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The Final thesis

The Impact of colorectal cancer screening program on Mortality in Lithuania

(title)

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1. ABSTRACT

Introduction: Lithuania's colorectal cancer (CRC) screening program originated in June 2009 and from January 2014 onwards, the program covers a population aged between 50 to 74. CRC screening program is based on reducing the incidence and mortality by removal of advanced adenoma and the early detection of the disease.

Aim: To assess the impact of colorectal cancer screening on the mortality rates in Lithuania

Methods: This study consists of a retrospective review of prospectively maintained data extracted from the National Colorectal Cancer Screening database of all individuals aged 50-74 who participated in the national colorectal screening program between the years 2013-2019 in Lithuania. The data on survival was extracted from the same database. We performed statistical data analysis using R statistical software package V 4.2.2 (2022-10-31) (© 2022 The R Foundation for Statistical Computing), RStudio 2022.07.2 Build 576 © 2009–2022 RStudio, PBC.

Results: 4% of individuals, who tested negative on the fecal immunochemical test (FIT) died, as compared to 5% of FIT-positive patients, who either had a normal colonoscopy or had adenoma, polyp, or normal tissues on colonoscopy biopsy; 8 % of patients, who had high-grade dysplasia died as well as 19% of those, that had biopsy-proven CRC. The mortality risk in FIT-positive individuals who did not undergo screening colonoscopy was significantly (78%) higher than in those, who completed their colonoscopy (9% vs 5%). Overall, completing FIT screening is associated with a reduced risk of death over 5 years.

Conclusions: There is a strong correlation between the results of CRC screening results and the overall risk of death over the period of 5 years. Completing CRC screening in FIT-positive patients is associated with a 78 % reduction in the risk of death.

Keywords: Colorectal cancer, Screening, Fecal immunochemical test, Colonoscopy, Mortality

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
CRC	Colorectal cancer
IBD	Inflammatory bowel disease
DNA	Deoxyribose nucleic acid
gFOBT	Guaiac Fecal occult blood test
FIT	Fecal Immunochemical Test
CS	Colonoscopy
DCBE	Double-contrast barium enema
CTC	Computed tomographic colonography
CCE	Colon capsule endoscopy
FDA	US Food and Drug Administration
FS	Flexible sigmoidoscopy
GI	Gastrointestinal tract
GP	General Practitioner
NHIF	National Health Insurance Fund

3. LIST OF TABLES AND FIGURES

4. INTRODUCTION

4.1 EPIDEMIOLOGY OF COLORECTAL CANCER

Colorectal cancer (CRC) in terms of incidence and mortality was recorded to be the third and the second most common cancer worldwide with new cases of 1.9 million and a 10% mortality of 935,000 patients in the year 2020 (1). In Europe, it was recorded to be the second and third leading cause of death caused by cancer among men and women with an estimated number of deaths of about 242,000 in the year 2018 (2). In Lithuania, it is reported to be the second most common cancer with 1892 men and women diagnosed with CRC, accounting for about 11.4% of all cancer diagnoses (3). This is currently the third most cancer burden in the country (4).

4.2 PATHOGENESIS OF CRC

CRC progresses from a polyp that begins as an aberrant crypt evolving into a neoplastic precursor lesion and then into cancer during a 10–15-year time period (5). The cell of origin is currently assumed to be a stem cell or a stem cell-like cell resulting from a progressive accumulation of epigenetic and genetic alterations that are capable of creating several alterations in the tumor-suppressor gene by inactivating it and in turn activating oncogenes (6,7). Globally, two major distinct pathways are identified to form the precursor lesion: the adenoma-carcinoma pathway causing about 70-90% of CRCs and the serrated neoplasia pathway causing 10-20% of CRC pathways (5). Although CRC can affect all the parts of the colon, 50% of the localizations are present in the distal part involving the sigmoid and the rectum (8).

4.3 RISK FACTORS

Various risk factors can influence the diagnosis of CRC and some of them can be age, family history and genetics, history of polyps or CRC, IBD, diet, obesity, and sedentary lifestyle, and smoking and alcohol consumption. The risk of CRC increases with age and most of the screening programs target those who are 50 years old and above. (9,10). People with a family history of CRC or genetic mutations like Lynch syndrome or familial adenomatous polyposis are studied to have a higher risk of developing CRC (11). Previous history of the disease or polyps increases the risk of future CRC reoccurrence or development (12). The presence of a history of IBD such as ulcerative colitis or Crohn’s disease has an increased probability of developing CRC due to the association with dysplastic colonic mucosa (13). A study of 693 patients in Iran evaluated patients for the associations of colon adenoma with diabetes and

obesity and found that there was an increase in precancerous lesion findings in the aforementioned groups signifying the increased risk of CRC in obese and sedentary life-leading patients (14). Association of smoking with CRC in a meta-analysis showed that there was an increase in the risk of developing CRC up to 27% with which current smokers had a higher risk than former (15). The authors of this study suggested that this could be due to the increased carcinogens in the smoke leading to damage in cell DNA and thereby creating mutations in the lining of the colon and rectum which in turn could develop into cancer (15).

