Ann Ig. 2024 Mar 7. doi: 10.7416/ai.2024.2618. Online ahead of print.

# Screening for colorectal cancer by full colonoscopy in first-degree relatives of colorectal cancer patients: a multicentric study by the Italian League for the Fight against Cancer

Giacomo Diedenhofen[1], Augusto Morgia[1], Nicola Sinnona[2], Alberto Pacchiarotti[2], Anna Fiaschetti[2], Vito Forte[2], Mauro Tosoni[3], Fabrizio Liberati[3], Sandro Boschetto[3], Enrico Zepponi[3,4], Pietro Marogna[5], Alessandra Manca[5], Marco Bisail[5,6], Annarita Vestri[1], Alessandro Rossi[2,7]

*Received: 2023 December 5*
*Accepted after revision: 2024 February 20*
*Published online ahead of print: 2024 March 7*

*Keywords: Colorectal cancer; cancer screening; secondary prevention; colonoscopy; familial cancer*
*Parole chiave: Cancro del colon-retto; screening del cancro; prevenzione secondaria; colonscopia; cancro familiare*

**Abstract**

***Background.*** *Colorectal cancer currently presents the third-highest incidence of cancers worldwide, making secondary prevention through screening programs for colorectal cancer, usually by Fecal Occult Blood Testing, an essential preventive medicine intervention. First-degree relatives of colorectal cancer patients are a particularly at-risk group, with indications to consider direct screening by full colonoscopy. Colonoscopy is considered the gold standard for diagnosing colorectal cancer, as it has high sensitivity and specificity, and is both a diagnostic and therapeutic tool. However, it requires significant organizational and financial resources, and has a small but relatively higher risk of complications as opposed to fecal occult blood testing. The present study aimed to assess the appropriateness of a screening program without age restrictions of CRC by full colonoscopy in asymptomatic, first-degree adult relatives of patients with colorectal cancer, aiming both to actively increase screening coverage and to determine the detection rate of precancerous lesions and colorectal cancer in this population.*
***Study Design.*** *Uncontrolled interventional study – colorectal cancer screening by full colonoscopy for at-risk population.*
***Methods.*** *The Italian League for the Fight against Cancer started a colorectal cancer screening program by full colonoscopy for first-degree relatives of colorectal cancer patients in 1998 in the province of Latina, Lazio Region, Italy. The program was expanded*

[1] *Department of Public Health and Infectious Diseases, Specialization School in Health Statistics and Biometrics, Sapienza University of Rome, Italy*
[2] *San Marco Clinic, Latina, Italy*
[3] *San Camillo de' Lellis Hospital, Rieti, Italy*
[4] *LILT Rieti, Italy*
[5] *Sassari University Hospital, Sassari, Italy*
[6] *LILT Sassari, Italy*
[7] *LILT Latina, Santa Maria Goretti Hospital, Latina, Italy*

Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

*to the provinces of Rieti, Lazio Region, and Sassari, Sardinia Region, in 2014 and 2016 respectively, and was concluded in 2018. Subjects were actively and voluntarily recruited by the study's working group. Subjects that had already been subjected to a full colonoscopy in the preceding 5 years were excluded from this study. Identified neoplastic lesions were treated either directly or referred to the Day Hospital setting, and histologically diagnosed following World Health Organization guidelines.*

***Results.*** *In total, 2,288 subjects (age range 15-88, mean 52.3 yrs, M/F = 946/1,204) were screened by colonoscopy, of which 103 (4.5%) were incomplete and 2,173 (95.0%) complete, with data on colonoscopy performance missing for 12 participants. Out of 468 positive outcomes on colonoscopy, diagnosis for 422 (204M/173F), 19.4% of total subjects, was adenomatous polyps and 46 (20M/20F), 2.1% of total subjects, was colorectal cancer. Female sex was a protective factor against a positive test outcome, with a 35% reduction compared to male sex, with OR=0.64 95%CI (0.52-0.80). On the other hand, being over 50 years of age was found to be a risk factor, making a positive outcome more than twice as likely, with OR=2.3 95%CI (1.8-2.9). Subjects over 50 also had significantly more instances of multiple adenomas being found, however the size distribution of found adenomas was not significantly different between subjects under and over 50, despite size being a predictor of risk of neoplastic progression.*

***Conclusions.*** *Given the high detection rate of precancerous lesions and colorectal cancer in the studied population, it is our opinion that guidelines should continue to recommend earlier and more frequent screening in first-degree relatives of patients with colorectal cancer, and, barring the introduction of more cost-effective and/or lower risk procedures with a similar efficacy profile, maintain the use of colonoscopy as the main screening option.*

## Introduction

Colorectal cancer (CRC) currently presents the third-highest incidence (10% of diagnosed cases) and second highest mortality (9.4% of cancer deaths) of cancers worldwide, as evidenced by the WHO's GLOBOCAN 2020 estimates (1).

In 2020, it represented one of the top five most frequently diagnosed cancers in Italy, with 12% of all cancers diagnosed among men and 11.2% of all diagnosed among women (2).

The data from the Cancer Registry of the province of Latina (part of the Lazio Region in central Italy, with a population of 563 thousand residents in 2018) referring to 2018, follows the national trend: among men, colorectal cancer represents 13.9% of all diagnosed cancers, and among women 12.2% (3).

From 2008 to 2016, the incidence rate of many cancers decreased significantly in both sexes and all age groups. Colorectal cancer was one of these, decreasing 3.0% on average per year in men and women between 50 and 69 years of age (the age group subjected to population screening). The latest available Italian national data for colorectal cancer shows a slight decrease compared to 2015, but it nonetheless remains a cancer with high incidence in both sexes (4, 5). Despite being one of the main cancers diagnosed in the population, the incidence of CRC in Italy has thus been declining in recent years, a fact that can also be attributed to ongoing national efforts at secondary prevention (6).

Secondary prevention, or the early detection and treatment of precancerous lesions and early-stage cancer, has been shown to significantly reduce the incidence and mortality of colorectal cancer. The pioneering work in this field was published in the late 60s and 70s (7) showing remarkable results that were nonetheless hampered by significant limitations in study design and the use of sigmoidoscopy, a procedure that had a small but significant risk of complications. In 1967 however, Greegor introduced the first fecal occult blood test (FOBT) (8), based on a guaiac card test that could be self-administered at home. Promising results and the introduction of a practically risk-free testing device did not however eliminate the risk for biases in these studies, and it wasn't until 1996 that properly designed RCTs confirmed these promising preliminary outcomes (9-11). In this context, various public healthcare providers started their own screening programs by FOBTs at the regional and local level in Italy (12-14), confirming these results and paving the way for the introduction of a unified national cancer screening program in 2004 (15).

