 (100)	44 (100)				
Did not know any possible complication during an UGIE	44 (100)	44 (100)				
Complication awareness	Test, mean (SD)	Retest, mean (SD)	ICC	95% CI	Mean difference	Bland-Altman limits
Colonoscopy complications knowledge score (0–7)	0.1 (0.4)	0.1 (0.3)	0.89	0.79–0.94	0.0	-0.4; 0.5
Awareness of possible complications during a colonoscopy (0–26)	12.2 (4.4)	13.4 (4.3)	0.78	0.59–0.88	-1.2	-8.3; 5.9
Awareness of possible complications during an UGIE (0–20)	9.6 (4.0)	11.0 (3.8)	0.83	0.64–0.91	-1.4	-6.8; 4.0
Perceived cancer severity	Test, mean (SD)	Retest, mean (SD)	ICC	95% CI	Mean difference	Bland-Altman limits
Perceived severity of CRC diagnosis (0–28)	17.0 (2.2)	17.6 (2.2)	0.84	0.70–0.91	-0.6	-3.6; 2.5
Perceived severity of GC diagnosis (0–28)	17.8 (1.9)	18.0 (2.0)	0.58	0.22–0.77	-0.2	-4.5; 4.0

CI, confidence interval; CRC, colorectal cancer; FOBT, faecal occult blood testing; GC, gastric cancer; ICC, intraclass correlation coefficient; UGIE, upper GI endoscopy.

1, Supplemental digital content 3, <http://links.lww.com/EJGH/A941>).

Attitudes towards screening

In a population of individuals not yet invited for a regional CRC screening program, intention to adhere was evaluated (Table 4). In both interviews, 98% (n = 43) reported intention to undergo CRC screening in the future with total agreement between teste and retest (K = 1.0 and overall PA = 1.00).

Participants who responded positively were subsequently asked whether they would prefer colonoscopy or FOBT as initial screening test. Moderate test-retest reliability was obtained (K = 0.46, 95% CI 0.04–0.88). Overall, PA for test-retest was 0.91 (0.76–0.97) indicating that 91% of participants gave the same answer in the test and retest. Specific PA for test-retest for this question were 0.90 (95% CI 0.76–0.97) for colonoscopy and 0.33 (95% CI 0.06–0.76) for FOBT, showing a fair agreement between test and retest when the answer is

FOBT and an almost perfect agreement when the answer is colonoscopy.

Substantial test-retest reliability was obtained (K = 0.66, 95% CI 0.03–1.00) for the intention to undergo UGIE for GC screening combined with a screening colonoscopy. Overall, PA for test-retest was 0.98 (0.86–1.00) indicating that 98% of participants gave the same answer in the test and retest. Specific PA for test-retest for this question were 0.98 (95% CI 0.86–1.00) for answer accept and 0.50 (95% CI 0.03–0.97) for answer unwilling, showing a moderate agreement between test and retest when the answer is unwilling and an almost perfect agreement when the answer is accepted.

Discussion

The PERCEPT-PREVENT is a valid and reliable tool to assess intention to adhere to CRC and GC screening. Additionally, this tool can be used to evaluate preferences in the CRC screening method, namely colonoscopy and FOBT. Knowledge on possible symptoms, risk factors and

Table 4. Attitudes towards screening

	Test n (%)	Retest n (%)	Kappa 95% CI	Proportions of agreement (95% CI)
Did not received invitation for screening	44 (100)	44 (100)		
Intention to undergo CRC screening			1.00	1.00 (0.90–1.00)
Unwilling	1 (2)	1 (2)		1.00 (0.05–1.00)
Accept	43 (98)	43 (98)		1.00 (0.90–1.00)
Preferred primary method of screening			0.46 (0.04–0.88)	0.91 (0.76–0.97)
FOBT	6 (14)	2 (5)		0.33 (0.06–0.76)
Colonoscopy	37 (86)	41 (95)		0.90 (0.76–0.97)
Intention to undergo UGIE for GC screening combined with a screening			0.66 (0.03–1.00)	0.98 (0.86–1.00)
colonoscopy				
Unwilling	1 (2)	2 (4)		0.50 (0.03–0.97)
Accept	43 (98)	42 (95)		0.98 (0.86–1.00)

CI, confidence interval; CRC, colorectal cancer; FOBT, faecal occult blood testing; GC, gastric cancer; UGIE, upper GI endoscopy.

screening tests as well as perceived severity of cancer diagnosis can be easily measured. Barriers to screening, including perceived negative health consequences of screening, financial barriers, time constraints, access barriers and perceived efficacy of testing can be quantified. Furthermore, this tool estimates knowledge on possible complications of endoscopic procedures, as well as individual risk factors that can increase the likelihood of endoscopy-related complications.

Although several Eastern studies reported the use of questionnaires based on the HBM, in Western countries, there is scarce data in CRC screening uptake predictors as well as estimation of barriers to screening. Sung J *et al.* first described a questionnaire based on the HBM, developed to estimate predictors of CRC uptake in Chinese residents of Hong Kong [15]. Using this tool, it was possible to link the low compliance to CRC screening to lower knowledge and higher perceived barriers to screening. A multicentric study in the Asia-Pacific region, using the same tool, compared knowledge, perceived severity of CRC and access barriers between low- and high-test participation countries [14]. A cross-sectional study performed in Saudi Arabia also used a questionnaire based in the HBM which was converted to an Arabic version [22]. A total of 71% of the surveyed individuals were willing to undergo CRC screening. A preference to colonoscopy screening over FOBT was noted, as the later was associated with no willingness to undergo screening. An ulterior nationwide study aimed to estimate predictors of CRC screening uptake [23]. Further eastern cross-sectional studies reported the use of surveys on CRC risk perception based in the HBM and focused on financial barriers to screening [24,25].

A Korean study aimed to determine associations between perceived risk of GC and socio-demographic, lifestyle, health, and psychological factors [26]. Furthermore, a systematic review aimed to identify barriers and facilitators of GC screening [27]. Most included studies were from Eastern countries, mainly Korea. The most reported barriers were lack of signs, fear of screening procedures, fear of screening outcomes, cost of screening, and embarrassment. Nonetheless, there is no data in GC risk perception tools to measure its impact in participation rates.

Our study provides the first validation of a tool to assess risk perception in digestive cancer for Western countries. Indeed, this questionnaire enables simultaneous evaluation of risk perception in the setting of CRC and GC screening. Furthermore, it also allows detailed

evaluation on the perception of endoscopy-related complications. After validation, the PERCEPT-PREVENT tool can be easily used in future studies to estimate adherence to CRC and GC screening and identify barriers to screening, leading ultimately to an informed and accurate decision-making process in health policies. The applicability of the survey in Western countries enables its use outside the Portuguese population and may be useful to perform further studies on CRC and GC screening, which may inform health policies across Europe.

We acknowledge some limitations in our study. The authors were not blinded to the intent of the backward translation and were familiar with the original questionnaire, which can provide bias. The amount of time necessary to complete in the questionnaire may limit its use, especially if applied by an untrained interviewer. Interviewer bias may also be acknowledged, yet measures were established to minimize this risk, which included training sessions that approached procedures in conducting the survey and quality control measures as well as the use of a standardized interview protocol. Motivated participants, willing to complete the survey in two different occasions, may have overestimated the presented reliability results. Additionally, the survey was applied in a predominantly urban population of the northern region of Portugal, which may limit the generalized use of the PERCEPT-PREVENT tool. Nonetheless, the English version of the questionnaire (Supplementary Appendix 2, Supplemental digital content 2, <http://links.lww.com/EJGH/A940>) provides a basis for further adaptation in Western countries with different native languages, at least in comparable urban settings.

Further studies using the PERCEPT-PREVENT tool may reinforce its role in risk perception assessment. Trends in the willingness to undergo CRC and GC screening may be estimated. Additionally, intention to adhere to CRC screening according to the screening method may be appraised. Moreover, comparison of knowledge, barriers and perceived cancer severity may be established between screening participants and unscreened individuals.

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Mário Dinis-Ribeiro, Diogo Libânio and João Carlos Silva designed the study. João Carlos Silva and Diogo Libânio performed the research and analyzed the data.

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Conflicts of interest

There are no conflicts of interest.

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2. Adherence, risk perception, and attitudes towards colorectal cancer screening: a road to individualized screening?

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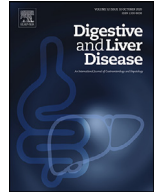
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Alimentary Tract

Adherence, risk perception, and attitudes towards colorectal cancer screening: A road to individualized screening? ☆

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ABSTRACT

Background & Aims: Colorectal cancer (CRC) ranks second globally in cancer-related deaths and there is ongoing debate on the best populational screening strategy. This study aimed to evaluate individuals' intention to adhere to CRC screening, screening method preference, and barriers to screening.

Methods: Cross-sectional study conducted in northern Portugal, where a populational fecal occult blood test (FOBT) program is implemented. The validated PERCEPT-PREVENT tool was administered across 3 groups: a) not yet invited to screening b) accepted FOBT screening, and c) primary colonoscopy screening.

Results: A total of 397 participants completed the PERCEPT-PREVENT questionnaire and were compared by screening status. Intention to adhere was reported at a high rate (95 %; $n = 354$) and was positively influenced by knowledge of the screening rationale (OR8.96, 95 %CI 3.61-22.25). Most were unaware of symptoms (64 %; $n = 253$), risk factors (68 %; $n = 271$), and associated screening procedure risks (58 %; $n = 230$). Lower barrier scores for FOBT (7 ± 3) compared to colonoscopy (10 ± 3) were observed for screening naïve respondents ($p < 0.001$). Previous FOBT screening led to a lower preference for colonoscopy (previous FOBT screening 56 % vs not yet invited to screening 75 % vs previous primary colonoscopy 90 %; $p < 0.001$).

Discussion: A greater understanding of the screening rationale enhances adherence. FOBT was highly accepted among never-screened participants. Colonoscopy should be offered to FOBT decliners, as personalized screening approaches could improve participation rates.

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1. Introduction

Colorectal cancer (CRC) is the most frequently diagnosed malignancy and the second leading cause of cancer mortality worldwide, and the burden is expected to rise [1,2]. Implementation of screening initiatives has positively impacted CRC early detection and mortality rates, with the largest decreases in mortality rates seen in countries with longstanding screening programs and higher screening uptake [3–5].

There is debate regarding the best strategy for populational-based CRC screening. In Europe, most countries have implemented organized invitational screening programs based on fecal occult

blood testing (FOBT) [6,7]. In contrast, colonoscopy screening is offered as the primary screening method in Poland and Germany [7,8]. European recommendations endorse organized populational FOBT-based programs (namely by fecal immunochemical testing - FIT) targeting average-risk individuals aged between 50 and 75 years [9,10]. Yet, it is stated that depending on local factors, namely adherence rates and availability of colonoscopy, primary screening by colonoscopy or sigmoidoscopy is also acceptable [9].

Screening uptake is largely influenced by the patient's risk perception (risk of CRC and screening procedures) and by existing barriers to screening (e.g., negative health consequences of screening, access to testing, financial burden, and time constraints). The perception of endoscopy-related complications may also influence adherence rates, as unscreened individuals may overestimate the risk of complications from a colonoscopy [11]. Even in countries with well-organized screening programs, participation rates are suboptimal, negatively impacting screening effectiveness [2,7,12]. The

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French national CRC screening program reported a participation rate of 34.2 %, consistent with prior findings indicating rates below 50 % [12–14]. Data from the European Health Interview Survey (2018–2020) estimate suboptimal fecal testing participation rates in Lithuania (36.3 %), Belgium (36.1 %), and Croatia (29.2 %) [15].

Intention to adhere to CRC screening, considering preferences for FOBT or colonoscopy as the primary screening method, and the influence of risk perception on CRC screening adherence rates, remains poorly characterized in European countries. Assessing risk perception is crucial for selecting the preferred screening modality, identifying factors associated with non-adherence, and overcoming existing barriers.

This study aimed to assess patients' perspectives about CRC screening (knowledge of CRC risk factors and symptoms, preferences for the primary screening method, intention to adhere, perception of screening procedure risks) and to identify barriers to screening.

2. Methods

2.1. Study design and procedures

This was a cross-sectional study including asymptomatic individuals aged 50–75 years eligible for CRC screening in the northern region of Portugal where a fully reimbursed populational FIT-screening program was implemented in 2018 under the coordination of the Northern Portugal Regional Health Administration (ARSN). Eligible citizens are directly invited by regular mail, initially through an awareness letter. Within 25–35 days, a kit for stool sample testing is sent, accompanied by instructions on how to perform the test and deliver it in person to the Primary Care Center [16]. Individuals with a positive FIT result (cut-off of 20 µg/g) are referred for a sedated colonoscopy at the nearest National Health Service (NHS) hospital, scheduled within 90 days of the positive result [16,17]. Parallel to populational screening program, primary care physicians can still refer healthy individuals for a screening sedated colonoscopy at private clinics, which are reimbursed by the Portuguese National Health Service and incur no costs for patients. The study protocol was approved by the Ethical committees of the 3 institutions involved in the study, namely, ARSN, *Unidade Local de Saúde Gaia e Espinho*, and *Instituto Português de Oncologia do Porto*. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), guidelines for reporting observational studies were used [18].

The study design relied on the comparison of four predefined groups: a) individuals not yet invited to screening; b) individuals who refused FOBT screening; c) individuals who accepted FOBT screening [c1) negative FOBT; c2) positive FOBT and accepted subsequent colonoscopy; c3) positive FOBT and refused subsequent colonoscopy]; d) individuals who underwent CRC screening through primary colonoscopy. Exclusion criteria encompassed symptomatic patients (e.g., diarrhea, constipation, abdominal pain, weight loss, hematochezia); anemia; previous CRC, Gastric Cancer (GC), or colorectal polyps; known hereditary cancer risk (including first-degree relatives with CRC and/or GC); previous colectomy; previous gastrectomy; inflammatory bowel disease; cognitive impairment; inability and/or refusal to answer the questionnaire.

Contacts of eligible individuals were extracted from the ARSN database based on their screening status from November 2021 to April 2022. Screening status assessment and data extraction were completed in August 2022. FOBT-positive individuals scheduled for colonoscopy from May 2023 to September 2023 were additionally included. Participants in this study were randomly selected through a stratified random sample, according to sex and age

group (50–59 years old and 60–74 years old). Given that all eligible age cohorts had been invited by the start of the study, individuals not yet invited to screening, identified in the ARSN database, included those who had recently reached the eligible screening age and those whose invitation letters had not been delivered due to logistical constraints. Individuals who underwent CRC screening through primary colonoscopy (outside the populational program) were recruited from 3 different private endoscopy units, from July 2022 to April 2023, after assessment of inclusion and exclusion criteria.

2.2. PERCEPT-PREVENT tool

The previously validated [19] PERCEPT-PREVENT tool questionnaire (supplementary appendix A.1 and A.2), was applied through telephonic interview, within a period of up to 6 months after the screening status assessment, from September 2022 to September 2023. In brief, this tool measures: 1) knowledge of symptoms, risk factors, and screening methods; 2) intention to participate in CRC screening; 3) preferred method of CRC screening (detailing fully reimbursed sedated colonoscopy or FOBT) 4) barriers to screening; 5) perceptions towards endoscopy-related complications. Interviews were conducted by 2 Gastroenterology nurses after three formal training sessions and informed verbal consent was obtained from all participants. The PERCEPT-PREVENT answers were collected in an electronic database, and each patient received a code number to secure anonymization. Sociodemographic data including age, gender, educational level, and monthly income were registered.

2.2.1. Sample size calculation and statistical analysis

The primary endpoint of the study used for sample size calculation was the intention to adhere to FOBT or colonoscopy. Considering previously reported FIT adherence rates between 35–68 % and colonoscopy adherence rates between 18–38 % [10], 65 patients in each group were needed to demonstrate a 23.5 % difference between estimated mean adherence to FIT (51.5 %) and colonoscopy, (28.0 %), with 95 % confidence interval (CI), an error of 0.05, and a power of 80 %.

Statistical Package for Social Sciences (SPSS) program version 28 (IBM Corporation, Armonk, NY) was used. Categorical variables are summarized as frequencies and percentages. As appropriate χ^2 test or Fisher's exact test was used to compare categorical variables. Normal distribution was examined using histogram visual inspection. Continuous variables were expressed in means and standard deviation (variables with normal distribution) or median and interquartile range (variables with skewed distributions). Independent samples t-test or independent samples Mann-Whitney U test were used to compare two groups. Mean overall FOBT and colonoscopy barrier scores were compared using the paired-samples t-test. The analysis of variance (ANOVA) test or the independent samples Kruskal-Wallis test were used to assess the differences among multiple groups. Following a significant result, the Bonferroni adjustment was applied to the pairwise comparisons.

To evaluate predictors of adherence to CRC screening and preference for the primary screening method, the domains of the PERCEPT-PREVENT tool as well as sociodemographic characteristics were assessed. Independent variables with at least marginal association with the outcome variable ($p < 0.100$) in univariate analysis were included in the multivariate logistic regression model. Variables with a significant association with the dependent variables were identified after adjustment using the Backward-Wald methodology (cut-off for entry 0.05; cut-off for exclusion 0.10). Odds Ratio (OR) with 95 %CI was calculated for each variable independently associated with the outcome variable. The model's goodness of fit and discriminatory ability were evaluated through the Hosmer-Lemeshow goodness-of-fit test and ROC curve analysis. All

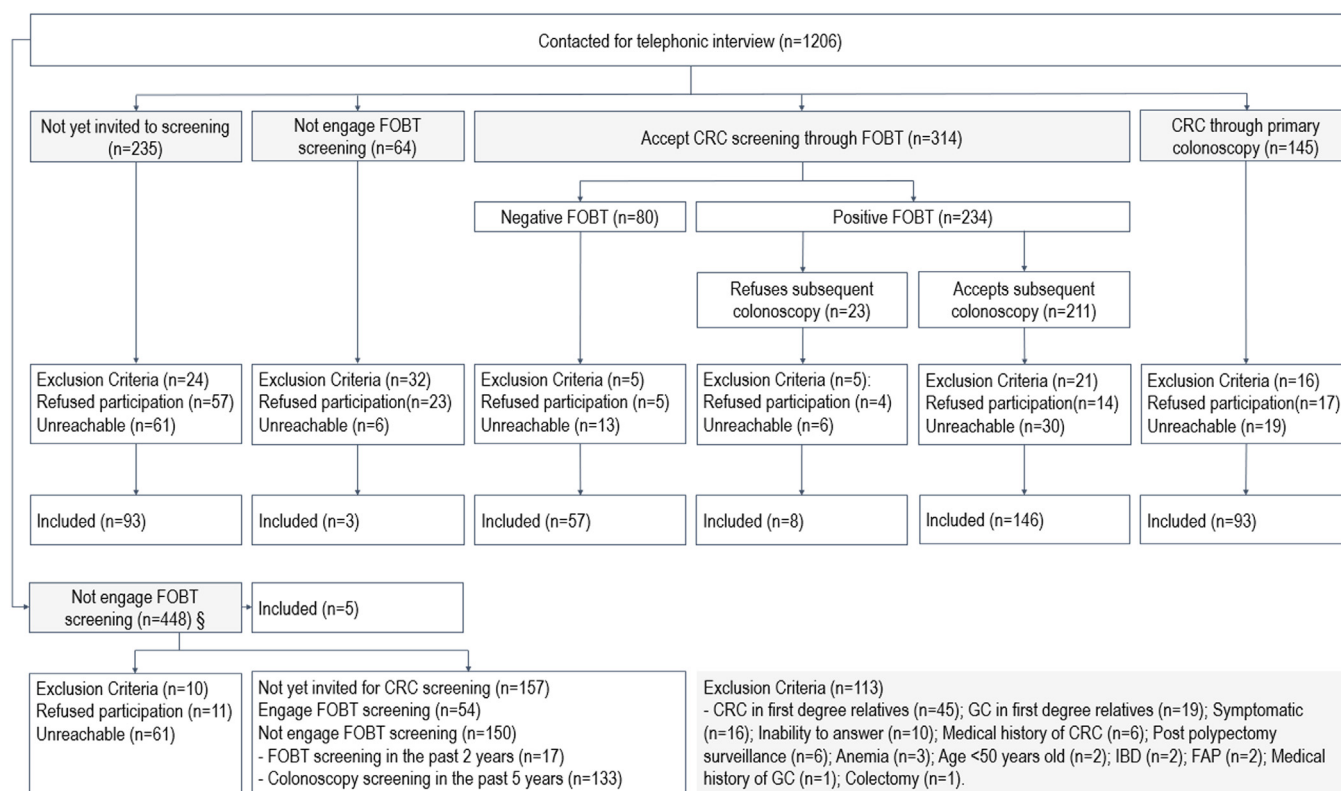


Fig. 1. Study population and recruitment procedures according to the screening status. § Additional round of telephonic interviews targeting individuals registered as non-adherent in the ARSN CRC screening database. CRC, Colorectal Cancer; FAP, Familial Adenomatous Polyposis; FOBT, Fecal Occult Blood Test; GC, Gastric Cancer; IBD, Inflammatory Bowel Diseases.

reported *p*-values are two-tailed, with a *p*-values less than 0.05 indicating statistical significance.

3. Results

3.1. Study population and recruitment procedures

A total of 1206 individuals were contacted for telephonic interviews, of which 196 were unreachable, 131 refused to participate and 113 met exclusion criteria. As the number of participants who refused FOBT screening fell below the sample size estimation an additional round of telephonic interviews was conducted focusing on this group, wherein the PERCEPT-PREVENT survey was adjusted to initially address screening uptake questions, with only those participants who definitively refused CRC screening proceeding to complete the entire questionnaire. Fig. 1 provides a comprehensive overview of recruitment data and participant allocation.

Of the 1,093 individuals eligible for inclusion, 70.1 % (*n* = 766) agreed to participate in the study. Of these, 405 completed the PERCEPT-PREVENT tool survey, while 361 solely reported data on their screening status. The 405 participants who completed the questionnaire were allocated based on their screening status (93 individuals not yet invited to screening, 8 individuals who refused FOBT screening, 211 individuals who accepted FOBT screening [negative FOBT *n* = 57; positive FOBT and accepted subsequent colonoscopy *n* = 146; positive FOBT and refused subsequent colonoscopy *n* = 8]), and 93 individuals who underwent CRC screening through primary colonoscopy. The number of participants who refused FOBT screening fell below the sample size estimation, rendering a comparative analysis unfeasible, thus only descriptive analysis was conducted. Thus, three main groups were de-

fined for further comparison: individuals not yet invited to screening (*n* = 93), individuals who accepted FOBT screening (*n* = 211), and individuals who underwent CRC screening through primary colonoscopy (*n* = 93). With respect to sociodemographic characteristics, individuals not yet invited to screening were generally younger (*p* < 0.001), more frequently employed (*p* < 0.001), less often married (*p* < 0.001), and less likely to have only a basic education level (*p* = 0.018). Bonferroni-adjusted pairwise comparisons showed comparable results between the FOBT screening and primary colonoscopy screening groups with regard to age, marital status, and educational level. Furthermore, no significant difference in educational level was observed between individuals not yet invited to screening and those screened through primary colonoscopy. Characterization of the sociodemographic features is displayed in Table 1.

3.2. Attitudes towards screening

Data on the intention to adhere to CRC screening was retrieved in 373 cases. Participants reporting intention to adhere to CRC screening (95 %; *n* = 354) were subsequently asked whether they would prefer colonoscopy or FOBT as the initial screening test. Overall, preference for colonoscopy as the primary screening test was reported in 69 % (*n* = 261).

Among the 93 individuals not yet invited to screening, 75 % (*n* = 70) preferred colonoscopy as the primary screening method, while the remaining 25 % (*n* = 23) opted for FOBT. Preference for colonoscopy was significantly lower among individuals who accepted FOBT screening (56 %; *n* = 110) compared to those who had not yet been invited to screening (75 %; *n* = 70) and those who underwent primary colonoscopy screening (90 %; *n* = 81) (Table 2). Among participants who accepted FOBT screening, preference for

Table 1
Sociodemographic characteristics.

	Total [§] (N = 397)	Not yet invited to screening(N = 93)	FOBT screening(N = 211)	Primary colonoscopy screening(N = 93)	p-values
Female, n (%)	207 (52)	48 (52)	105 (50)	54 (58)	0.407
Age, median (IQR)	56 (51–62)	51 (50–52)	60 (55–66)	57 (52–64)	<0.001 ^a
Married, n (%)	245 (63)	36 (40)	146 (70)	63 (68)	<0.001 ^a
Basic educational level [¶] , n (%)	217 (56)	39 (43)	127 (61)	51 (56)	0.018 ^{a, b}
Active worker, n (%)	228 (59)	70 (79)	100 (49)	58 (64)	<0.001
Intermediate or high monthly income, n (%)	99 (67)	4 (67)	72 (64)	23 (79)	0.346

[§] Excludes individuals who refused FOBT screening.[¶] Sub-high school educational attainment.^{a-b} Bonferroni-adjusted pairwise comparisons showing no significant differences between groups (a FOBT screening and primary colonoscopy screening; b not yet invited to screening and primary colonoscopy screening). IQR, Interquartile Range; CRC, Colorectal cancer; sD, Standard deviation.**Table 2**
Attitudes towards screening.

	Total [§] (N = 397)	Not yet invited to screening(N = 93)	FOBT screening(N = 211)	Primary colonoscopy screening(N = 93)	p-values
Intention to undergo CRC screening, n (%)	354 (95)	92 (100)	183 (92)	79 (96)	0.012
Preferred primary method of CRC screening					<0.001
• FOBT, n (%)	117 (31)	23 (25)	85 (44)	9 (10)	
• Colonoscopy, n (%)	261 (69)	70 (75)	110 (56)	81 (90)	
Previous screening [¶] , n (%)	64 (16)	0 (0)	38 (18)	26 (28)	0.050
Medical recommendation, n (%)	237 (60)	0 (0)	146 (69)	91 (98)	<0.001
Regular follow-up with primary care physician, n (%)	381 (96)	89 (96)	201 (96)	91 (98)	0.639
Health insurance, n (%)	117 (30)	25 (27)	61 (29)	31 (33)	0.616
Information on CRC screening tests from any means of communication, n (%)	236 (59)	53 (57)	112 (53)	71 (76)	<0.001
CRC in 2nd degree relatives or acquaintances, n (%)	115 (29)	30 (32)	49 (23)	36 (39)	0.017
Perceived CRC severity (0–28), mean (sD)	18 (3)	18 (3)	18 (4)	19 (3)	<0.001

[§] Excludes individuals who refused FOBT screening.[¶] FOBT >2 years ago and or colonoscopy >10years ago. CI, Confidence Interval; CRC, Colorectal Cancer; FOBT, Fecal Occult Blood Test; sD, Standard deviation.

colonoscopy over FOBT was significantly higher in FOBT-positive respondents who agreed to undergo a follow-up colonoscopy (61.2 %; $n = 85$), with 56.5 % interviewed after endoscopic screening, compared to those who underwent only FOBT, whether negative or positive but refusing a follow-up colonoscopy (44.6 %; $n = 25$) ($p = 0.035$). Additionally, in the primary colonoscopy group, 33 % ($n = 31$) of participants reported that they were previously invited to FOBT but opted for endoscopic screening.

A higher rate of individuals in the primary colonoscopy group received medical recommendation for CRC screening ($p < 0.001$) and information on CRC tests ($p < 0.001$). The proportion of participants regularly followed up by primary care physicians ($p = 0.639$) and with health insurance (0.616) did not differ significantly across groups. Subjective perception of emotional and familiar distress in the case of CRC diagnosis was significantly higher in the primary colonoscopy group compared to FOBT (19 ± 3 vs 18 ± 4 ; $p < 0.001$) and individuals not yet invited to screening (19 ± 3 vs 18 ± 3 ; $p = 0.019$). Table 2 details data on cues to action and attitudes towards CRC screening.

