
Medical University of Gdańsk
Faculty of Medicine

Doctoral Thesis

# Epidemiology and diagnostics of colorectal cancer and its precursor lesions based on data from Polish Colonoscopy Screening Program.

(pol.) Epidemiologia i diagnostyka raka jelita grubego oraz zmian prekursorowych raka jelita grubego na podstawie danych z Programu Badań Przesiewowych Raka Jelita Grubego.

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## Abbreviations

AADR, advanced adenoma detection rate;
ADR, adenoma detection rate;
AE, adverse event;
AJCC, American Joint Committee on Cancer
BMI, body mass index;
CRC, colorectal cancer;
ICD, International Classification of Diseases;
ITT, intention-to-treat;
NFZ, National Health Fund Registry;
OR, odds ratio
PCSP, Polish Colonoscopy Screening Program;
PESEL Registry, Population Registry;
PP, per-protocol.
TNM, The TNM (Tumor, Nodes, Metastases) Classification of Malignant Tumors
WHO, World Health Organization

## Keywords

Colorectal cancer, colon cancer, detection, risk of death, complication, injury colonoscopy, screening, obesity, colorectal cancer epidemiology

## Abstract

***Introduction***

Colorectal cancer (CRC) is one of the most prevalent and fatal cancers both in Poland and worldwide. Due to that fact many countries, including Poland have established national screening programs for colorectal cancer. Recently, it has been proven that screening in colorectal cancer lowers the prevalence and improves survival[1]. In Poland asymptomatic individuals between 50 and 66 years old are either invited to participate or participate in an opportunistic manner in Polish Colonoscopy Screening Program (PCSP) which facilitates colonoscopy as a screening tool.

An accepted paradigm states that most of colorectal cancers (CRC) develop from precursor lesions, i.e. colorectal adenomas[2]. The phenomenon is called adenoma-to-carcinoma sequence. This model assumes that natural history of CRC follows a certain pathway. Once initial mutations appear normal epithelium of colon and rectum transforms into colorectal adenoma. Following this, adenomas transform into advanced adenomas. After crucial mutations, advanced adenoma transforms into colorectal cancer, which if not detected and treated progresses through stages, from stage I to, finally, stage IV as defined by American Joint Committee on Cancer (AJCC)[3].

Screening for CRC is crucial as it enables diagnosis of less advanced disease and therefore offers the possibility of curing patients[4]. However, colonoscopy-based screening, offers even more as it enables not only detection of early CRCs but also the removal of precursor lesions – colorectal adenomas. Latter is especially of interest. On one hand it may greatly reduce both CRC incidence and mortality. On the other removal of precancerous lesions is associated with the need of performing endoscopic procedures, such as polypectomies which may lead to a greater number of adverse events (AEs) when compared to standard diagnostic colonoscopy.

As mentioned, use of colonoscopy as a diagnostic and therapeutic modality for CRC and its precursor lesions is increasing both in Poland and worldwide[5,6]. It is however associated with sever periprocedural adverse effects among others including bleeding and bowel perforation. These may lead not only to unplanned hospitalization of patients undergoing colonoscopy but also mortality. Data from literature on rates of these events are not robust, and it is yet to be determined whether colonoscopy is safe as a screening tool on populational level.

Increased body mass, most often expressed with use of body mass index (BMI) is a known risk factor both for the development of CRC and its precursor lesions[7,8]. Some researchers indicated that obesity enhances the rate of normal to adenoma sequence, but not adenoma to early carcinoma sequence[9]. It therefore possible that the dynamics of CRC formation and CRC progression are both influenced by obesity, but do not follow the same pattern of change. This could lead to an altered distribution of CRC stages in obese individuals, what however has not been explored to date.

This doctoral thesis consists of two original studies which analyze the data from Polish Colonoscopy Screening Program. First of the two entitled "Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study" assess the safety of colonoscopy as a screening tool on populational level. Second, entitled "Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in the Polish Colonoscopy Screening Program" assess the distribution of stages of colorectal cancer in patients diagnosed with colorectal cancer during screening colonoscopy in relation to BMI category.

***Aims***

**Publication 1**

The aim of this study was to compare mortality and hospitalization rate 6 weeks before and 30 days after the actual or virtual date of colonoscopy in the screening or control group of the PCSP.

**Publication 2**

Primary the aim of this study was to assess whether the stage of CRC detected in overweight and obese individuals in a screening setting differs from individuals with normal body weight. A secondary aim of this study was to elucidate whether overweight and obesity influence the overall survival (OS) of patients diagnosed with CRC.