It should however be noted that, despite the well-established effectiveness of CRC screening and its importance in preventative healthcare, to the point that it is a core performance indicator of the regional public healthcare systems in Italy (16), significant gaps remain in reaching satisfactory levels of screened population. The Italian National Screening Observatory (ONS) reports that in 2019, out of the general population invited to FOBT screening (ages 50-69 in most regions, despite national guidelines aiming for ages 50-74), only 41.6% responded. Of these, only 45% of subjects with a positive outcome on FOBT underwent colonoscopy within 30 days from

the outcome, the Italian Colorectal Screening Group (GISCOR) acceptable standard being >90%. Even more worryingly, more than 20% of subjects with a positive outcome nonetheless refused to undergo colonoscopy entirely. The most recent ONS report, for 2020, paints an even more dire picture due to significant difficulties and reductions in screening volumes during the COVID-19 pandemic (17).

On a wider perspective, the latest OECD report showed that Italy maintained a higher than OECD average percentage of people aged 50-74 years who had fecal occult blood test at least once in their life by 2014, with 49.1% compared to the OECD's average 40.4%. While this is better than the OECD average, it should also be noted that Germany reached a percentage of 81.0% in the same survey (18).

While there has been a successful effort to improve and expand both screening programs and treatment options, the risk of developing CRC remains high in certain populations, including first-degree relatives of patients with CRC (19). These individuals have a two to four-fold increased risk of developing the disease compared to the general population, depending on both the number and age of affected relatives (20-22). A recent study also suggests that even first-degree relatives of patients with CRC precursor lesions (colorectal polyps) present an increased risk of CRC, evidencing both the importance of screening programs and the particular risk profile of this population (23). The Italian cancer screening program maintains a provision for the application of full colonoscopy as a direct form of secondary prevention and eventual treatment of at-risk populations, as full colonoscopy is a highly sensitive screening method for the detection of colorectal cancer and precancerous lesions. However, this provision remains limited by age restrictions. While CRC screening is currently the most effective means of reducing both the mortality and incidence of this malignancy, screening modes for first-degree relatives of patients with CRC are more nuanced than the simple application of the FOBT, and depend on a number of factors including age of the affected patient, age of the screened relative and possible genetic mutations (24). However, the cost and risk effectiveness of using full colonoscopy as a direct screening and secondary prevention strategy is still a matter of ongoing debate (25, 26).

Within this wider context, starting in 1998 the LILT ("Lega Italiana per la Lotta contro i Tumori", Italian League for the Fight against Cancer) started a colorectal cancer screening program by full colonoscopy for first-degree relatives of patients with colorectal cancer (CRC) in the province of Latina, Lazio Region, which ran successfully thanks to external funding and the work of LILT volunteers and was expanded to the provinces of Rieti, Lazio Region, and Sassari, Sardinia Region, in 2014 and 2016 respectively. The screening program had to be interrupted in 2018, due to a lack of sufficient further funding. Colonoscopy was chosen as the screening tool as it is considered the gold standard for diagnosing CRC, with high sensitivity and specificity, and is both a diagnostic and therapeutic tool. However, it requires significant organizational and financial resources, and has a small but relatively higher risk of complications as opposed to FOBTs, which, while it can be used as a direct screening tool (27-29), makes it preferable as a second line diagnosis and treatment approach following positive FOBT results in general population screening (30).

The present study aimed to assess the appropriateness of a screening program without age restrictions of CRC by full colonoscopy in asymptomatic, first-degree adult relatives of patients with colorectal cancer, with preliminary results published in 2008 (31). Specifically, we aimed both to actively increase the screening coverage and to determine the detection rate of precancerous lesions and colorectal cancer by full colonoscopy screening in this population, to contribute to the growing body of evidence to better determine the optimal approach to CRC prevention in this at-risk population.

## Materials and methods

The participating centers of this program were the Latina operational center with 2,078 subjects (91.3%), the Rieti center with 137 subjects (6%) and the Sassari center with 62 subjects (2.7%).

Approval for the study was granted by the LILT Latina ethics committee both in 1998 for the start of the study and, subsequently, in 2009 to expand the study to the Rieti and Sassari centers. The study actively recruited first-degree, adult relatives of patients affected by CRC who were directly contacted by members of the working team (oncologist, endoscopist, pathologist, nurses and volunteers). These relatives were informed about their increased risk profile and counselled on the possible steps they could undertake to mitigate it, including colonoscopy. Written informed consent forms to the procedure, and to the gathering of relevant patient data to study and evaluate the secondary prevention program,

were obtained after consulting with a working team physician. Subjects that had already been subjected to a full colonoscopy in the preceding 5 years were excluded from this study.

Endoscopy was always performed by two operators (endoscopist physician and specialized nurse) and in conscious sedation in the majority of cases, with some subjects requesting deep sedation. As it is standard, patients prepared for the procedure with a specific diet in the 3 days preceding it, followed by the ingestion of 4lt of a polyethylene glycol (PEG) solution in the preceding 24 hours. During the procedure, in the absence of contraindications to biopsy, endoscopic polypectomies were performed on any polyps not exceeding 1cm in size. For larger polyps, polypectomy was deferred to the *Day Hospital* setting, following additional controls for blood count and coagulation indexes (PT, PTT, INR). For voluminous lesions with a suspicion of malignancy, and/or frankly heteroplastic formations, no less than 5 biopsies were performed per lesion.

Biopsied material was fixed with 10% neutral buffered formalin solution, macroscopically described, sectioned where deemed necessary, included in paraffin and histologically diagnosed following WHO guidelines.