3.3. Non-adherence to CRC screening

A total of 512 individuals registered as non-adherent to FOBT in the ARSN CRC screening database were contacted over two rounds of interviews (Figure 1; supplementary figure 1). A total of 150 individuals underwent CRC screening outside the organized screening program (84 % colonoscopy and 11 % FOBT). A total of 8 individuals (5 %) truly refused CRC screening, with 75 % ($n = 6$) reporting low perceived testing need scores (0–3). Reasons for non-adherence included fear of complications during screening procedures ($n = 5$), COVID-19 pandemic restrictions ($n = 2$), and perceived low risk of

CRC ($n = 1$). Only 8 FOBT-positive individuals refused colonoscopy, 4 of them due to fear of complications.

3.4. Knowledge and barriers to CRC screening

Overall knowledge of CRC symptoms and risk factors was low, as 64 % ($n = 253$) did not know any CRC symptom and 68 % ($n = 271$) did not know any CRC risk factor. Individuals screened through primary colonoscopy scored lower for the risk factor awareness score ($p = 0.002$), detailing the perception of having CRC risk factors (Table 3).

In 89 % ($n = 352$) of interviews, participants classified the need to screen healthy individuals aged 50 years or older for CRC as a “great need” and a lower perceived testing need score was noted in the FOBT screening group ($p = 0.006$) compared to individuals not yet invited to screening. The mean test knowledge score (2 points attributed to each known test) was 4 ± 1 , with most participants (88 %; $n = 356$) recognizing FOBT and colonoscopy as the only possible CRC screening methods. Colonoscopy was rated as the most accurate screening test (primary colonoscopy 100 % vs not yet invited to screening 99 % vs FOBT screening 78 %; $p < 0.001$). On the other hand, FOBT was pointed as the safest (not yet invited to screening 99 % vs primary colonoscopy 88 % vs FOBT screening 82 %; $p < 0.001$) and less costly method (not yet invited to screening 98 % vs primary colonoscopy 74 % vs FOBT screening 66 %; $p < 0.001$).

Significantly lower overall barrier scores were observed for FOBT compared to colonoscopy among individuals not yet invited to screening (FOBT 7 ± 3 vs Colonoscopy 10 ± 3 ; $p < 0.001$) and those who accepted FOBT screening (FOBT 4 ± 3 vs Colonoscopy 11 ± 5 ; $p < 0.001$). In contrast, comparable scores were found for

Table 3
Knowledge and barriers to colorectal cancer screening.

Knowledge	Total [§] (N = 397)	Not yet invited to screening(N = 93)	FOBT screening(N = 211)	Primary colonoscopy screening(N = 93)	p-values
Did not know any symptom, n (%)	253 (64)	68 (73)	138 (65)	47 (50)	0.005
Symptom knowledge score (1–9), median (IQR)	3 (2–3)	3 (3–4)	2 (1–3)	3 (2–3)	0.002
Did not know any CRC risk factor, n (%)	271 (68)	60 (65)	157 (74)	54 (58)	0.013
Risk factor knowledge score (1–12), median (IQR)	4 (3–5)	5 (4–5)	4 (3–6)	4 (4–5)	0.053
Perceived risk score (0–2), median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–0)	0.677
Risk factor awareness score (0–12), median (IQR)	2 (0–4)	2 (0–4)	2 (0–4)	1 (0–2)	0.002
Test knowledge score (0–10), mean (sD)	4 (1)	4 (1)	4 (1)	5 (1)	0.003
Perceived testing need score “great need”, n (%)	352 (89)	90 (97)	178 (84)	84 (90)	0.006
Barriers to FOBT screening					
Perceived negative health consequences of FOBT (0–16), median (IQR)	2 (0–4)	4 (4–4)	1 (0–3)	3 (0–4)	<0.001
Perceived financial burden of FOBT (0–4), median (IQR)	2 (1–2)	2 (2–2)	1 (0–2)	1 (1–2)	<0.001
Perceived time constrain to FOBT (0–4), median (IQR)	1 (0–1)	1 (0–1)	0 (0–1)	1 (0–1)	<0.001
Perceived access barrier to FOBT (0–4), median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	0 (0–1)	0.059
Perceived negative efficacy of FOBT (0–4), median (IQR)	1 (0–1)	1 (0–1)	0 (0–1)	1 (1–1)	<0.001
Overall perceived barriers to FOBT screening (0–32), mean (sD)	5 (3)	7 (3)	4 (3)	6 (3)	<0.001
Barriers to colonoscopy screening					
Perceived negative health consequences of colonoscopy screening (0–16), mean (sD)	6 (3)	5 (2)	7 (3)	4 (3)	<0.001
Perceived financial burden of colonoscopy screening (0–4), mean (sD)	2 (1)	2 (0)	2 (1)	1 (1)	<0.001
Perceived time constrain to colonoscopy screening (0–4), median (IQR)	1 (0–1)	1 (1–1)	1 (0–1)	1 (0–1)	<0.001
Perceived access barrier to colonoscopy screening (0–4), median (IQR)	1 (0–1)	1 (1–1)	1 (0–1)	0 (0–1)	<0.001
Perceived negative efficacy of colonoscopy screening (0–4), median (IQR)	1 (0–1)	1 (1–1)	0 (0–1)	0 (0–1)	<0.001
Overall perceived barriers to colonoscopy screening (0–32), mean (sD)	10 (4)	10 (3)	11 (5)	7 (3)	<0.001
Colonoscopy complication awareness					
Did not know any complication, n (%)	230 (58)	89 (96)	124 (59)	17 (18)	<0.001
Colonoscopy-related complication knowledge score (1–7), median (IQR)	1 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)	0.573
Awareness of possible complications during a colonoscopy (0–26), mean (sD)	14 (4)	14 (4)	13 (4)	14 (5)	0.976
Did not know any risk factor for complications, n (%)	341 (86)	92 (99)	194 (92)	55 (60)	<0.001
Risk factor for colonoscopy-related complication knowledge score (1–12), median (IQR)	1 (1–2)	1 (1–1)	1 (1–2)	1 (1–2)	0.657
Perceived complication risk score (0–2), median (IQR)	0 (0–2)	0 (0–0)	0 (0–2)	0 (0–2)	0.338

[§] Excludes individuals who refused FOBT screening. CI, Confidence Interval; CRC, Colorectal Cancer; FOBT, Fecal Occult Blood Test; IQR, Interquartile Range; sD, Standard deviation.

individuals screened through primary colonoscopy (FOBT 6 ± 3 vs Colonoscopy 6 ± 4 ; $p = 0.382$).

When considering screening through FOBT, participants screened by this method scored significantly lower across all domains compared to individuals not yet invited to screening, except for access barriers ($p = 0.059$). Bonferroni-adjusted pairwise comparisons showed comparable results between FOBT screening and primary colonoscopy screening groups in all barrier domains, except for a higher perceived negative efficacy of FOBT testing ($p < 0.001$) in the primary colonoscopy group.

Regarding barriers to colonoscopy screening, participants screened by this method scored significantly lower for financial burden, time constraints, and access barriers. Bonferroni-adjusted pairwise comparisons for perceived negative health consequences of colonoscopy ($p = 0.105$) and perceived efficacy of testing ($p = 0.311$) did not differ compared to individuals not yet invited to screening and FOBT-screened, respectively.

Overall, knowledge of colonoscopy-related complications and their risk factors was low, with 58 % ($n = 230$) and 86 % ($n = 341$) of participants not knowing about any possible complications or their risk factors, respectively. Table 3 details perceived barriers to FOBT and colonoscopy, as well as the perception of colonoscopy-related complications.

3.5. Predictors of adherence and preference over the primary screening method

In univariate analysis, younger age ($p < 0.001$), active work status ($p = 0.002$), CRC in second-degree relatives or acquaintances ($p = 0.044$), no prior screening invitation ($p = 0.009$), higher perceived testing need score ($p < 0.001$), lower perceived negative health consequences of colonoscopy screening ($p < 0.001$) and lower perceived time constrain to colonoscopy screening ($p = 0.010$) were associated with higher intention to undergo CRC screening (regardless of the primary screening method) (Table 4). After adjusting for the aforementioned factors, active work status (OR 5.42, 95 %CI 1.26–23.36) and higher perceived testing need score (OR 8.96, 95 %CI 3.61–22.25) were independently associated with the intention to adhere to CRC screening, irrespective of screening method preference.

Predictors of preference for colonoscopy over FOBT as the primary screening method were evaluated. In univariate analysis, younger age ($p = 0.013$), CRC in second-degree relatives or acquaintances ($p < 0.001$), no prior screening invitation ($p < 0.001$), higher CRC risk factor knowledge score ($p = 0.018$), higher perceived testing need score ($p < 0.001$), lower perceived negative health consequences of colonoscopy screening (p

Table 4

Predictors of adherence and preference over the primary screening method.

	Intention to adhere to CRC screening				Preference for colonoscopy over FOBT as primary screening method			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR	p-values	aOR	95 % CI	OR	p-values	aOR	95 % CI
Female	1.20	0.690			1.36	0.161		
Younger age	1.11	<0.001			1.04	0.013		
Married	0.71	0.495			1.06	0.788		
Intermediate or high educational level	¥	0.995			1.15	0.540		
Active worker	5.10	0.002	5.42	1.26–23.36	1.42	0.123		
Intermediate or high monthly income	§	0.997			0.86	0.692		
Medical recommendation	0.51	0.173			1.32	0.214		
Regular follow-up with primary care physician	2.57	0.233			1.99	0.168		
Health insurance	1.69	0.356			1.09	0.718		
Information on CRC screening tests from any means of communication	1.95	0.141			1.31	0.223		
CRC in second-degree relatives or acquaintances	8.00	0.044			2.46	<0.001	2.20	1.26–3.86
Higher Perceived CRC severity	0.98	0.818			0.99	0.979		
No prior screening invitation	14.87	0.009			2.71	<0.001	2.55	1.53–4.22
Higher symptom knowledge score	2.18	0.169			1.10	0.246		
Higher risk factor knowledge score	3.80	0.076			1.14	0.018		
Higher risk factor awareness score	1.20	0.144			1.06	0.233		
Higher test knowledge score	1.69	0.091			1.00	0.965		
Higher perceived testing need score	9.60	<0.001	8.96	3.61–22.25	3.71	<0.001	3.61	1.69–7.70
Lower perceived negative health consequences of FOBT	0.89	0.334			0.92	0.185		
Lower perceived financial burden of FOBT	1.81	0.120			0.94	0.700		
Lower perceived time constrain to FOBT	0.62	0.288			0.75	0.169		
Lower perceived access barrier to FOBT	0.96	0.921			1.03	0.868		
Lower perceived negative efficacy of FOBT	1.13	0.697			0.90	0.527		
Lower perceived negative health consequences of colonoscopy screening	1.28	<0.001			1.14	<0.001	1.08	1.01–1.17
Lower perceived financial burden of colonoscopy screening	1.38	0.395			1.73	0.002		
Lower perceived time constrain to colonoscopy screening	2.46	0.010			1.41	0.070		
Lower perceived access barrier to colonoscopy screening	1.67	0.065			1.21	0.254		
Lower perceived negative efficacy of colonoscopy screening	1.56	0.085			1.09	0.536		
Higher colonoscopy-related complication knowledge score	0.68	0.197			1.31	0.025	1.42	1.10–1.84
Higher awareness of possible complications during a colonoscopy	0.95	0.362			0.96	0.147		
Higher risk factor for colonoscopy-related complication knowledge score	1.27	0.476			1.84	0.018		

CI, Confidence Interval; CRC, Colorectal Cancer; FOBT, Fecal Occult Blood Test; OR, Odds Ratio.

¥ The high odds ratio value is not displayed, which may be due to the fact that none of the respondents with intermediate or high educational levels reported unwillingness to undergo CRC screening.

§ The high odds ratio value is not displayed, which may be due to the fact that none of the respondents with intermediate or high monthly income reported unwillingness to undergo CRC screening.

< 0.001), lower perceived financial burden of colonoscopy screening ($p = 0.002$), higher colonoscopy-related complication knowledge score ($p = 0.025$) and higher scores for knowledge on risk factors for colonoscopy-related complications ($p = 0.018$) were associated with preference for colonoscopy over FOBT. In multivariate analysis, CRC in second-degree relatives or acquaintances (OR 2.20, 95 %CI 1.26–3.86), no prior screening invitation (OR 2.55, 95 %CI 1.53–4.22), higher perceived testing need score (OR 3.61, 95 %CI 1.69–7.70), lower perceived negative health consequences of colonoscopy screening (OR 1.08, 95 %CI 1.01–1.17) and higher scores for knowledge on colonoscopy-related complications (OR 1.42, 95 %CI 1.10–1.84) were independently associated with preference for colonoscopy over FOBT as primary method of CRC screening. Combined, the results from the Hosmer-Lemeshow goodness-of-fit test ($X^2 = 4.0$; $df = 8$; $p = 0.853$) and ROC curve analysis ($AUC = 0.72$, 95 %CI 0.67–0.78; $p < 0.001$) indicate that the logistic regression model calibrates well to

the observed outcomes and exhibits an acceptable discriminatory power.

3.6. Timing of the interview impact on risk perception

Individuals referred to colonoscopy after a positive FOBT ($n = 146$) were randomly contacted before (43 %; $n = 63$) and after (57 %; $n = 83$) the procedure. There were no differences between groups across the PERCEPT-PREVENT tool key domains, namely preferred screening method, colonoscopy complication knowledge score, and overall barriers to colonoscopy screening (supplementary table 1). The heightened intention to undergo screening among those interviewed before the procedure (100 % vs 91 %; $p = 0.017$) may be attributed to these individuals already having a colonoscopy scheduled.

4. Discussion

This is the first European study designed to assess preference for the primary CRC screening method with simultaneous measurement of CRC risk perception. Participants reported their preferred screening strategy rather than being assigned one, reflecting adherence rates to FOBT and colonoscopy. The inclusion of individuals not yet invited to organized CRC screening allowed for an unbiased assessment of adherence trends. Risk perception was evaluated using the validated PERCEPT-PREVENT tool, providing objective measurements of knowledge and barrier domains [19].

Intention to adhere to CRC screening was reported at a high rate and was positively influenced by knowledge of the screening rationale. Preference for colonoscopy over FOBT as the primary method of screening was observed. Nonetheless, a quarter of individuals naïve to CRC screening preferred FOBT, and those screened by this method opted for endoscopic screening at a lower rate. In brief, most individuals initially screened through primary colonoscopy intended to continue using this method, whereas, nearly half of those screened with FOBT reported a willingness to maintain the same screening approach. Among the remaining individuals initially screened with FOBT, the majority shifted their preference toward colonoscopy, likely influenced by the recent referral for colonoscopy following a positive result. Lower barrier scores for FOBT compared to colonoscopy were observed among never-screened individuals. No prior screening invitation, higher perceived testing need, CRC in second-degree relatives/acquaintances, lower perceived negative consequences of colonoscopy, and higher complication knowledge were identified as independent predictors of a preference for endoscopic screening over FOBT.

Adherence rates vary widely depending on the adopted CRC screening strategy [7,20]. In countries with fully rolled-out programs with fecal tests (e.g., Netherlands, Denmark, Slovenia) and those offering colonoscopy as an alternative screening method (e.g., Germany, Austria, Luxemburg), participation rates were highest, reaching up to 75 % [7,21]. In our study, 95 % reported intention to adhere to CRC screening, surpassing previous studies [7,15,20,22]. The authors admit a trend towards higher population coverage for CRC screening in northern Portugal due to active involvement of primary care physicians following target screening standards predefined for several primary care health services. Accordingly, Portugal reported the highest colonoscopy utilization rate, surpassing 40 %, among countries with established fecal test-based screening programs [15]. Furthermore, full reimbursement of screening tests, including FIT, colonoscopy and sedation, may contribute to a greater intention to adhere to CRC screening, as reflected in the low scores for financial constraints and the negligible impact of health insurance on screening uptake observed in our sample.

Most European countries have implemented organized screening programs using FIT as the primary screening method [7,15,20,23]. While the Dutch national FIT-based screening program reported a participation rate of 72 %, Poland's once-only colonoscopy screening had a participation rate of only 18 % in the first two years [21,24]. The Spanish COLONPREV trial [25] (FOBT 34.2 % vs colonoscopy 24.6 %) and the Swedish SCREESCO trial [26] (FOBT 55.5 % vs colonoscopy 35.1 %) reported higher participation rates for fecal tests compared to colonoscopy. Additionally, the NordICC trial reported an overall adherence to colonoscopy of 42.0 % [23,27]. Our results indicate a preference for endoscopic screening among individuals who have never been screened. Notably, previous studies have invited participants to undergo either FOBT or colonoscopy, rather than inquiring about their preference for the primary screening method. Makaroff K et al, found that 77.4 % of individuals aged ≥ 50 preferred annual FOBT over

a colonoscopy every 10 years [28,29], and the CONFIRM trial reported that 43.4 % of those declining participation preferred a specific screening test (58.5 % FOBT vs 40.6 % colonoscopy) [30]. However, prior colonoscopy was the main cause of trial ineligibility (39.9 %) [30,31]. Similarly, in our sample, most participants classified as non-adherent had previously undergone screening (mostly through colonoscopy) and were not included. Thus, previously reported adherence rates (29 %) may have been underestimated [16], and optimized integration of screening colonoscopy data from private units with the regional database could enhance the exclusion of screened individuals. Addressing organizational challenges and implementing targeted interventions are crucial for increasing screening uptake. Reminders, whether delivered through letters, text messages, or automated voice recordings, have been shown to effectively boost participation among non-adherent individuals [32,33]. In addition, patient navigation interventions, which involve personalized counseling provided by a trained healthcare provider, are a known strategy to improve CRC screening uptake and promote equity in healthcare [13,34–36]. Virtual health assistants, as recently described, can further enhance screening by providing personalized recommendations that simulate high-quality patient-provider communication, elicit individual preferences, empower decision-making, and promote screening uptake [37,38]. The integration of artificial intelligence (AI) into organized screening programs offers significant opportunities for advancement, including streamlined organizational and auditing processes, automated tracking of non-adherent individuals, and targeted interventions via periodic reminders and personalized counseling delivered by AI-driven conversational agents [37].

Programs incorporating both fecal tests and colonoscopy as primary screening methods were associated with a greater reduction in mortality [39]. Colonoscopy is offered as an alternative for opportunistic screening in several countries [7,15,20,40]. In Germany, adherence rose from 66–68 to 77–80 % following the inclusion of colonoscopy as an alternative to FOBT, mainly due to an increase in colonoscopy uptake [40]. In a study from Coronado et al, the offer of a blood-based screening test to those who declined FIT screening, boosted CRC screening by 17.5 % [41]. Our results reinforce the potential of personalized screening, including the option of colonoscopy as an alternative primary screening method, to increase participation rates.

Risk perception and attitudes towards CRC screening were rarely evaluated in Western countries [22,42–47]. In line with previous findings, despite a strong willingness to undergo screening, there was a low level of knowledge regarding CRC symptoms and risk factors [22]. This underscores the necessity for enhancing literacy in digestive health. It is important to acknowledge that measuring the intention to adhere may significantly overestimate the actual uptake of screening tests, particularly in a population with limited knowledge of CRC risk and screening practices [22]. The discrepancy between the low knowledge scores and the high reported intention to participate in CRC screening, as observed in our sample, may be partially attributed to social desirability bias.

We acknowledge some limitations in our study. The study relies on measures susceptible to bias such as selective memory, social desirability, or attribution bias. Yet, the timing of the interview did not unequivocally impact risk perception. Healthy user bias may have contributed to an overestimation of the intention to adherence to CRC screening, as participants willing to complete the telephone survey (70.1 % of the eligible sample) are likely more health-conscious and thus more prone to undergo screening. Conversely, individuals with lower health awareness may have been less inclined to undergo screening tests and more likely to decline participation in the telephone interview, which could partially explain the low number of respondents who refused FOBT screening, despite a second round of interviews targeting eight times the re-

quired sample size. The high rate of individuals registered as non-adherent in the CRC screening database, who reported not receiving invitations, may be attributed to logistical issues (e.g., incorrect addresses, mailing failures) or response bias (social desirability). Moreover, the survey was conducted regionally rather than nationally.

Further health economic evaluations, considering the obtained estimates of preference for colonoscopy and FOBT may lead to an optimization of the screening strategy. Such models may include the evaluation of an individualized population-based screening strategy that offers colonoscopy as an alternative to FOBT. Additionally, prospective studies comparing willingness to undergo screening and preference for the primary screening method with the actual uptake of specific screening tests could bolster our findings.

Conflict of interest

The authors would like to submit a manuscript entitled “Adherence, risk perception, and attitudes towards colorectal cancer screening: a road to individualized screening?” for consideration for publication in *Digestive and Liver Disease*. João Carlos Silva, Mário Dinis-Ribeiro, Fernando Tavares and Diogo Libânio declare no conflict of interest for this article.

Author contributions

Mário Dinis-Ribeiro, Diogo Libânio, and João Carlos Silva designed the study. João Carlos Silva and Diogo Libânio performed the research and analyzed the data. Mário Dinis-Ribeiro, Diogo Libânio, and Fernando Tavares received the paper for critically important intellectual content.

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Supplementary materials

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2.1. Author's reply: "Improving screening participation: the need for socioeconomic considerations and psychological interventions in colorectal cancer programs"

João Carlos Silva, Mário Dinis-Ribeiro, Diogo Libânio

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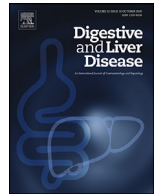
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Author's reply: "Improving screening participation: The need for socioeconomic considerations and psychological interventions in colorectal cancer programs"^{*}

Dear Editor,

We sincerely appreciate Jianyu Lv's et al. interest in our recently published article, "Adherence, risk perception, and attitudes towards colorectal cancer screening: a road to individualized screening?" [1]. Their thoughtful commentary [2] offers valuable insights, and we wish to further enrich the discussion by presenting a few additional points that complement their perspective.

Previous data indicated that colorectal cancer (CRC) screening participation rates tend to be lower among younger individuals, those in rural areas, males, disadvantaged groups with lower socioeconomic and educational levels, migrants, and individuals with sparser contact with the health system [3,4]. In our study, while socioeconomic status was not formally stratified and compared, monthly income and educational level were assessed and can be interpreted as surrogate indicators. Neither higher monthly income nor higher educational level was associated with a higher intention to adhere to CRC screening or a preference for colonoscopy over fecal tests, in our sample. Nevertheless, this remains a critical issue in the context of CRC screening, as individuals with lower socioeconomic status are expected to encounter greater barriers to screening [5]. It is noteworthy that our sample is confined to the northern region of Portugal, predominantly covering urban areas. Future nationwide studies could potentially diversify the study population and further strengthen the generalizability of our findings.

Regarding psychological factors that may influence screening uptake, it is widely recognized that prior screening experience can influence subsequent decision-making and, in turn, impact adherence rates. In our sample, the perceived negative health consequences of screening, which included feelings of fear and embarrassment associated with fecal occult blood test (FOBT) and colonoscopy were measured. Consequently, the psychological impact of prior screening experience (among those previously submitted to FOBT and/or colonoscopy) on the intention to adhere was indirectly evaluated. While the study design did not specifically target psychological reactions to prior screening experiences and their impact on screening uptake, it was observed that nearly half of those initially screened with fecal tests later shifted their preference to colonoscopy, likely due to the recent referral for colonoscopy following a positive result. Nevertheless, no differences were observed in the key domains of the PERCEPT-PREVENT tool between individuals referred for colonoscopy following a

positive FOBT who were randomly contacted both before and after the procedure. Moreover, psychological factors were evaluated in detail across the study sample using the perceived cancer severity score, which primarily focused on anxiety related to a potential CRC diagnosis, pessimism, and the perception of familial burden.

Undoubtedly, technological innovations can play a central role in personalizing cancer screening strategies and optimizing participation rates. Although assessing the potential of technological innovations, such as artificial intelligence (AI), was beyond the scope of our study, it should still be explored, regardless of considerations regarding the adopted screening methods. As previously discussed [1], AI has the potential not only to optimize screening recruitment through personalized virtual health assistants but also to facilitate quality auditing processes, automate the tracking of non-adherent individuals, and enable targeted interventions through periodic reminders [6,7]. Although still distant from practical implementation, the capacity to personalize CRC screening based on clinical-demographic characteristics, genetic risk, and microbiome data positions AI as a critical tool in advancing digestive cancer screening.

In summary, we deeply appreciate the valuable insights offered by Jianyu Lv et al. in their thoughtful commentary, which has contributed to further enriching the discussion surrounding our study. As emphasized, both socioeconomic status and psychological factors are critical determinants shaping screening outcomes, while technological innovations have the potential to mitigate barriers to screening and enhance participation in CRC screening in the future.

Declaration of competing interest

The authors would like to submit a manuscript entitled "Author's Reply: Improving Screening Participation: The Need for Socioeconomic Considerations and Psychological Interventions in Colorectal Cancer Programs" for consideration for publication in *Digestive and Liver Disease*. João Carlos Silva, Mário Dinis-Ribeiro, and Diogo Libânio declare no conflict of interest for this article.

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3. Gastric cancer screening: intention to adhere and patients' perspective

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ORIGINAL ARTICLE

Gastric Cancer Screening: Intention to Adhere and Patients' Perspective

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ABSTRACT

Background and Aims: Gastric cancer (GC) is the third cause of cancer mortality worldwide. A screening strategy that combines an upper gastrointestinal endoscopy (UGIE) with a screening colonoscopy may be cost-effective in intermediate-risk regions. This study aimed to evaluate the intention to adhere to combined endoscopic screening and assess knowledge of GC symptoms, risk factors, and barriers to screening.

Methods: Cross-sectional study enrolling individuals eligible for CRC screening in northern Portugal, where a populational fecal occult blood test (FOBT) program is implemented. The validated PERCEPT-PREVENT tool was applied across three groups: (a) not yet invited to CRC screening, (b) FOBT-positive referred to colonoscopy, and (c) primary colonoscopy screening.

Results: A high acceptance rate was observed for combined endoscopic screening (94%; $n = 264$) [not yet invited to CRC screening 98% ($n = 90$) vs. FOBT-positive referred to colonoscopy 90% ($n = 103$) vs. primary colonoscopy 97% ($n = 71$); $p = 0.017$], with the vast majority reporting intention to adhere in the setting of full reimbursement (97%; $n = 255$). Most respondents were unaware of any possible GC symptom (76%; $n = 213$), risk factor (73%; $n = 205$), and UGIE-related complication (85%; $n = 237$). Regular follow-up with the primary care physician (Odds Ratio (OR) 27.59, 95% confidence interval (CI) 2.99–254.57), lower perceived negative health consequences of UGIE (OR 1.40, 95% CI 1.13–1.74), and lower perceived financial burden (OR 2.46, 95% CI 1.04–5.85) were the only factors independently associated with a higher intention to undergo combined screening.

Conclusions: Willingness to undergo combined endoscopic screening was notably high and positively impacted by lower perceived barriers. Additional efforts should be undertaken to improve levels of digestive health literacy.

1 | Introduction

Gastric cancer (GC) is the fifth most common cancer and the third cause of cancer mortality worldwide [1]. Currently, screening for GC is performed only in high-incidence countries (age-standardized incidence rate [ASR] ≥ 20 per 100,000, such as Japan and Korea [29.9 and 41.3, respectively]) [2]. A cost-utility European analysis found that combining

an upper GI endoscopy (UGIE) with a screening colonoscopy may also be cost-effective in intermediate-risk regions (ASR $\geq 10/100,000$) [3]. This suggests that in Europe, if a colorectal cancer (CRC) screening program is already in place (through fecal occult blood testing [FOBT] or stand-alone colonoscopy), countries with intermediate incidence of GC might benefit from adding a screening UGIE to a screening colonoscopy [4].