***Material and methods***

**Publication 1**

This was a randomized health services study nested in a registry of population of present and future participants of the PCSP, RHS registration number: 007_2015_1_RHS. Persons 55–64 years old living in the area covered by the PCSP from 2012 through 2015 were assigned in a 1:1 ratio to a group invited for screening colonoscopy (n=338,477) or a matched group that would be invited 5 years later (controls, n=338,557). All subjects in the screening group were assigned proposed screening colonoscopy dates (actual dates when invitees confirmed or rescheduled colonoscopy) and those in the control group were assigned virtual dates corresponding to the matched individuals from the screening group. In the screening group, 55,390 subjects (16.4%) underwent screening colonoscopy. Mortality and hospitalization data were obtained from National Registries. We compared mortality and rate of hospitalization between the groups for defined intervals before and after colonoscopy date. Hospitalizations were divided into related and unrelated to colonoscopy based on ICD codes by 3 specialists. Continuous data were described by using means, standard deviations, medians, and interquartile ranges and compared by using t-test or Wilcoxon rank-sum test. Categorical data were described by using frequencies and compared by using chi-

squared test or Fisher exact test. All tests were two-sided. P-value <0.05 was considered to denote statistically significant differences.

**Publication 2**

This study was a cross-sectional analysis performed on data from a prospectively maintained database of the Polish Colonoscopy Screening Program on 163,129 individuals who underwent screening colonoscopy between January 2007 and December 2011. Chi-squared test and tests for trend were used to investigate differences between CRC stage distribution stratified by BMI and by BMI and gender. Univariable and multivariable logistic regression models were used to investigate the associations between advanced CRC and patient's BMI, gender, age, and family history of CRC. Probability of overall survival stratified by stages and BMI was estimated using the Kaplan–Meier method. Survival curves were compared using log-rank test. Univariable and multivariable Cox proportional hazard models were used to estimate hazard ratios of death according to CRC stage, patient's BMI, gender, age, and family history of CRC. Forward stepwise selection at the 0.1 significance level was used for variable selection in multivariable models. BMI was included in all multivariable models regardless of its significance. All tests were two-sided. P-value <0.05 was considered to denote statistically significant differences.

***Results***

**Publication 1**

In the intention to treat analysis, there were no significant differences in mortality between the colonoscopy group and control group (0.22% vs 0.22%; risk difference less than 0.01%; p=0.913). The overall rate of unplanned hospitalization was significantly higher for the colonoscopy group (2.39% vs 2.31% for the control group; risk difference, 0.08%; 95% CI, 0.01%–0.15%; p=0.026) for the entire observation period. This was due to the higher rate of hospitalizations after screening (1.10% vs 1.01% for the control group; risk difference, 0.09%; 95% CI, 0.04%–0.14%; p<0.001) including higher proportion of hospitalizations that were assessed as related to colonoscopy (0.24% vs 0.22% for the control group; risk difference, 0.02%; 95% CI, 0.00%–0.05%; p=0.046). In the per-protocol analysis, the overall rate of hospitalizations did not differ significantly between control and screening colonoscopy groups (1.87% vs 1.90%; p=0.709). However, screening colonoscopy did increase rates of related hospitalizations after the date of screening (from 0.14% to 0.31%; p<0.001).

**Publication 2**

Overweight and obese individuals presented with a less advanced CRC in the screening setting (p=0.014). This trend was the most pronounced in males (p=0.001). Univariable and multivariable analyses revealed that obesity was a negative predictor of detection of advanced CRC with odds ratio 0.72 (95% confidence interval 0.52–1.00; p=0.047). Furthermore, overweight and obesity were not statistically significant predictors of risk of death (p=0.614 and p=0.446, respectively).

***Conclusions***

Presented studies provide novel insight into the field of diagnostics and epidemiology of colorectal cancer and its precursor lesions. The first publication provides high quality evidence that colonoscopy is safe as a screening tool on a populational level. Second publication provides new evidence that obese screenees, especially males, present with a less advanced colorectal cancer, when compared to non-obese.

In conclusion, considering the populational safety of colonoscopy and distinct prevalence and stage distribution of CRC in obese individuals it should be feasible to introduce additional public health campaigns encouraging participation in screening programs. These campaigns could especially focus on people with obesity.

## **Streszczenie** *(pol.)*


***Wstęp***

Rak jelita grubego (RJG) jest jednym z najczęstszych i najbardziej śmiertelnych nowotworów złośliwych zarówno w Polsce jak i na świecie. Z tego względu wiele Państw, włączając w to Polskę, wdrożyło narodowe programy badań przesiewowych w kierunku raka jelita grubego. W ostatnim czasie udowodniono, że badania przesiewowe w przypadka raka jelita grubego zmniejszają częstość występowania tej choroby i poprawiają przeżywalność[1]. W Polsce bezobjawowe osoby między 50 a 66 rokiem życia są zapraszane lub zgłaszają się samodzielnie do Programu Badań Przesiewowych Raka Jelita Grubego (PBP RJG), który wykorzystuje kolonoskopię jako narzędzie przesiewu.