Quantitative data were summarized by descriptive statistics (mean, standard deviation, median, interquartilic range); categorical data were summarized by counts and percentages. To assess differences or associations between subgroups we perform chi square test (or Fisher exact test when appropriate) for categorical data; t-test was used to compare quantitative data. We performed a logistic regression, the dependent variable is the outcome (positive/negative), to determine the independent

Table 1 - Population Characteristics

**Population Characteristics (N = 2288)**

| Variables | Category | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Sex | Male | 946 | 41.3% | 44.0% | 44% |
| | Female | 1204 | 52.6% | 56.0% | 100% |
| | Missing | 138 | 6.0% | / | / |
| Age (years) | ≤49 | 984 | 43.0% | 43.1% | 43.1% |
| | ≥50 | 1297 | 56.7% | 56.9% | 100.0% |
| | Missing | 7 | 0.3% | / | / |
| Participating Center | Latina | 2089 | 91.3% | 91.3% | 91.3% |
| | Rieti | 137 | 6.0% | 6.0% | 97.3% |
| | Sassari | 62 | 2.7% | 2.7% | 100.0% |
| Colonoscopic Examination | Complete | 2173 | 95.0% | 95.5% | 95.5% |
| | Incomplete | 103 | 4.5% | 4.5% | 100.0% |
| | Missing | 12 | 0.5% | / | / |
| Diagnostic outcome | Negative | 1729 | 75.6% | 78.5% | 78.5% |
| | Adenomatous polyp | 428 | 18.7% | 19.4% | 97.9% |
| | CRC | 46 | 2.0% | 2.1% | 100.0% |
| | Missing | 85 | 3.7% | / | / |
| Distribution of adenomatous polyps by max. size (N = 428) | ≤5 mm | 192 | 44.9% | 52.0% | 52.0% |
| | 6-9 mm | 46 | 10.7% | 12.5% | 64.5% |
| | 10-19 mm | 50 | 11.7% | 13.6% | 78.0% |
| | 20-29 mm | 37 | 8.6% | 10.0% | 88.1% |
| | >30 mm | 44 | 10.3% | 11.9% | 100.0% |
| | Missing | 59 | 13.8% | / | / |
| Presence of multiple adenomatous polyps (N = 428) | No | 326 | 76.2% | 76.2% | 76.2% |
| | Yes | 102 | 23.8% | 23.8% | 100.0% |

predictors, we calcolate the Odds ratio with the 95% confidence interval.

Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

## Results

In total, 2,288 subjects were screened by colonoscopy, with the population characteristics summarized in table 1. A time distribution of subjects screened by year, is shown in Fig.1.

Performed colonoscopies were recorded as incomplete for 103 participants (4.5%) and complete (cecal intubation) for 2,173 (95.0%), with data on colonoscopy performance missing for 12 participants.

Looking at outcomes by sex (Tab. 2), we note that the screened participants for whom this variable was recorded (N = 2,150), included 946 males (44%) and 1,204 females (56%), with a mean age of 51.9±12.5 (median 51.9, IQR 43-61, range 19-88) and 52.4±12.4 (median 52, IQR 43-61, range 15-88) years, respectively. No significant statistical difference was found between age and sex.

However, a significant difference ($p<0.001$) was found in the bivariate analysis between sex and outcome: males shared a higher percent of the positive outcomes (53.3%) than femalesw (46.7%) on screening. No significant differences linked to sex were found between those who had complete or incomplete exams.

Going into an analysis of positive outcomes, separating them between the finding of polyps of variable degrees of dysplasia and the confirmed diagnosis of carcinoma, a more complete picture came in, evidencing how the difference in outcomes by sex is mostly driven by the higher percent of positive finding of polyps in males (54.1%) as opposed to females (45.9%) (Fig. 2). While the positive finding of carcinoma was evenly split by sex, it should still be noted that as a percentage of the screened population this represented a slightly higher percent incidence between the male (2.15%) and female (1.75%) population.

An analysis of the distribution of adenomatous polyps by maximum recorded size, and of the presence of single or multiple polyps, showed no significant statistical difference linked to sex.

It must be considered that individuals aged 50 to 69 in the general population are already covered by recommended screenings, while those aged 20 to 49 only have a generic recommendation to undergo checks (always within the context of familiarity). To

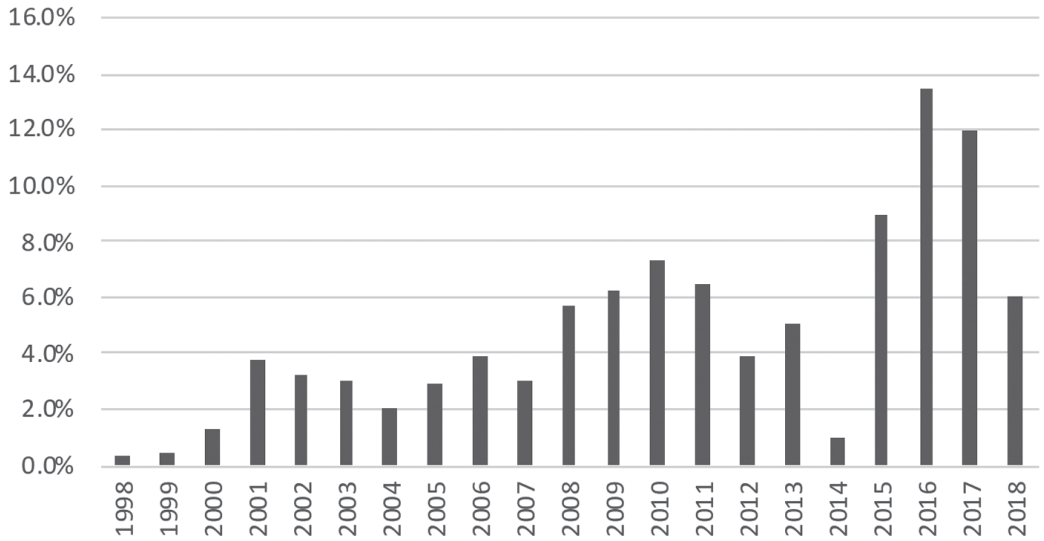


Figure 1 - Time distribution of subjects screened by colonoscopy, by percent of total

Table 2 – Age and outcomes by sex, p-values calculated by (a) t-test and (b) Pearson's chi-squared test