The abovementioned cost-utility analysis assumed full compliance with endoscopic screening although it is known that adherence to screening procedures is suboptimal and even in countries with well-established GC screening programs the adherence rates are up to 56.2% [3, 5]. However, there are no studies evaluating adherence rates to UGIE screening in intermediate-risk countries, namely regarding combined screening (CRC and GC). Furthermore, it is crucial to investigate factors influencing participation rates, particularly risk perception (regarding the risk of developing GC, which is influenced by knowledge of symptoms and risk factors), as well as knowledge of screening procedure risks. It is also important to explore barriers to screening (perceived complication risk, access to testing, financial burden, and time constraints) which may negatively impact screening uptake.

Thus, the aim of this study was to estimate adherence to GC screening, considering a strategy that combines a UGIE with a screening colonoscopy. Secondary aims included the evaluation of the knowledge of GC risk factors and symptoms, assessing the perceived risk of screening procedures, and characterizing barriers to screening.

2 | Methods

2.1 | Study Design and Procedures

This was a cross-sectional study including asymptomatic individuals aged 50–75 years eligible for CRC screening in the northern region of Portugal where a populational FIT-screening program was implemented in 2018 under the coordination of the Northern Portugal Regional Health Administration (ARSN). The study protocol was approved by the Ethical committees of the three institutions involved in the study, namely ARSN, *Unidade Local de Saúde Gaia e Espinho*, and *Instituto Português de Oncologia do Porto*. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), guidelines for reporting observational studies were used [6].

Eligible citizens are directly invited for CRC screening by regular mail, initially through an awareness letter, and subsequently a kit for stool sample testing (1-sample FIT) is sent, along with instructions on how to perform the test and deliver it to the Primary Care Center [7]. Those who test positive are invited to undergo a pre-colonoscopy assessment, performed by the primary care physician, and then referred for a sedated colonoscopy at the nearest Portuguese National Health Service (NHS) hospital. Both CRC screening tests, namely FIT and colonoscopy, are offered free of charge. All FITs (OC-Auto Sampling 3, Eiken Chemical Co., Ltd.) undergo analysis at a centralized laboratory that uses a cut-off of 100 ng/mL (equivalent to 20 µg/g) [8]. A centralized information platform (Electronic Screening Management Platform) oversees all pertinent outcomes of the organized screening program [7].

Gastric cancer screening is neither implemented nor recommended, although primary care physicians are allowed to order UGIE (and colonoscopies) at their discretion. These endoscopic

procedures are performed in clinics and the patients incur no costs, being those supported by the NHS. The NHS also covers sedation costs for colonoscopy, but not for stand-alone UGIE. However, in the northern region of Portugal, if a patient is prescribed a colonoscopy with sedation plus a non-sedated UGIE, most private clinics do not charge additional costs for UGIE sedation. In the case of stand-alone UGIE, the NHS covers the cost of the UGIE, but the patient covers sedation costs (around 80–120€).

This cross-sectional study evaluated the intention to adhere to UGIE for GC screening, considering a strategy that combines a UGIE with a screening colonoscopy. According to this strategy, UGIE would be offered to individuals scheduled for a screening colonoscopy, whether due to a positive FIT result or as part of primary colonoscopy screening. To ensure that estimates of intention to adhere to combined endoscopic screening were not biased by previous exposure to FIT and/or colonoscopy, individuals not yet invited to CRC screening were also enrolled. Thus, intention to undergo combined screening was compared across three predefined groups: (a) individuals not yet invited to CRC screening, (b) FOBT-positive individuals referred to colonoscopy, and (c) individuals who underwent CRC screening through primary colonoscopy outside of the organized CRC screening program.

Inclusion criteria were asymptomatic individuals aged 50–75 years eligible for populational FOBT screening. Individuals who tested negative for FOBT and those who refused colonoscopy after a positive FOBT were excluded. Further exclusion criteria encompassed symptomatic patients (e.g., diarrhea, constipation, abdominal pain, weight loss, hematochezia); anemia; previous CRC, GC, or colorectal polyps; known hereditary cancer risk (including first-degree relatives with CRC and/or GC); previous colectomy; previous gastrectomy; inflammatory bowel disease (IBD); dementia; inability, and/or refusal to answer the questionnaire.

The individuals eligible for CRC screening selected for participation in this study were randomly extracted from the ARSN database based on their screening status from November 2021 to April 2022. Screened participants were randomly selected through a stratified random sample, according to sex and age group (50–59 years old and 60–74 years old). Individuals who had reached the CRC screening age but had not yet been invited for screening were also selected from the ARSN database. Individuals who underwent CRC screening through primary colonoscopy (outside the populational program) were recruited from three different private endoscopy units, from July 2022 to April 2023, after assessment of inclusion and exclusion criteria.

2.2 | PERCEPT-PREVENT Tool

A previously validated questionnaire on GC risk perception (PERCEPT-PREVENT tool) was used, targeting (1) knowledge of GC symptoms and risk factors; (2) perceived severity of GC; (3) perceived benefits of combined screening; (4) barriers to screening; and (5) perceptions toward endoscopy-related complications. The complete version of the PERCEPT-PREVENT

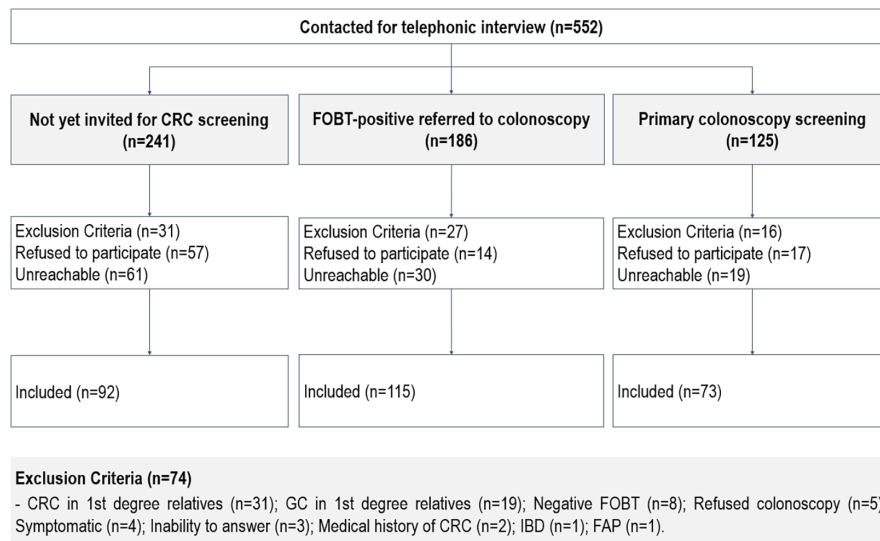


FIGURE 1 | Study population according to the screening status. CRC, colorectal cancer; FAP, Familial adenomatous polyposis; FOBT, Fecal occult blood test; GC, Gastric cancer; IBD, Inflammatory bowel disease.

tool has been previously detailed [9] and is also presented as a Appendices S1 and S2.

The PERCEPT-PREVENT tool questionnaire was applied through telephonic interview, within a period of up to 6 months after the screening status assessment, from September 2022 to September 2023. Interviews were conducted by two dedicated gastroenterology nurses after three formal training sessions and informed verbal consent was obtained from all participants. The PERCEPT-PREVENT answers were recorded in an electronic database, and each patient received a code number to secure anonymization. Besides questionnaire answers, sociodemographic data including age, gender, educational level, and monthly income were registered.

2.3 | Sample Size Calculation and Statistical Analysis

Due to the lack of previous estimates on adherence to UGIE combined with a screening colonoscopy, the authors considered preliminary data previously published [9]. Thus, considering an expected adherence of 95%, with a 95% confidence interval (CI), an error of 0.05, and a power of 80%, the required number of participants is 73.

Statistical Package for Social Sciences (SPSS) program version 27 (IBM Corporation, Armonk, NY) was used. Categorical variables are summarized as frequencies and percentages. As appropriate χ^2 test or Fisher's exact test was used to compare categorical variables. Normal distribution was examined using histogram visual inspection. Continuous variables were expressed in means and standard deviation (variables with normal distribution) or median and interquartile range (variables with skewed distributions). Independent samples *t*-test or independent samples Mann-Whitney *U* test were used to compare two groups. The analysis of variance (ANOVA) test or the independent samples Kruskal-Wallis test were used to assess the differences among multiple groups. Following a significant

result, the Bonferroni adjustment was applied to the pairwise comparisons.

To identify predictive factors for willingness to undergo UGIE for GC screening combined with a screening colonoscopy, the domains of the PERCEPT-PREVENT tool were evaluated, as well as sociodemographic characteristics. Independent variables with at least marginal association with the outcome variable ($p < 0.100$) in univariate analysis were included in the multivariate logistic regression model. Variables with a significant association with the dependent variables were identified after adjustment using the Backward-Wald methodology (cut-off for entry 0.050; cut-off for exclusion 0.100). Odds Ratio (OR) with 95% CI was calculated for each variable independently associated with the outcome variable. The model's goodness of fit and discriminatory ability were evaluated through the Hosmer-Lemeshow goodness-of-fit test and ROC curve analysis. All reported *p*-values are two-tailed, with a *p*-value < 0.050 indicating statistical significance.

3 | Results

3.1 | Study Population and Recruitment Procedures

A total of 552 individuals were contacted for telephonic interview of which 110 were unreachable, 88 refused to participate, and 74 met exclusion criteria. In total, 280 participants were included: 92 not yet invited to CRC screening, 115 FOBT-positive referred to colonoscopy, and 73 who underwent CRC screening through primary colonoscopy. Figure 1 displays the study population according to the screening status.

The mean age was 57 ± 8 years, and 55% ($n = 153$) were female. Regarding sociodemographic characteristics, 56% ($n = 154$) had a basic educational level (sub-high school educational attainment) and 60% ($n = 163$) reported an active work status. Most participants indicated consistent follow-up with their primary care physician (98%; $n = 274$), while only 25% ($n = 71$) reported

having additional health insurance besides NHS. Further information on the sociodemographic characteristics is provided in Table 1.

3.2 | Attitudes Toward Screening

Overall, the acceptance of combined screening was high (94%; $n=264$). A total of 97% ($n=255$) were willing to undergo combined screening if fully reimbursed [not yet invited to CRC screening 100% ($n=90$) vs. FOBT-positive referred to colonoscopy 93% ($n=96$) vs. primary colonoscopy 97% ($n=69$); $p=0.023$].

Despite the absence of formal recommendations on GC screening in Europe, 34% ($n=96$) received medical recommendation for GC screening [not yet invited to CRC screening 4% ($n=4$) vs. FOBT-positive referred to colonoscopy 32% ($n=37$) vs. primary colonoscopy 75% ($n=55$); $p<0.001$]. Among FOBT-positive individuals referred to colonoscopy, 83% ($n=95$) underwent the procedure at an NHS hospital as part of the organized screening program in northern Portugal, where concomitant UGIE was not permitted. Notably, out of the 188 participants who underwent colonoscopy (115 FOBT-positive referred to colonoscopy and 73 who underwent CRC screening through primary colonoscopy), 93 (49%) were submitted to the procedure at a private endoscopy unit outside the organized screening program. A total of 60% ($n=56$) underwent combined screening and the intention to adhere to UGIE combined with a screening colonoscopy did not differ based on the previously adopted screening strategy (UGIE combined with colonoscopy 96% vs. colonoscopy alone 97%; $p=1.000$) (Figure 2). The proportion of participants regularly followed up by primary care physicians ($p=0.244$) and with health insurance (0.725) did not differ significantly across groups.

TABLE 1 | Sociodemographic characteristics ($n=280$).

Female, n (%)	153 (55)
Age, mean (SD)	57 (8)
Married, n (%)	166 (60)
Basic educational level, n (%)	154 (56)
Active worker, n (%)	163 (60)
Intermediate monthly income (500–1000€), n (%)	28 (45)
Regular follow-up with primary care physician, n (%)	274 (98)
Health insurance, n (%)	71 (25)
Informed on GC screening tests from any means of communication, n (%)	152 (55)
GC in second-degree relatives or acquaintances, n (%)	67 (24)
Second-degree relatives with GC, n (%)	35 (52)

Abbreviations: GC, Gastric cancer; SD, Standard deviation.

Despite the overall comparisons yielding a significant difference regarding perceived GC severity ($p=0.002$), Bonferroni-adjusted pairwise comparisons showed a significant difference only between individuals not yet invited to screening and those FOBT-positive referred to colonoscopy (19 ± 2 vs. 17 ± 3 ; $p=0.002$). Table 2 details data on cues to action and attitudes toward GC screening.

3.3 | Knowledge and Barriers to GC Screening

Perceived testing need scores were globally high, and 99% ($n=91$) of participants not yet invited to CRC screening were classified as a “great need” to screen healthy individuals aged 50years old or older for GC (Table 3). Despite this, overall knowledge of GC symptoms and risk factors was low as 76% ($n=213$) did not know any possible GC symptom and 73% ($n=205$) did not know any risk factor. The risk factor awareness score, which detailed the perception of having GC risk factors, was significantly lower in individuals screened for CRC through primary colonoscopy ($p<0.001$). Furthermore, knowledge of Hp infection status was reported at a significantly higher rate in individuals who underwent CRC screening through primary colonoscopy [not yet invited to CRC screening 10% ($n=9$) vs. FOBT-positive referred to colonoscopy 59% ($n=68$) vs. primary colonoscopy screening 78% ($n=57$); $p<0.001$].

Significantly higher scores for perceived negative health consequences of UGIE were apparent in participants submitted to colonoscopy after a positive FOBT ($p<0.001$). Lower scores for perceived financial burden were obtained in the primary colonoscopy screening group ($p<0.001$). No differences were found across groups for the remaining barrier domains (Table 3). A total of 85% ($n=237$) were unaware of any potential complications arising from a screening UGIE, and 98% ($n=273$) did not know its risk factors. The scores for complication knowledge and its risk factors did not differ across groups (Table 3).

3.4 | Predictors of Adherence to Combined Endoscopic Screening

In univariate analysis, younger age ($p=0.013$), higher educational level ($p=0.048$), active work status ($p=0.013$), regular follow-up with the primary care physician ($p=0.014$), previous information on GC screening tests ($p=0.030$), higher perceived testing need score ($p=0.044$) and lower perceived negative health consequences of UGIE ($p=0.002$) were significantly associated with willingness to undergo combined screening. Variables with at least marginal association with the outcome variable ($p<0.100$) were also included in the multivariable model (Table 4). On multivariate analysis, regular follow-up with the primary care physician (OR 27.59, 95% CI 2.99–254.57), lower perceived negative health consequences of UGIE (OR 1.40, 95% CI 1.13–1.74), and lower perceived financial burden (OR 2.46, 95% CI 1.04–5.85) were independently associated with the intention to accept UGIE combined with a screening colonoscopy. The results from the Hosmer–Lemeshow goodness-of-fit test ($\chi^2=7.58$; $df=8$; $p=0.475$) and ROC curve analysis (AUC=0.82, 95% CI 0.70–0.94; $p<0.001$) indicate that the logistic regression model calibrates well to the observed outcomes and exhibits a considerable discriminatory power.

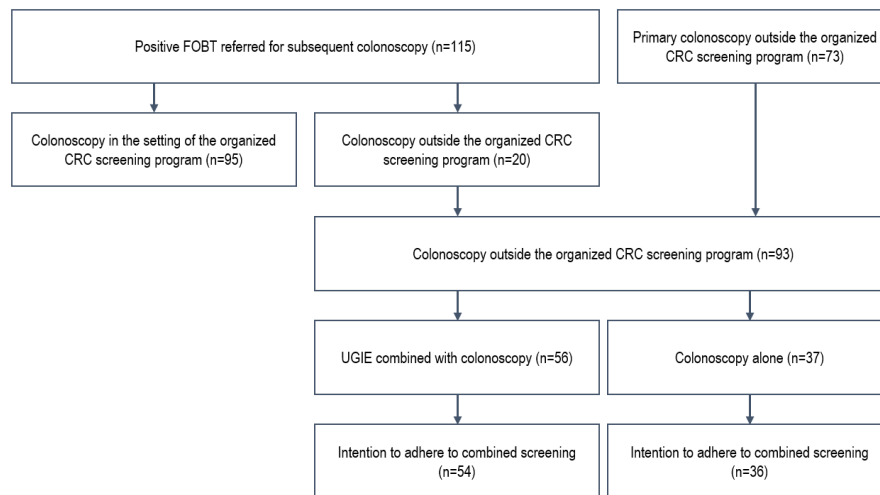


FIGURE 2 | Combined endoscopic screening in individuals referred for a screening colonoscopy. CRC, colorectal cancer; FOBT, Fecal occult blood test; UGIE, Upper gastrointestinal endoscopy.

4 | Discussion

A high acceptance rate was observed for combined endoscopic screening, especially in the setting of full reimbursement. Overall, knowledge of GC symptoms, risk factors, and UGIE-related complications were low. Regular follow-up with the primary care physician, lower perceived negative health consequences of UGIE, and lower perceived financial burden were the only factors independently associated with a higher intention to undergo combined screening.

Combined GC and CRC endoscopic screening may be cost-effective in intermediate-risk regions (ASR 10–20/100,000) [3, 4, 10]. Combining a UGIE with a screening colonoscopy in individuals aged 50 to 75 years appears to be a valuable strategy for GC screening. Two recent meta-analyses evaluated the diagnostic yield of UGIE in FOBT-positive subjects undergoing colonoscopy [11, 12]. Choe et al. report a 0.5% prevalence of GC, unsupportive of routine UGIE screening for patients with a positive FIT [11]. Yet, among the four included studies, only in one case GC was diagnosed, with a prevalence of 1.23% in a sub-sample of FIT-positive/colonoscopy-negative subjects who underwent UGIE [11]. In contrast, Shah et al. report that same-day UGIE in FOBT-positive subjects undergoing colonoscopy yields approximately 25% more malignancies than colonoscopy alone [12]. The latter review encompassed 21 studies: six employed FIT, 11 used guaiac-based FOBTs, and the remaining four did not specify the type of FOBT used. The pooled prevalence of upper gastrointestinal (UGI) cancers was 0.8% (95% CI 0.4–1.6). For UGI clinically significant lesions (CSL), which were defined as lesions potentially explaining occult blood loss (e.g., polyps, ulcers, vascular lesions), the prevalence was 30.4% (95% CI 20.7–42.2). In comparison, the prevalence of colonic cancers was 3.3% (95% CI 1.8–6.0) and colonic CSL (e.g., tubular adenomas, advanced adenomas) was 31.9% (95% CI 23.9–41.1). Additionally, the prevalence of UGI CSL and UGI cancers in FOBT-positive subjects was comparable, regardless of the presence or absence of colonic pathology. Both reviews present limitations, notably the inclusion of symptomatic individuals [11, 12]. Moreover, in

the latter meta-analysis not only GC but all UGI neoplasms were accounted [12]. However, when considering a screening strategy that combines GC and CRC screening, the role of UGIE extends beyond diagnosing gastric neoplasms, as it enables the diagnosis of precancerous conditions such as chronic atrophic gastritis and intestinal metaplasia, which are particularly prevalent in countries with a higher incidence of GC [13]. In intermediate to high-risk regions, diagnosis and surveillance of patients with precancerous gastric conditions are cost-effective and endorsed by European recommendations [14, 15]. Considering an increase in the detection of precancerous conditions and GC through combined endoscopic screening, it must be acknowledged that most European CRC screening programs are based on FOBT, which restricts GC screening to individuals who test positive [16, 17].

In a prior cost-utility analysis for GC screening in intermediate-risk regions, full compliance with endoscopic screening was assumed [3, 10]. However, it is recognized that in countries with well-established GC screening programs, the adherence rates fall below 100% [5]. Even in high-risk regions, the highest pooled adherence rates, reported in studies based on self-reported screening uptake, reached up to 56.2% [5, 18–24]. Time trends of screening uptake in Korea based on the analysis of the National Cancer Screening Program databases favor endoscopic screening which increased from 31.1% in 2002 to 72.5% in 2011 [25–29]. In this high-risk region, the organized GC screening program adherence rate has nearly doubled, increasing from 38.2% in 2009 to 70.2% in 2022, surpassing the increase in uptake observed in the Japanese GC screening program [30]. Overall, data on adherence to endoscopic screening are scarce and no estimates on combined endoscopic screening uptake were available. In our study, considering participants naïve to digestive cancer screening, 98% were willing to undergo combined endoscopic screening. The slightly lower rate observed among FOBT-positive individuals referred to colonoscopy, along with the higher scores for perceived negative health consequences of UGIE, may be related to a prior preference for non-invasive testing and previous experience with stand-alone colonoscopy within the organized CRC screening program.

TABLE 2 | Attitudes toward GC screening.

	Total (N=280)	Not yet invited to CRC screening (N=92)	FOBT-positive referred to colonoscopy (N=115)	Primary colonoscopy screening (N=73)	p
Willing to undergo UGIE for GC screening combined with a screening colonoscopy, <i>n</i> (%)	264 (94)	90 (98)	103 (90)	71 (97)	0.017
Willingness to pay for a UGIE, if combined with a screening colonoscopy					0.023
Fully reimbursed, <i>n</i> (%)	255 (97)	90 (100)	96 (93)	69 (97)	
The cost of a UGIE under sedation, <i>n</i> (%)	9 (3)	0 (0)	7 (7)	2 (3)	
Underwent UGIE combined with a screening colonoscopy, <i>n</i> (%)	56 (30)	0 (0)	1 (1)	55 (75)	<0.001
Medical recommendation, <i>n</i> (%)	96 (34)	4 (4)	37 (32)	55 (75)	<0.001
Regular follow-up with primary care physician, <i>n</i> (%)	274 (98)	88 (96)	114 (99)	72 (99)	0.244
Health insurance, <i>n</i> (%)	71 (26)	25 (27)	26 (23)	20 (27)	0.725
Information on GC screening tests from any means of communication, <i>n</i> (%)	152 (56)	52 (57)	52 (47)	48 (67)	0.029
GC in second-degree relatives or acquaintances, <i>n</i> (%)	67 (24)	26 (28)	23 (20)	18 (25)	0.378
Perceived GC severity (0–28), mean (SD)	18 (3)	19 (2)	17 (3)	18 (2)	0.002

Abbreviations: CI, Confidence interval; CRC, colorectal cancer; FOBT, Fecal occult blood test; GC, Gastric cancer; SD, Standard deviation; UGIE, Upper gastrointestinal endoscopy.

TABLE 3 | Knowledge and barriers to GC screening.

Knowledge	Total (N= 280)	Not yet invited to CRC screening (N= 92)	FOBT-positive referred to colonoscopy (N= 115)	Primary colonoscopy screening (N= 73)	p
Did not know any symptom, n (%)	213 (76)	72 (78)	90 (78)	51 (70)	0.352
Symptom knowledge score (1–9), median (IQR)	3 (3–4)	4 (3–5)	4 (3–4)	3 (2–4)	0.027
Did not know any risk factor, n (%)	205 (73)	58 (63)	97 (84)	50 (68)	0.002
Risk factor knowledge score (1–12), median (IQR)	4 (3–4)	4 (3–4)	4 (3–4)	3 (3–4)	0.393
Perceived risk score (0–2), median (IQR)	0 (0–1)	0 (0–2)	0 (0–2)	0 (0–0)	0.101
Risk factor awareness score (0–12), median (IQR)	1 (0–2)	1 (1–3)	1 (0–2)	0 (0–1)	<0.001
Knowledge of <i>Helicobacter pylori</i> infection status, n (%)	134 (48)	9 (10)	68 (59)	57 (78)	<0.001
Positive <i>Helicobacter pylori</i> , n (%)	14 (10)	0 (0)	6 (9)	8 (14)	0.536
Perceived testing need score “great need,” n (%)	257 (92)	91 (99)	99 (87)	67 (92)	0.006
Barriers to UGIE screening					
Perceived negative health consequences of UGIE (0–16), median (IQR)	6 (4–8)	4 (4–6)	7 (4–9)	4 (4–8)	<0.001
Perceived financial burden of UGIE (0–4), median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)	1 (1–2)	<0.001
Perceived time constrain to UGIE (0–4), median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	0.772
Perceived access barrier to UGIE (0–4), median (IQR)	1 (0–1)	1 (1–1)	1 (0–1)	1 (0–1)	0.654
Perceived negative efficacy of UGIE (0–4), median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	0.113
Overall perceived barriers to UGIE screening (0–32), mean (SD)	10 (3)	9 (2)	11 (3)	9 (3)	<0.001
UGIE complication awareness					
Did not know any UGIE complication, n (%)	237 (85)	92 (100)	97 (84)	48 (66)	<0.001
UGIE-related complication knowledge score (1–7), median (IQR)	2 (1–2)		2 (1–3)	2 (1–2)	0.220
Awareness of possible complications during a UGIE (0–20), mean (SD)	10 (10)	10 (4)	10 (3)	11 (4)	0.210
Did not know any risk factor for UGIE- related complication, n (%)	273 (98)	91 (99)	113 (98)	69 (95)	0.206
Risk factor for UGIE-related complication knowledge score (1–12), median (IQR)	1 (1–1)		1 (1–2)	1 (1–1)	0.157

Abbreviations: CI, Confidence interval; CRC, colorectal cancer; FOBT, Fecal occult blood test; GC, Gastric cancer; IQR, Interquartile range; SD, Standard deviation; UGIE, Upper gastrointestinal endoscopy.

TABLE 4 | Predictors of adherence to combined endoscopic screening.

	Willingness to undergo UGIE combined with a screening colonoscopy			
	Univariate analysis		Multivariate analysis	
	OR	<i>p</i>	aOR	95% CI
Female	2.09	0.164		
Younger age	1.08	0.013	1.02	0.92–1.13
Married	1.35	0.568		
Intermediate or high educational level	3.63	0.048	2.39	0.51–11.23
Active worker	4.42	0.013	2.25	0.46–10.97
Intermediate or high monthly income	1.47	0.761		
Regular follow-up with primary care physician	9.29	0.014	27.59 ^a	2.99–254.57
Health insurance	2.31	0.278		
Information on GC screening tests from any means of communication	3.67	0.030	2.48	0.52–11.93
GC in second-degree relatives or acquaintances	0.94	0.918		
Higher perceived GC severity	1.01	0.891		
Higher GC symptom knowledge score	1.89	0.126		
Higher GC risk factor awareness score	0.79	0.176		
Higher perceived testing need score	2.43	0.044	1.44	0.30–6.85
Lower perceived negative health consequences of UGIE	1.31	0.002	1.40 ^a	1.13–1.74
Lower perceived financial burden of UGIE	1.72	0.085	2.46 ^a	1.04–5.85
Lower perceived time constrain to UGIE	1.60	0.247		
Lower perceived access barrier to UGIE	1.48	0.367		
Lower perceived negative efficacy of UGIE	1.31	0.502		
Higher UGIE-related complication knowledge score	1.57	0.402		
Higher awareness of possible complications during a UGIE	1.01	0.993		

Abbreviations: aOR, Adjusted odds ratio; CI, Confidence interval; CRC, colorectal cancer; GC, Gastric cancer; OR, Odds ratio; UGIE, Upper gastrointestinal endoscopy.

^aAdjusted odds ratio, for variables retained in the final model using the Backward–Wald methodology.