Powszechnie uznany paradygmat stanowi, że raki jelita grubego rozwijają się ze zmian prekursorowych, tj. gruczolaków jelita grubego[2]. To zjawisko nazywane jest sekwencją gruczolak-rak. Model ten zakłada, że naturalna historia rozwoju raka jelita grubego przebiega według określonej ścieżki. Po zaistnieniu początkowych mutacji prawidłowa śluzówka okrężnicy i odbytnicy przekształca się w gruczolaka. Następnie gruczolaki zamieniają się w zaawansowane gruczolaki. Gdy dojdzie do kolejnych mutacji zaawansowany gruczolak przekształca się w raka jelita grubego, który, jeżeli nie zostanie wykryty i leczony odpowiednio szybko, rozwija się w kolejnych stadiach zawansowania – od stadium I do IV zgodnie z definicją American Joint Committee on Cancer (AJCC)[3].

Prowadzenie przesiewu w kierunku RJG jest kluczowe, gdyż pozwala na wykrycie mniej zawansowanej choroby i w efekcie wyleczenie pacjenta[4]. Programy wykorzystujące kolonoskopię do prowadzenia przesiewu umożliwiają nie tylko wykrycie wczesnych zmian nowotworowych, ale również usuwanie zmian prekursorowych – gruczolaków jelita grubego. Z jednej strony umożliwia to zmniejszenie częstości występowania oraz śmiertelności z powodu RJG. Z drugiej, usuwanie zmian prekursorowych związane jest z koniecznością wykonywania procedur endoskopowych, takich jak polipektomie, które mogą spowodować większą ilość zdarzeń niepożądanych w porównaniu z diagnostyczną kolonoskopią.

Jak wspomniano, wykorzystanie kolonoskopii jako narzędzia diagnostyczno-terapeutycznego w przypadku raka jelita grubego wzrasta zarówno w Polsce jak i na świecie[5,6]. Kolonoskopia związana jest z występowaniem zdarzeń niepożądanych, takich jak krwawienie oraz perforacja jelita. Mogą one prowadzić nie tylko do nieplanowanych hospitalizacji, ale również być przyczyną śmierci pacjentów. Dane literaturowe dotyczące częstości występowania zdarzeń niepożądanych po kolonoskopii powodujących hospitalizację lub zgon są ograniczone. Wciąż brak jest przekonujących dowodów na bezpieczeństwo kolonoskopii jako narzędzia skriningowego na poziomie populacyjnym.

Zwiększona masa ciała, najczęściej wyrażana przy pomocy indeksu masy ciała (en. body mass index, BMI) jest znanym czynnikiem ryzyka zarówno dla rozwoju raka jelita grubego jak i zmian prekursorowych raka jelita grubego[7,8]. Niektórzy badacze wskazywali, że otyłość może zwiększać tempo powstawania gruczolaków z prawidłowego nabłonka jelit, nie mając jednocześnie takiego samego wpływu na tempo transformacji nowotworowej z gruczolaka w raka[9]. W związku z tym możliwe jest, że otyłość wpływa zarówno na dynamikę powstawania raka jelita grubego jak i na dynamikę progresji raka jelita grubego, jednak w różny sposób. Taka sytuacja może doprowadzać do zmienionej dystrybucji stadiów zawansowania raka jelita grubego u osób z otyłością, co dotychczas nie było badane.

Ten przewód doktorski składa się z dwóch badań oryginalnych analizujących dane z Programu Badań Przesiewowych Raka Jelita Grubego. Pierwsza praca pt. "Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study" ocenia bezpieczeństwo kolonoskopii jako narzędzia skriningowego na poziomie populacyjnym. Druga pt. "Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in the Polish Colonoscopy Screening Program" ocenia dystrybucję stopni zaawansowania raka jelita grubego u pacjentów zdiagnozowanych z rakiem jelita grubego podczas przesiewowej kolonoskopii w relacji do kategorii BMI pacjentów.

## *Cele*

### Publikacja 1

Celem tego badania było porównanie śmiertelności oraz częstości hospitalizacji 6 tygodni przed i 30 dni po faktycznej i wirtualnej dacie kolonoskopii w przesiewowym oraz kontrolnym ramieniu badania osadzonego w PBP RJG.

### Publikacja 2

Pierwszorzędowym celem badania była ocena czy stopień zawansowania raka jelita grubego wykrytego u osób z nadwagą i otyłością podczas badania przesiewowego różni się od osób z prawidłową masą ciała. Drugorzędowym celem pracy była ocena czy nadwaga i otyłość wpływają na przeżycia całkowite pacjentów zdiagnozowanych z rakiem jelita grubego.