**Age and outcomes by sex (N = 2150)**

| Variables | | Male (N = 946) | | Female (N = 1204) | | p-value |
|---|---|---|---|---|---|---|
| Age expressed as mean ± SD, median, IQR, range) | | 51.93 ± 12.46, 51.92, 43-61, 19-85 | | 52.37 ± 12.38, 52.00, 43-61, 15-88 | | 0.413[a] |
| | **Category** | **Frequency** | **Valid Percent** | **Frequency** | **Valid Percent** | |
| Diagnostic outcome | Negative | 698 | 75.4% | 947 | 83.0% | <0.001[b] |
| | Adenomatous polyp | 208 | 22.5% | 174 | 15.2% | |
| | CRC | 20 | 2.2% | 20 | 1.8% | |
| | Missing | 20 | / | 63 | / | / |
| Distribution of adenomatous polyps by max. size (N = 382) | ≤5 mm | 94 | 48.5% | 72 | 49.0% | 0.591[b] |
| | 6-9 mm | 27 | 13.9% | 18 | 12.2% | |
| | 10-19 mm | 28 | 14.4% | 21 | 14.3% | |
| | 20-29 mm | 17 | 8.8% | 20 | 13.6% | |
| | >30 mm | 28 | 14.4% | 16 | 10.9% | |
| | Missing | 14 | / | 27 | / | / |
| Presence of multiple adenomatous polyps (N = 382) | No | 157 | 75.5% | 141 | 81.0% | 0.192[b] |
| | Yes | 51 | 24.5% | 33 | 19.0% | |

this end, the ages were divided according to two large classes, ≤49 years and ≥50 years (Tab. 3). As could be expected by the generally higher incidence of cancers and pre-cancerous lesions with increasing age, a statistically significant difference can be found with respect to the two age groups ($p<0.001$), with positive outcome values respectively equal to 14.3% and 27.5%. This is evidenced for all outcomes in Fig. 3. While we also see a statistically significant difference in the presence of multiple adenomatous lesions between the two groups ($p<0.001$), no significant difference in the distribution of the maximum recorded size of pre-cancerous lesions was found.

Further subdividing these age groups by sex reflects the above identified trends very clearly, giving us a more complete picture (Fig.4).

The results of the logistic regression, considering the outcome (positive/negative) as the dependent variable, showed that female sex was a protective factor against a positive test outcome, with a 35% reduction compared to male sex, with OR=0.64 95%CI (0.52-0.80). On the other hand, being over 50 years of age was found to be a risk factor, making a positive outcome more than twice as likely, with OR=2.30 95%CI (1.82-2.90).

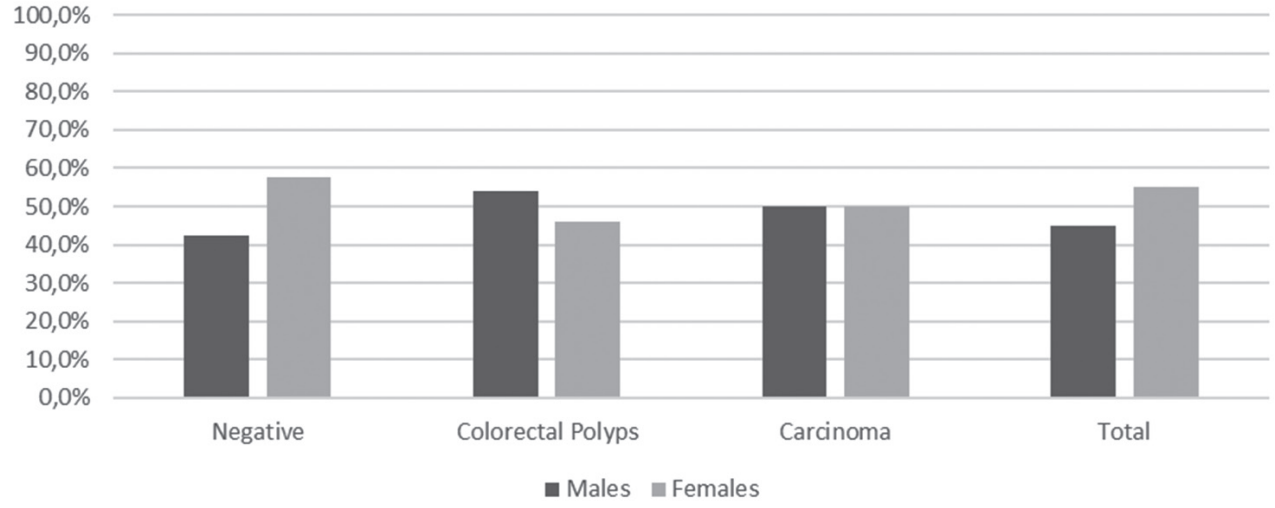


Figure 2 - Percent of outcomes by sex

Table 3 - Performed colonoscopies by age and outcome, p-values calculated by Pearson's chi-squared test

**Outcomes by age (N = 2281)**

| Variables | | Age (years) ≤ 49 (N = 984) | | Age (years) ≥ 50 (N = 1297) | | |
|---|---|---|---|---|---|---|
| | Category | Frequency | Valid Percent | Frequency | Valid Percent | p-value |
| Diagnostic outcome | Negative | 806 | 84.7% | 918 | 73.7% | <0.001 |
| | Adenomatous polyp | 134 | 14.1% | 293 | 23.5% | |
| | CRC | 12 | 1.3% | 34 | 2.7% | |
| | Missing | 32 | / | 52 | / | / |
| Distribution of adenomatous polyps by max. size (N = 427) | ≤5 mm | 68 | 59.1% | 124 | 49.0% | 0.290 |
| | 6-9 mm | 15 | 13.0% | 31 | 12.3% | |
| | 10-19 mm | 14 | 12.2% | 36 | 14.2% | |
| | 20-29 mm | 7 | 6.1% | 29 | 11.5% | |
| | >30 mm | 11 | 9.6% | 33 | 13.0% | |
| | Missing | 19 | / | 40 | / | / |
| Presence of multiple adenomatous polyps (N = 427) | No | 117 | 87.3% | 209 | 71.3% | <0.001 |
| | Yes | 17 | 12.7% | 84 | 28.7% | |

## Discussion and conclusions

Our cecal intubation rate (CIR) of 95,5% was in line with similar studies using conscious sedation (32, 33) and higher than a number of other studies that had made more limited use of sedation, which reached a CIR of 82-85% (34, 35). No serious adverse events (e.g. perforation, bleeding) were recorded, a testament to the expertise of the operators involved, as the procedure does still carry a small risk of complications, with 0.4 to 0.6 perforations and 0.2 to 6.8 bleeding events per 1000 colonoscopies registered in other studies (36-38).

In our study, 19.4% of first-degree relatives of CRC patients who underwent colonoscopy were positive for adenomatous polyps and 2.1% were positive for carcinoma. Of those over 50 years of age, 23.5% were positive for adenomatous polyps and 2.7% were positive for carcinoma, while our screened population below the age of 50 presented an incidence of adenomatous polyps of 14.1% and of CRC of 1.3%. These figures are similar to those in other studies (34, 39-43), though there is a range of results and classification approaches to adenomatous lesions may vary. It should be noted that our screened population below the age of 50 showed a significantly lower incidence of positive outcomes compared to the population over 50 in the same study. This was evident both in the number of positive diagnostic outcomes (adenomas and CRC) and multiple adenomas found. It should be noted, however, that the size distribution of found adenomas was not significantly different between subjects under and over 50, despite size being a predictor of risk of neoplastic progression. While the lower age may explain the lower incidence of lesions and CRC, among other factors simply due to a reduced time for precancerous lesions to develop into cancer, we wish to stress that it is well established that first-degree relatives have a higher risk than the general population of developing CRC, both in absolute terms over their lifetime and in those subjects under 50 (22, 43).