Overall, intention to adhere to GC screening exceeded previous reports based on self-reported data, which may be explained by the proposed joint screening strategy. Lee YC. et al. describe a combined screening strategy for both GC and CRC in Taiwan. Individuals eligible for CRC screening were randomly invited to receive either the standard FIT or an FIT supplemented with a *Helicobacter pylori* stool antigen test (HPSA). Interestingly, the addition of the HPSA test increased the screening program's participation rate by 13.9% compared to FIT-only testing [31]. Thus, combined screening may potentiate both GC and CRC screening uptakes.

Risk perception and attitudes toward GC screening were rarely evaluated in Western countries. Several Eastern studies have been designed to identify predictors of adherence and measure GC risk perception [18–20, 22, 26]. An 80% intention to undergo GC screening, accompanied by a moderate level of knowledge

regarding GC risk factors and warning symptoms was described in China [32, 33]. A systematic review, which included 13 studies (nine from Asia, three from the Middle East, and one from the USA), identified sociodemographic characteristics such as age, educational level, and employment as facilitators of GC screening [34]. In contrast, fear of the screening procedure, fear of the screening outcome, costs, embarrassment, and lack of signs were the most commonly reported barriers [34]. Alghamdi G. et al. reported a moderate level of knowledge about the risk factors and symptoms of GC in Saudi Arabia [35]. GC risk perception was evaluated in a Western study before and after an educational program, revealing that compared to responses prior to the educational presentation, fewer participants expressed concerns about cost, pain, and taking time off work, but were slightly more concerned about the findings of the UGIE [36]. The low levels of knowledge identified in our study underscore the need to improve literacy in digestive health.

This European study marks the inaugural attempt to evaluate knowledge and risk perception in GC, alongside estimating the adherence rate to combined endoscopic screening in intermediate-risk regions. Knowledge of GC symptoms, risk factors, and screening procedure risks was evaluated through the PERCEPT-PREVENT tool, previously validated for an objective measurement of knowledge and barrier domains [9].

The authors acknowledge the study's identifiable limitations, which rely on measures susceptible to bias, such as selective memory, social desirability, or attribution bias. Furthermore, healthy user bias should also be considered, as participants willing to participate and available to complete the survey through a telephonic interview may be more prone to engage in health-promoting behaviors. Additionally, the survey was conducted regionally rather than nationally.

Economic analysis may be revisited considering the adherence estimates obtained in the present study for combined endoscopic screening. Additional prospective observational studies confronting self-reported willingness to undergo combined screening with screening uptake may be developed within the context of pilot GC screening programs. Comparing alternative strategies for combined screening, such as the intention to adhere to FOBT combined with HPSA versus combined endoscopic screening, could provide valuable insights into adherence estimates for digestive cancer screening and the strategic management of endoscopic capacity.

Author Contributions

Mário Dinis-Ribeiro, Diogo Libânio, and João Carlos Silva designed the study. João Carlos Silva and Diogo Libânio performed the research and analyzed the data. Fernando Tavares, Mário Dinis-Ribeiro, and Diogo Libânio revised the paper for critically important intellectual content.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.



4. Exploring the perceived risk of complications in endoscopic screening procedures

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Exploring the Perceived Risk of Complications in Endoscopic Screening Procedures

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Keywords

Gastrointestinal endoscopy · Cancer screening · Early cancer detection · Endoscopy-related complications · Adverse events · Preventive medicine · Risk perception

Abstract

Background and Aims: Endoscopy holds a pivotal role in colorectal (CRC) and gastric cancer screening, and adherence rates might be impacted by the patient's risk perception, encompassing concerns about complications during endoscopic screening procedures. This study aimed to evaluate how individuals perceive the risk of complications associated with undergoing a screening colonoscopy and upper gastrointestinal endoscopy (UGIE). **Methods:** This is a cross-sectional study enrolling individuals eligible for CRC screening in northern Portugal, where a populational fecal occult blood test program is implemented. The validated PERCEPT-PREVENT tool was applied through telephonic interviews in 2 groups: (a) never-screened and (b) already submitted to endoscopic

screening. **Results:** Among the 217 included healthy participants, 61% ($n = 133$) and 83% ($n = 181$) were unaware of any possible complications from colonoscopy and UGIE, respectively. Never-screened individuals less frequently reported a high complication risk perception (colonoscopy: 19% vs. 45%, $p < 0.001$; UGIE: 14% vs. 41%, $p < 0.001$). A lower risk perception for UGIE complications was associated with a higher willingness to undergo UGIE combined with a screening colonoscopy (OR: 2.30, 95% confidence interval: 1.42–3.70). Participants who underwent combined screening reported less frequently a high complication risk perception (colonoscopy: 27% vs. 61%, $p < 0.001$; UGIE: 28% vs. 54%, $p = 0.006$) and scored higher for complication awareness (colonoscopy: 14 ± 5 vs. 11 ± 4 , $p < 0.001$; UGIE: 11 ± 4 vs. 9 ± 3 , $p < 0.001$) compared to those who had only undergone colonoscopy. **Discussion:** Enhancing risk perception and knowledge of complications associated with endoscopic screening procedures offers an opportunity to increase adherence rates.

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Perceção do risco de complicações em procedimentos endoscópicos de rastreio

Palavras Chave

Endoscopia digestiva · Rastreio oncológico · Detecção precoce · Complicações · Eventos adversos · Medicina preventiva · Perceção do risco

Resumo

Objetivos: A endoscopia digestiva desempenha um papel central no rastreio de neoplasias do trato digestivo. A adesão ao rastreio pode ser influenciada pela perceção do risco de complicações. O objetivo deste estudo foi avaliar a perceção do risco de complicações associadas à colonoscopia e à endoscopia digestiva alta (EDA) em contexto de rastreio.

Métodos: Estudo transversal com inclusão de indivíduos elegíveis para o programa de rastreio de cancro colorretal, implementado na região norte de Portugal. O questionário PERCEPT-PREVENT, previamente validado, foi aplicado através de entrevistas telefónicas em 2 grupos: a) sem rastreio prévio, e b) rastreio endoscópico prévio. **Resultados:** Foram incluídos 217 participantes, dos quais 61% ($n = 133$) e 83% ($n = 181$) desconheciam qualquer complicação da colonoscopia e da EDA, respetivamente. Indivíduos sem rastreio prévio reportaram com menor frequência uma perceção alta do risco de complicações (colonoscopia: 19% vs. 45%, $p < 0,001$; EDA 14% vs. 41%, $p < 0,001$). Uma menor perceção do risco de complicações da EDA associou-se a uma maior intenção de aceitar a EDA combinada com uma colonoscopia de rastreio (OR: 2,30, IC95%: 1,42–3,70). Participantes previamente submetidos a rastreio combinado reportaram, com menor frequência, uma perceção alta do risco de complicações (colonoscopia: 27% vs. 61%, $p < 0,001$; EDA: 28% vs. 54%, $p = 0,006$) e obtiveram pontuações mais altas no reconhecimento das possíveis complicações (colonoscopia: 14 ± 5 vs. 11 ± 4 , $p < 0,001$; EDA: 11 ± 4 vs. 9 ± 3 , $p < 0,001$) quando comparados com indivíduos submetidos apenas a colonoscopia.

Discussão: Otimizar o conhecimento sobre as complicações dos procedimentos endoscópicos de rastreio oferece uma oportunidade para aumentar as taxas de adesão.

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Introduction

Gastrointestinal (GI) endoscopy is a minimally invasive procedure that carries a risk of complications, which may be heightened by additional diagnostic or therapeutic interventions. Informed consent must be obtained before each procedure to ensure patient autonomy and is signed by the patient or, in cases of incapacity, by their legal representative [1]. In this context, medicolegal issues are increasingly relevant even for commonly performed endoscopic procedures such as a screening colonoscopy [2].

GI endoscopy plays a fundamental role in digestive cancer screening [3]. In Europe, most countries have implemented populational colorectal cancer (CRC) screening programs based on fecal occult blood testing (FOBT), while colonoscopy screening is offered as the primary method in Poland [4, 5]. Upper GI endoscopy (UGIE) is the primary screening method for gastric cancer (GC) in high-incidence countries (age-standardized incidence rate ≥ 20 per 100,000) [6]. For intermediate-risk regions, with an age-standardized incidence rate between 10 and 20 per 100,000, UGIE may have a role for primary screening if cost-effectiveness is proven [3]. Data from Portuguese cost-utility analyses concluded that endoscopic screening for GC was cost-effective when combined with a screening colonoscopy [7, 8]. Therefore, endoscopic screening can be considered based on local settings, including the costs of endoscopic procedures and the availability of endoscopic resources [3, 8].

Apart from concerns about patient autonomy and medicolegal issues, patients' risk perception, particularly regarding complications, may impact digestive cancer screening uptake. Adherence to screening encompasses the perceived risk of developing cancer but also the perceived barriers, particularly the risk of complications during endoscopic screening procedures. A previous study comparing never-screened individuals with individuals previously screened for CRC evaluated the complication risk perception and found that never-screened individuals were more likely to overestimate the risk of complications from a colonoscopy than patients already submitted to screening (38% vs. 19%; $p = 0.04$) [9].

This study aimed to assess the perceived risk of endoscopy-related complications within the context of CRC and GC screening. Additionally, the study aimed to measure the impact of perceived complication risk on screening uptake.

Materials and Methods

Study Design and Procedures

This was a cross-sectional study including asymptomatic individuals aged 50–75 years eligible for CRC screening in the northern region of Portugal where a populational fecal immunochemical test (FIT) screening program was implemented in 2018 under the coordination of *Administração Regional de Saúde do Norte* (ARSN). The study protocol was approved by the Ethical Committees of the 3 institutions involved in the study, namely, ARSN, *Unidade Local de Saúde Gaia Espinho*, and *Instituto Português de Oncologia do Porto*. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies were used [10].

In the populational FIT screening program, eligible citizens are directly invited by regular mail, initially through an awareness letter, and subsequently, a kit for stool sample testing is sent, along with instructions on how to perform the test and deliver it to the Primary Care Center [11]. Those who test positive are invited to undergo a pre-colonoscopy assessment, performed by the primary care physician, and then referred for a sedated colonoscopy at the nearest Portuguese National Health Service (NHS) hospital. Both screening tests, namely, FIT and colonoscopy, are offered free of charge. All FITs (OC-Auto Sampling 3, Eiken Chemical Co., Ltd.) undergo analysis at a centralized laboratory, while a centralized information platform (Electronic Screening Management Platform) oversees all pertinent outcomes of the organized screening program.

GC screening is neither implemented nor recommended, although primary care physicians are allowed to order UGIE (and colonoscopies) at their discretion. These endoscopic procedures are performed in clinics, and the patients incur no costs, being those supported by the NHS. The NHS also covers sedation costs for colonoscopy but not for stand-alone UGIE. However, in the northern region of Portugal, if a patient is prescribed a colonoscopy with sedation plus a non-sedated UGIE, most private clinics do not charge additional costs for UGIE sedation. In the case of stand-alone UGIE, the NHS covers the cost of the UGIE, but the patient covers sedation costs (around EUR 80–120).

The study design relied on the comparison of two predefined groups: (a) never-screened individuals and (b) patients already submitted to endoscopic screening

(primary colonoscopy, colonoscopy after a positive FOBT, or primary colonoscopy combined with UGIE), with or without sedation. Individuals who tested negative for FOBT as well as FOBT-positive individuals who refused colonoscopy screening were excluded. Further exclusion criteria encompassed patients with either upper or lower GI symptoms (e.g., diarrhea, constipation, abdominal pain, weight loss, hematochezia, dysphagia, heartburn, nausea, vomiting, hematemesis); anemia; previous CRC, GC, or colorectal polyps; precancerous gastric conditions; known hereditary cancer risk (including first-degree relatives with CRC and/or GC); previous colectomy; previous gastrectomy; inflammatory bowel disease; dementia; inability and/or refusal to answer the questionnaire.

Contacts of individuals eligible for CRC screening were extracted from the ARSN database based on their screening status from November 2021 to April 2022. Participants were randomly selected through a stratified random sample, according to sex and age groups (50–59 years old and 60–74 years old). Screening status assessment and data extraction were completed in August 2022. Individuals who underwent CRC screening through primary colonoscopy (outside the populational program) were recruited from 3 different private endoscopy units, from July 2022 to April 2023, after assessment of inclusion and exclusion criteria.

Percept-Prevent Tool

A previously validated risk perception questionnaire (PERCEPT-PREVENT tool) that targets both CRC and GC as well as endoscopy-related complications was used [12]. In the section of the survey focusing on barriers to screening, negative health consequences of colonoscopy and UGIE were assessed, including the perception of possible corporal harm (defined as “complication risk perception”), physical discomfort, fear, and embarrassment. Knowledge of possible endoscopy-related complications was evaluated in two steps. First, participants were asked to enumerate known complications for colonoscopy and UGIE (“complication knowledge score”). Subsequently, participants were presented with a detailed list and instructed to identify which were, in their perspective, possible complications of a sedated colonoscopy and UGIE (“awareness of possible complications”). The complete version of the PERCEPT-PREVENT tool has been previously detailed [12] and is also presented as an online supplementary appendix (for all online suppl. material, see <https://doi.org/10.1159/000543180>) (online suppl. appendix 1 and 2).

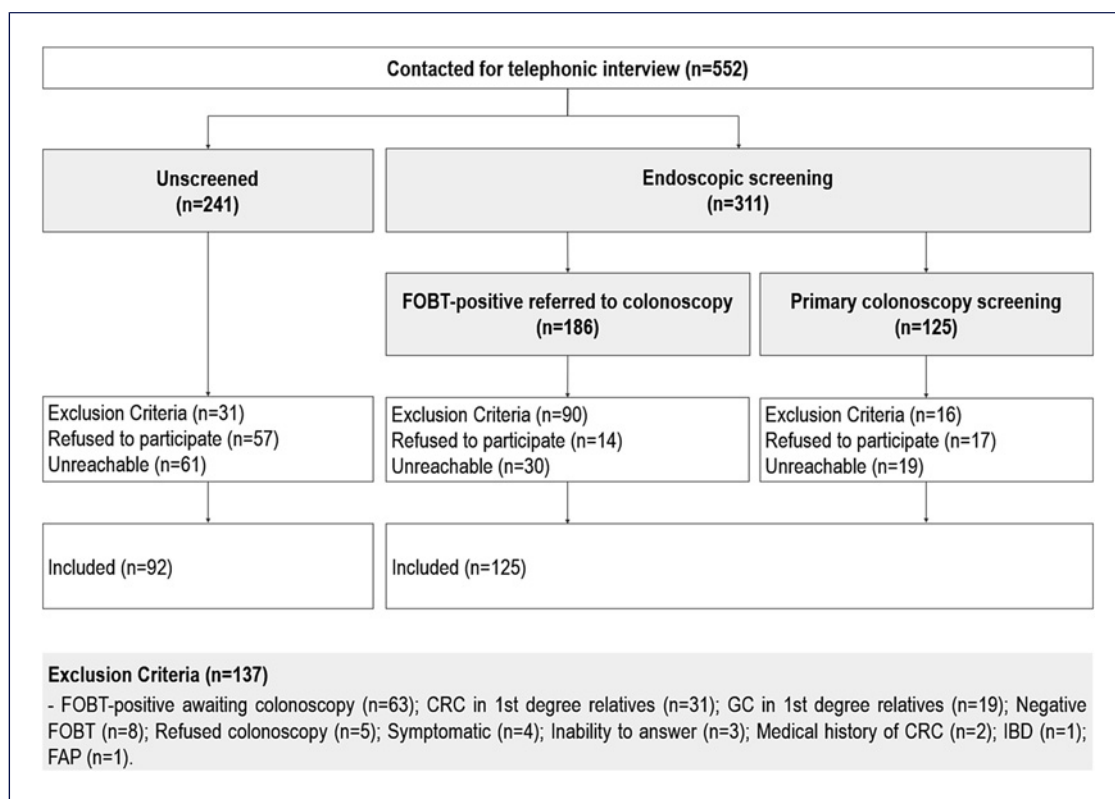


Fig. 1. Study population according to the screening status. CRC, colorectal cancer; FAP, familial adenomatous polyposis; FOBT, fecal occult blood test; GC, gastric cancer; IBD, inflammatory bowel disease.

The PERCEPT-PREVENT tool questionnaire was administered remotely via telephonic interview, within a period of up to 6 months after the screening status assessment, from September 2022 to September 2023. Interviews were conducted by 2 gastroenterology nurses after three formal training sessions, and informed verbal consent was obtained from all participants. The PERCEPT-PREVENT answers were recorded in an electronic database, and each patient received a code number to secure anonymization. Sociodemographic data including age, gender, educational level, and monthly income were registered.

Sample Size Calculation and Statistical Analysis

The primary endpoint of the study, used for sample size calculation, was the perceived risk of colonoscopy complications. Considering previously reported complication rate perception of 38% for never-screened and 19% for screened individuals [9], we calculated that 85 participants in each group were needed to demonstrate a 19% difference between groups, with a 95% confidence interval (CI), an error of 0.05, and a power of 80%.

Statistical Package for Social Sciences (SPSS) program version 28 (IBM Corporation, Armonk, NY) was used. Categorical variables are summarized as frequencies and percentages. As appropriate, the χ^2 test or Fisher's exact test was used to compare categorical variables. Normal distribution was examined using histogram visual inspection. Continuous variables were expressed in means and standard deviation (variables with normal distribution) or median and interquartile range (variables with skewed distributions). The independent samples *t* test or independent samples Mann-Whitney U test were used to compare two groups. Spearman's correlation coefficient was used to evaluate the correlation between complication risk perception scores. To assess the impact of risk perception on screening uptake (intention to undergo CRC screening, preferred method of CRC screening, and willingness to undergo UGIE combined with a screening colonoscopy), the domains of the PERCEPT-PREVENT tool targeting perception of colonoscopy and UGIE complications were evaluated. All reported *p* values are two-tailed, with a *p* value <0.050 indicating statistical significance.

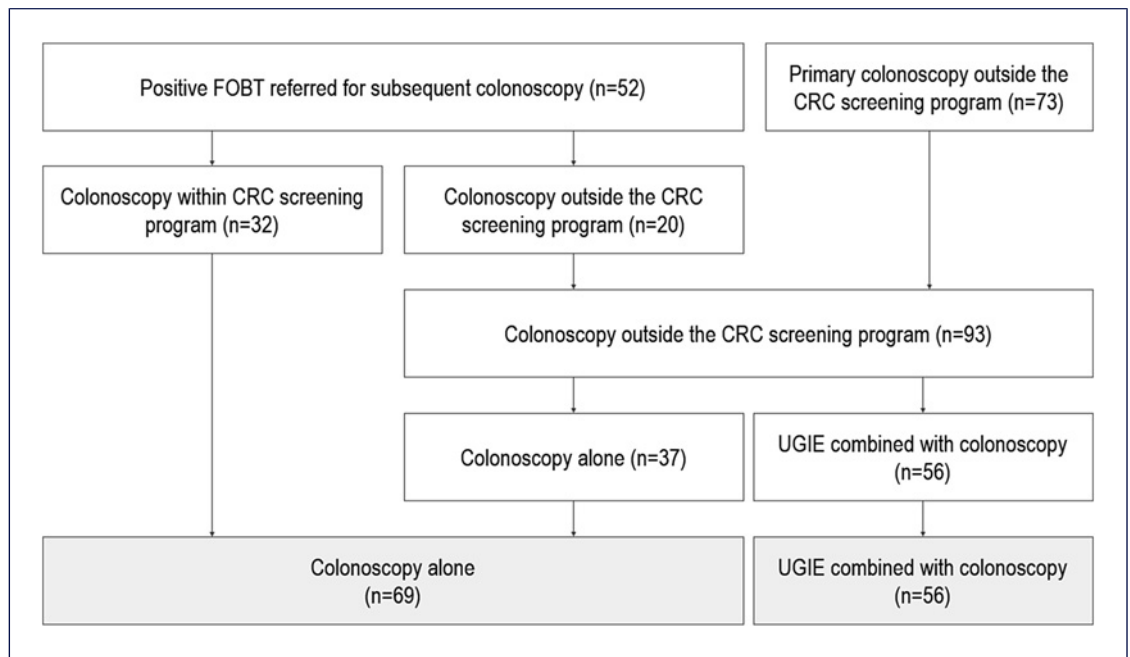


Fig. 2. CRC and GC endoscopic screening. CRC, colorectal cancer; FOBT, fecal occult blood test; UGIE, upper gastrointestinal endoscopy.

Results

Study Population and Recruitment Procedures

A total of 552 individuals were contacted for telephonic interviews. Of these, 137 met exclusion criteria, 110 were unreachable, and 88 refused to participate in the telephone interviews, regardless of their screening status (Fig. 1). A total of 217 healthy participants were included, comprising 92 never-screened individuals and 125 who had already undergone endoscopic screening. Among screened participants, 32 (26%) underwent colonoscopy within the organized CRC screening program and the remaining 93 (74%) were screened in private endoscopy units. Previous screening through FIT and/or colonoscopy was reported in 13.6% ($n = 17$). Accordingly, none of the individuals in the never-screened group reported previous screening. Concerning screened respondents, most were submitted to UGIE combined with a screening colonoscopy (60%; $n = 56$) (Fig. 2).

The mean age was 55 ± 7 years, and 56% ($n = 122$) were female. Regarding sociodemographic features, 57% ($n = 121$) were married, 53% ($n = 112$) had a basic educational level (sub-high school educational attainment), and 29% ($n = 62$) had health insurance. Data on sociodemographic characteristics and attitudes toward digestive cancer screening are shown in Table 1.

Risk Perception of Endoscopy-Related Complications

Overall, knowledge of complications was low: 61% ($n = 133$) and 83% ($n = 181$) of the individuals did not know (did not name) any possible complication for colonoscopy and UGIE, respectively. In detail, among participants who reported knowledge of at least one possible complication (colonoscopy: $n = 84$; UGIE: $n = 36$), perforation and bleeding were the most commonly identified complications (colonoscopy: 96% and 41%, respectively; UGIE: 97% and 36%, respectively).

Never-screened individuals less frequently reported a high complication risk perception, both for colonoscopy (19% vs. 45%; $p < 0.001$) and UGIE (14% vs. 41%; $p < 0.001$). There was a strong positive correlation between the perceived complication risk for colonoscopy and UGIE ($r = 0.68$; $p < 0.001$).

Irrespective of previously reported knowledge on colonoscopy and UGIE complications, participants were subsequently presented with a detailed list of complications and instructed to identify which, in their perspective, were possible complications of a screening colonoscopy and UGIE (Table 2). A higher rate of affirmative answers was obtained for perforation (colonoscopy: 96%, $n = 185$; UGIE: 94%, $n = 175$), bleeding (colonoscopy: 84%, $n = 147$; UGIE: 79%, $n = 132$), and infection (colonoscopy: 63%, $n = 100$; UGIE: 56%, $n = 84$). There were no significant differences across groups,

Table 1. Sociodemographic characteristics and attitudes towards digestive cancer screening ($n = 217$)

Female, n (%)	122 (56)
Age, mean (SD)	55 (7)
Married, n (%)	121 (57)
Basic educational level, n (%)	112 (53)
Active worker, n (%)	141 (67)
Intermediate monthly income (EUR 500–1,000), n (%)	22 (43)
Regular follow-up with primary care physician, n (%)	212 (98)
Health insurance, n (%)	62 (29)
Informed on CRC screening tests from any means of communication, n (%)	141 (65)
CRC in second-degree relatives or acquaintances, n (%)	63 (29)
Second-degree relatives with CRC, n (%)	32 (15)
Intention to undergo CRC screening, n (%)	210 (97)
Preferred primary method of CRC screening, n (%)	
FOBT	49 (23)
Colonoscopy	161 (77)
Informed on GC screening tests from any means of communication, n (%)	100 (47)
GC in second-degree relatives or acquaintances, n (%)	52 (24)
Second-degree relatives with GC, n (%)	26 (12)
Willing to undergo UGIE for GC screening combined with a screening colonoscopy, n (%)	206 (95)

CRC, colorectal cancer; GC, gastric cancer; SD, standard deviation.

except for the higher perceived risk of allergy to drugs administered during the procedure among endoscopically screened respondents (colonoscopy: 71% vs. 45%, $p = 0.005$; UGIE: 62% vs. 40%, $p = 0.016$) and higher perceived risk of infection in never-screened participants (colonoscopy: 79% vs. 56%, $p = 0.005$; UGIE: 67% vs. 50%, $p = 0.045$). Death was acknowledged as a possible adverse outcome of colonoscopy by 65% ($n = 98$) and of UGIE by 60% ($n = 96$).

For both colonoscopy (90%; $n = 194$) and UGIE (97%; $n = 211$), most participants did not know any factor that increases the risk of endoscopy-related complications (Table 3). Among the 22 participants (10%) who reported knowledge of risk factors for colonoscopy complications, 86% ($n = 19$) identified inadequate bowel preparation, while 18% ($n = 4$) mentioned anticoagulants, antiplatelets, or bleeding disorders. Only 6 participants (3%) reported knowledge of risk factors for UGIE complications, and 3 of these specified inadequate fasting.

Impact of the Perceived Risk of Endoscopy-Related Complications on Screening Uptake

Concerning CRC screening, complication risk perception and complication knowledge did not impact either intention to adhere or the preference for any screening method (online

suppl. Table 1). However, a lower risk perception for UGIE complications was significantly associated with a higher willingness to undergo an UGIE combined with a screening colonoscopy (OR: 2.25, 95% CI: 1.29–3.92).

Among participants already submitted to endoscopic screening, those submitted to combined screening reported less frequently a high complication risk perception for both colonoscopy (27% vs. 61%; $p < 0.001$) and UGIE (28% vs. 54%; $p = 0.006$) when compared with individuals submitted to colonoscopy alone (online suppl. Table 2). Additionally, in this subset of individuals, a significantly higher proportion of participants reported knowledge of at least two possible colonoscopy complications (45% vs. 26%; $p = 0.030$). Awareness of complications was also higher in the combined screening group (colonoscopy: 14 ± 5 vs. 11 ± 4 , $p < 0.001$; UGIE: 11 ± 4 vs. 9 ± 3 , $p < 0.001$). In the latter, bleeding (colonoscopy: 91% vs. 70%, $p = 0.005$; UGIE: 88% vs. 66%, $p = 0.008$), infection (colonoscopy: 78% vs. 35%, $p < 0.001$; UGIE: 76% vs. 21%, $p < 0.001$), and cardiorespiratory complications (colonoscopy: 73% vs. 43%, $p < 0.017$; UGIE: 64% vs. 22%, $p < 0.001$) were correctly identified in a significantly higher rate. Likewise, death was more frequently considered as a potential adverse outcome of colonoscopy (84% vs. 50%; $p < 0.001$) and of UGIE (75% vs. 47%; $p = 0.003$).