## *Materiał i metody*

### Publikacja 1

Badanie to było randomizowanym badaniem usług medycznych (RHS, randomized health services study) osadzonym w rejestrze dotychczasowych i przyszłych pacjentów PBP RJG. Numer rejestracyjny RHS 007_2015_1_RHS. Osoby w wieku 55-64 lat mieszkające w rejonie, w którym prowadzony był PBP w latach 2012-2015 były przypisane w stosunku 1:1 do grupy zaproszonej na badanie przesiewowe (gr. Kolonoskopową, n=338,477) oraz grupy z zaplanowanym zaproszeniem na datę o 5 lat późniejszą (gr. kontrolna, n=338,557). Wszystkim pacjentom z ramienia

przesiewowego przypisano datę kolonoskopii (uwzględniając ewentualną zmianę daty na życzenie pacjenta). Pacjentom z grupy kontrolnej przypisano datę kolonoskopii wirtualnej korespondującą do daty faktycznej kolonoskopii dla sparowanej osoby z grupy przesiewanej, jednak o 5 lat późniejszą. W ramieniu przesiewowym 55,690 (16.4%) pacjentów zostało poddanych kolonoskopii. Dane dotyczące śmiertelności i częstości hospitalizacji zostały pobrane z Rejestrów Krajowych. Porównano śmiertelność i częstość hospitalizacji pomiędzy grupami w zdefiniowanych interwałach dla okresów przed i po dacie kolonoskopii. Hospitalizacje zostały zakwalifikowane jak związane lub niezwiązane z kolonoskopią na podstawie kodów ICD przez 3 lekarzy specjalistów. Dane ciągłe zostały opisane przy pomocy średnich, odchyleń standardowych, median oraz rozstępów międzykwartylowych i porównane przy pomocy testu t-studenta oraz testu Wilcoxona. Dane kategoryczne zostały opisane przy pomocy częstości i porównane przy pomocy testu chi-kwadrat oraz testu Fishera. Wszystkie testy były dwustronne. Wartość $p<0.05$ wskazywała na istotność statystyczną różnic.

**Publikacja 2**

Badanie to było przekrojową analizą wykonaną na danych z prospektywnie utrzymywanej bazy danych 163,129 pacjentów PBP RJG którzy poddani zostali przesiewowej kolonoskopii między Styczniem 2007 a Grudniem 2011. Test chi-kwadrat i test dla trendu zostały wykorzystane do określenia różnic pomiędzy dystrybucją stopni zawansowania RJG w zależności od kategorii BMI oraz kategorii BMI i płci. Jedno- i wieloczynnikowa analiza regresji logistycznej została wykorzystana do określenia związku pomiędzy zawansowanym RJG a BMI, płcią, wiekiem i pozytywnym wywiadem rodzinnym w kierunku występowania RJG pacjentów. Prawdopodobieństwa całkowitego przeżycia w zależności od stopnia zawansowania i kategorii BMI zostały oszacowane przy pomocy metody Kaplana-Meiera. Krzywe przeżywalności zostały porównane przy pomocy testu log-rank. Jedno- i wieloczynnikowe modele proporcjonalnego hazardu Coxa zostały wykorzystane do oszacowania stosunku ryzyka (hazard ratio, HR) śmierci w zależności od stopnia zawansowania RJG, kategorii BMI, płci, wieku i wywiadu rodzinnego w kierunku RJG. Postępująca selekcja krocząca na poziomie istotności 0.1 została wykorzystana do oceny zmiennych w modelach wieloczynnikowych. BMI zostało włączone do wszystkich analiz wieloczynnikowych niezależnie od osiągniętej istotności. Wszystkie testy były dwustronne. Wartość $p<0.05$ wskazywała na istotność statystyczną różnic.

***Wyniki***

**Publikacja 1**

W analizie intencji leczenia (ITT, intention-to-treat) nie wykazano istotnych statystycznie różnic pomiędzy grupą kolonoskopową a kontrolą (0.22% vs 0.22%; różnica ryzyka < 0.01%; p=0.913). Całkowita częstość nieplanowanych hospitalizacji była statystycznie istotnie większa dla grupy kolonoskopowej (2.39% vs 2.31% dla kontroli; różnica ryzyka, 0.08%; 95% CI, 0.01%–0.15%; p=0.026) dla całego okresu obserwacji. Wynikało to z wyższej częstości hospitalizacji po wykonaniu badania przesiewowego (1.10% vs 1.01% dla kontroli; różnica ryzyka, 0.09%; 95% CI, 0.04%–0.14%; p<0.001) włączając w to większą proporcję hospitalizacji określonych jako związane z kolonoskopią (0.24% vs 0.22% dla kontroli; różnica ryzyka, 0.02%; 95% CI, 0.00%–0.05%; p=0.046). W analizie według protokołu badania (PP, per protocol) całkowita częstość hospitalizacji nie różniła się istotnie pomiędzy grupą kolonoskopową o kontrolną (1.87% vs 1.90%; p=0.709). Jednak w grupie kolonoskopowej wystąpiła zwiększona częstość hospitalizacji związanych z kolonoskopią występujących po dacie przesiewu (od 0.14% do 0.31%; p<0.001).