Like smoking, alcohol could also create damage to DNA of the cell linings of the colon and rectum and have shown to have an increased risk of attaining CRC by 21% when linked with heavy consumption of alcohol i.e., 30g or more alcohol per day (16). Other factors such as diet or other existing diseases could also contribute to the risk of developing CRC.

4.4 PREVENTION STRATEGIES

Despite continuous improvement in treatment strategies, 40% of patients still die from the disease which leads to an understanding that there is still room for improvement in the management of the disease involving various preventative strategies, early detection, and treatment (8). Treatment and improvement of prevention strategies for CRC before the final decades of the 19th century were mostly misjudged to be palliative and did not aim to achieve a cure. This led to diagnosis during an advanced stage of the disease when the patients sought medical treatment attention (17). However, in the 2nd decade of the 20th century, the initial idea of cancer being characteristically systemic at the beginning of the disease changed to an understanding that the disease develops from a single localized cell and then thereby progresses into advanced stages of disease when systemic (18). Further refinement of the theory helped provide greater insight that led to pursuing curative therapy for early staged disease detection and removal of polyps (17). Several prevention strategies can be implemented to reduce the risk of CRC in a population and they can be classified into primary and secondary prevention strategies.

4.4.1 PRIMARY PREVENTION

Primary prevention strategies involve tackling certain measures affecting risk factors. One of the primary prevention methods that can theoretically prevent at least 70% of colon cancers is maintaining a healthy lifestyle with dietary modifications (19). Some studies have shown the association of red meat with increased risk for CRC due to possible reasons of total fat, protein, saturated fat, iron, or carcinogens being a part of the major source (19). A case-control study in

the UK concluded that intake of dietary fibre was inversely associated with the risk to develop CRC (20). Some authors have also concluded the protective role of calcium and vitamin D and dairy intake while others also brought up less verified components such as magnesium, garlic, omega fatty acids, folate, and Vitamin B6 to have a positive impact on disease risk (20–25). Obesity has been shown to have consistent associations with the high-risk development of CRC as well as worse outcomes post-diagnosis (26–28). A review of 29 studies revealed that for every increase in 5 kg/m2 in body mass index, 24% of CRC increase for men and 9% for women was studied (26). Alcohol consumption, although controversial, has been reported as having increased risk in individuals with moderate to heavy alcohol intake (29). While currently there are no widely accepted chemo-preventive indications for CRC, some or several pharmaceuticals have demonstrated primary preventive effects against CRC (9). Aspirin and COX-2 selective inhibitors are two of the most investigated agents in regards to CRC prevention and regular usage of these agents has shown potential capability in reduction of incidence in individuals at both, average and high. (30,31). However, it is quite important to weigh potential benefits over risks in this approach to minimize side effects as with any other medical treatment. In the general population, benefits are usually outweighed by risks although some individuals at increased risk for colorectal neoplasia have been supported with this approach (30).

4.4.2 SECONDARY PREVENTION

Secondary prevention strategies involve interventions or screening methods establishing the early diagnosis of cancer or preneoplastic lesions in selected groups of the population that is at average or increased risk (32). Early diagnosis of the disease can drastically impact the prognosis of the disease, as a 5-year survival with CRC is between 50% and 60 % (33) with a higher survival rate of 75% to 90% in its initial stages and a survival rate less than 15% in advanced stages (34). Most of the CRCs detected after the presence of signs and symptoms could typically indicate disease at its advanced stage and could not, thereby, contribute to a positive effect on the prognosis of the disease (35). Hence this makes an understanding that early detection of the disease in a population could have great importance on the prognosis of the disease (35). Here is where CRC screening comes into action. Not everyone is likely to be benefitted from the program but those who are a part of the average risk population including men and women surpassing the age of 50 without any symptoms, family history, or personal history of CRC (35). In the year 2000, the European Union member states received recommendations from the Advisory Committee on Cancer Prevention to implement and use

the screening program for the asymptomatic population above 50 years old (36). There are about three screening methods available: stool-based, imaging, and endoscopy tests for early detection and screening (37).

4.4.2.1 STOOL-BASED TESTS

4.4.2.1.1 Guaiac-based faecal occult blood test (gFOBT)

gFOBT works by detecting the presence of heme from hemoglobin in a stool sample based on the properties of alpha-guaiaconic acid, a phenolic compound extracted from Guaiacum trees. The addition of hydrogen peroxide on guaiac paper causes the oxidization of alpha-guaiaconic acid, a process that usually requires a long time, turning it into blue. However, the presence of heme catalyzes the process within seconds and causes an immediate reaction resulting in the change of colour to blue (38,39). Although this screening method was one the most cost-effective and non-invasive, it, unfortunately, has a lot of disadvantages carried along. (9) One of them is the fact that there are a lot of strict dietary restrictions implemented before the testing and that it can induce false-positive tests due to the ability to be catalysed by any peroxidase, like the heme present in meat, leading to unnecessary colonoscopies (9,38,40). On the contrary, false negative cases experienced were due to the ingestion of a large amount of Vitamin C (41). In addition to the dietary restrictions, patients needed to repeat the sample three consecutive times to achieve the aimed sensitivity (42). Finally, there is difficulty in the detection of polyps with g FOBT as polyps do not bleed and reduced sensitivity in identifying advanced adenoma (43).