Table 2. Awareness of possible complications during endoscopic screening procedures

	Total (N = 217)	Never-screened (N = 92)	Endoscopically screened (N = 125)	p value
<i>Colonoscopy</i>				
Awareness of possible complications during a colonoscopy (0–26) ^a , mean (SD)	13 (4)	14 (4)	13 (5)	0.089
Abdominal pain, n (%)	52 (33)	12 (28)	40 (35)	0.375
Fever, n (%)	9 (6)	1 (3)	8 (8)	0.335
Nausea and/or vomiting, n (%)	46 (32)	13 (38)	33 (30)	0.368
Headache and/or dizziness, n (%)	25 (18)	5 (19)	20 (18)	0.920
Perforation, n (%)	185 (96)	69 (96)	116 (96)	0.991
Bleeding, n (%)	147 (84)	53 (90)	94 (80)	0.109
Infection, n (%)	100 (63)	38 (79)	62 (56)	0.005
Injury in other organs (e.g., spleen rupture), n (%)	2 (4)	0 (0)	5 (5)	1.000
Acute appendicitis, n (%)	1 (3)	1 (14)	0 (0)	0.200
Acute diverticulitis, n (%)	1 (3)	1 (14)	0 (0)	0.219
Cardiorespiratory complications ^b , n (%)	60 (58)	18 (49)	42 (64)	0.139
Allergy to drugs administered during the procedure, n (%)	75 (63)	18 (45)	57 (71)	0.005
Death, n (%)	98 (65)	30 (63)	68 (67)	0.617
<i>UGIE</i>				
Awareness of possible complications during a UGIE (0–20) ^a , mean (SD)	10 (4)	10 (4)	10 (4)	0.480
Abdominal pain, n (%)	38 (25)	6 (15)	32 (29)	0.079
Fever, n (%)	7 (5)	2 (6)	5 (5)	0.730
Nausea and/or vomiting, n (%)	57 (39)	13 (35)	44 (40)	0.573
Headache and/or dizziness, n (%)	31 (22)	6 (18)	25 (24)	0.453
Perforation, n (%)	175 (94)	68 (93)	107 (95)	0.664
Bleeding, n (%)	132 (79)	48 (83)	84 (77)	0.389
Infection, n (%)	84 (56)	33 (67)	51 (50)	0.045
Cardiorespiratory complications ^b , n (%)	50 (47)	16 (42)	34 (50)	0.435
Allergy to drugs administered during the procedure, n (%)	65 (54)	17 (40)	48 (62)	0.016
Death, n (%)	96 (60)	29 (58)	67 (61)	0.728

SD, standard deviation; UGIE, upper gastrointestinal endoscopy. ^aCalculated by summing the score for each possible complication ("yes": 2 points; "do not know": 1 point; "no": 0 points). ^bIncludes acute myocardial infarction, thrombosis, stroke, and arrhythmia.

Discussion

Individuals who had never undergone screening had a lower perception of the risk of complications from a screening colonoscopy and UGIE. Overall, the knowledge of complications and their risk factors was low. Bleeding and perforation were the most commonly recognized complications for both colonoscopy and UGIE. A lower perceived risk of UGIE complications was significantly associated with a higher willingness to undergo UGIE combined with a screening colonoscopy. Moreover, among respondents who have already undergone endoscopic screening, those who underwent combined screening reported a lower complication risk perception, along with a heightened awareness of potential complications.

Complication risk perception has been scarcely characterized in Western countries, with research primarily focusing on complications associated with colonoscopy [9, 13]. A US cross-sectional study, targeting patients scheduled for a screening colonoscopy, evaluated patient's understanding of the procedure's benefits, risks, and alternatives [14]. A total of 48% described at least one risk of the procedure, and only 3% described the minimal required elements for informed consent. King-Marshall et al. [15] conducted a study evaluating patient and caregiver understanding of the colonoscopy procedure and confirmed that 27% of patients provided an incorrect or vague definition of colonoscopy and only 2% provided a definition that correctly detailed the procedure characteristics and purpose. The notably low knowledge of complications associated with endoscopic screening

Table 3. Perceived risk of endoscopy-related complications

	Total (N = 217)	Never-screened (N = 92)	Endoscopically screened (N = 125)	p value
<i>Colonoscopy</i>				
Perceived complication risk, median (IQR)	1 (1–3)	1 (1–2)	1 (1–3)	0.034
High risk ^a , n (%)	68 (34)	16 (19)	52 (45)	<0.001
Did not know any complication, n (%)	133 (61)	89 (97)	44 (35)	<0.001
Complication knowledge score (1–7), median (IQR)	2 (1–2)	1 (1–1)	2 (1–2)	0.129
Complication knowledge score ≥2, n (%)	43 (20)	0 (0)	43 (34)	<0.001
Did not know any risk factor, n (%)	194 (90)	91 (99)	103 (83)	<0.001
Risk factor knowledge score (1–12), median (IQR)	1 (1–2)	1 (1–1)	1 (1–2)	0.727
Risk factor knowledge score ≥2, n (%)	6 (3)	0 (0)	6 (5)	0.032
<i>UGIE</i>				
Perceived complication risk, median (IQR)	1 (1–3)	1 (1–1)	1 (1–3)	0.016
High risk ^b , n (%)	56 (29)	12 (14)	44 (41)	<0.001
Did not know any complication, n (%)	181 (83)	92 (100)	89 (71)	<0.001
Complication knowledge score (1–7), median (IQR)	2 (1–2)		2 (1–2)	
Complication knowledge score ≥2, n (%)	21 (10)	0 (0)	21 (17)	<0.001
Did not know any risk factor, n (%)	211 (97)	91 (99)	120 (96)	0.196
Risk factor knowledge score (1–12), median (IQR)	1 (1–2)		1 (1–2)	
Risk factor knowledge score ≥2, n (%)	1 (1)	0 (0)	1 (1)	0.579

IQR, interquartile range; SD, standard deviation; UGIE, upper gastrointestinal endoscopy. ^aAnswered “agree” or “strongly agree” to “Colonoscopy may be harmful to the body (e.g., bowel perforation)”. ^bAnswered “agree” or “strongly agree” to “UGIE may be harmful to the body”.

procedures, as identified in our sample, reinforces the need for additional efforts to increase health literacy in the general population. It is essential to strengthen the interaction between individuals scheduled for endoscopic screening procedures, their close relatives, and healthcare professionals, particularly primary care physicians, gastroenterologists, and nurses. This increased engagement is pivotal to ensuring thorough communication regarding the potential complications associated with these procedures. By fostering a more robust dialogue, healthcare professionals can provide a comprehensive explanation of the associated risks and benefits, thereby promoting informed decision-making and addressing any concerns raised by patients or their relatives.

A prospective US study evaluated risk perception facing the scenario of unwillingness to undergo a screening colonoscopy due to fear of suffering a complication and reported a higher perceived risk of complications from colonoscopy in never-screened respondents (38%) as opposed to in previously screened participants (19%) [9]. In Germany, where the CRC screening program has offered colonoscopy as primary

screening method since 2002 [16], a cross-sectional study concluded that concerns about colonoscopy were independent predictors of compliance with screening recommendations [17]. In the latter study, 36% (95% CI: 28.1–44.3) of the non-screened versus 7.8% (95% CI: 2.6–13.0) of the screened group reported to be afraid of complications caused by colonoscopy [17]. In contrast, our results show that never-screened participants have a lower perceived risk of colonoscopy complications and suggest that the perceived risk of complications may not be a determining factor for CRC screening uptake. Nonetheless, the observed difference in complication risk perception may be explained by the fact that individuals who had previously undergone endoscopic screening were instructed to read the informed consent form prior to the endoscopic procedure and received clarification regarding the potential complications. Never-screened participants were not exposed to the informed consent process that is required prior to endoscopic screening. However, exposure to health literacy campaigns, discussions of endoscopic procedures during primary care appointments, or

contact with relatives or acquaintances who had undergone such procedures may have influenced their perception of the risk of complications. However, even among respondents who underwent colonoscopy and had previously been exposed to informed consent, knowledge of complications and their risk factors was suboptimal. Improving risk perception and knowledge of complications associated with endoscopic screening procedures presents an opportunity to boost adherence rates and reduce the burden of medicolegal litigation.

A systematic review on barriers and facilitators to GC screening, including mostly Eastern studies, concluded that fear of the screening procedure was the most commonly reported barrier [18]. Fear of undergoing UGIE was pointed out as the reason for nonadherence by 38.1% of participants in a cross-sectional Chinese study and by 8.4% in the Korean National Cancer Screening Survey [19–21]. As previously reported, a lower perception of the negative health consequences of UGIE was independently associated with a higher intention to undergo combined screening [22]. Our results reinforce the impact of complication risk perception in the acceptance of combined screening.

To our knowledge, this is the first European study to simultaneously measure the risk perception of endoscopic-related complications for both colonoscopy and UGIE in a screening setting. Utilization of the previously validated PERCEPT-PREVENT tool enabled an objective assessment of risk perception [12].

Our study presents some limitations. The presented results rely on measures susceptible to bias, including selective memory, social desirability, or attribution bias. Notably, respondents who underwent endoscopic screening procedures were recently informed about the potential complications, which may explain the higher knowledge scores obtained. The impact of complication risk perception in CRC screening uptake may have been underestimated since individuals who tested negative for FOBT, as well as FOBT-positive individuals who either declined screening colonoscopy or were waiting for its scheduling, were excluded. Details on colonoscopy completeness (including reasons for incomplete procedures), the number of previous endoscopic procedures, and any history of colonoscopy-related complications, which could affect the perception of complication risk, were not retrieved. Furthermore, the survey primarily was conducted regionally rather than nationally.

Further prospective, nationwide studies are necessary to confirm our findings, especially through the application of the survey before and after an educational program. Measuring the perceived risk of complications could extend beyond the screening context to other therapeutic endoscopic procedures, with the adaptation of the PERCEPT-PREVENT tool for high-risk procedures offering valuable

insights, particularly regarding medicolegal concerns. Moreover, educational campaigns focused on complication risk perception should be integrated at the primary care level and disseminated through social media and other communication platforms. Having primary care physicians initiate the informed consent process by explaining the procedure, along with establishing direct communication channels for patients to connect with healthcare providers at endoscopy units to address specific concerns, could further enhance their understanding of the associated risks.

Acknowledgments

Gastroenterology nurses Cláudia Rocha and Cátia Ribeiro conducted the telephone interviews.

Statement of Ethics

This study protocol was reviewed and approved by the Ethical Committees of the 3 institutions involved in the study, namely, *Administração Regional de Saúde do Norte (ARSN)*, *Unidade Local de Saúde Gaia Espinho*, and *Instituto Português de Oncologia do Porto*. Since the regional CRC screening program is performed and operationalized by ARSN, this organization provided random telephonic contacts of participants, after Data Protection Committee's approval. The questionnaire was applied through telephonic interview, and informed verbal consent was obtained from all participants after explanation of aims of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mário Dinis-Ribeiro, Diogo Libânio, and João Carlos Silva designed the study. João Carlos Silva and Diogo Libânio performed the research and analyzed the data. Fernando Tavares, Mário Dinis-Ribeiro, and Diogo Libânio revised the paper for critically important intellectual content.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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Chapter VI – Real-world data on the impact of digestive cancer screening

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1. An organized fecal immunochemical test-based screening program affects colorectal cancer early diagnosis and survival in the short term

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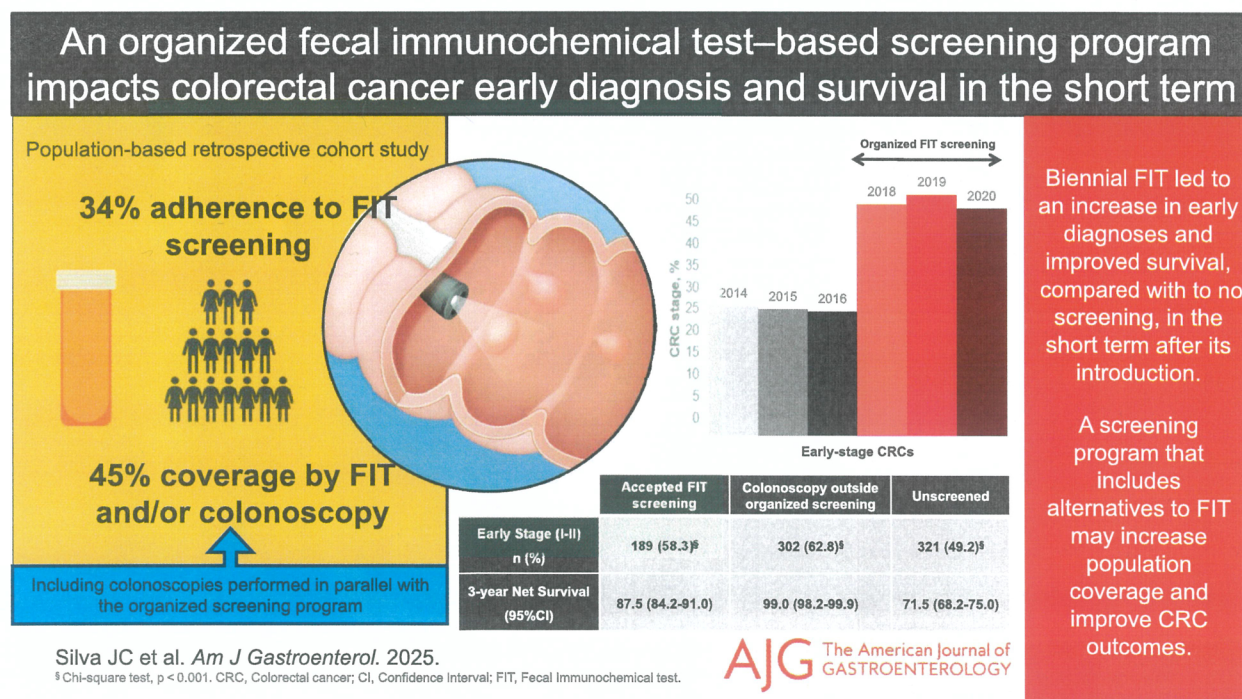
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An Organized Fecal Immunochemical Test–Based Screening Program Affects Colorectal Cancer Early Diagnosis and Survival in the Short Term

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INTRODUCTION: In 2018, a biennial fecal immunochemical test (FIT) screening program for colorectal cancer (CRC) was introduced in northern Portugal, targeting 1.1 million residents aged 50–74 years. The aim of this study was to evaluate trends in CRC incidence, early diagnosis, and survival before and after the program's implementation.

METHODS: This was a population-based retrospective cohort study in northern Portugal. Data on CRC cases diagnosed between 2014 and 2020 were retrieved from the Portuguese National Cancer Registry. Early diagnosis was defined as stage I/II tumors. Net survival estimates for 2014–2016 vs 2018–2020 were compared. Data from Portuguese National Cancer Registry were linked to the FIT-based screening program of the Northern Portugal Regional Health Administration for the years 2018–2020 to assess screening outcomes.



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RESULTS: Between 2018 and 2020, the first 3 years of the program, 482,938 invitations for FIT screening were sent, resulting in an adherence rate of 34.4% (165,895). The negative predictive value of FIT was 99.95% (95% CI: 99.94–99.96). Overall, coverage by FIT and/or colonoscopy was 44.9%. The proportion of early cancers was significantly higher among individuals who accepted FIT screening (58.3%) or underwent colonoscopy (62.8%) compared with unscreened individuals (49.2%) ($P < 0.001$). Net survival rates at 1 year and 3 years were significantly higher among individuals who accepted FIT screening or underwent colonoscopy compared with those who remained unscreened ($P < 0.001$).

DISCUSSION: Biennial FIT led to an increase in early diagnoses and improved survival, compared with no screening, in the short term after its introduction. A screening program that includes alternatives to FIT may increase population coverage and improve CRC outcomes.

KEYWORDS: colorectal cancer; cancer screening; early detection of cancer; gastrointestinal endoscopy; preventive medicine

ABBREVIATIONS: APC, annual percentage change; ARSN, Northern Portugal Regional Health Administration; CEU, contracted endoscopy units; CRC, colorectal cancer; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; NHS, National Health Service; RON, National Cancer Registry of Portugal

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/D796>; <http://links.lww.com/AJG/D797>

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related mortality, with the burden expected to rise (1,2). Several methods for CRC screening have been described, including colonoscopy, sigmoidoscopy, multitarget stool DNA test, CT colonography, capsule endoscopy, guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and blood-based tests (3–5). Most studies comparing the impact of different screening methods on CRC incidence and mortality primarily focused on sigmoidoscopy or gFOBT (4,6). There are limited data on the long-term effects of FIT and colonoscopy on CRC outcomes (7,8).

Implementation of screening initiatives has positively affected CRC early detection and mortality rates, with the largest decreases in mortality rates seen in countries with longstanding screening programs and higher screening uptake (9–11). In Europe, most countries have implemented organized invitational screening programs based on gFOBT (12–14). By contrast, colonoscopy screening is offered as the primary screening method in Poland (5,13). European recommendations endorse organized populational FOBT-based programs targeting average-risk individuals aged between 50 and 75 years (15). Yet, it is stated that depending on local factors, namely adherence rates and availability of colonoscopy, primary screening by colonoscopy or sigmoidoscopy, is also acceptable (15). The aim of this study was to analyze trends in CRC incidence, early diagnosis, and survival before and after the implementation of the FIT-based screening program.

METHODS

Study design and participants

This population-based retrospective cohort study was conducted in northern Portugal to evaluate CRC incidence, early diagnosis, and survival before and after the implementation of a FIT-based screening program (detailed in Supplementary Appendix 1, <http://links.lww.com/AJG/D797>). Individuals who had undergone endoscopic procedures (colonoscopy within the 10 years

or sigmoidoscopy within the 5 years preceding the year under analysis), as well as those under surveillance for familial syndromes or inflammatory bowel disease, were excluded from the organized FIT-based screening program. Two periods were then compared—the initial period comprised the 3 years (2014–2016) that preceded the screening program start, whereas the subsequent period included the first 3 years of the program (2018–2020). It was decided to exclude the period between January 1 and December 31, 2017, during which pilot programs took place (16).

The study protocol was approved by the ethics committees of the participating institutions, including the Northern Portugal Regional Health Administration (ARSN) and the Portuguese National Cancer Registry (RON). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology, guidelines for reporting observational studies were used (17).

Data retrieval

Data were obtained from 2 independent sources: the RON and the ARSN databases. The RON database provided information on CRC cases in northern Portugal. The date of cancer diagnosis was determined by the first histological confirmation. CRC cases were first recoded from the International Classification of Diseases ICD-O-3 to ICD-10 (18), considering the following cancer sites: C18 (Malignant neoplasm of colon), C19 (Malignant neoplasm of rectosigmoid junction), and C20 (Malignant neoplasm of rectum). Only malignant invasive cases were analyzed. Subsites for the anatomical location of CRC were not studied.

Comprehensive data on FIT participation and results were obtained from ARSN CRC screening database. Individuals registered in the database as meeting the exclusion criteria for the population-based FIT screening program (e.g., colonoscopy within the 10 years before the year under analysis) were not included in the analysis. Individuals with inconclusive FIT results

who did not undergo a subsequent test for clarification were analyzed together with positive FIT cases. Individuals who received an invitation but did not complete the test, as well as those whose FIT was conducted more than 2 years ago, were collectively analyzed as “nonupdated FIT participants.”

Within the Portuguese National Health System (NHS), individuals could access CRC screening either through the organized FIT-based program or through physician-initiated colonoscopy referrals (Supplementary Appendix 1, <http://links.lww.com/AJG/D797>). Thus, data on colonoscopies conducted at contracted endoscopy units (CEU) outside NHS facilities, beyond the scope of the organized screening program, were collected. As determining the indication for each colonoscopy was not feasible, all procedures were included, extending beyond those performed solely for screening purposes. This Supplementary Data were obtained by identifying primary care physicians’ prescriptions for sedated colonoscopies issued for CEU from 2018 to 2020, using each individual’s NHS identification number.

We linked data from RON with the initial 3 years of the organized ARSN FIT-based screening program using the Portuguese NHS identification number. Although the analysis primarily focuses on outcomes from the initial 3 years of screening (2018–2020), we extended the observation period to include diagnoses recorded in the RON through the end of 2023, ensuring adequate follow-up. Data on FIT participation and

results were cross-referenced with records of colonoscopy uptake occurring during the study period (2018–2020). Cancer cases were classified based on the year of the FIT result, considering a 2-year time frame for diagnosis. The colonoscopy setting was further analyzed for FIT-positive participants (NHS hospital or CEU). In addition, FIT-negative patients who underwent colonoscopy, as well as those who declined FIT screening but had colonoscopy at CEU, were identified.

To assess the impact of the implemented screening program (2018–2020) on early detection and survival, 3 groups were compared: (a) individuals who participated in the FIT screening program [a1. those with a negative FIT result; a2. those with a positive FIT result who underwent colonoscopy; a3. those with a positive FIT result who declined colonoscopy], (b) individuals who underwent colonoscopy outside the organized screening program, and (c) unscreened individuals, defined as those with no record of either a FIT within the past 2 years as part of the organized screening program or a colonoscopy performed at an NHS-contracted endoscopy unit. Figures 1 and 2 provide a detailed overview of the study design and the CRC screening program implemented in northern Portugal.

Incidence and mortality

Data on CRC incidence were retrieved from RON, and mortality data were obtained from Statistics Portugal for the periods

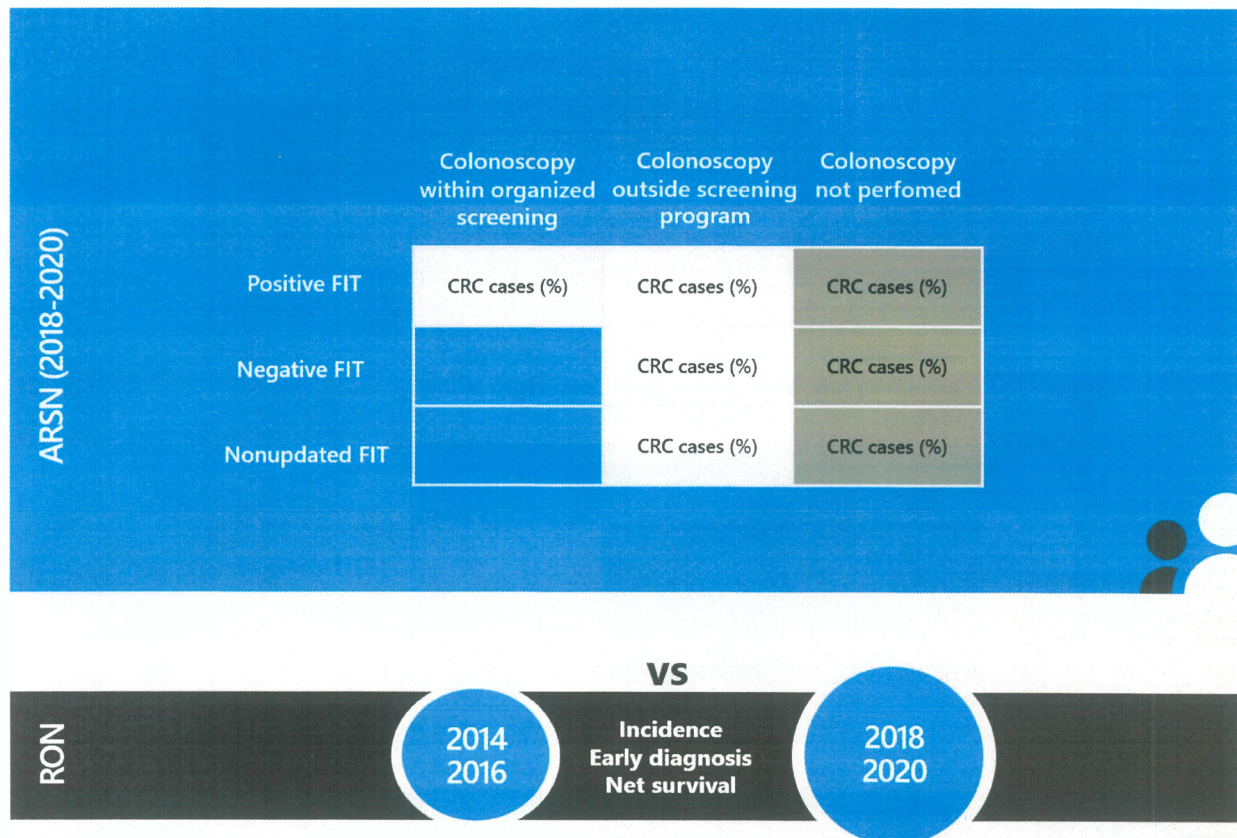


Figure 1. Study design. ARSN, Northern Portugal Regional Health Administration; CRC, colorectal cancer; FIT, fecal immunochemical test; RON, National Cancer Registry of Portugal.

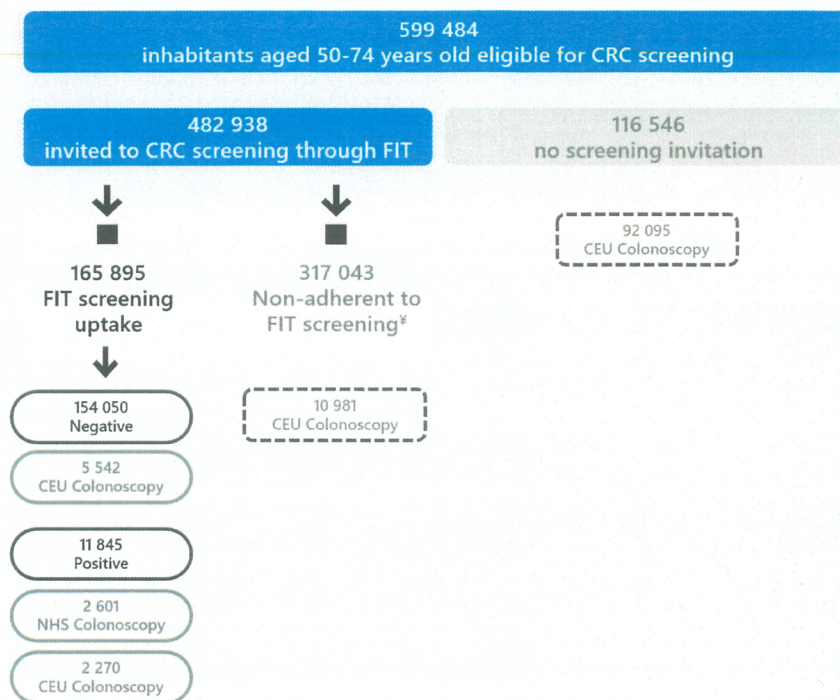


Figure 2. Colorectal cancer screening uptake in 2018–2020. * Includes individuals who received an invitation but did not complete the test and those whose FIT was conducted >2 years. CEU, contracted endoscopy units; CRC, colorectal cancer; FIT, fecal immunochemical test; NHS, National Health System.

2014–2016 and 2018–2020. Age-standardized incidence and mortality rates were computed for 5-year age groups and per calendar period. The number of person-years at risk was calculated as the total amount of individual times at risk during the period of observation. Age-standardized incidence and mortality rates were calculated by the direct method, using the 2013 European standard population, and were expressed per 100,000 person-years (19).

Staging

Cancer cases were classified according to the pathological and clinical TNM Classification of Malignant Tumors at the time of diagnosis and divided according to tumor staging (I–IV). Early stage was defined as stage I–II, whereas advanced stage was defined as stage III–IV. Comparison between proportions of TNM staging groups (I–II, III–IV) was made using Pearson χ^2 with confidence intervals (CIs) for proportions differences (20).

Survival

Given that cancer cases were collected from population-based cancer registries, data on the cause of death were lacking. To overcome this limitation, net survival rates were estimated using the Pohar-Perme estimator (21). Comparisons of 1-year and 3-year net survival rates were made between the 2 study periods. R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org) was used.

RESULTS

Coverage by FIT and/or colonoscopy

Over the first 3 years of the screening program, 482,938 invitations for FIT screening were sent, resulting in a 34.4%

adherence rate (165,895 individuals) (Figure 2). Among the 317,043 individuals with nonupdated FIT, including 316,910 who received an invitation but did not complete the test and 133 whose last FIT was performed more than 2 years earlier, 10,981 (3.5%) underwent colonoscopy outside the organized screening program.

Furthermore, among the 116,546 individuals who underwent endoscopic procedures at CEU during the study period and who were neither invited to FIT screening nor registered as meeting exclusion criteria in the screening program database, 92,095 (79.0%) underwent colonoscopy (alone or combined with UGIE), whereas the remaining 24,451 (21.0%) underwent UGIE alone.” In our analysis, the latter were categorized as “no screening invitation.” However, this classification does not imply that these individuals represent the entire population of eligible participants who may have been unintentionally omitted from the organized screening program in northern Portugal nor should this proportion be interpreted as an estimate of adherence.