**Publikacja 2**

W badaniu przesiewowym osoby z nadwagą i otyłością zostały zdiagnozowane z mniej zaawansowanymi RJG (p=0.014). Trend ten był najwyraźniej zauważalny u mężczyzn (p=0.001). Jedno- i wieloczynnikowe analizy wykazały, że otyłość była negatywnym predyktorem wykrycia zaawansowanego RJG ze stosunkiem szans (OR, odds ratio) 0.72 (95% CI 0.52-1.00; p=0.047). Ponadto nadwaga i otyłość nie były istotnymi statycznie predyktorami ryzyka zgonu (odpowiednio, p=0.614 oraz p=0.446)

***Wnioski***

Zaprezentowane badania dostarczają nowych informacji w zakresie diagnostyki i epidemiologii raka jelita grubego i jego zmian prekursorowych. Pierwsza publikacja dostarcza wysokiej jakości dowodów, że kolonoskopia jest bezpiecznym narzędziem przesiewowym na poziomie populacyjnym. Druga publikacja dostarcza nowych dowodów, że osoby otyłe poddawane przesiewowi, a zwłaszcza mężczyźni, diagnozowane są z mniej zaawansowanymi rakami jelita grubego w porównaniu do nieotyłych.

Biorąc pod uwagę bezpieczeństwo populacyjne kolonoskopii oraz odmienną częstość i dystrybucję stopni zaawansowania RJG u osób otyłych uzasadnione może być wprowadzenie dodatkowych kampanii społecznych zachęcających do uczestnictwa w programie przesiewowym. Tego typu kampanie mogą w szczególności skupione być na osobach z otyłością.

## Introduction

Colorectal cancer (CRC) is one of the most prevalent and fatal cancers both in Poland and worldwide. Due to that fact many countries, including Poland have established national screening programs for colorectal cancer. Recently, it has been proven that screening in colorectal cancer lowers prevalence and improves survival[1]. In Poland asymptomatic individuals between 50 and 66 years old are either invited to participate or participate in an opportunistic manner in Polish Colonoscopy Screening Program (PCSP) which facilitates colonoscopy as a screening tool.

An accepted paradigm states that most of colorectal cancers (CRC) develop from precursor lesions, i.e. colorectal adenomas (Figure 1)[2]. The phenomenon is called adenoma-to-carcinoma sequence. This model assumes that natural history of CRC follows a certain pathway. Once initial mutations appear normal epithelium of colon and rectum transforms into colorectal adenoma. Following this, adenomas transform into advanced adenomas. After crucial mutations, advanced adenoma transforms into colorectal cancer, which if not detected and treated progresses trough stages, from stage I to, finally, stage IV as defined by American Joint Committee on Cancer (AJCC)[3]. However, other pathways of colorectal carcinogenesis have also been described, including the serrated pathway. This pathway may be responsible for up to 30% of colorectal cancers and is yet to be well understood [10,11].