4.4.2.1.2 Fecal immunochemical test (FIT)

FIT is a screening tool that detects blood in stool using a specific antibody against human hemoglobin. Since FIT has lesser dietary restrictions and observer bias as compared to gFOBT, it has a comparatively higher specificity for both adenomas and cancers (44,45). Although more expensive than gFOBT, FIT is more compliant and convenient for patients to use, due to the requirement for fewer samples (46). Speaking in terms of sensitivity and specificity, it is 79% and 94% according to a study in 2014 (47).

4.4.2.1.3 Fecal DNA testing

The stool DNA testing can detect large cells from colorectal neoplasms in the stool, due to their sloughing off or remarkable exfoliative nature, which makes them release these cells into the lumen, which then thereby provides a DNA biomarker in the stool, helping to detect CRC

earlier (48). The sensitivity of fecal DNA is 92% and specificity is 87%, although it often provides false positive test results which would thereby require colonoscopy (CS) to recheck and confirm the diagnosis (49).

4.4.2.2 IMAGING TESTS

4.4.2.2.1 Double-contrast barium enema (DCBE)

DCBE is a fairly old method that was considered safe and used in the past but less frequently now due to new methods available instead. Here, the colon is distended with air after coating the mucosa with barium, both of which are rectally conducted and are then studied with the help of an X-ray. Sensitivity for DCBE is only recorded to be about 50% for polyps greater than 10mm and there is a high occurrence of false positive results due to poor bowel preparation (50,51).

4.4.2.2.2 Computed tomography colonography (CTC)

CTC, also called the virtual CS, was developed in the mid-1990s and 2016 and approved by the US Food and Drug Administration for colorectal cancer screening (52). Here, the reconstructed images of the air-distended colon by Computed tomography (CT) and Magnetic resonance imaging (MRI), are thereby used to provide a two-to-three-dimensional image of the lumen of the colon (53). There has been a lot of variation in different studies about the diagnostic values of CTC, however, the introduction of newer methods and techniques has led to CTC developing its sensitivity and specificity closer to that of CS when speaking in terms of CRC detection (54). Per-person sensitivity and specificity for the adenomas sized ≥ 10mm were studied to be 67% to 94% and 86% to 98% (55) and ≥ 6mm were 73%–98% and 80%–93% respectively (56). Speaking about the risk of colonic perforations, compared to CS, CTC due to being minimally invasive has a lower risk of perforation and bleeding and is preferred by patients due to the lack of usage of sedation (57). When preparing for a CTC procedure, preparation of the bowel is quite necessary and consists of three components; dietary restriction, fluid and fecal tagging, and colon catharsis (58). Major drawbacks of CTC could involve, follow-up with the means of CS if results were positive, as excision or biopsy could not be performed by CTC, and the other drawback is the exposure to radiation (54,59). Finally, there have been many studies regarding the incidental extracolonic findings that can be detected, which can be addressed as an advantage but on the contrary, also lead to unnecessary anxiety of the patient along with overdiagnosis and overtreatment (9,55).

4.4.2.3 ENDOSCOPIC TESTS

4.4.2.3.1 Colon capsule endoscopy (CCE)

CCE is an FDA-approved endoscopy method in which patients are given a capsule containing a tiny wireless video camera which is swallowed, thereby taking images as it passes through the colon (60). CCE is usually performed in average-risk patients not as a screening option but in those with incomplete CS or in those who refuse or have contradictions for CS, and its role is still rapidly evolving (61). CCE requires adequate bowel preparation but does not require sedation or alteration in medications or diet (62). Although patients usually prefer CCE over CS, CCE is an expensive camera-only visualization test that cannot help in the removal or biopsy in the presence of a polyp (63,64). A study conducted on asymptomatic patients using high-quality CS as a standard for comparison showed that CCE was able to identify subjects with at least one adenoma ≥ 6mm, with sensitivity and specificity of 88% and 82% while those with adenomas ≥10mm of 92% and 95% (65).

4.4.2.3.2 Flexible Sigmoidoscopy (FS)

FS is a procedure performed every 5 years, that allows visualization of lesions, biopsy, and removal of polyps in the left side of the colon, from the rectum until the splenic flexure, using a 60cm long flexible endoscope (66,67). Sedation during the procedure is often not required it can be usually performed by trained surgeons, primary care clinicians, gastroenterologists, and advanced practitioners (66). However, when lesions are present on the right side or proximal part of the colon, detection is often missed, making FS less sensitive as compared to CS (68). Perforation of the colon was one of the most seen complications as seen in a Medicare study of the population with 0.88 perforation rates per 1000 sigmoidoscopies (69). Positive FS often requires follow-up with CS, although polyps of smaller size can be biopsied or excised using FS, lesions larger than 1.0cm are usually excised during these follow-up CS (67).