Our findings evidence the increased risk for males and for subjects above 50 in our studied population, a trend that is in line both with those seen in similar studies on first-degree relatives and in the general population (22, 24).

The study presents a number of limitations that should be taken into consideration. Unfortunately, we are not able to calculate the exact adhesion rate to the screening program of the population at risk, as we do not know the exact number of all first-degree relatives of each index-colon cancer patient. The study does not contain a control group, even if we had paired the at-risk population over 50 with general population controls in the same age group undergoing screening colonoscopies, it would not have been possible to do the same with our at risk population below the age of 50, a problem arising from the study being designed as a screening program without age restrictions for at-risk adults. Healthy controls with no indication for colonoscopy could not be included due to ethical reasons linked to the risk of complications associated with the procedure. While we did find that the size

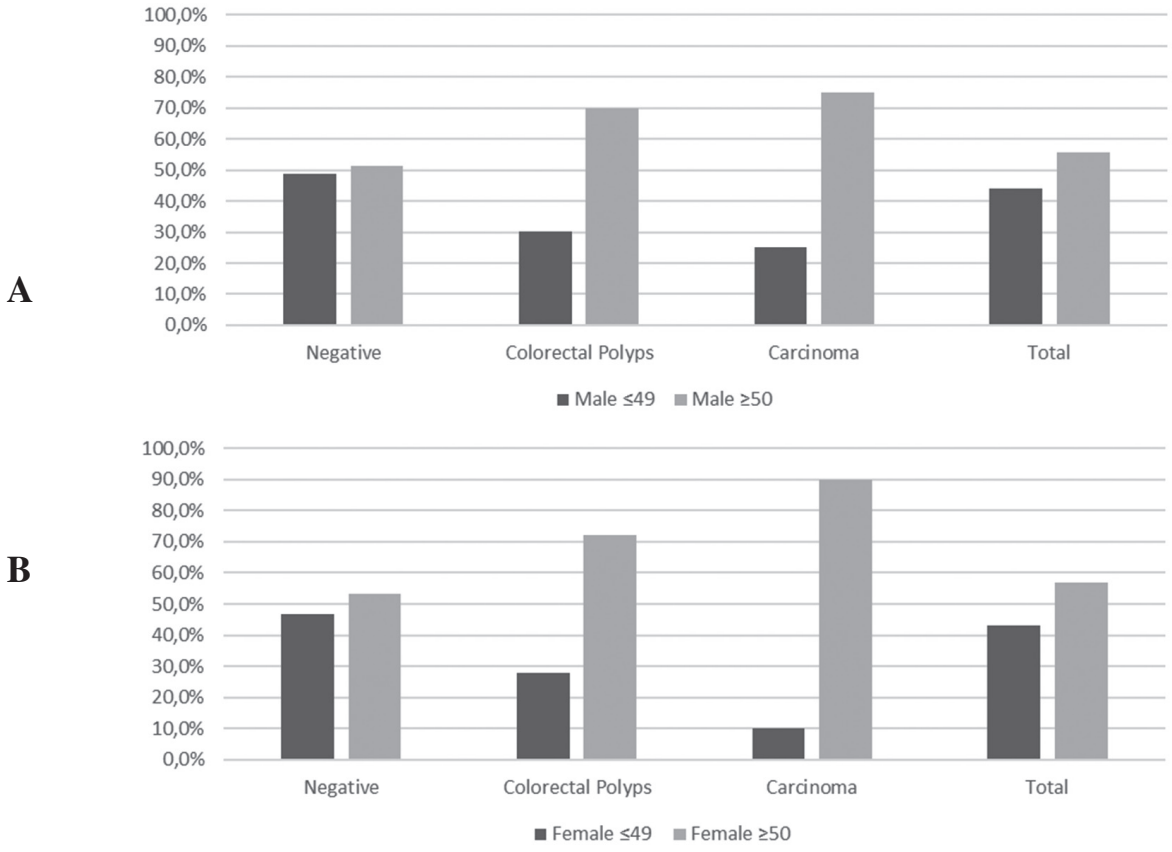


Figure 4 - Percent of outcomes by age and sex. A: male; B: Female

distribution of adenomas found in our population was not significantly different for both age and sex, we do not have comprehensive histological data at our disposal to further evaluate the risk profile of these adenomas beyond their size.

On the subject of the wider context of screening for CRC within which our study is situated, we note that the Italian National Screening Observatory (ONS) data for the 2014-2020 period, relating to the screening of the general Italian population, shows a similar percentage of adenomatous polyps and carcinomas (17.8% and 2.9% of total performed colonoscopies, respectively) identified in subjects over 50 who underwent colonoscopy, after having already resulted positive by FOBT (17). An italian study evaluating the prevalence of familial risk in subjects that resulted positive to FOBT screening in the general population, evidenced a prevalence of 12% of first-degree relatives of CRC patients, while confirming the increased risk for pathologically significant lesions in these subjects (44). This hints to an important issue of outreach in screening this

Table 4 - Logistic Regression Results

| Variables | Sign. | Exp(B) | 95% C.I. for EXP(B) | |
|---|---|---|---|---|
| | | | Inferior | Superior |
| Sex | 0.000 | 0.644 | 0.518 | 0.799 |
| Age (years, ≤ 49 or ≥ 50) | 0.000 | 2.296 | 1.820 | 2.896 |

at-risk population, as they should access screening sooner than the general population and there is no need to risk a possible false negative on FOBT testing when colonoscopy is an available and appropriate screening option. We note that our studied population presented a similar incidence of lesions found on direct colonoscopic screening to those found in the general population that had already resulted positive to FOBT. This is not meant as a direct comparison between these methodologies but aims to underline the importance of outreach and colonoscopic screening in first-degree relatives of CRC patients. A significant part of our screening program was represented by the active outreach to relatives of CRC patients and the work of LILT volunteers, who allowed us to provide a valuable service to our screened population but also inevitably meant the program had to eventually conclude in 2018.