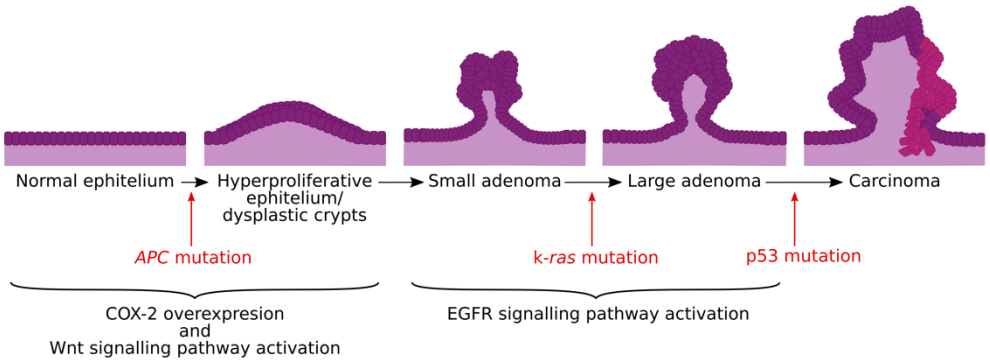


*Figure 1 Overview of the adenoma to carcinoma sequence*

Screening for CRC is crucial as it enables diagnosis of less advanced disease and therefore offers the possibility of curing patients[4]. Screening modalities for colorectal cancer include FOBT (fecal occult blood test), FIT (fecal immunochemical test), sigmoidoscopy and colonoscopy[12]. Each of these methods has its advantages and limitations. Colonoscopy-based screening is the most demanding as it requires bowel preparation and highly trained personnel. On the other hand, it is the only method that enables not sole detection of early CRCs but also the removal of precursor lesions in the entirety of the large bowel. Latter is especially important. Firstly, it may greatly reduce both CRC incidence and mortality. Secondly, removal of precancerous lesions is associated with the need of performing endoscopic procedures, such as polypectomies which may lead to a greater number of adverse events (AEs) when compared to standard diagnostic colonoscopy.

The Polish Colonoscopy Screening Program was first introduced in the year 2000 and since then has been steadily developed to include more comprehensive data on screened individuals as well as to increase the yearly number of screenees. As it has been previously described in detail, consists of two major arms[13–17]. In the first one, which was started in year 2000, asymptomatic individuals aged 50-65 years old are eligible for screening in an opportunistic manner – i.e. every willing individual can be screened provided he or she meets inclusion criteria and does not meet exclusion criteria. In the second arm which was started in year 2012, citizens aged 55-64 years old are invited to screening by a letter invitation [13].

The design and capacity of PCSP is unique in Europe and worldwide. To date it has included over 500 000 individuals with increasing annual recruitment trend. Therefore, it plays not only a critical clinical role in polish healthcare policy, but also as great of a role in scientific research. Since the commencement of the program the team have used the acquired data for epidemiological analyses and trials. Unique design of PCSP enables robust cross-sectional analyses as well as conducting randomized health services studies. Furthermore, the program is cooperating with other national screening programs in foreign countries including Austria, Denmark, Norway, The Netherlands, Portugal, Spain and Sweden.

As mentioned, use of colonoscopy as a diagnostic and therapeutic modality for CRC and its precursor lesions is increasing[5,6]. It may be however associated with periprocedural adverse events including bleeding and bowel perforation. These may lead not only to unplanned hospitalization of patients undergoing colonoscopy but also mortality. Data from literature on rates of these events are not robust, and it is yet to be determined whether colonoscopy is safe as a screening tool on the populational level.

Increased body mass, most often expressed with use of body mass index (BMI) is a known risk factor both for the development of CRC and its precursor lesions[7,8]. Some researchers indicated that obesity enhances the rate of normal to adenoma sequence, but not adenoma to early carcinoma sequence[9]. It is therefore possible that the dynamics of CRC formation and CRC progression are both influenced by obesity, but do not follow the same pattern of change. This could lead to an altered distribution of CRC stages in obese individuals. It has however not been explored to date.

This doctoral thesis consists of two original studies which analyze the data from Polish Colonoscopy Screening Program. First of the two entitled "Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study" assess the safety of colonoscopy as a screening tool on populational level. Second, entitled "Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in the Polish Colonoscopy Screening Program" assess the distribution of stages of colorectal cancer in patients diagnosed with colorectal cancer during screening colonoscopy in relation to BMI category.

## Aims of the studies

**Publication 1**

*Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study*

The aim of this study was to compare mortality and hospitalization rate 6 weeks before and 30 days after the actual or virtual date of colonoscopy in the screening or control group of the PCSP.

**Publication 2**

*Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in the Polish Colonoscopy Screening Program*

Primary the aim of this study was to assess whether the stage of CRC detected in overweight and obese individuals in a screening setting differs from individuals with normal body weight. A secondary aim of this study was to elucidate whether overweight and obesity influence the overall survival (OS) of patients diagnosed with CRC.

## Conclusions

Presented studies provide novel insight into the field of diagnostics and epidemiology of colorectal cancer and its precursor lesions. In the first publication we have provided high quality evidence that colonoscopy is safe as a screening tool on a populational level. However, it may be associated with a small but significant increase in unplanned hospitalizations, especially after the colonoscopy is completed. Therefore, colonoscopy screening programs should not be considered as a substantial burden for both populations and healthcare providers. Nevertheless, the financial consequences of additional hospitalizations should be taken into account when performing cost-effectiveness analyses.

Second publication provides new evidence that obese screenees, especially males, present with a less advanced colorectal cancer, when compared to non-obese. Considering the fact that incidence of CRC in obese individuals is higher it may suggest that increasing the uptake of these patients into screening programs may create survival benefit in this group.

Considering the safety of colonoscopy and distinct prevalence and stage distribution of CRC in obese individuals it should be feasible to introduce additional public health campaigns encouraging participation in screening programs. These campaigns could especially focus on people with obesity.