4.4.2.3.3 Colonoscopy (CS)

CS is a procedure that enables visualization of the colon, rectum, and terminal portion of the ileum using a 120cm to 160 cm long flexible fibreoptic endoscope, performed every 10 years if the patient belongs to the category of average to high risk for CRC (67,70). It is considered to be a “gold standard” screening test for CRC as it is noted to have high sensitivity and acceptable specificity in the detection of adenomas, also allowing to perform a biopsy and removal of the same, all during one test (67). However, like in any other procedure, CS weighs

some disadvantages which mostly are related to the requirement of extensive bowel preparation before the procedure, possible sedation of the patient and its side effects and possible perforation, major bleeding, and infection of 0.1% -0.2%, with increased risk in elderly or comorbid patients (67,70). Another limitation involves increased cost and requirement of specialized equipment and well-trained endoscopist which highly limit its overall availability (67).

TABLE 1: SCREENING TOOLS BENEFITS, DRAWBACKS, AND MORTALITY REDUCTION RATE

Intervention	Benefits	Drawbacks	Reduction of CRC mortality rates
gFOBT	Inexpensive, easy to perform at home, non-invasive procedure. Has a role in CRC mortality reduction.	False positive results, dietary restrictions, repeated sampling. Has low sensitivity and specificity.	15%-33% (71).
FIT	Non-invasive and have higher sensitivity and specificity compared to gFOBT. Fewer dietary restrictions and occurrence of false positive tests compared to gFOBT.	Requirement of follow-up CS. Possible false positives and negatives can occur, certain drugs and dietary restrictions (72).	40% (73).
Fecal DNA testing	Non-invasive, easy to perform at home, require no dietary or drug restriction, and has higher sensitivity for the detection of advanced precancerous lesions than FIT (49).	Expensive and if positive, require subsequent evaluation with CS, decreased specificity than FIT and CS, and decreased sensitivity for	54% (75).

	Adherence to positive test results on follow-up CS, mostly involving right-sided lesions. (74) Testing frequency is every 3 years, making it more convenient than annual testing. (67)	adenomas ≤9mm (67).	
DCBE	Non-invasive, cheaper, and with lesser complications than CS, sedation is often not required, able to detect polyps greater than 1cm (76).	Radiation exposure of the patient, and inability to excise the lesion for biopsy thereby requirement of follow-up (77). Various factors determine the accuracy of the test (76). Requirement of a well-trained radiologist to interpret images.	Unknown
CTC	No requirement for sedation or analgesia, less invasive than CS, ability to view the appendix and extracolonic structures other than the mucosa of the	Small radiation exposure, patient anxiety due to extracolonic findings, bowel preparation, the requirement of a contrast agent, and the requirement of a	68% (79,80).

	colon, has a high sensitivity for polyps ≥10mm, more patient uptake than CS (78).	well-trained radiologist, may miss small polyps (78). A colonoscopy is required to confirm positive findings.	
CCE	Non-invasive intervention that does not require sedation or dietary adjustments, is safer than CS, has better tolerance of patients as compared to CS, and is possible to completely visualize the colon, including the cecum and ileocecal valve (81).	Intense bowel preparation, inability to remove polyp during visualization process thereby follow-up CS requirement, reduced accuracy in detecting smaller lesions than in CS, missed lesions, expensive and decreased availability in all screening (81).	Unknown
FS	Prevents incidence of both distal and proximal colon cancers, decreases mortality of distal colon cancers, sedation not necessary, lesser complications than CS, able to detect and remove small polyps present in the	Inability to detect and remove right-sided polyps, the requirement of follow-up CS in case of positive FS to fully evaluate the rectum and colon, possible complications such as bowel perforation and bleeding,	Overall mortality was reduced by 28%, and distal CRC mortality reduction by 43% (83).

	distal colon and rectum, lesser intense bowel preparation and less expensive than CS (82).	technical difficulties that interfere with FS reaching adequate depth, and absence of sedation reduce patient uptake of the test (82).	
CS	High sensitivity for both cancer and all precancerous lesions, ability to diagnose and treat at one go, long examination gap (10 years) if test results are normal, a significant reduction in the incidence and mortality of CRC, and cost-effective (82).	Requirement of intense bowel cleansing, high risk for bowel perforation, aspiration pneumonitis due to deep sedation and after-procedural bleeding, quality dependence of the test on operator skills for detection of cancer and other lesions plus selecting the right surveillance and screening intervals after CS (82).	Overall CRC mortality reduction of 67%. 65% right-sided colon and 75% left-sided colon cancer mortality reductions (84).