Accounting for endoscopic procedures conducted outside the organized screening program, the overall coverage by FIT and/or colonoscopy was 44.9% (compared with 34.4% adherence to the FIT-based screening program). This represents an absolute increase in coverage of 10.5% (Absolute Risk Difference 10.5%; 95% CI: 10.3%–10.7%) relative to FIT screening alone.

Colonoscopy uptake among FIT-positive individuals

Among the 11,845 individuals who tested positive for FIT, 2,601 (22.0%) accepted a follow-up colonoscopy at an NHS hospital. Including follow-up colonoscopies performed at CEU, the overall acceptance rate reaches 41.1% ($n = 4,871$). The acceptance rate

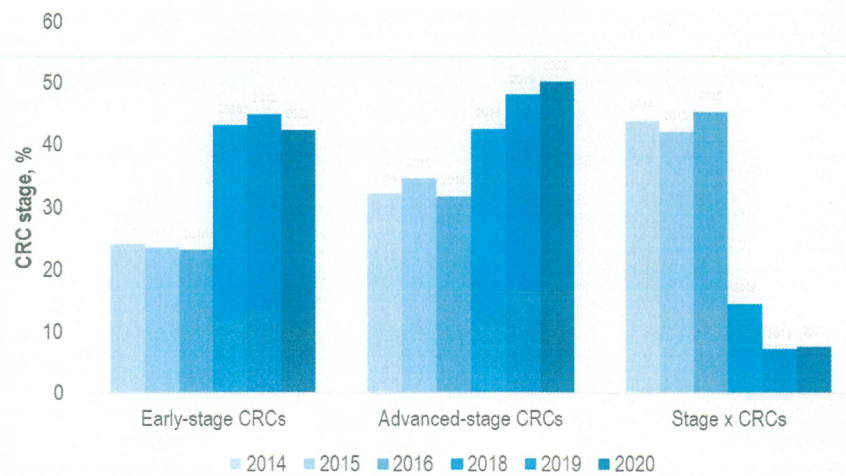


Figure 3. Proportion of early-stage and advanced-stage colorectal cancers within all colorectal cancer cases by calendar year. CRC, colorectal cancer; Stage x, tumor stage cannot be assessed.

was 59.3% in 2018 and 55.4% in 2019 but dropped to 20.7% in 2020 (Supplementary Table 1, <http://links.lww.com/AJG/D797>).

Incidence and mortality rates

CRC incidence decreased by 36.2%, from 85.0 per 100,000 in 2014 to 54.2 per 100,000 in 2020 (Supplementary Figure 1a, <http://links.lww.com/AJG/D796>). CRC incidence declined by 9.6% after the implementation of the screening program (from 83.5 per 100,000 in 2016 to 75.5 per 100,000 in 2018). During the period from 2014 to 2016, the annual percentage change (APC) was -0.9% (95% CI: -3.9 to 2.3). By contrast, from 2018 to 2020, the APC was -15.4% (95% CI: -18.5 to -12.1).

The mortality rate declined by 9.8%, from 29.6 deaths per 100,000 in 2014 to 26.7 deaths per 100,000 in 2020 (Supplementary Figure 1b, <http://links.lww.com/AJG/D796>). The APC was -0.3% per year (95% CI: -6.8 to 6.6) from 2014 to 2016. By contrast, from 2018 to 2020, the APC was -4.4% per year (95% CI: -7.7 to -1.0).

Early-stage (I/II) CRC

The proportion of early-stage (I/II) CRC diagnoses has increased over time (Figure 3). Between 2014 and 2020, the proportion of early-stage CRC cases increased by 18.1% (95% CI: 15.6 to 20.7).

Notably, after the implementation of organized screening (2018–2020), there was a significant rise in early-stage detection, with an increase of 19.9% (95% CI: 18.5 to 21.3) compared with the prescreening period (2014–2016). To account for the potential confounding effect of unassessed tumor stage (Tx) cases, a sensitivity analysis was performed including only cases with known T stage. Among these, the proportion of early-stage (I/II) diagnoses increased from 41.8% in 2014–2016 to 48.3% in 2018–2020, corresponding to an absolute increase of 6.5% (95% CI: 4.7–8.3; $P < 0.001$).

Net survival rates

Overall, 1-year and 3-year net survival rates showed no significant change between the 2 periods. The 1-year net survival was 82.0% (95% CI: 81.2–82.8) for 2014–2016 and 82.9% (95% CI: 82.0–83.7) for 2018–2020. Similarly, the 3-year net survival was 67.0% (95% CI: 66.0–67.9) for 2014–2016 and 67.7% (95% CI: 66.7–68.8) for 2018–2020.

Impact of FIT-based screening on early detection and survival

Overall, 165,895 individuals participated in FIT screening, 103,076 underwent colonoscopy outside the organized screening program, and 330,513 remained unscreened (Table 1; Figure 2). The detection of early-stage CRC (stage I–II) at diagnosis was

Table 1. Colorectal cancer cases according to the screening status in the period 2018–2020

	Total			Colonoscopy within organized screening			Colonoscopy outside screening program			Colonoscopy not performed ^a		
	CRC cases	Total	%	CRC cases	Total	%	CRC cases	Total	%	CRC cases	Total	%
Positive FIT ^b , n (%)	292	11,845	2.47	80	2,601	3.08	59	2,270	2.60	153	6,974	2.19
Negative FIT, n (%)	75	154,050	0.05				20	5,542	0.36	55	148,508	0.04
Non-updated FIT ^c , n (%)	899	317,043	0.28				116	10,981	1.06	783	306,062	0.26
Not invited, n (%)	498	116,546	0.43				457	92,095	0.50	41	24,451	0.17

CRC, colorectal cancer; FIT, fecal immunochemical test; NHS, National Health System.

^aNo records of NHS-funded colonoscopies during the study period (2018–2020), either in NHS hospitals or contracted endoscopy units.

^bBoth positive and inconclusive FIT results were analyzed together.

^cIncludes individuals who received an invitation but did not complete the test and those whose FIT was conducted >2 yr.

Table 2. Tumor stage according to previous exposure to CRC detection tests (2018–2020)

	Early stage (I–II)	Advanced stage (III–IV)
Accepted FIT screening CRC cases (% of total)	189 (58.3)	135 (41.7)
Colonoscopy outside organized screening CRC cases (% of total)	302 (62.8)	179 (37.2)
Unscreened CRC cases (% of total)	321 (49.2)	332 (50.8)
Overall CRC cases (% of total)	812 (55.7)	646 (44.3)

CRC, colorectal cancer; FIT, fecal immunochemical test.

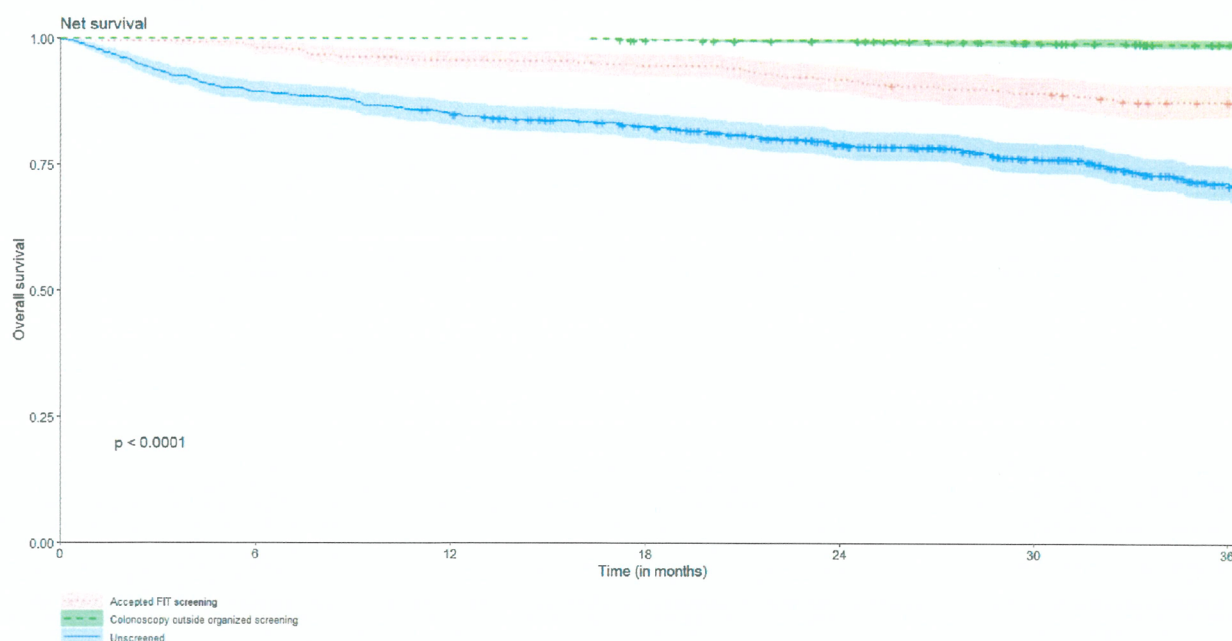
significantly associated with previous exposure to CRC detection tests ($P < 0.001$). Early-stage detection was highest among individuals who underwent colonoscopy outside the organized screening program (62.8%; $n = 302$), followed by those who accepted FIT screening (58.3%; $n = 189$), and lowest among unscreened individuals (49.2%; $n = 321$). The difference in early-stage detection between those who underwent colonoscopy without previous FIT and those who remained unscreened was 13.6% (95% CI: 5.9–21.3), whereas the difference between those who underwent FIT screening and those who remained unscreened was 9.1% (95% CI: 0.2–18.0). Table 2 details the distribution of tumor stage according to previous exposure to CRC detection tests.

Net survival was significantly higher among individuals who participated in FIT screening or underwent colonoscopy outside the organized screening program compared with those who remained unscreened (Figure 4). Among unscreened individuals, 1-year net survival was 85.2% (95% CI: 82.8–87.7), and 3-

year net survival was 71.5% (95% CI: 68.2–75.0), both significantly lower than the net survival rates observed in individuals who accepted FIT screening (1-year net survival: 95.7%; 95% CI: 93.6–97.8; 3-year net survival: 87.5%; 95% CI: 84.2–91.0). Survival rates were highest among those who underwent colonoscopy outside the organized screening program, with 1-year net survival at 100% and 3-year net survival at 99.0% (95% CI: 98.2–99.9).

FIT diagnostic accuracy

CRC was diagnosed in 2.47% (292 out of 11,845) of FIT-positive individuals, compared with 0.05% (75 out of 154,050) of FIT-negative individuals (Table 1). FIT demonstrated a sensitivity of 79.56% (95% CI: 75.10–83.60), a specificity of 93.02% (95% CI: 92.89 to 93.15), and a negative predictive value of 99.95% (95% CI: 99.94–99.96). The false-negative (FN) rate of FIT was 20.44% (95% CI: 16.40–24.90), whereas the false-positive rate was 6.98% (95% CI: 6.85–7.11).

**Figure 4.** Net survival according to previous exposure to FIT and/or colonoscopy. FIT, fecal immunochemical test.

DISCUSSION

This study provides evidence on the effectiveness of a population-based screening program using fecal tests, emphasizing FIT diagnostic accuracy. It also delivers a comprehensive analysis of CRC outcomes by examining data from periods before and after its implementation. A key strength lies in the integration of data from 2 comprehensive registries. Notably, incorporating data on colonoscopies performed outside organized screening offers a broader perspective on the NHS's endoscopic capacity.

Over the first 3 years of the FIT-based screening program in northern Portugal, a rise in early detection and improved survival among screened individuals highlighted the program's impact compared with the absence of screening. Adherence to the FIT-based screening program was 34%, whereas overall coverage by FIT and/or colonoscopy, accounting for colonoscopy availability within the Portuguese Health System, reached 45%.

Our findings align with observations from European countries that have implemented FIT-based screening programs, demonstrating an overall decrease in CRC incidence (8,10,22). Age-standardized incidence rates steadily decreased throughout the study period, yet this reduction was significantly more expressive after the implementation of the regional FIT screening program. Similarly, Bucchi et al reported a sustained 28% reduction in annual CRC incidence 8 years after the implementation of organized FIT screening in northern Italy (22). In accordance with the Dutch FIT program, early-stage CRC diagnosis increased more expressively after the implementation of organized screening (8). When comparing the 2 study periods, 2014–2016 and 2018–2020, 1-year and 3-year net survival did not significantly change, suggesting that a longer evaluation of the screening program may be needed (8,23–25). Nevertheless, net survival was significantly higher among individuals who participated in FIT screening or underwent colonoscopy outside the organized screening program in the 2018–2020 period compared with those who remained unscreened. The positive impact of FIT-based screening on mortality is supported by evidence beyond European settings, including in the United States, where CRC screening is not uniformly implemented at a regional or national level (26). Moreover, in a large-scale, population-based prospective cohort study in Taiwan, Chiu et al demonstrated that biennial FIT screening was associated with a 34% reduction in advanced-stage CRC and a 40% reduction in CRC mortality (27). Thus, our findings are consistent with previous research and reinforce the effectiveness of FIT-based population screening, further supporting its positive impact on CRC outcomes (22,26–29).

Adherence rates vary considerably depending on the CRC screening strategy used, with many European countries adopting organized programs that use FIT as the primary screening method (13,30–32). While the Dutch national FIT-based screening program reported a participation rate of 72%, Poland's once-only colonoscopy screening had a participation rate of only 18% in the first 2 years (8,33). Data from randomized controlled trials also point at higher participation rates for fecal tests compared with colonoscopy (COLONPREV trial—FIT 34.2% vs colonoscopy 24.6%; SCREESCO trial—FIT 55.5% vs colonoscopy 35.1%; NordICC trial—colonoscopy 42.0%) (7,32,34,35). Accordingly, a US cross-sectional study concluded that most individuals preferred annual FIT over colonoscopy every 10 years, with 77.4% of those aged 50 years and older

favoring FIT (36–38). Adherence to FIT screening in our study was 34%, consistent with previously published data (16,30,39).

Although FIT serves as a valuable screening tool, it is not a highly accurate test (40). In 2 meta-analyses, the pooled sensitivity ranged from 72% to 79%, and the pooled specificity ranged from 87% to 94%. (41,42). In our sample, the use of a 20 µg/g cutoff for FIT yielded a sensitivity of 80% and a specificity of 93%, consistent with findings from previous reviews. Notably, the sensitivity of quantitative FIT assays can be improved by lowering the threshold for a positive result (43). For instance, the Dutch CRC screening program increased the cutoff from 15 to 47 µg/g to alleviate the colonoscopy burden, maintaining an overall FIT sensitivity of approximately 82% (8,44). While reducing the cutoff enhances sensitivity and lowers the FN rate, it also places greater strain on colonoscopy resources.

In European countries with established fecal test-based screening programs, such as the Netherlands, Denmark, and Belgium, colonoscopy acceptance rates after a positive FIT range from 75% to 90% (45–47). By contrast, studies conducted in the United States report follow-up colonoscopy rates under 80% (48–51). In our study, the 20.7% acceptance rate observed in 2020 contrasts with the higher rates of 59.3% in 2018 and 55.4% in 2019, likely resulting from delays caused by the COVID-19 pandemic rather than unwillingness to undergo endoscopic screening (52–55).

Previous studies emphasize that the highest CRC screening adherence rates are observed in countries with fully implemented organized programs based on fecal tests and those offering colonoscopy also as a primary screening option (8,10,30). Moreover, programs incorporating both fecal tests and colonoscopy as primary screening methods were associated with a greater reduction in mortality (13,23,30,31,56). In European countries offering colonoscopy as an alternative, endoscopic screening uptake ranged between one-half and almost two-thirds in most countries (30). Among countries with established fecal test-based screening programs, Portugal reported the highest colonoscopy utilization rate, exceeding 40% (30). However, overall knowledge of colonoscopy complications and their associated risk factors remains low (57,58). Accordingly, in our study, colonoscopy outside organized screening increased the coverage by any CRC detection test by 10.5%. In Germany, adherence rose from 66%–68% to 77%–80% after the inclusion of colonoscopy as an alternative to fecal tests, mainly due to an increase in colonoscopy uptake (56). Previous data from northern Portugal showed that a quarter of screening-naïve individuals preferred FOBT, and those who chose this method were less likely to opt for endoscopic screening (59). Regarding the provision of alternative screening options, a randomized trial conducted in the United States found that offering a blood-based screening test to individuals who declined FIT resulted in a 17.5% increase in screening uptake (3). Our results highlight the potential of personalized screening approaches, leveraging the health system's comprehensive screening capacity, to improve participation rates.

The authors acknowledge the limitations of this study, which focused on a regional rather than a national CRC screening program. Given its retrospective design, our study is subject to length and lead time bias that could have overestimated survival estimates. Length time bias may have led to over-representation of indolent tumors, whereas lead time bias may have artificially inflated survival by advancing the time of diagnosis without

altering prognosis. To mitigate these limitations, we also evaluated CRC incidence and mortality rates alongside net survival, as they are less affected by length and lead time biases and showed consistent reductions after the screening program implementation. It was not feasible to determine the indications for endoscopic procedures performed at CEU, including those performed in individuals with a negative FIT result. Consequently, symptomatic participants may have been included alongside those undergoing endoscopic screening, something that is well known to occur in the screening setting (60). The analysis is confined to the initial 3 years of the screening program, which limits the evaluation of its long-term effects. Although the observation period extends through the end of 2023, the completeness of diagnosis registration in the RON declines in more recent years, increasing the risk of under-reporting. However, this affected homogeneously all groups, so no significant bias is foreseen. After the implementation of the CRC screening program, the increase in the proportion of early-stage diagnoses may have been overestimated, as it coincided with a decline in the proportion of unassessed tumor stages. However, the sensitivity analysis confirmed that the observed increase in early-stage diagnoses was not solely due to a reduction in Tx cases. In 2020, the COVID-19 pandemic significantly disrupted the northern Portuguese screening program by delaying invitations and postponing colonoscopies after positive FIT results, thereby reducing overall screening participation. In addition to the impact of the organized FIT-based screening program, other factors could have contributed to the observed decline in incidence rates. These include diagnostic delays during the COVID-19 pandemic, particularly evident in 2020, potential under-reporting in cancer registry data, and improvements in health-related behaviors that may have reduced the prevalence of key risk factors. Nevertheless, the observation period extended until the end of 2023. Therefore, the decline in CRC incidence cannot be attributed solely to colonoscopy delays in 2020, as our analysis included CRC cases diagnosed up to 2 years after the FIT result. It could be hypothesized that, in the absence of pandemic-related restrictions, the screening program might have resulted in an even greater reduction in incidence rates.

Further nationwide studies with longer follow-up periods could strengthen and expand on our findings. In addition, future health economic evaluations of individualized population-based screening strategies, including both FIT and colonoscopy, could provide valuable insights to inform health policy decisions on CRC screening.

Our findings demonstrate that the implementation of a population-based screening program in northern Portugal enhanced early detection and improved survival among screened individuals, consistent with reports from other organized screening programs (8,30). Furthermore, the comprehensive screening capacity of the health system, encompassing both the organized screening program and endoscopy units contracted by the NHS, has played a critical role in optimizing coverage by FIT and/or colonoscopy. Looking forward, a more individualized approach to CRC screening, such as offering primary colonoscopy to those who decline FIT, combined with the synergistic integration of various cancer screening programs, could further strengthen public health efforts to reduce the overall cancer burden.

CONFLICTS OF INTEREST

Guarantor of the article: João C. Silva, MD.

Specific author contributions: M.D.-R., D.L., J.C.S., M.J.B. and F.: Tavares designed the study. P.L.-S., J.C.S. and D.L.: performed the research and analyzed the data. M.D.-R., D.L., M.J.B. and F.T.: revised the paper for critically important intellectual content. All authors approved the submitted final draft.

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Potential competing interests: The authors report no conflicts of interest.

Data availability: Data from the present study will not be made available upon request.

Study Highlights

WHAT IS KNOWN

- ✓ The implementation of fecal immunochemical test (FIT)-based screening programs can reduce colorectal cancer (CRC) incidence and mortality by enabling the resection of premalignant lesions and early cancer detection in FIT-positive individuals, but varying participation rates affect overall screening effectiveness.

WHAT IS NEW HERE

- ✓ The FIT screening adherence rate was 34%, whereas overall coverage by any CRC detection test, including colonoscopies performed in parallel with the FIT-based program, reached 45%.
- ✓ Shortly, within 3 years, early diagnosis and survival rates were higher among FIT participants than nonparticipants.
- ✓ A health system's comprehensive approach, incorporating organized FIT screening and colonoscopy, improves population coverage and CRC outcomes.
- ✓ Population data are essential to overcome potential observation bias.

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2. Impact of a FIT-based colorectal cancer screening program on gastric cancer incidence, early diagnosis and patients' survival

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ORIGINAL ARTICLE

Impact of a FIT Based Colorectal Cancer Screening Program on Gastric Cancer Incidence, Early Diagnosis and Patients' Survival

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ABSTRACT

Background and Aims: In countries with an intermediate incidence of gastric cancer (GC), it has been suggested that offering an upper gastrointestinal endoscopy (UGIE) to individuals referred for a screening colonoscopy following a positive result in the fecal immunochemical test (FIT) may be cost-effective. This study was designed to evaluate the impact of a FIT-based screening program on GC incidence, early diagnosis, and mortality.

Methods: Population-based retrospective cohort study in northern Portugal. Data on GC cases were retrieved from the Portuguese National Cancer Registry (RON). GC stage at diagnosis (with early stages defined as T1) and net survival estimates were compared between 2014 and 2016 and the first 3 years of the FIT-based screening program (2018–2020), during which 165,967 tests were performed.

Results: The odds of GC detection were significantly higher among FIT-positive individuals compared to those with a negative result (OR = 2.87; 95% CI: 1.76–4.49). Of the 10,372 individuals who completed FIT screening and underwent colonoscopy, 51% ($n = 5281$) also underwent UGIE. The proportion of early-stage diagnoses increased by 14% (95% CI: 12–15), and 3-year net survival improved from 42% (95% CI: 40–43) to 48% (95% CI: 47–50).

Discussion: Despite the absence of a formal GC screening program, more than half of FIT-screened individuals who underwent colonoscopy also underwent UGIE. The period following the implementation of FIT-based screening was associated with increased early-stage detection and improved survival. These findings support the potential value of offering UGIE combined with colonoscopy for FIT-positive individuals, at least in regions with intermediate GC incidence.

Abbreviations: ARSN, Northern Portugal Regional Health Administration; ASR, age-standardized rate; CRC, colorectal cancer; FIT, fecal immunochemical test; NHS, National Health Service; RON, National Cancer Registry of Portugal; UGIE, upper gastrointestinal endoscopy.

1 | Introduction

Gastric cancer (GC) is the fifth most common cancer and the third cause of cancer mortality worldwide [1]. Currently, screening is limited to high-incidence countries, defined by an age-standardized incidence rate (ASR) ≥ 20 per 100,000, such as Japan (ASR 29.9 per 100,000) and Korea (ASR 41.3 per 100,000) [2]. In the setting of colorectal cancer (CRC) screening, it has been previously suggested that false positive results in the fecal occult blood test (FOBT) could arise from the small amount of blood loss from the upper segments [3]. Since hemoglobin is degraded as it moves through the gastrointestinal (GI) tract, the fecal immunochemical test (FIT), which has higher specificity for lower GI bleeding, may also yield positive results in patients with upper gastrointestinal cancer [4]. Combined endoscopic screening for GC and CRC may be cost-effective in intermediate-risk regions (ASR 10–20 per 100,000) [5–7]. Therefore, in countries with fully rolled-out CRC screening programs and an intermediate incidence of GC, there may be a benefit from adding an Upper Gastrointestinal Endoscopy (UGIE) to a screening colonoscopy [7].

In the screening setting, the role of UGIE extends beyond diagnosing gastric neoplasms, as it allows the diagnosis of precancerous conditions such as chronic atrophic gastritis and gastric intestinal metaplasia (GIM) [8]. In intermediate to high-risk regions, where these conditions are particularly prevalent, surveillance of patients with precancerous gastric conditions is cost-effective and should preferably target high-risk GIM phenotypes, including corpus-extended GIM, operative link on GIM assessment (OLGIM) stages III/IV, the incomplete GIM subtype, persistent refractory *Helicobacter pylori* infection, and individuals with a first-degree family history of GC [9–11].

A systematic review evaluating opportunistic GC screening in subjects with a positive FOBT undergoing colonoscopy found that same-day UGIE detects approximately 25% more malignancies than colonoscopy alone [3]. The pooled prevalence of upper gastrointestinal cancers was 0.8% (95% CI: 0.4–1.6), with no significant difference observed between FOBT-positive individuals with or without colonic pathology [3]. Data from the Dutch CRC screening program revealed that, although significantly more cancers proximal to the colon (including upper gastrointestinal, oral cavity, nose, and throat cancers) were detected in those testing positive for FIT, the 3-year cumulative incidence remained below 1% [12]. However, it is important to note that the Netherlands is considered a low-risk region for GC (ASR < 10 per 100,000) [13]. The impact of a population-based FIT screening program on GC incidence, early diagnosis, and survival in intermediate-risk regions, such as northern Portugal, remains to be fully elucidated. Moreover, the outcomes of combined screening approaches remain insufficiently characterized, with limited data available to evaluate their real-world effectiveness and potential synergistic effects.

This study was designed to evaluate the impact of the organized FIT-based screening program on GC incidence, early diagnosis, and mortality.

2 | Methods

2.1 | Study Design and Participants

This population-based retrospective cohort study conducted in northern Portugal aimed to evaluate the impact of the FIT screening program (detailed in Appendix S1) on GC incidence, early diagnosis, and survival. Individuals who have undergone lower endoscopic procedures (colonoscopy within the past 10 years or sigmoidoscopy within the past 5 years) and those under surveillance for familial syndromes or inflammatory bowel disease were excluded. It was not feasible to evaluate prior exposure to UGIE within FIT-based screening, and this was not used as an exclusion criterion. Two periods were then compared: the initial period comprised the 3 years (2014–2016) that preceded the screening program start, while the subsequent period included the first 3 years of the program (2018–2020). It was decided to exclude the period between January 1 and December 31, 2017, during which pilot programs took place [14].

GC screening is not implemented or formally recommended in northern Portugal. However, primary care physicians can prescribe both UGIE and colonoscopy at their discretion, parallel to the organized CRC screening program, which currently offers colonoscopy (without UGIE) to FIT-positive individuals (Appendix S1). These procedures are performed at contracted endoscopy units outside National Health Service (NHS) hospitals, with all costs covered by the NHS.

The study protocol was approved by the ethics committees of the participating institutions, including the Northern Portugal Regional Health Administration (ARSN) and the National Cancer Registry of Portugal (RON). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies were used [15].

2.2 | Data Retrieval

Data were obtained from two independent sources: the RON and the ARSN databases.

The RON database provided information on CRC and GC cases in northern Portugal. The date of cancer diagnosis was mainly determined by the first histological confirmation. GC cases were recoded from the ICD-O-3 to ICD-10, considering the cancer site C16 (“Malignant neoplasm of stomach”) [16]. Only malignant invasive cases were analyzed. Subsites for the anatomical location were not studied.

Comprehensive data on FIT participation and results were obtained from the ARSN CRC screening database. Individuals meeting the exclusion criteria for the population-based FIT screening were not included in the analysis. Individuals with inconclusive FIT results who did not undergo a subsequent test for clarification were analyzed together with positive FIT cases.

Individuals who were not invited, those who received an invitation but did not complete the test, and those whose FIT was conducted more than 2 years ago were collectively analyzed as ‘non-updated FIT participants’.