Further studies should focus on assessing the safety of colonoscopy specifically in overweight and obese individuals, as this has proven to be a differing subgroup of individuals. Moreover, more studies investigating the changes in CRC formation and progression rates dependent on patient-specific factors, including body mass, are still warranted.

## List of publications and bibliometrics

**Publication 1**

Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study

**Spychalski P* (corresponding author),** Kobiela J*, Wieszczy P, Pisera M, Pilonis N, Rupinski M, Bugajski M, Regula J, Kaminski MF. [1]

Clin Gastroenterol Hepatol. 2020 Jun;18(7):1501-1508.e3.

doi: 10.1016/j.cgh.2019.09.010.

Bibliometrics: Impact Factor: 8.549 MNiSW: 140.000

**Publication 2**

Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in the Polish Colonoscopy Screening Program

**Spychalski P (corresponding author),** Kobiela J, Wieszczy P, Kamiński MF, Reguła J.

United European Gastroenterol J. 2019 Jul;7(6):790-797.

doi: 10.1177/2050640619840451.

Bibliometrics: Impact Factor: 3.549 MNiSW: 100.000

Summary of bibliometrics:

**Impact Factor: 12.098**

MNiSW: 240.000

## Publications

Further please find the publications constituting this doctoral thesis. Please consider that both publications and both supplementary materials are attached in an as-published form, hence the formatting differs across the documents.

*These authors should be considered as equal co-first authors.

Clinical Gastroenterology and Hepatology 2020;18:1501–1508

# Mortality and Rate of Hospitalization in a Colonoscopy Screening Program From a Randomized Health Services Study


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**BACKGROUND & AIMS:** **It is difficult to quantify adverse events related to screening colonoscopy due to lack of valid and adequately powered comparison groups. We compared mortality and rate of unplanned hospitalizations among subjects who underwent screening colonoscopies within the Polish Colonoscopy Screening Program (PCSP) vs unscreened matched controls in Poland.**

**METHODS:** **Persons 55–64 years old living in the area covered by the PCSP from 2012 through 2015 were assigned in a (1:1) to a group invited for screening colonoscopy (n = 338,477) or a matched group that would be invited 5 years later (controls, n = 338,557). All subjects in the screening group were assigned proposed screening colonoscopy dates (actual dates when invitees confirmed or rescheduled colonoscopy) and those in the control group were assigned virtual dates corresponding to the matched individuals from the screening group. In the screening group, 55,390 subjects (16.4%) underwent screening colonoscopy. Mortality and hospitalization data were obtained from National Registries. We compared mortality and rate of hospitalization between the groups for defined intervals before and after colonoscopy date. Hospitalizations were divided into related and unrelated to colonoscopy based on ICD codes by 3 specialists. Our primary aim was to compare mortality and hospitalization 6 weeks before and 30 days following the actual or virtual date of colonoscopy in the screening or control group.**

**RESULTS:** **In the intent to treat analysis, overall there were no significant differences in mortality between the colonoscopy group and control group (0.22% vs 0.22%; risk difference less than .01%; 95% CI, decrease of 0.02% to 0.02%; $P = .913$). The overall rate of unplanned hospitalization was significantly higher for the colonoscopy group (2.39% vs 2.31% for the control group; risk difference, 0.08%; 95% CI, 0.01%–0.15%; $P=.026$) for the entire observation period. This was due to the higher rate of hospitalizations after screening (1.10% vs 1.01% for the control group; risk difference, 0.09%; 95% CI, 0.04%–0.14%; $P < .001$) including higher proportion of hospitalizations that were assessed as related to colonoscopy (0.24% vs 0.22% for the control group; risk difference, 0.02%; 95% CI, 0.00%–0.05%; $P = .046$). In the per-protocol analysis, the overall rate of hospitalizations did not differ significantly between control and screening colonoscopy groups (1.87% vs 1.90%; $P=.709$). However, screening colonoscopy did increase rates of related hospitalizations after the date of screening (from 0.14% to 0.31%; $P < .001$).**

[a]Authors share co-first authorship.

*Abbreviations used in this paper:* AE, adverse event; CRC, colorectal cancer; ICD, International Classification of Diseases; ITT, intention-to-treat; NFZ, National Health Fund Registry; PCSP, Polish Colonoscopy Screening Program; PESEL Registry, Population Registry; PP, per-protocol.

Most current article



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CONCLUSIONS: **In an analysis of data from the PCSP, we found high-quality evidence that colonoscopy as a screening intervention does not increase mortality before or after colonoscopy. However, it may be associated with a small but significant increase in unplanned hospitalizations, especially after the colonoscopy is completed.**

*Keywords:* Colon Cancer; Detection; Risk of Death; Complication; Injury.