4.5 CRC SCREENING PROGRAM IN LITHUANIA

The CRC screening program in Lithuania was first introduced in June 2009, screening all people aged 50-74 from January 2014 (85). The primary aim of the screening program was to increase the detection of early staged cancers and identification of precancerous polyps so that interventions and treatments could limit the advancement of cancer and thereby reduce both incidence and mortality caused by CRC in the screened population (85). There are four services

provided by the screening program which include: (1) Providing information about the program which includes FIT in it too, (2) Referral for CS, (3) CS with or without biopsy, (4) Pathological examination and diagnosis (85). Every two years Lithuanian residents are invited by the program to get FIT done. The three main FIT tests that are registered in Lithuania include AQ4 PolyCheck (Veda Lab, Alençon, France), MediSmart (Lobeck Medical Ltd., Frick, Switzerland), and IFOB (SureScreen Diagnostics Ltd., Derby, UK) (85). The system of invitation of the screening population is not centrally organized and the population generally receives a leaflet with information from their respective general practitioners (GP) about the screening (4). The screening individual then receives a FIT kit along with information on how to sample fecal specimens accurately to test oneself, after which he or she reviews the processed kit with the results along with their GP, concluding this particular service. Based on the positive test result, individuals are registered and referred by their GP to perform CS, whereas, if the test result is negative, individuals are advised to repeat the test in 2 years time period (4). When the referral for CS is done by the GP, the patient is provided with information about the technique of bowel preparation that needs to be conducted beforehand. The patient receives a bowel preparation kit that contains Macrogel 4000 with sodium sulphate, sodium hydro carbonate, and sodium and potassium chloride, of which one packet contains 75g for 15-20kg body weight dissolved in 1L of water (85). The performance of CS is carried out under sedation with Midazolam by the anesthetist (4). The final report of the CS along with the biopsy results, if performed, are provided and sent to the referring physician for further evaluation and explanation of the results to the patient. This concludes the referral for the CS step (85). If cancer is suspected, it is recommended to attain at least five samples of the biopsy and sent them to the respective pathological centers for further examination and diagnosis, and the results will be provided to both the GP and the institution where the CS was initially performed (85). If CS results were normal, it could mean that FIT need not be performed earlier than after 10 years time period (85). The funding of the program is performed by the National Health Insurance Fund (NHIF) which consists of a steering committee involving representatives of surgeons, epidemiologists, endoscopy specialists, primary care physicians, and pathologists as well as NHIF and the Ministry of Health representatives, who assesses and monitors the program (4). This is a Medicare database performed to assess the impact of CRC screening on the mortality rates of the screening population in Lithuania, aged 50 to 74 from the years 2013-2019, based on the data obtained from the National Cancer database.

5. METHODS

5.1 DATA SOURCE

The anonymous data of the population aged 50-74 from the years 2013 to 2019, who participated in the CRC screening program were extracted from the statistical database of the NHIF, which provided both, the participation in different services of screening indicated by specific codes, as well as the fact and the year of death. No data on the cause of death was provided.

5.2 DATA ANALYSIS

We performed statistical data analysis using R statistical software package V 4.2.2 (2022-10-31) (© 2022 The R Foundation for Statistical Computing), RStudio 2022.07.2 Build 576 © 2009–2022 RStudio, PBC.

We presented the characteristics of the qualitative variables in frequency tables with absolute numbers and percentages in the appropriate subgroup of the sample. We used Pearson's Chi-square (X2) criterion for statistically significant differences between nominal variables for the evaluation of the respective groups. We evaluated the effect sizes between the respective subgroups of the sample with nominal variables using Cramer's V effect sizes. We consider the effect size to be tiny if Kramer's V r< 0.05, very small if Kramer's V 0.05<=r < 0.1, small if Kramer's V 0.1<=r < 0.2, medium if Kramer's V 0.2< =r < 0.3, large if Kramer's V 0.3<=r < 0.4 and very large if Kramer's V r≥ 0.4 (“funder2019”) rules). For the assessment of Odds Ratio (OR) relationships, we created a univariate logistic regression equation.

Relationships between variables were considered statistically significant when the p-value was less than 0.05 ($p < 0.05$), and the statistical power of the test 1-ß was equal to 0.95 (1-ß = 0.95).

6. RESULTS

Anonymized data of a total of 1,543,766 individuals were retrieved from the database between 2013 and 2019, of whom 1,521,551 took part in the screening program. It was not possible to retrieve data of the non-participants of the screening program from the database for comparison. The number of persons who participated in the screening program annually is shown in Table 2 below, and Table 3 includes the codes given to each screening intervention and the total number of people who underwent each screening technique. Table 4 displays the correlation between each interventional code to the screened population, in terms of survival and mortality and Figure 1 depicts the same graphically. Figure 2 illustrates the survival and

mortality rates among patients with positive FIT results who underwent CS, those with positive FIT results who did not undergo CS, and those with positive FIT results who underwent CS. Figure 3 shows the survival and mortality rates between people who had a positive FIT and underwent a CS and those who had a positive FIT but underwent no CS. Figure 4 compares the survival and mortality rates between those with a negative FIT who did not perform CS and those with a positive FIT who did not undergo CS and Figure 5 compares the same between those with negative FIT results who did not perform a CS and those with positive FIT results who performed CS.