Data on endoscopic procedures performed at contracted endoscopy units outside NHS facilities, beyond the scope of the organized screening program, were collected. Since determining the indication for each participant was not feasible, all procedures were included, extending beyond those performed solely for screening purposes. This supplementary data were obtained by identifying primary care physicians’ prescriptions for colonoscopies and/or UGIE issued for contracted endoscopy units from 2018 to 2020, using each individual’s NHS identification number.

We linked data from RON with the initial 3 years of the organized ARSN FIT-based screening program using the Portuguese NHS identification number. While the analysis primarily focuses on outcomes from the initial 3 years of screening, we extended the observation period to include diagnoses recorded in the RON through the end of 2023, ensuring adequate follow-up. Data on FIT participation and results were cross-referenced with records

of UGIE and/or colonoscopy uptake occurring during the study period (2018–2020). GC cases were classified based on the year of the FIT result, including positive and negative results, considering a 2-year time frame for diagnosis. Individuals diagnosed with GC more than 2 years after completing a FIT, regardless of the result, were allocated to the non-updated FIT group.

To evaluate the impact of the implemented screening program on GC early detection, participants were stratified by prior FIT exposure. Those who underwent FIT as part of CRC screening were compared to non-updated FIT participants. Figure 1 illustrates the study design.

2.3 | Incidence and Mortality

Data on GC incidence were retrieved from RON, and mortality data were obtained from Statistics Portugal for the periods 2014 to 2016 and 2018 to 2020. Age-standardized incidence and mortality rates were computed for 5-year age groups and per calendar period. Age-standardized incidence and mortality rates were calculated by the direct method, using the 2013 European standard population, and were expressed per 100,000 person-years

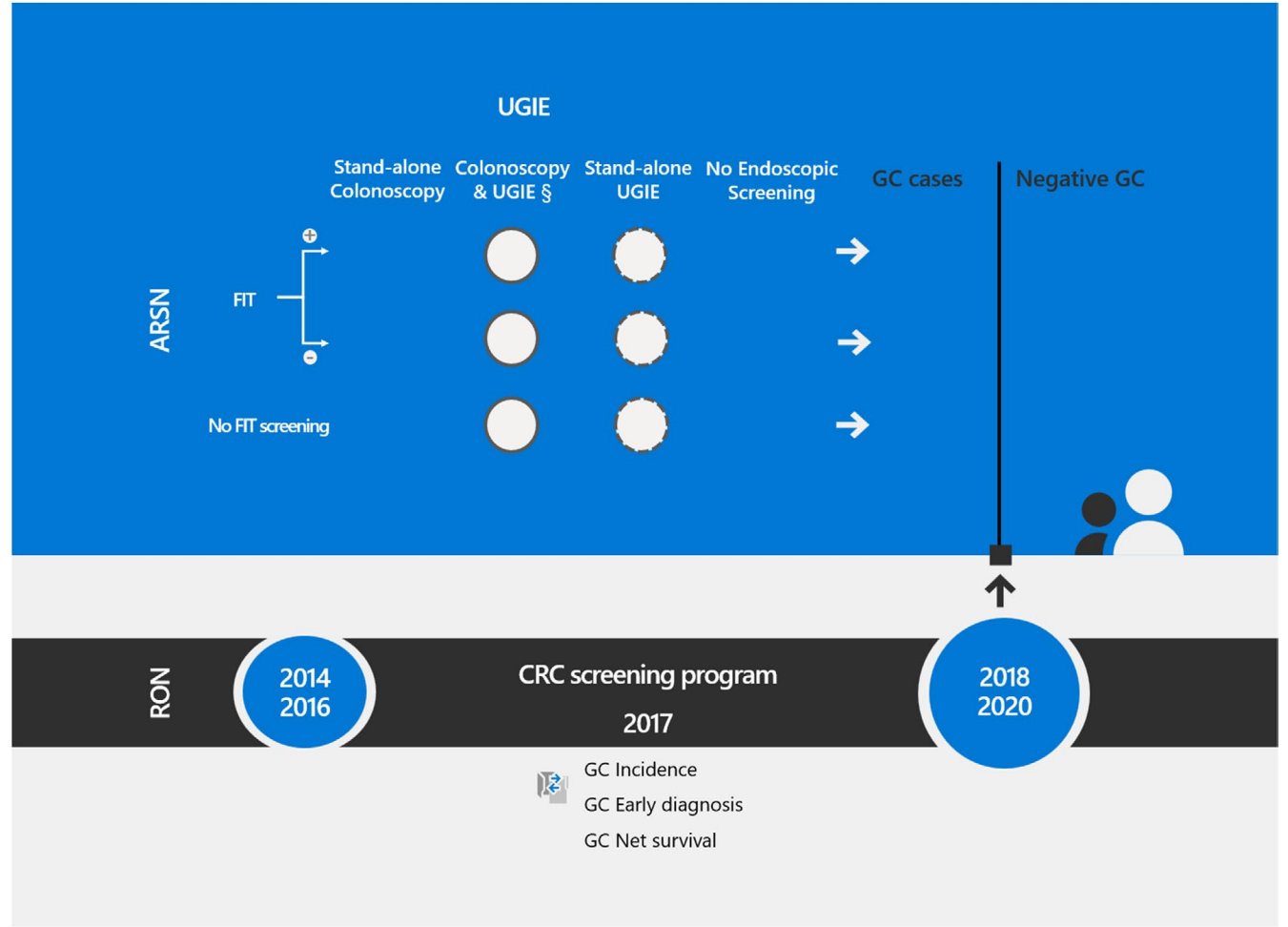


FIGURE 1 | Study design. § Includes both colonoscopy and upper gastrointestinal endoscopy procedures conducted simultaneously, as well as procedures performed separately, within the timeframe from January 1, 2018, to December 31, 2020. ARSN, Northern Portugal Regional Health Administration; CRC, Colorectal Cancer; GC, Gastric Cancer; FIT, Fecal Immunochemical Test; RON, National Cancer Registry of Portugal; UGIE, Upper Gastrointestinal Endoscopy.

[17]. Annual percentage change (APC) in incidence and mortality was estimated using log-linear regression models fitted to the age-standardized rates, with 95% confidence intervals calculated from the regression coefficients and their standard errors.

2.4 | Staging

Cancer cases were categorized based on the extent of tumor invasion (T1, T2, T3, and T4) and classified according to the pathological and clinical TNM system at the time of diagnosis. Early-stage was defined as T1. The comparison of proportions of T cases was conducted using Pearson's chi-squared test, along with confidence intervals (CIs) for proportion differences [18].

2.5 | Survival

Given that cancer cases were collected from population-based cancer registries, data on the cause of death were lacking. To overcome this limitation, net survival rates were estimated using the Pohar–Perme estimator [19]. Life tables of all-cause mortality, from Statistics Portugal, stratified by single year of age, sex, and calendar year were used. Comparisons of 1-year and 3-year net survival rates were made between the two study periods. Net survival was age-standardized using the International Cancer Survival Standard [20]. R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org) was used.

3 | Results

3.1 | Impact of FIT-Based Screening on Gastric Cancer Outcomes

During the first 3 years of the FIT-based screening program, 165,967 tests were performed, of which 7% ($n = 11,856$) were positive (Table 1). The odds of GC detection were significantly higher among individuals with a positive FIT result (0.2%; 24/11,856) than among those with a negative result (0.07%; 109/154,111), with an odds ratio of 2.87 (95% CI: 1.76–4.49; $p < 0.001$). Of those with a positive FIT result, 4864 (41%) underwent follow-up colonoscopy, and 1316 (27%) of these also underwent UGIE during the study period. Among FIT-negative individuals, 5508 (4%) still underwent colonoscopy, of whom 3965 (72%) also underwent UGIE. Overall, of those screened for CRC through FIT, 10,372 underwent colonoscopy with UGIE performed concurrently in 51% of cases ($n = 5281$).

Among individuals with a positive FIT, the GC detection rate was 0.2% (95% CI: 0.1–0.3). Detection was significantly higher in those who underwent stand-alone UGIE (4.3%) compared with UGIE combined with colonoscopy (0.2%), colonoscopy alone (0.1%), or neither procedure (0.2%) ($p < 0.001$). Among individuals with a negative FIT, detection was also significantly higher in those who underwent stand-alone UGIE (0.5%) than in those who underwent UGIE combined with colonoscopy (0.3%), colonoscopy alone (0.0%), or neither procedure (0.1%) ($p < 0.001$). Similarly, in the non-updated FIT group, the highest detection was observed in individuals

TABLE 1 | Gastric cancer cases by fecal immunochemical test screening and endoscopy exposure.

	Gastric cancer cases	Total	Gastric cancer detection (%)
Positive FIT ^a , n (%)	24	11,856	0.2
• Colonoscopy alone	4	3548	0.1
• UGIE combined with colonoscopy	3	1316	0.2
• Stand-alone UGIE	2	46	4.3
• Neither colonoscopy nor upper endoscopy performed	15	6946	0.2
Negative FIT, n (%)	109	154,111	0.07
• Colonoscopy alone	0	1543	0
• UGIE combined with colonoscopy	12	3965	0.3
• Stand-alone UGIE	10	1972	0.5
• Neither colonoscopy nor upper endoscopy performed	87	146,631	0.06
Non-updated FIT ^b	749	433,517	0.2
• Colonoscopy alone	7	3930	0.2
• UGIE combined with colonoscopy	57	13,751	0.4
• Stand-alone UGIE	10	1665	0.6
• Neither colonoscopy nor upper endoscopy performed	675	414,171	0.2

Abbreviations: FIT, fecal immunochemical test; UGIE, upper gastrointestinal endoscopy.

^aBoth positive and inconclusive FIT results were analyzed together.

^bIncludes individuals who were not invited, those who received an invitation but did not complete the test, and those whose FIT was conducted more than 2 years ago.

undergoing stand-alone UGIE (0.6% vs. 0.4%, 0.2%, and 0.2%, respectively; $p < 0.001$) (Table 1). A sensitivity analysis excluding individuals who underwent stand-alone UGIE was conducted. Among those with a positive FIT, differences in GC detection across subgroups were not statistically significant ($p = 0.476$). However, significant differences remained in the negative FIT and non-updated FIT groups ($p < 0.001$), with higher detection rates among individuals who underwent UGIE combined with colonoscopy.

Restricting the analysis to cases with known T stage, the proportion of T1 diagnoses was comparable across subgroups (Table 2), except among individuals who underwent FIT screenin. In this subgroup, the rate of early-stage GC diagnosis was significantly higher among those who underwent UGIE, either alone or in combination with colonoscopy, compared to those who did not undergo any endoscopic procedures (54% vs. 27%; $p = 0.017$). Furthermore, among individuals screened with FIT, the T1 detection rate was lower in those without endoscopic evaluation than in individuals who underwent neither FIT nor endoscopy (27% vs. 43%; $p = 0.010$).

3.2 | Incidence and Mortality Rates

Age-standardized incidence rate declined from 44 per 100,000 in 2014 to 32 per 100,000 in 2020 (Figure S1). Following the implementation of population-based FIT screening, GC incidence increased from 43 per 100,000 in 2016 to 44 per 100,000 in 2018. Between 2014 and 2016, the APC in GC incidence was -1.04% (95% CI: -1.68% to -0.39%). From 2018 to 2020, the decline accelerated, with an APC of -14.39% (95% CI: -23.26% to -4.50%).

The age-standardized mortality rate declined from 27 per 100,000 in 2014 to 21 per 100,000 in 2020, representing a 21% reduction over the study period (Figure S1). Between 2014 and 2016, the APC was -2.82% (95% CI: -5.12% to -0.46%), and from 2018 to 2020, the APC was -4.37% (95% CI: -9.52% to 1.08%).

3.3 | Early-Stage Gastric Cancers (T1)

The proportion of early-stage detection rose from 10% in 2014 to 22% in 2020, representing an increase of 13% (95% CI: 10–15). A 14% increase in T1 diagnoses (95% CI: 12–15) was observed when comparing the periods 2014–2016 and 2018–2020. To account for the potential confounding effect of unassessed tumor stage (Tx) cases, a sensitivity analysis was performed including only cases with known T stage. Among these, the proportion of T1 diagnoses increased from 27% in 2014–2016 to 32% in 2018–2020, corresponding to an absolute increase of 5% (95% CI: 3–8; $p < 0.001$). Figure 2 illustrates the proportions of T1 GC cases.

3.4 | Net Survival Rates

Net survival significantly improved between the two study periods (Figure 3). The 1-year net survival increased from 60% (95% CI: 59–61) in 2014 to 2016 to 67% (95% CI: 66–68) in 2018 to 2020. Similarly, 3-year net survival rose from 42% (95% CI: 40–43) to 49% (95% CI: 47–50) during the same periods.

TABLE 2 | Stage at diagnosis stratified by fecal immunochemical test screening and endoscopy exposure.

Stage at diagnosis <i>n</i> (%)	FIT and UGIE (stand-alone or combined with colonoscopy)		FIT and neither colonoscopy or UGIE performed		Non-updated FIT ^a and UGIE (stand-alone or combined with colonoscopy)		Non-updated FIT ^a and neither colonoscopy or UGIE performed	
	FIT and colonoscopy alone	FIT and colonoscopy combined with colonoscopy	FIT and colonoscopy or UGIE performed	FIT and colonoscopy or UGIE performed	Non-updated FIT ^a and UGIE (stand-alone or combined with colonoscopy)	Non-updated FIT ^a and UGIE (stand-alone or combined with colonoscopy)	Non-updated FIT ^a and neither colonoscopy or UGIE performed	Non-updated FIT ^a and neither colonoscopy or UGIE performed
• T1	1 (33.3)	14 (53.8)	23 (27.4)	23 (27.4)	33 (53.2)	33 (53.2)	3 (60.0)	229 (43.0)
• T2	2 (66.7)	7 (26.9)	9 (10.7)	9 (10.7)	5 (8.1)	5 (8.1)	1 (20.0)	98 (18.4)
• T3	0 (0)	4 (15.4)	30 (35.7)	30 (35.7)	17 (27.4)	17 (27.4)	0 (0)	103 (19.4)
• T4	0 (0)	1 (3.8)	22 (26.2)	22 (26.2)	7 (11.3)	7 (11.3)	1 (20.0)	102 (19.2)
• Tx	1	1	18	18	5	5	2	143

Abbreviations: FIT, fecal immunochemical test; Tx, tumor stage cannot be assessed; UGIE, upper gastrointestinal endoscopy.

^aIncludes individuals who received an invitation but did not complete the test, as well as those whose fecal immunochemical test was conducted more than 2 years ago.

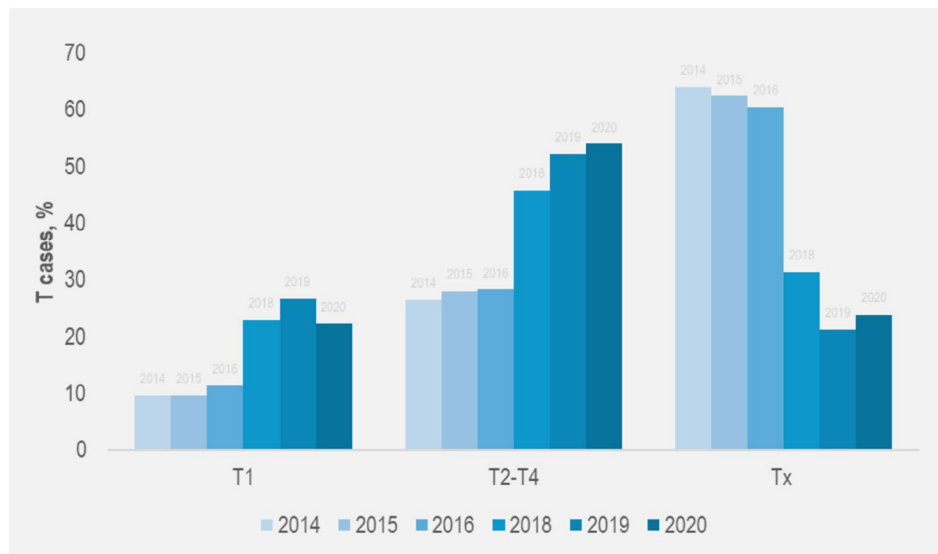


FIGURE 2 | Proportion of early-stage and advanced-stage gastric cancers within all gastric cancer cases by calendar year. Tx, tumor stage cannot be assessed.

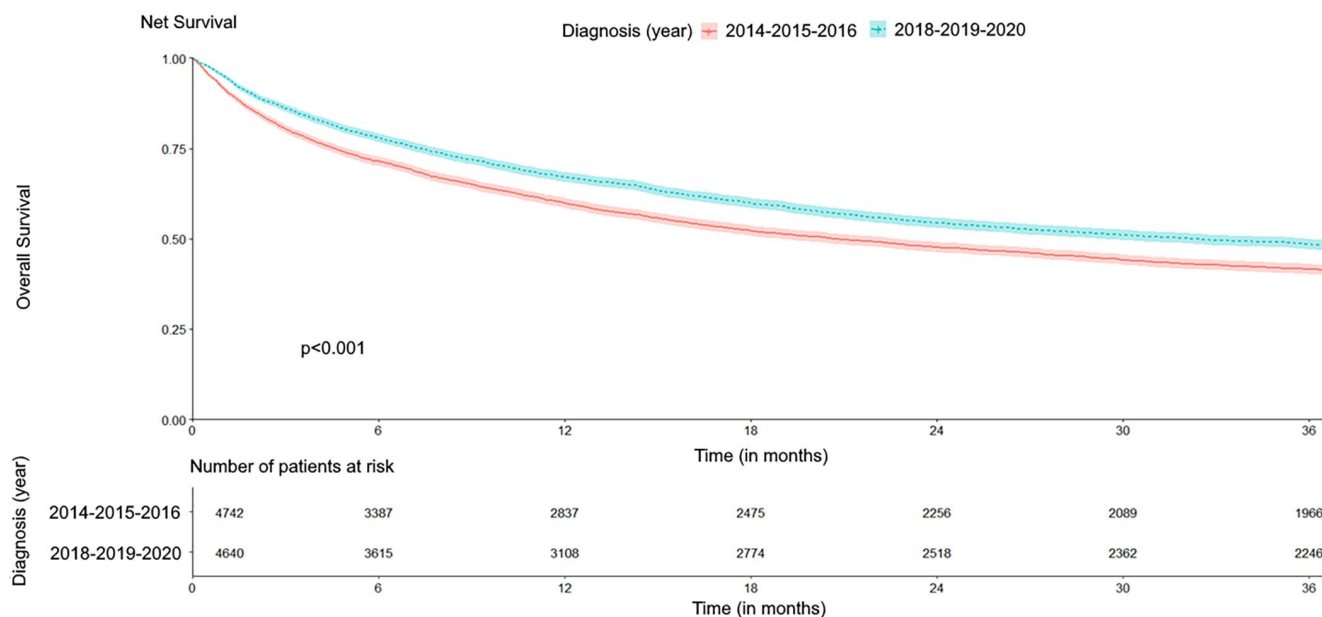


FIGURE 3 | Net survival for gastric cancer before and after the implementation of the fecal immunochemical test screening program.

4 | Discussion

In an intermediate-risk region for GC, this study sheds new light on how a FIT-based screening program may influence GC incidence, early detection, and mortality. By integrating data from two comprehensive registries, it was possible to perform a detailed assessment of endoscopic coverage across northern Portugal. The use of population-level data further strengthened the evaluation of combined colonoscopy and UGIE utilization, providing unbiased real-world evidence of its impact on GC outcomes. In northern Portugal, a cost-utility analysis had previously compared three screening strategies: stand-alone UGIE; UGIE combined with a CRC screening colonoscopy after a positive FIT result; and pepsinogens serologic screening. It concluded that an UGIE for GC screening every 5 years was

cost-effective only if combined with a screening colonoscopy [5]. These results were later confirmed by a subsequent economic evaluation [6] and further support the relevance of our study.

Among individuals who were invited to participate in CRC screening and accepted, the odds of GC detection were significantly higher in those who tested positive. Despite the absence of a formal GC screening program in northern Portugal, over half of FIT-screened individuals undergoing colonoscopy also underwent UGIE. Following the implementation of organized FIT screening and compared to the preceding period, GC early detection and survival increased over time.

Even though we observed an encouraging increase in early GC diagnosis and survival following the implementation of the CRC

screening program, concurrent factors must be considered. A trend toward increased early detection and improved survival had already been observed in northern Portugal prior to the implementation of FIT screening, with several contributing factors having been proposed [13]. These include improvements in technology (e.g., high-definition endoscopes with integrated virtual chromoendoscopy), enhanced training in early neoplasia detection, and quality improvement initiatives, all identified as relevant contributors [13]. The European Society of Gastrointestinal Endoscopy (ESGE) position statement on performance measures for UGIE serves as an example of a meaningful quality improvement effort, which may partially explain the improved GC outcomes observed following its publication in 2016 [21]. Although we do not expect these factors to have changed substantially between the two periods under analysis, the improved GC outcomes cannot, based on our study design, be solely attributed to the FIT screening program alone. Nevertheless, the implementation of the FIT screening program may have also expanded colonoscopy coverage, which in turn could have indirectly facilitated access to endoscopic procedures and increased UGIE uptake.

Currently, there is insufficient evidence to recommend UGIE for FIT-positive individuals in western populations. Sah et al. [3] reported a pooled prevalence of upper gastrointestinal cancers of 0.8% (95% CI: 0.4–1.6) in their systematic review and meta-analysis, including mostly western studies, which exceeds the 0.2% (95% CI: 0.1–0.3) GC detection rate observed among FIT-positive individuals in our sample. However, two key methodological differences must be considered when establishing this comparison. First, the meta-analysis included both FIT and guaiac-based FOBT, which may have influenced the diagnostic performance of fecal testing. Second, GC cases accounted for 51% of the upper gastrointestinal cancers reported, potentially limiting the comparability of prevalence estimates.

A large-scale study conducted through the Korean National Cancer Screening Program assessed the 3-year risk of cancers proximal to the colon following FIT-based screening [4]. In this high-risk region, the 3-year incidence of GC was 1.1% among individuals without a CRC diagnosis within the first year after FIT, compared to 2.6% among those diagnosed with CRC [4]. In the former study, the risks of esophageal and GC were higher among FIT-positive individuals and did not differ based on the diagnosis of CRC. Given that South Korea presents an ASR exceeding 20 per 100,000, the observed benefit in GC detection among FIT-positive individuals was further reinforced.

Drawing on the largest population-based study within a western FIT-based CRC screening program, data from the Dutch cohort provide compelling evidence regarding the incidence of GC among screened individuals [12]. Those with a positive FIT result exhibited a significantly elevated risk (hazard ratio: 1.55) of malignancies proximal to the colon. However, the 3-year cumulative incidence in this group remained below 1%. It must be noted that the Dutch study considered all cancers proximal to the colon, including oral cavity, nose/throat, esophageal, gastric, small bowel undefined, duodenum (including the papilla of Vater), jejunum, and ileum. When the analysis was restricted to GC alone, the 3-year incidence among FIT-positive individuals remained well below the 0.2% detection rate observed in our

cohort, supporting prior estimates and suggesting a higher GC incidence in Northern Portugal [13]. However, it should be noted that our study did not restrict the period between a positive FIT result and GC diagnosis to 3 years, which may at least partially explain the observed difference.

Building on two previously published cost-utility analyses, GC screening may be cost-effective if UGIE is combined with a screening colonoscopy [5–7]. Prior estimates on the adherence to a combined screening strategy pointed at a 94% intention to accept UGIE combined with a screening colonoscopy [22]. Yet, in this cross-sectional study using the PERCEPT-PREVENT survey through telephonic interviews, the risk of bias, such as social desirability and healthy user bias, must be acknowledged [23]. Although adherence to combined endoscopic screening was not measured in the present study, UGIE and colonoscopy were combined for over 50% of the study population screened for CRC through FIT and colonoscopy. The implementation of the CRC screening program, rather than the FIT result alone, may have contributed to increased UGIE uptake. In the absence of an organized GC screening program and considering that the decision to perform UGIE alongside colonoscopy was made by NHS primary care physicians rather than by the individuals themselves, it is reasonable to expect that a combined screening strategy may achieve relatively high participation rates in northern Portugal.

A fundamental limitation of the combined screening strategy lies in the restriction of UGIE availability to individuals with a positive FIT result [5–7]. By confining GC screening to a narrower subset of the eligible population, this approach departs from the comprehensive and inclusive framework that typically defines organized screening initiatives [24]. The potential impact of this targeted strategy on early GC diagnosis and survival remains insufficiently studied to date [12]. Nonetheless, our findings suggest that the implementation of the regional CRC screening program was associated with meaningful gains in GC early detection and survival, highlighting the potential benefits of expanded endoscopic coverage and facilitated access to UGIE within organized FIT-based programs.

The authors recognize this study's limitations. Firstly, a regional rather than a national FIT screening program was analyzed. Secondly, it was not feasible to determine the indications for endoscopic procedures performed at contracted endoscopy units, including those performed in individuals with a negative FIT result. Consequently, symptomatic participants were included alongside those undergoing endoscopic screening. While the unintentional inclusion of symptomatic participants is a well-known occurrence in the screening setting [3], the authors acknowledge that the impact of FIT screening in GC detection rates may have been overestimated in our sample. In fact, individuals who underwent stand-alone UGIE were presumably more likely to be symptomatic, which could have inflated detection rates; however, the sensitivity analysis excluding this subgroup yielded similar results. Furthermore, the positive predictive value of alarm symptoms for upper gastrointestinal cancer in the general population is low, and early-stage GC often presents asymptotically [25–27]. Moreover, the study design did not account for key risk factors such as *Helicobacter pylori* infection, smoking, family history, or socioeconomic

status, which may have influenced both the likelihood of undergoing UGIE and the risk of GC. While our analysis is centered on the initial 3 years of the FIT screening program, the observation period extends through the end of 2023. Although the interval between FIT completion and diagnosis was not formally assessed, a two-year period was considered for allocation purposes. A previous study adopted a three-year interval, assuming that beyond this period neoplasms proximal to the colon could no longer be reliably considered detectable at the time of FIT testing [12]. In our study, although a shorter interval was applied, GC cases diagnosed beyond 2 years were not excluded and were analyzed within the non-updated FIT subgroups. The increase in the proportion of early-stage diagnoses from 2018 may have been overestimated, as it coincided with a decline in the proportion of unassessed tumor stages. However, the sensitivity analysis confirmed that the observed increase in early-stage diagnoses was not solely due to a reduction in Tx cases. Due to its retrospective design, our study may be affected by lead-time and length biases. Slow-growing tumors could be overrepresented, and earlier detection might have extended observed survival without altering prognosis. To help mitigate these effects, we also analyzed incidence and mortality, which are less influenced by timing-related biases. Furthermore, the non-standardized and opportunistic use of UGIE in our setting may limit the generalizability of the findings to healthcare systems with different structures or limited endoscopy resources. Implementation in resource-constrained settings would require careful evaluation of feasibility, cost-effectiveness, and alignment with national health policies [5, 24]. Ultimately, our analysis was restricted to gastric epithelial lesions and did not encompass other gastric lesions (e.g., mesenchymal tumors, peptic ulcer disease), as well as esophageal, duodenal, or head and neck malignancies [28].

Studies performed at a national level with longer follow-up periods could further reinforce our findings. Assessment of annual treatment proportions will be essential to better characterize stage-specific trends. Moreover, the evaluation of combined UGIE and colonoscopy in the context of pilot projects may offer a clearer assessment of their effect on GC outcomes, as these would result exclusively from screening procedures. Future health economic evaluations of individualized screening strategies that consider offering UGIE not only to individuals referred for colonoscopy following a positive FIT result, but also to those undergoing primary colonoscopy, may provide valuable insights to inform health policy decisions on digestive cancer screening.