Despite the clear scientific consensus on screening, significant work remains to be done to reach more widespread adoption and overcome barriers to screening access. This also underlines the importance of programs such as the one presented in this study, as active outreach to more at-risk populations becomes even more important in a context where general population screening is still not as widespread as one could expect (45). This matter has become even more pressing in the aftermath of the COVID-19 pandemic, as cancer screening programs have been significantly affected both internationally (46, 47) and in Italy (48, 49). Screening is a time-sensitive medical intervention, and delays and backlogs created by the pandemic could result in several late diagnosed cases, making it imperative that screening programs receive the resources to not only continue as before but also make up for what was lost. It will be particularly necessary to monitor even more closely the cases most at risk to develop a cancer, such as the at-risk population presented here.

Our findings provide further evidence for the appropriateness of full colonoscopy as a secondary prevention strategy in first-degree relatives of patients with colorectal cancer, and evidence the need for targeted and active management of this at-risk population. The high detection rate of precancerous lesions and colorectal cancer in this population underscores the importance of regular screening by full colonoscopy. Given the high risk of developing colorectal cancer in this population, it is our opinion that guidelines should continue to recommend earlier and more frequent screening in first-degree relatives of patients with colorectal cancer, and, barring the introduction of more cost-effective and/or lower risk procedures with a similar effectiveness profile, maintain the use of colonoscopy as the main screening option.

**Funding and Competing Interests**
This study was supported by the Rotary Club Latina, Rotary Club Rieti and Rotary
Club Sassari, with the patronage of District 2080 Rotary (LAZIO - SARDEGNA).
The authors declare no conflicts of interest.
**Acknowledgements**
We thank Dr. Lucrezia Mosillo and Dr. Marta Mosillo for their support and putting the LILT Latina operative spaces at our disposal. We also thank Dr. Marina Bellia for her work and oversight as President of the LILT Latina ethics committee.

## Riassunto

***Screening colonscopico del cancro del colon-retto in parenti di primo grado di pazienti affetti da cancro del colon-retto: uno studio multicentrico della Lega Italiana per la Lotta contro i Tumori***

**Premesse.** Il cancro del colon-retto è attualmente il cancro con la terza più alta incidenza a livello mondiale, e i programmi di screening, solitamente effettuati tramite esame del sangue occulto nelle feci, rappresentano un intervento di medicina preventiva essenziale per contrastarlo. I parenti di primo grado di pazienti affetti da cancro del colon-retto sono un gruppo particolarmente a rischio, con indicazione di considerare direttamente lo screening in colonscopia. La colonscopia è considerata il gold standard per la diagnosi di cancro del colon-retto, ha alta sensibilità e specificità, ed è un mezzo sia diagnostico che terapeutico. Come mezzo di screening richiede però importanti risorse organizzative e finanziarie, ed ha un piccolo ma relativamente maggiore rischio di complicanze rispetto al test sangue occulto nelle feci. Il presente studio mirava a valutare l'appropriatezza di un programma di screening senza restrizioni di età per il cancro del colon-retto tramite colonscopia completa in adulti parenti di primo grado asintomatici di pazienti con cancro del colon-retto, con l'obiettivo sia di aumentare attivamente la copertura dello screening sia di determinare il tasso di individuazione di lesioni precancerose e di cancro del colon-retto in questa popolazione.

**Disegno dello studio.** Studio interventistico non controllato – screening colonscopico del cancro del colon-retto per popolazione a rischio.

**Metodi.** La Lega Italiana per la Lotta contro i Tumori ha avviato un programma di screening colonscopico del cancro del colon-retto per parenti di primo grado di pazienti affetti da cancro del colon-retto nel 1998, nella provincia di Latina, Lazio, Italia. Il programma è stato esteso alle province di Rieti, Lazio, e Sassari, Sardegna, rispettivamente nel 2014 e 2016, e si è concluso nel 2018. I soggetti partecipanti sono stati reclutati attivamente e volontariamente dal gruppo di lavoro dello studio. I soggetti già sottoposti a colonscopia nei 5 anni precedenti sono stati esclusi dallo studio. Le lesioni neoplastiche identificate sono state trattate direttamente oppure, ove appropriato,

riferite al setting di *Day Hospital*, con diagnosi istologica eseguita secondo linee guida dell'Organizzazione Mondiale della Sanità.

**Risultati.** Sono stati sottoposti a screening colonscopico 2,288 soggetti (età 15-88, età media 52, M/F = 946/1204), di cui 2,173 (95.0%) hanno completato l'esame. Di 468 soggetti positivi allo screening colonscopico, 422 (204M/173F), 19.4% del totale, sono stati diagnosticati come affetti da polipi adenomatosi e 46 (20M/20F), 2.1% del totale, da cancro del colon-retto. Il sesso femminile è risultato come un fattore protettivo contro l'outcome positivo, con una riduzione del 35% rispetto al sesso maschile, con OR = 0.64 95%CI (0.52-0.80). L'età maggiore di 50 anni invece risulta essere un fattore di rischio il quale più che raddoppia le possibilità di outcome positivo, con OR = 2.3 95%CI (1.8-2.9). I soggetti sopra ai 50 anni hanno presentato anche significativamente più casi di adenoma multipli diagnosticati, si nota però che la distribuzione delle dimensioni degli adenomi trovati tra soggetti sopra e sotto ai 50 anni di età non è risultata significativamente differente, malgrado questa sia un predittore di rischio di progressione neoplastica.

**Conclusioni.** Dato l'alto rischio di sviluppare il cancro del colon-retto in questa popolazione, siamo dell'opinione che le linee guida dovrebbero continuare a raccomandare screening precoci e più frequenti, colonscopici, nei parenti di primo grado di pazienti affetti da cancro del colon-retto, salvo l'introduzione di procedure con maggior profilo di costo-efficacia e minor rischio, che mantengano però un simile grado di accuratezza diagnostica.