In summary, 4% of individuals, who tested negative on the fecal immunochemical test (FIT) died, as compared to 5% of FIT-positive patients, who either had normal CS or had adenoma, polyp, or normal tissues on colonoscopy biopsy; 8 % of patients, who had high-grade dysplasia died as well as 19% of those, that had biopsy-proven CRC. The mortality risk in FIT-positive individuals who did not undergo screening colonoscopy was significantly (78%) higher than in those, who completed their colonoscopy (9% vs 5%). Overall, there seems to be an association between the findings of the CRC screening program and the 5-year overall risk of death.

TABLE 2: POPULATION PARTICIPATED BY YEARS

Years	Number of people (N=1,521,551)
2013	114,436
2014	230,364
2015	204,493
2016	228,205
2017	224,599
2018	236,095
2019	255,899

TABLE 3: PARTICIPATION BY CODES

Codes	Description of code	No. of people (n)
3019	Referral of the patient to a specialist doctor for a colonoscopy	23,878
3024	Information on early diagnosis of colon cancer and evaluation of FIT results – found FIT positive (+)	52,748
3023	Information on early diagnosis of colon cancer and evaluation of FIT results – found FIT negative (-)	1,393,305

3026	Examination and evaluation of colonoscopy biopsy material - tissue found to be normal (normal)	1,567
3027	Examination and evaluation of colonoscopy biopsy material - polyp identified	4,106
3028	Examination and evaluation of colonoscopy biopsy material- adenoma identified	15,063
3029	Examination and evaluation of colonoscopy biopsy material- an adenoma with high-grade dysplasia was found	2,508
3031	Examination and evaluation of colonoscopy biopsy material- carcinoma identified	832
3421	Examination and evaluation of colonoscopy biopsy material - other pathological changes	84

TABLE 4: ASSOCIATION OF SURVIVAL AND MORTALITY TO EACH CODE

Code	**Alive**	**Dead**
3019	22,027 (92%)	1,851 (8%)
3024	48,074 (91%)	4,674 (9%)
3023	1,335,406 (96%)	57,899 (4%)
3026	1,491 (95%)	76 (5%)
3027	3,908 (95%)	198 (5%)
3028	14,297 (95%)	766 (5%)
3029	2,296 (92%)	212 (8%)
3031	670 (81%)	162 (19%)
3421	82 (98%)	2 (2%)