In brief, our results demonstrate that the implementation of a population-based FIT screening program has had a positive impact on GC outcomes, including improved early detection and survival. Furthermore, a relatively high proportion of individuals underwent both UGIE and colonoscopy, suggesting a potentially high acceptance of organized combined endoscopic screening. Our study paves the way for further exploration of combined screening strategies across European countries, incorporating both endoscopic and non-invasive approaches, such as the joint use of FIT and *Helicobacter pylori* stool antigen testing. Aligning concurrent cancer screening programs could strengthen public health efforts to reduce the overall burden of cancer.

Author Contributions

Mário Dinis-Ribeiro, Diogo Libânio, João Carlos Silva, Maria José Bento and Fernando Tavares designed the study. João Carlos Silva, Mário Dinis-Ribeiro, Pedro Leite-Silva and Diogo Libânio performed the research and analyzed the data. Mário Dinis-Ribeiro, Diogo Libânio, Maria José Bento and Fernando Tavares revised the paper for critically important intellectual content.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** hel70071-sup-0001-DataS1.zip.



Chapter VII - Discussion and Conclusions

DISCUSSION

The current research project systematically examined patients' risk perception (encompassing both cancer risk and screening procedures risk) and assessed their preferences for CRC and GC screening strategies. Furthermore, real-world outcomes, including adherence, early detection, and survival, were analyzed following the implementation of a population-based FIT screening program in Northern Portugal.

The first study presented in this thesis synthesizes data on GC screening to complement the wider available evidence on CRC screening^{25,27,75,117,173-175}. After a comprehensive assessment, only Japan and South Korea have implemented population-based screening, offering both UGIS and UGIE. The review demonstrates that GC screening reduces mortality, with UGIE providing the highest detection rates.

To measure risk perception, a previously validated^{12,13} questionnaire on CRC risk perception, based on the HBM, underwent forward/backward translation, as well as cultural adaptation and further adaptation to address GC screening and complication risk perception. Validation of the PERCEPT-PREVENT tool was a necessary step to enable subsequent exploration of personalized screening and of synergistic screening approaches across three cross-sectional studies.

In the initial cross-sectional study, a clear preference for colonoscopy over fecal tests as the primary screening method was evident, yet 25% of naïve participants preferred FIT as the primary screening method. Knowledge assessment showed that 64% could not identify any symptoms and 68% were unaware of risk factors. Our results are aligned with previous studies showing that, despite a strong willingness to undergo screening, knowledge of CRC symptoms and risk factors remains low¹⁸⁰. It is important to acknowledge that measuring the intention to adhere may significantly overestimate the actual uptake of screening tests due to social desirability bias, a phenomenon that was particularly evident in populations with

limited knowledge of CRC risk and screening practices^{180,181}. In the second cross-sectional study, self-reported willingness to undergo UGIE combined with colonoscopy reached 94%. However, 76% and 73% were unfamiliar with any potential GC symptoms and risk factors, respectively. Previous studies from Eastern countries have also reported moderately high intention to undergo GC screening, despite moderate to low levels of knowledge¹⁸²⁻¹⁸⁴. The third observational study found that 19% of never-screened and 45% of screened participants perceived a high risk of colonoscopy complications, while for UGIE, the figures were 14% and 41%, respectively. While this contrasts with previous data suggesting that never-screened individuals were more likely to overestimate the risk of complications, 61% and 83% could not identify any potential complications of colonoscopy and UGIE, respectively¹⁴. A striking lack of awareness concerning the risk of complications, as reported in previous studies^{14,104,185,186}, rather than an assessment of low risk, probably explains our results.

The results of our real-world studies evaluating CRC outcomes after FIT implementation reinforce both the importance of screening and its effectiveness at the population level, as evidenced by enhanced early detection and survival. Our findings also indicate that, while adherence to FIT is high (34%), coverage can be increased if alternatives to fecal tests are offered. This was shown in the cross-sectional study, in which 25% of naïve participants preferred FIT while 69% overall preferred colonoscopy, and it was further reinforced by real-world data showing a 10% increase in coverage when colonoscopies performed in parallel with the organized screening program were included. Contracted endoscopy units were shown to complement the organized FIT-based program by ensuring timely performance of colonoscopy, allowing some flexibility in the choice of unit or endoscopist, and offering the possibility of combination with UGIE.

Our results can also contribute to the implementation of GC screening. In real-world settings without a formal GC screening program, more than 50% of individuals who completed FIT and colonoscopy also underwent UGIE. In the scenario of a screening program,

this rate may approach the 94% acceptance observed in our cross-sectional study. Moreover, although the FIT program is not primarily intended to detect GC, it was associated with improved outcomes, including higher rates of early detection and survival.

In summary, this thesis advances the concept of personalized screening, allowing individuals to choose between FIT and colonoscopy, and the concept of synergistic screening, combining UGIE for GC screening with colonoscopy. It adopts a perspective that integrates self-reported willingness to undergo digestive cancer screening with real-world adherence data, while also measuring the impact of FIT screening on the early detection and survival of CRC and GC using population-based data

This discussion seeks to contextualize the findings within the existing body of literature, highlighting their significance for cancer screening practices. It will focus on three key domains: personalized screening strategies, synergistic approaches to cancer screening, and the comprehensive assessment of risk perception.

1. Expanding coverage through personalized CRC screening strategies

The optimal approach for CRC screening remains a subject of ongoing debate. In addition to policy and financial factors, choosing an appropriate population-based screening strategy, including the primary screening method, can affect participation rates and, consequently, the effectiveness of an organized program. Concisely, a screening test that reaches higher acceptance in a given population has the potential to maximize screening coverage. When real-world data are considered, a stark contrast is evident between the 72% participation rate in the biennial FIT screening program in the Netherlands and the 18% uptake of a once-in-a-lifetime colonoscopy in Poland^{27,42}.

A cost-utility analysis conducted in Portugal evaluated biennial FIT, colonoscopy every 10 years, and the absence of screening. Biennial FIT was the most cost-effective option, with an incremental cost-effectiveness ratio (ICER) of €2,694 per quality-adjusted life year (QALY),

significantly lower than the €103,633 per QALY estimated for colonoscopy^{4,5}. Furthermore, implementing a FIT-based screening program would require a 1.3% increase in colonoscopy capacity, compared to a 31% increase necessary for a colonoscopy-based program⁷. However, the analysis relied on adherence estimates from European and North American studies, assuming acceptance rates of 50% for FIT and 38% for colonoscopy, without real-world data from the Portuguese population⁷.

While noninvasive CRC screening with FIT has gained broad support, evidence remains limited regarding its comparative acceptability over colonoscopy, highlighting the need for more robust data on patient preferences. Variability in participation rates across countries underscores the significant impact of regional differences on screening uptake and preferences for the primary screening method^{7,8,43}. These findings highlight the need for a deeper understanding of local screening behaviors and preferences to optimize program effectiveness. Indeed, in an era of personalized and precision medicine, a one-size-fits-all approach may not be adequate when more than one screening method is available.

As part of the present project, the initial cross-sectional study evaluated individuals' intention to adhere to CRC screening and their preferences regarding the primary screening method¹⁸⁷. Overall, 95% of participants expressed an intention to undergo CRC screening, surpassing the findings of previous studies^{7,43,180,188}. A clear preference for colonoscopy over fecal tests as the primary screening method was evident across our sample, yet these findings warrant further analysis. Among participants not yet invited to screening, 25% preferred FOBT as the primary screening method. Most individuals (90%) initially screened through primary colonoscopy intended to continue using this method, whereas half of those previously screened with FIT expressed a willingness to transition to endoscopic screening. This shift was particularly evident among participants who had recently been referred for colonoscopy following a positive FIT result, suggesting that prior screening experiences strongly influence future preferences. Our results complement previous data that tended to point to higher

acceptance of fecal tests^{41,143-145,189}. The Spanish COLONPREV trial registered participation rates of 34.2% for FIT and 24.6% for colonoscopy¹⁴⁴. Furthermore, the Swedish SCREESCO trial reports an adherence rate of 55.5% for FIT and 35.1% for colonoscopy¹⁴⁵. Despite the tendency favouring less invasive tests, both trials assigned participants to FOBT or colonoscopy without considering their preference for the primary screening method, potentially overlooking factors influencing adherence^{144,145}. Within the European setting, the NordICC trial reported an overall adherence to colonoscopy of 42%, ranging from 33% in Poland to 61% in Norway^{41,143}. In the US, despite a historically high acceptance of colonoscopy, a cross-sectional study designed to assess patient preferences for screening tests reported that 77% of individuals over 50 years expressed a preference for annual FIT over colonoscopy every 10 years¹⁹⁰⁻¹⁹². The CONFIRM trial, conducted in the US, reported that 43% of those declining participation expressed a preference for a specific screening test, with 58.5% favouring FIT and 40.6% opting for colonoscopy¹⁸⁹. Nevertheless, prior colonoscopy was the primary reason for ineligibility, accounting for nearly 40% of exclusions^{189,193}.

In our cross-sectional assessment, barriers to CRC screening were generally lower for fecal tests compared to colonoscopy. A higher perception of the potential negative health consequences associated with colonoscopy contributed to a stronger preference for non-invasive testing. Interestingly, a greater knowledge of the complications associated with a screening colonoscopy was independently linked to a preference for colonoscopy over FIT as the primary CRC screening method. As reinforced in our third cross-sectional study, complication risk perception did not negatively impact CRC screening uptake¹⁹⁴. This is explained on the one hand by greater awareness among previously screened individuals, and on the other by limited knowledge among those naïve to screening. Absence of a prior screening invitation, a higher perceived need for testing, and a history of CRC in second-degree relatives or acquaintances were additionally identified as independent predictors of a preference for colonoscopy over fecal tests. Nonetheless, it is important to acknowledge that

the study findings may have been influenced by biases, including recall bias, social desirability bias—particularly in estimates of intention to adhere—and attribution bias¹⁹⁵⁻¹⁹⁷. Additionally, healthy user bias could have led to an overestimation of both the intention to adhere to CRC screening and the preference for colonoscopy screening. Participants who were willing to complete the telephone survey are likely more health-conscious, making them more prone to participate in screening initiatives and undergo invasive procedures.

To overcome potential observation bias in adherence estimates from the previous cross-sectional study, we conducted a population-based retrospective cohort study including all eligible individuals for the first three years of the Northern Portuguese screening program. The effectiveness of organized, population-based CRC screening is largely shaped by adherence rates, as higher participation can lead to a more pronounced impact on incidence, early diagnosis, and mortality²⁴⁻²⁶. Adherence to the FIT-based screening program was 34%, while overall coverage by FIT and/or colonoscopy, accounting for colonoscopy availability within the *Sistema Nacional de Saúde* (SNS), reached 45%. These results align with our cross-sectional assessment, in which most participants classified as non-adherent had previously undergone colonoscopy. Colonoscopies performed in parallel with the organized screening program, largely initiated through referrals from primary care physicians, contributed to a 10% increase in uptake of CRC detection tests, emphasizing that maximizing the SNS capacity improved overall coverage, with open-access colonoscopy¹⁹⁸ complementing FIT-based screening programs. Accordingly, a systematic review and meta-analysis of CRC screening programs found that offering individuals a choice between fecal tests and colonoscopy was associated with a greater reduction in mortality compared to programs with a single screening modality¹⁹⁹. In the US, a randomized trial found that offering a blood-based test to individuals who declined FIT increased screening uptake by 17.5%¹⁴⁶. Moreover, in Germany, the participation rate increased by up to 12% following the inclusion of colonoscopy as an

alternative to fecal tests, primarily due to greater colonoscopy uptake, even in an opportunistic setting¹⁰⁴.

The impact of the structured CRC screening program in Northern Portugal became evident within just three years. Despite the 20% false-negative rate, early-stage cancers were significantly more frequent among individuals who participated in FIT-based screening than among those who remained unscreened (58% vs. 49%), and three-year net survival was also higher (87.5% vs. 72%). Our findings align with previous research and confirm the effectiveness of FIT-based screening, supporting its positive impact on CRC outcomes^{75,117,173-175}. In the Dutch FIT program, 66.7% of screening-detected CRC was early stage (vs 46.2%), and mortality fell by 22%²⁷. Similarly, Bucchi *et al.* reported a 28% sustained reduction in CRC incidence eight years after organized FIT screening began in Northern Italy⁷⁵. Beyond the European context, a 33% lower risk of death from CRC after FIT screening was reported in the US¹⁷³. Moreover, a Taiwanese prospective cohort study showed that biennial FIT screening reduced advanced-stage CRC by 34% and CRC mortality by 40%¹¹⁷. Altogether, these findings highlight both the effectiveness of FIT screening and the potential of personalized approaches to enhance CRC outcomes by aligning screening strategies with individual preferences. However, the Northern Portuguese retrospective cohort study has some limitations, including reduced colonoscopy uptake during the COVID-19 pandemic and the inability to determine the clinical indications for endoscopic procedures performed at contracted endoscopy units.

Overall, our findings show that population-based screening with noninvasive tests is effective and well accepted. Additionally, our results allow us to suggest implementing a personalized screening approach, namely offering primary colonoscopy to individuals who decline FIT or as an alternative to FIT, within the capacity of the health system, as a strategy to further enhance overall coverage.

2. Strategies for the implementation of GC screening in intermediate-risk regions

Several screening methods have been proposed for GC detection, either individually through UGIE or by combining non-invasive tests (e.g., UGIS, serum pepsinogen I/II levels, serum anti-Hp IgG or HPSA) with endoscopy^{126-128,130}. Nevertheless, the optimal screening method and the impact of the different GC screening methods on mortality have been sparsely characterized. Therefore, we conducted a systematic review and meta-analysis to detail and characterize GC screening programs and compare screening methods regarding adherence, diagnostic yield and impact on mortality. We found that organized GC screening is confined to Eastern countries, with no established programs reported in the West. Japan and South Korea have implemented nationwide screening initiatives, offering UGIE and UGIS to asymptomatic healthy individuals¹⁷⁻¹⁹. In China, endoscopic screening is available in some high-risk regions^{132,200}. Overall, screening has demonstrated a significant impact in reducing GC mortality^{126,128}. Endoscopic screening was associated with higher diagnostic yield, including improved early detection rates, compared to UGIS and serologic testing¹²⁸. While noninvasive tests generally yielded higher participation rates, comparative data remain scarce¹²⁸.

The main limitation of our review was the significant heterogeneity in adherence estimates, despite careful study selection, quality assessment, and subgroup analysis. A previous meta-analysis focusing exclusively on endoscopic screening reported a 40% reduction in the relative risk of GC mortality, further reinforcing the role of UGIE¹²⁶. Our results were further corroborated by two subsequent meta-analyses, one of which highlighted a trend toward increased uptake of endoscopic screening over time^{201,202}. Based on these findings, we suggest that GC screening programs should preferentially be based on UGIE given the higher diagnostic yield^{126,128}. Patient discomfort and tolerance may be a concern due to its invasive nature, but with the wider availability of sedation, this should not deter us from recommending the most sensible diagnostic method. The use of transnasal

endoscopy or the offer of a less invasive test (e.g., UGIS) may be considered in the settings of limited access to sedation²⁰³. Taking the Korean screening program as an example, although both UGIE and UGIS are offered, since 2018, endoscopy has become the preferred method, with UGIS reserved for individuals unable to tolerate the procedure²⁰⁴.

After identifying the most accurate diagnostic method, it is equally important to consider factors such as adherence and cost-effectiveness, especially in intermediate-risk countries. Adherence is indeed a critical consideration in this context, as it directly influences the effectiveness and feasibility of GC screening. Data from our systematic review and meta-analysis indicate that the highest pooled adherence rate among studies based on self-reported screening uptake reached 56%¹²⁸. However, these adherence estimates were for stand-alone UGIE and not for combined screening. Notably, previous economic analyses on combined endoscopic screening assumed full adherence as a baseline for cost-effectiveness modeling²¹. This highlighted the need to understand the factors influencing the intention to undergo GC screening, to assess the willingness to accept UGIE combined with screening colonoscopy, and to incorporate realistic adherence rates into future economic analyses to better inform policy and optimize screening outcomes.

To build on this, we conducted a cross-sectional study to evaluate the intention to undergo UGIE combined with a screening colonoscopy. In Northern Portugal, the intention to adhere to combined endoscopic screening reached an acceptance rate of 94%, with most individuals expressing a willingness to participate under conditions of full reimbursement²⁰⁵. In our sample, self-perceived risk of GC was generally low and was not influenced by the fact that the study was conducted in an intermediate-risk region. Key factors independently associated with a higher intention to undergo combined screening included a lower perceived financial burden and lower perceived negative health consequences of UGIE²⁰⁵. These findings were further confirmed in a subsequent cross-sectional study targeting complication risk perception assessment, showing that a lower risk perception for UGIE complications was

associated with a higher willingness to undergo UGIE combined with a screening colonoscopy¹⁹⁴.

Our studies were pivotal in assessing risk perception for UGIE combined with colonoscopy. As in the prior study, the main limitations of our cross-sectional analysis of GC risk perception are its regional scope and the potential introduction of healthy user bias. Nevertheless, a Portuguese retrospective study, published only later, reported a 95% acceptance rate for combined screening, corroborating our findings²⁰⁶. Previous studies focusing on GC screening alone were also aligned with our results. A systematic review on barriers and facilitators to GC screening, including mostly Eastern studies, concluded that fear of the screening procedure was the most commonly reported barrier¹⁸⁴. Fear of undergoing UGIE was pointed out as the reason for non-adherence by 38.1% of participants in a cross-sectional Chinese study and by 8.4% in the Korean National Cancer Screening Survey^{183,207,208}.

Data on population GC screening programs are scarce outside high-risk countries, such as Japan and Korea^{120,133}. In Europe, there are no population-based programs or sufficiently robust data that can serve as a direct comparator. However, two cost-effectiveness analyses have been performed^{4,21,22}. Both economic evaluations show that endoscopic screening is cost-effective in Portugal, if combined with a screening colonoscopy^{21,22}. Despite the favorable economic evaluation, no organized screening program has yet been formally implemented across intermediate-risk European countries.

We conducted a population-based retrospective cohort study to assess the impact of a FIT-based screening program on GC outcomes and to determine the proportion of individuals undergoing combined endoscopic screening, using population data to mitigate potential behavioral biases. Among FIT screened individuals referred for colonoscopy, more than half underwent concomitant UGIE. The decision to perform colonoscopy and/or UGIE was primarily made by general practitioners and influenced by regulatory limitations. Thus, this proportion likely underestimates the true intention to undergo combined screening. The

implementation of the FIT screening program expanded colonoscopy coverage, which in turn could have indirectly facilitated access to endoscopic procedures and increased the number of UGIEs performed. Notably, the implementation of FIT-based screening coincided with significant improvements in GC outcomes, with a 14% increase in early-stage diagnoses and an improvement in 3-year net survival from 42% to 49%. Our line of investigation is concordant with the European Union recommendations on cancer screening and with the efforts of the TOGAS project, which recently launched a pilot study on combined screening¹⁴⁸. It is also aligned with previous reviews suggesting routine UGIE screening for FIT-positive patients²⁸. Controversially, the Dutch screening cohort reported a higher detection rate of neoplasms proximal to the colon among FIT-positive individuals, although the 3-year cumulative incidence below 1% did not support a recommendation for combined screening²⁹. By contrast, in a high incidence setting like the Korean National Cancer Screening Program, the 3-year incidence of GC reached up to 2.6%¹⁷⁸. The encouraging results obtained in Northern Portugal must be considered in light of the study's limitations. Since we could not determine the indication for procedures at contracted units, symptomatic cases may have inflated the impact of FIT screening on GC detection rates. The improved GC outcomes cannot, based on our study design, be solely attributed to the FIT screening program alone, since the trend toward increased early detection and improved survival had already been observed prior to the implementation of FIT screening and could be explained by other contributing factors, such as usage of high-definition endoscopes with chromoendoscopy, enhanced training, and quality improvement initiatives^{23,209}.

In conclusion, GC screening through UGIE should be implemented in our country. UGIE is the most valid diagnostic method, has been suggested to be cost-effective in intermediate-risk regions, is highly accepted by patients—particularly when combined with colonoscopy with fully reimbursed sedation—and is associated with improved early detection and survival. These results highlight the transformative potential of integrated screening

programs in reducing the burden of GC, providing a compelling model for adoption and scalability in intermediate-risk settings worldwide.

3. Risk perception and health literacy in GI cancer: addressing knowledge gaps in endoscopic screening

Taken together, the findings from the three cross-sectional studies on risk perception highlight limited health literacy regarding digestive cancer symptoms, risk factors, and the potential risks of endoscopic screening procedures. Our results highlight the pressing need for targeted initiatives aimed at improving health literacy, which is critical for empowering individuals to make informed decisions about cancer screening participation and ultimately promoting more equitable and effective screening uptake.

Several interventions previously proposed could be implemented, including classic approaches such as community campaigns, public health initiatives (e.g., Digestive Cancer Day), and awareness-raising efforts involving public figures²¹⁰. Additionally, social media can serve as a valuable channel to improve health literacy, foster health education and facilitate wide dissemination of public health information²¹¹. Thus, targeting the eligible population with content on social media platforms represents an innovative approach to improving health literacy^{211,212}. Virtual health assistants can further enhance health literacy by providing personalized recommendations that simulate high-quality patient-provider communication, elicit individual preferences, empower decision-making, and promote screening uptake^{213,214}. Integration of AI may enable automated tracking of non-adherent individuals and delivery of targeted interventions through periodic reminders and personalized counseling by AI-driven conversational agents³⁷. Ultimately, these strategies should complement rather than replace the central role of primary care physicians, whose ongoing support and guidance remain essential to promoting informed participation in cancer screening⁹.

This thesis highlights the pressing need to strengthen health literacy as a strategy to overcome barriers to cancer screening and, ultimately, to lessen the burden of both CRC and GC. Moreover, it offers robust evidence to inform screening strategies in Northern Portugal, supporting the integration of colonoscopy as an alternative to FIT and advocating for the pioneering implementation of GC screening through the combination of UGIE and colonoscopy.

4. CONCLUSIONS

Globally, CRC is the third most diagnosed malignancy and constitutes a growing public health burden, which may be reduced through the implementation of population-based screening^{1,2}. While GC still ranks as the fifth most common cancer, population-based screening is neither widely implemented nor consensual in intermediate-risk regions¹⁶.

The present research project was designed to generate critical data to inform public health policies and consequently, further optimize the design of cancer screening programs. Although certain limitations have been acknowledged, which highlight the need for further research, several conclusions can nonetheless be drawn across three main domains: personalized screening strategies, potential synergies across cancer screening programs and individual risk perception.

Across our studies, FIT was well accepted among never-screened participants in Northern Portugal, confirming its value as a noninvasive and widely accessible tool. An analysis of the first three years following the implementation of an organized FIT-based screening program showed an increase in early detection and improved survival. Nevertheless, a considerable proportion still expressed a preference for colonoscopy and have performed colonoscopy outside the screening program. Additionally, endoscopic procedures performed parallel to the organized program substantially contributed to overall coverage by any CRC detection test. Offering colonoscopy to individuals who decline FIT could personalize the screening process, address individual preferences, and ultimately optimize population coverage.

GC screening is systematically implemented only in two high-risk countries, where organized programs have significantly reduced mortality, with endoscopic screening shown to yield higher detection rates¹²⁸. In Northern Portugal, the intention to adhere to a combined endoscopic screening approach reached 94%, highlighting the potential feasibility and

acceptability of implementing integrated screening programs in intermediate-risk European countries. Following the implementation of the FIT-based screening program in Northern Portugal, GC early-stage detection increased significantly, accompanied by improved survival rates. Notably, even in the absence of an organized GC screening program, more than 50% of individuals who completed FIT-based screening and underwent colonoscopy also received a UGIE.

Throughout the studies presented in this thesis, knowledge of CRC and GC symptoms and risk factors was consistently low, reinforcing the urgent need for initiatives to improve health literacy. A higher perceived testing need score, which reflects a better understanding of the rationale for screening, was an independent predictor of the intention to adhere to CRC screening. Likewise, lower perceived barriers, such as concerns about negative health consequences of UGIE and financial burden, were independently associated with a greater intention to accept UGIE combined with screening colonoscopy. In line with these findings, participants who underwent combined screening were less likely to report a high perceived risk of complications from colonoscopy and UGIE. Notably, the perceived risk of colonoscopy complications did not appear to discourage participation in CRC screening. Yet, this is explained by greater awareness among previously screened individuals and by limited knowledge among those not yet submitted to endoscopic procedures.

Our findings emphasize the potential for personalized CRC/GC screening strategies, such as offering colonoscopy as an alternative to individuals who decline FIT screening and also offering the possibility of upper GI screening. This tailored approach could increase population coverage and boost the effectiveness of organized screening programs. Furthermore, the high acceptance rates observed for combined endoscopic screening highlight its feasibility in intermediate-risk regions, paving the way for the implementation of GC screening programs. Importantly, there is an urgent need for targeted health literacy campaigns to bridge knowledge gaps. The synergistic integration of various cancer screening

programs has the potential to significantly enhance public health strategies. By leveraging shared resources and tailoring approaches to population needs, these combined efforts could effectively reduce the overall cancer burden and improve early detection.



Chapter VIII – Future Directions

FUTURE DIRECTIONS

The project embedded in this thesis represents a comprehensive effort to derive clear answers within the inherently complex and heterogeneous domain of digestive cancer screening. Our research plan was ultimately designed to generate conclusions with clear clinical relevance and to inform public health policy. While the results obtained contribute meaningfully to the optimization of screening strategies, they also highlight persisting knowledge gaps and raise new questions.

This research highlights three delineated avenues for future investigation: personalized screening strategies, potential synergies across cancer screening programs as well as individual risk perception and health literacy.

Concerning personalized screening initiatives, several key objectives can be pursued to enhance their effectiveness and implementation:

- Proactively offer colonoscopy to individuals who decline FIT screening within a prospective cohort and measure the resulting variation in adherence rates.
- Assess endoscopy capacity within the Portuguese healthcare system and conduct an economic analysis comparing the implementation of a personalized CRC screening strategy with a standard FIT-only approach.

In the setting of synergies across cancer screening programs, future research should explore the following aims:

- Conduct a pilot project to proactively offer UGIE to asymptomatic individuals referred for colonoscopy—either due to a positive FIT result or as part of an individualized primary screening approach—and evaluate adherence, the prevalence of premalignant conditions, and the detection rate of early-stage GC.
- Prospectively offer non-invasive combined fecal testing (FIT plus HPSA) and measure adherence. Evaluate the impact on long-term GC survival and cancer-

related mortality of a strategy that offers *Helicobacter pylori* eradication therapy to individuals testing positive on HPSA and combined UGIE and colonoscopy to those testing positive on FIT.

- In the primary care setting, compare synergic health interventions aimed at combined screening tests for different cancer types (e.g., breast cancer mammography and FIT, serum anti-*Helicobacter pylori* IgG antibodies and PSA) with the standard of care, and measure long-term outcomes.

Within the domain of individual risk perception assessment, several potential objectives can be listed:

- Prospectively compare individuals' willingness to undergo screening, as measured by the PERCEPT PREVENT tool, with the actual uptake of FIT and/or colonoscopy.
- Compare educational interventions delivered by healthcare professionals, AI-powered virtual assistants, or targeted content on social media platforms and evaluate their impact on digestive cancer risk perception using the PERCEPT PREVENT tool.
- Adaptation and validation of the PERCEPT-PREVENT tool for high-risk endoscopic procedures, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

By addressing these critical areas, future research will be instrumental in refining screening strategies that are grounded in robust evidence, centered on patient needs, and designed to be adaptable and sustainable in the face of evolving healthcare challenges, ultimately aiming to increase early detection and improve survival in digestive cancer.



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