## References


1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May; ***71***(3): 209-49. doi: 10.3322/caac.21660. Epub 2021 Feb 4.
2. AIRTUM Working Group. I Numeri del Cancro in Italia 2020 [Internet]. Brescia: Intermedia Editore; 2020 [cited 2023 May 15]. 11–28 p. Available from: https://www.aiom.it/wp-content/uploads/2020/10/2020_Numeri_Cancro-operatori_web.pdf [Last accessed: 2023 December 05].
3. Pannozzo F, Macci L, Curatella S, Bernazza E, Bugliarello E. I Tumori in provincia di Latina Rapporto 2018 [Internet]. Latina: Registro Tumori di Popolazione della Provincia di Latina; 2018 [cited 2023 May 15]. 10–20 p. Available from: https://www.registri-tumori.it/cms/sites/default/files/pubblicazioni/RTLT_2018_1.pdf [Last accessed: 2023 December 05].
4. AIRTUM Working Group. I Numeri del Cancro in Italia 2021 [Internet]. Brescia: Intermedia Editore; 2021 [cited 2023 May 15]. 50-52 p. Available from: https://www.aiom.it/wp-content/uploads/2021/10/2021_NumeriCancro_web.pdf [Last accessed: 2023 December 05].
5. AIRTUM Working Group. I Numeri del Cancro in Italia 2022 [Internet]. Brescia: Intermedia Editore; 2022 [cited 2023 May 15]. 54-56 p. Available from: https://www.aiom.it/wp-content/uploads/2022/12/2022_AIOM_NDC-web.pdf [Last accessed: 2023 December 05].
6. Zorzi M, Cavestro GM, Guzzinati S, Dal Maso L, Rugge M; AIRTUM Working Group. Decline in the incidence of colorectal cancer and the associated mortality in young Italian adults. Gut. 2020 Oct; **69**(10): 1902-3. doi: 10.1136/gutjnl-2019-320406. Epub 2019 Dec 16.
7. Gilbertsen VA, Nelms JM. The prevention of invasive cancer of the rectum. Cancer. 1978; **41**(3): 1137-9. doi: 10.1002/1097-0142(197803)41:3<1137::aid-cncr2820410350>3.0.co;2-g.
8. Greegor DH. Diagnosis of large-bowel cancer in the asymptomatic patient. JAMA. 1967 Sep 18; **201**(12): 943-5.
9. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996 Nov 30; ***348***(9040): 1467-71. doi: 10.1016/S0140-6736(96)03430-7.
10. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993 May 13; **328**(19): 1365-71. doi: 10.1056/NEJM199305133281901.
11. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996 Nov 30; **348**(9040): 1472-7. doi: 10.1016/S0140-6736(96)03386-7.
12. Crotta S, Castiglione G, Grazzini G, Valle F, Mosconi S, Rosset R. Feasibility study of colorectal cancer screening by immunochemical faecal occult blood testing: results in a northern Italian community. Eur J Gastroenterol Hepatol. 2004 Jan; **16**(1): 33-7. doi: 10.1097/00042737-200401000-00006.
13. Grazzini G, Castiglione G, Ciabattoni C, Franceschini F, Giorgi D, Gozzi S, et al. Colorectal cancer screening programme by faecal occult blood test in Tuscany: first round results. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP. 2004 Feb; **13**(1): 19-26. doi: 10.1097/00008469-200402000-00004.
14. Grazzini G, Castiglione G, Isu A, Mantellini P, Rubeca T, Sani C, et al. Colorectal cancer screening by fecal occult blood testing: results of a population-based experience. Tumori. 2000; **86**(5): 384-8. doi: 10.1177/030089160008600503.
15. Interventi urgenti per fronteggiare situazioni di pericolo per la salute pubblica [Internet]. Legge 138 May 26, 2004. Available from: https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2004-05-29&atto.codiceRedazionale=04A05690&elenco30giorni=false [Last accessed: 2023 December 05].
16. Carbone S, Campolongo A, Ceccolini C, Colandrea C, Di Fonzo G, Gallo M, et al. Monitoraggio dei LEA attraverso il Nuovo Sistema di Garanzia – Metodologia e risultati dell'anno 2020. Roma: Ministero della Salute - Direzione generale della programmazione sanitaria - Ufficio 6; 2023.
17. Osservatorio Nazionale Screening. Lo screening colorettale - Dati di attività dal 2014 al 2020 [Internet]. [cited 2023 May 15]. Available from: https://www.osservatorionazionalescreening.it/content/lo-screening-colorettale [Last accessed: 2023 December 05].