Figure 1 RELATIONSHIP BETWEEN SURVIVAL AND MORTALITY TO THE CODES

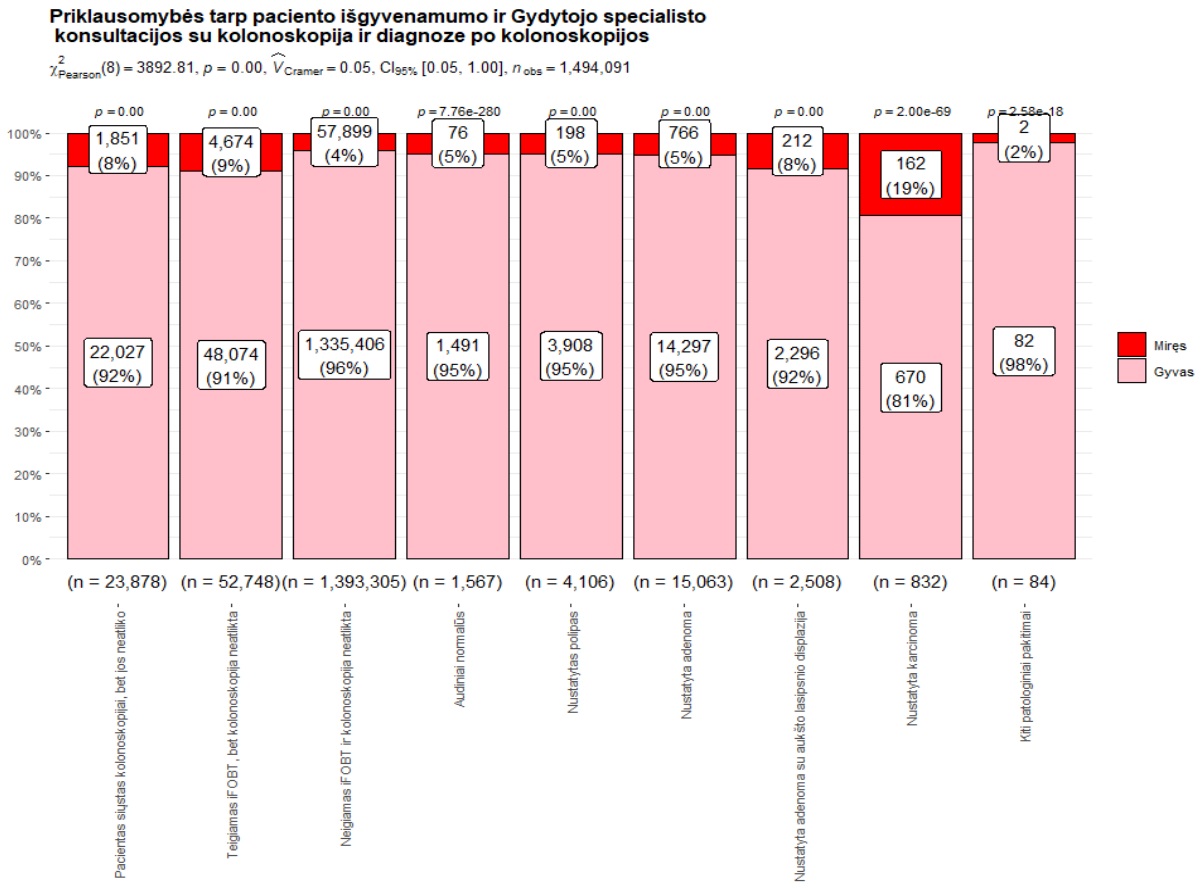


Figure 2 RELATION BETWEEN DEATH AND SURVIVAL IN NEGATIVE AND POSITIVE FIT WHO DID AND DID NOT PERFORM CS

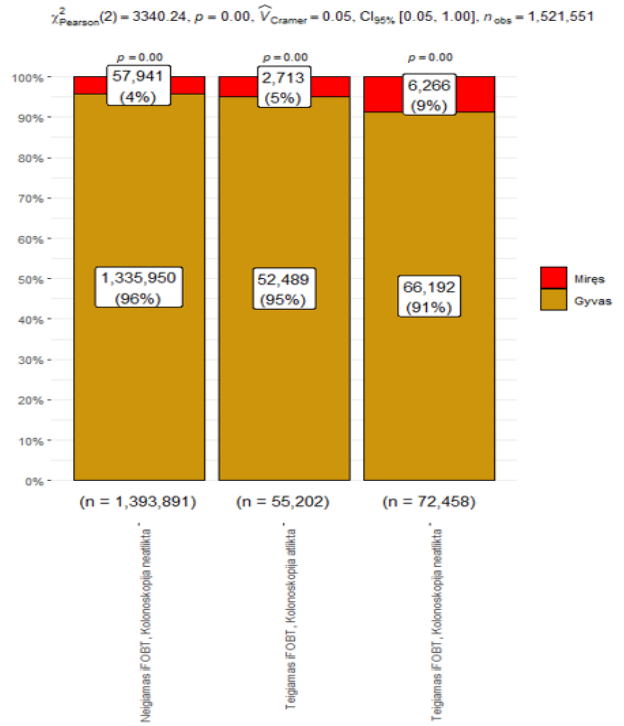


Figure 3 SURVIVAL AND MORTALITY IN POSITIVE FIT WHO PERFORMED CS VS WHO DID NOT PERFORM CS

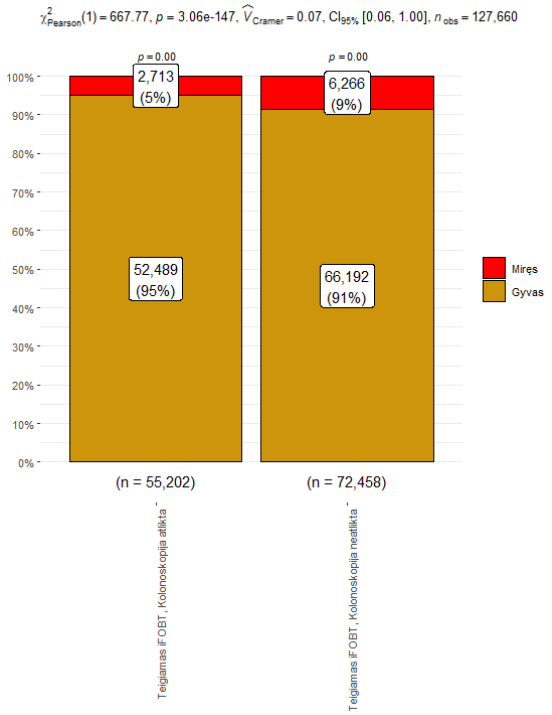


Figure 5 SURVIVAL AND MORTALITY IN NEGATIVE FIT WHO DID NOT PERFORM CS VS POSITIVE FIT WHO PERFORMED CS

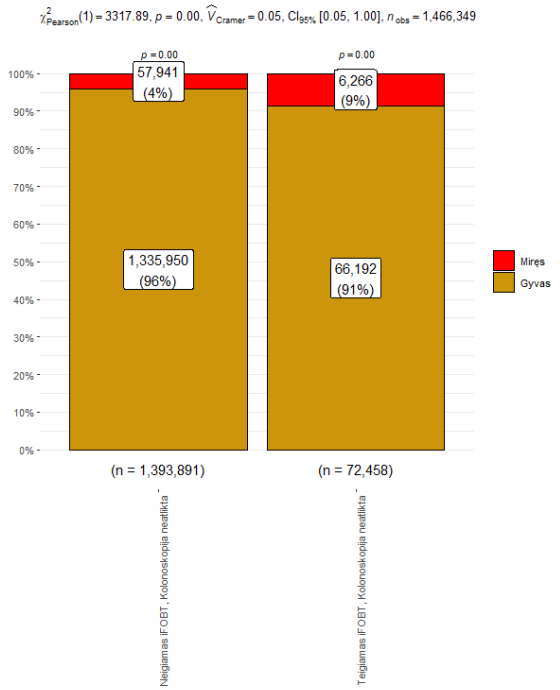
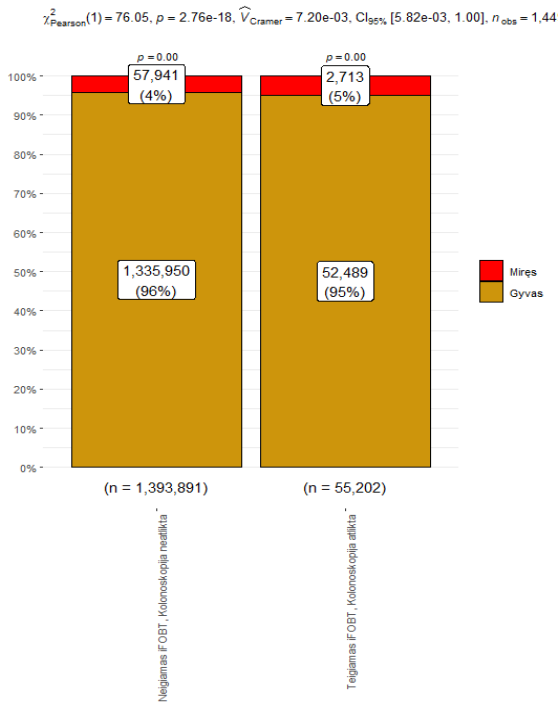


Figure 4 SURVIVAL AND MORTALITY IN NEGATIVE FIT WHO DID NOT PERFORM CS VS POSTIVE FIT WHO DID NOT PERFORM CS



7. DISCUSSION

We found from the analysis of the results that, participating in the screening program with the completion of CS after a positive FIT was associated with a significant reduction in mortality by 78%. The risk of death was found to be the highest in those after detection of carcinoma and adenoma with high-grade dysplasia during CS, and in those who did not perform CS after a positive FIT result. Therefore, completion in the performance of CS demonstrates a 78% reduction in risk of death versus not completing CS.

The major strength of our study was that our data were gathered from the national, population-based systematic registration, that was maintained prospectively, and provided a near-complete mortality registration of the population, which made it easier to determine what happened to the almost 1.5 million people that were screened. As a result, the analysis provides us with very valid data regarding overall survival and the participation and completion of screening which is a really strong point of the study. Regarding the limitations of the study, this registration is statistical and not medical, as it is not a clinical trial, and so we only received the statistical codes and not the medical description of each situation. Another drawback is the fact that we cannot determine the cause of death, whether it was due to CRC-related, procedural, surgical,

or other problems. Also, we were not able to obtain the data of the normal population who did not undergo screening, from the National database, which led to using mortality in the population with negative FIT negative and no performance of CS, as the control for the comparison of mortality in other groups.

Evaluating a different study by Michael Bretthauer et al., involved a randomized trial using CS as the intervention to screen a population of 84,585 participants from the year 2009 to 2014, to see if CRC risk was lower among those who underwent CS (86). The trial showed a reduction in the risk of CRC by 18%, although, using CS as the screening intervention itself could be quite costly, inefficient, and a waste of resources if needed to be performed on such a large amount of population as in our study. In addition to that, CS being an invasive procedure that requires intense bowel preparation and cleansing, could be found to be less convenient for people to perform as compared to FIT, which could reduce overall participation in the CRC screening program. Besides the bowel preparation, there may be also the risk of perforation and bleeding during the screening intervention. These risks could be easily avoided if CS is only performed on those who need it after a positive FIT, leaving the others with a negative FIT less exposed to the risk and the need for unnecessary physician-performed CS. This would also help save money and resources.

Our study suggests the importance of the completion and participation of individuals in the CRC screening program and how it can improve overall survival outcomes. The study also raises the practical issue of getting the information across to the participants about the screening process and highlights the need for healthcare professionals to inform and encourage people, under a specific age and risk to undergo screening, given the significant impact it can have on participant's health and in reducing mortality. Furthermore, it is clear that using FIT as a primary method can result in greater individual participation because it is non-invasive, simple to use, and can be administered without difficulty. This helps conserve resources and money compared to using CS screening directly. The relevance of doing CS after receiving a positive FIT test is further emphasized by our study because it can improve quality of life and survival rates.

Overall, our study highlights the importance of CRC screening in lowering disease burden, raising survival rates, and enhancing Lithuanian public health. It supports the ongoing growth of CRC screening programs in Lithuania and abroad by offering useful information for healthcare professionals, policymakers, and people thinking about CRC screening.

8. CONCLUSION

Our study confirms that there is a significant reduction in mortality in those who complete the CRC screening program than those who do not, and indicates that screening can help in detection in early stages when it is most curable, can point towards early diagnosis and treatment thereby increasing survival rates. Additionally, regular screening of the disease, especially in the precancerous stages, can also help remove and improve survival rates.

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