18. OECD. Health at a Glance 2019: OECD Indicators [Internet]. Paris: Organisation for Economic Co-operation and Development; 2019 [cited 2023 May 15]. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2019_4dd50c09-en [Last accessed: 2023 December 05].
19. Ponz de Leon M, Rossi G, di Gregorio C, De Gaetani C, Rossi F, Ponti G, et al. Epidemiology of colorectal cancer: the 21-year experience of a specialised registry. Intern Emerg Med. 2007 Dec 1; **2**(4): 269-79. doi: 10.1007/s11739-007-0077-z. Epub 2007 Nov 29.
20. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med. 1994 Dec 22; **331**(25): 1669-74. doi: 10.1056/NEJM199412223312501.
21. Guttmacher AE, Collins FS, Carmona RH. The family history--more important than ever. N Engl J Med. 2004 Nov 25; **351**(22): 2333-6. doi: 10.1056/NEJMsb042979.
22. Butterworth AS, Higgins JPT, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer Oxf. 1990. 2006 Jan; **42**(2): 216-7. doi: 10.1016/j.ejca.2005.09.023. Epub 2005 Dec 9.
23. Song M, Emilsson L, Roelstraete B, Ludvigsson JF. Risk of colorectal cancer in first degree relatives of patients with colorectal polyps: nationwide case-control study in Sweden. BMJ. 2021 May 4; **373**: n877. doi: 10.1136/bmj.n877.
24. Gruppo di Lavoro per lo Screening del Carcinoma del Colon Retto. Raccomandazioni per lo Screening del Carcinoma del Colon Retto. In: Ministero della Salute - Raccomandazioni per la pianificazione e l'esecuzione degli screening di popolazione per la prevenzione del cancro della mammella, del cancro della cervice uterina e del cancro del colon retto. Rome: Tipografia Graffiti; 2006: 55-74.
25. Cheng TI, Wong JM, Hong CF, Cheng SH, Cheng TJ, Shieh MJ, et al. Colorectal cancer screening in asymptomaic adults: comparison of colonoscopy, sigmoidoscopy and fecal occult blood tests. J Formos Med Assoc Taiwan Yi Zhi. 2002 Oct; **101**(10): 685-90.
26. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology. 2005 Aug; **129**(2): 422-8. doi: 10.1016/j.gastro.2005.05.056.
27. Winawer SJ, Zauber AG, Ho MN, Ho MN, O'Brien MJ, Gottlieb LS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993 Dec 30; **329**(27): 1977-81. doi: 10.1056/NEJM199312303292701.
28. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol. 1999 Apr; **34**(4): 414-20. doi: 10.1080/003655299750026443.
29. Scintu F, Canalis C, Capra F, D'Alia G, Giordano M, Mocci P, et al. [Colonoscopic screening in first-degree relatives of patients with sporadic colorectal cancer]. Ann Ital Chir. 2000; **71**(6): 693-9. Italian.
30. Lieberman DA, Weiss DG; Veterans Affairs Cooperative Study Group 380. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med. 2001 Aug 23; **345**(8): 555-60. doi: 10.1056/NEJMoa010328.
31. Sinnona N, Pacchiarotti A, Rossi A, Cecconi A, Angelini F. Secondary prevention of colorectal cancer conducted by the Italian League for the Fight against Cancer in the Province of Latina, Italy. Preliminary results. Eur J Oncol Environ Health. 2008 Mar; **13**(1): 41-6.
32. Nelson DB, McQuaid KR, Bond JH, Lieberman DA, Weiss DG, Johnston TK. Procedural success and complications of large-scale screening colonoscopy. Gastrointest Endosc. 2002 Mar; **55**(3): 307-14. doi: 10.1067/mge.2002.121883.
33. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med. 2000 Jul 20; **343**(3): 162-8. doi: 10.1056/NEJM200007203430301.
34. Pezzoli A, Matarese V, Rubini M, Simoni M, Caravelli GC, Stockbrugger R, et al. Colorectal cancer screening: results of a 5-year program in asymptomatic subjects at increased risk. Dig Liver Dis. 2007 Jan; **39**(1): 33-9. doi: 10.1016/j.dld.2006.09.001.
35. Thiis-Evensen E, Hoff GS, Sauar J, Vatn MH. Patient tolerance of colonoscopy without sedation during screening examination for colorectal polyps. Gastrointest Endosc. 2000 Nov; **52**(5): 606-10. doi: 10.1067/mge.2000.109804.
36. Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DSM. Adverse Events after Screening and Follow-up Colonoscopy. Cancer Causes Control. 2012 Feb; **23**(2): 289-96. doi: 10.1007/s10552-011-9878-5.
37. Kim SY, Kim HS, Park HJ. Adverse events related to colonoscopy: Global trends and future challenges. World J Gastroenterol. 2019 Jan 14; **25**(2): 190-204. doi: 10.3748/wjg.v25.i2.190.
38. Benazzato L, Zorzi M, Antonelli G, Guzzinati S, Hassan C, Fantin A; Veneto Screening Endoscopists Working Group. Colonoscopy-related adverse events and mortality in an Italian organized colorectal cancer screening program. Endoscopy. 2021 May; **53**(5): 501-8. doi: 10.1055/a-1228-9225.
39. Pariente A, Milan C, Lafon J, Faivre J. Colonoscopic screening in first-degree relatives of patients with "sporadic" colorectal cancer: a case-control study. The Association Nationale des Gastroentérologues des Hôpitaux and Registre Bourguignon des Cancers Digestifs (INSERM CRI 9505). Gastroenterology. 1998 Jul; ***115***(1): 7-12. doi: 10.1016/s0016-5085(98)70358-0.
40. Guillem JG, Neugut AI, Forde KA, Waye JD, Treat MR. Colonic neoplasms in asymptomatic first-degree relatives of colon cancer patients. Am J Gastroenterol. 1988 Mar; ***83***(3): 271-3.
41. Baker JW, Gathright JB, Timmcke AE, Hicks TC, Ferrari BT, Ray JE. Colonoscopic screening of asymptomatic patients with a family history of colon cancer. Dis Colon Rectum.

1990 Nov; **33**(11): 926-30. doi: 10.1007/BF02139100.
42. Armelao F, Paternolli C, Franceschini G, Franch R, Orlandi PG, Miori G, et al. Colonoscopic findings in first-degree relatives of patients with colorectal cancer: a population-based screening program. Gastrointest Endosc. 2011 Mar; **73**(3): 527-34.e2. doi: 10.1016/j.gie.2010.12.025.
43. Del Vecchio Blanco G, Cretella M, Paoluzi OA, Caruso A, Mannisi E, et al. Adenoma, advanced adenoma and colorectal cancer prevalence in asymptomatic 40- to 49-year-old subjects with a first-degree family history of colorectal cancer. Colorectal Dis. 2013 Sep; **15**(9): 1093-9. doi: 10.1111/codi.12263.
44. Castiglione G, Visioli CB, Zappa M, Grazzini G, Mallardi B, Mantellini P. Familial risk of colorectal cancer in subjects attending an organised screening programme. Dig Liver Dis. 2012 Jan; **44**(1): 80-3. doi: 10.1016/j.dld.2011.08.007. Epub 2011 Sep 16.
45. Ruthotto F, Papendorf F, Wegener G, Unger G, Dlugosch B, Korangy F, et al. Participation in screening colonoscopy in first-degree relatives from patients with colorectal cancer. Ann Oncol. 2007 Sep 1; **18**(9): 1518-22. doi: 10.1093/annonc/mdm200.
46. Alkatout I, Biebl M, Momenimovahed Z, Giovannucci E, Hadavandsiri F, Salehiniya H, et al. Has COVID-19 Affected Cancer Screening Programs? A Systematic Review. Front Oncol. 2021; **11**: 675038. doi: 10.3389/fonc.2021.675038.
47. Mayo M, Potugari B, Bzeih R, Scheidel C, Carrera C, Shellenberger RA. Cancer Screening During the COVID-19 Pandemic: A Systematic Review and Meta-analysis. Mayo Clin Proc Innov Qual Outcomes. 2021 Dec; **5**(6): 1109-17. doi: 10.1016/j.mayocpiqo.2021.10.003.
48. Buscarini E, Benedetti A, Monica F, Pasquale L, Buttitta F, Cameletti M, et al. Changes in digestive cancer diagnosis during the SARS-CoV-2 pandemic in Italy: A nationwide survey. Dig Liver Dis. 2021 Jun; **53**(6): 682-8. doi: 10.1016/j.dld.2021.02.021.
49. Fancellu A, Veneroni S, Santoru A, Meloni A, Sanna V, Ginesu GC, et al. How the COVID-19 pandemic has affected the colorectal cancer screening in Italy: A minireview. World J Gastrointest Oncol. 2022 Aug 15; **14**(8): 1490–8. doi: 10.4251/wjgo.v14.i8.1490.

Corresponding Author: Giacomo Diedenhofen, MD, Specialization School in Health Statistics and Biometry, Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy
e-mail: giacomo.diedenhofen@uniroma1.it