Colonoscopy as the primary method of screening for colorectal cancer (CRC) is becoming increasingly common, with several countries launching national screening programs worldwide.[1,2] Procedure-related adverse events (AEs), associated with periprocedural stress, bowel preparation, and examination itself, are the main concerns.[3,4] Most common serious AEs of colonoscopy include bleeding and bowel perforations and may lead to mortality or unplanned hospital admissions.[1] These are reported at variable rates that strongly depend on the study design and reporting methods.[1–4] Mortality rates and hospital admission rates are objective because they are provided by national registries and hospital billing systems. Main concerns regarding evidence on burden of screening colonoscopy as healthcare policy are reporting of AEs and lack of valid and adequately powered comparator arms in observational studies. Data from randomized trials on colonoscopy screening are missing. Most available studies report only crude mortality and hospitalization rates that are biased by background risks. Studies embedded within the Polish Colonoscopy Screening Platform (PCSP) are population-based comparative effectiveness studies designed to evaluate the performance characteristics and effectiveness of screening colonoscopy as a public health policy. Analyses of mortality and unplanned hospital admissions are essential in assessment of risk to benefit ratio of the policy. Comparative design of this randomized health services study offers the possibility to extract the rates related to screening colonoscopy as a healthcare policy from overall rates in matched control group.[5] Furthermore, studies use various endpoints that may be subjective, especially when reported by healthcare providers. Optimal endpoints to assess burden of colonoscopy may include mortality and hospital admission rates based on data from National Registry. Therefore, use of hard endpoints based on registry-level data along with a randomized controlled design should limit bias and increase the level of evidence.

## Aim of the Study

The aim of this study was to compare mortality and hospitalization rate 6 weeks before and 30 days after the actual or virtual date of colonoscopy in the screening or control group of the PCSP.

## Materials and Methods

This was a randomized health services study nested in a registry of population of present and future participants of the PCSP, RHS registration number: 007_2015_1_RHS.

### *Patients*

**Inclusion criteria.** All individuals aged 55–64 years living in the area covered by 25 centers participating in the organized CRC screening program in 2012–2015 were eligible for the study. Detailed descriptions of the screening methodology are available elsewhere; readers may especially refer to an article entitled "Design of the Polish Colonoscopy Screening Program: a randomized health services study", paragraph "Program Design".[6–12] Eligible individuals were drawn from the Population Registry (PESEL Registry) and randomly assigned in a 1:1 ratio to the group invited to screening colonoscopy in the year of drawing (screening group) or in 5 years' time (control group). The control group was not informed about their status as controls. The control group has been matched to colonoscopy group by date of invitation, sex, age, and place of residence. Therefore, if the screenee changed the date of the screening colonoscopy, the date of virtual colonoscopy in matched control was changed accordingly.

**Exclusion criteria for study enrollment.** The following individuals were excluded from the study:

- Message from neighbor/family/post office on death of screenee (not updated in Population Registry) before the date of draw
- Resident abroad (not updated in Population Registry)
- Return of unopened letter of invitation and/or reminder (address unknown)
- Diagnosis of CRC before the date of draw.

**Exclusion criteria for screening colonoscopy.** These individuals were not offered any screening but are included in the intention-to-treat (ITT) analysis.

- Individuals in need of long-lasting attention and nursing services (somatic, psychosocial, or mental disability)
- Severe cardiac or lung disease limiting routine daily activity
- Proctocolectomy or colectomy.

Excluded individuals with suspicious symptoms were advised to consult their physician for further investigations.

### Methods

Mortality data were obtained from the Ministry of Interior in Poland (PESEL Registry changes) and the National Cancer Registry and were based on death certificates. Hospital admissions' data were obtained from the National Health Fund Registry (NFZ). Health services in Poland are financed by the National Health Fund (NFZ), pursuant to the Act and the Regulation of the Minister of Health resulting thereof.[13] Hospital admissions were categorized by the type of admission, planned or unplanned, which was based on the billing codes of healthcare providers. The emergency admissions were qualified by a committee of 3 specialist medical doctors into categories described by the National Cancer Institute; AE reporting requirements were based on the review of International Classification of Diseases (ICD)-9 and ICD-10 coding, length of stay, and other available data. In the present analysis we have not divided unplanned hospitalizations by ICD code to analyze specific reasons for the hospitalization. This would be of interest; however, the complexity of the analysis requires a separate evaluation. Reviewers were blinded (were not able to identify group assignment).[14] On the basis of the relation with screening colonoscopy, the hospitalization episodes were qualified as unrelated, unlikely, possibly, probably, and definitely related to the endoscopy. Last two were considered as "related" to colonoscopy. Detailed definitions of categories and details regarding attribution are available in the Supplementary Material. Comparisons between the groups were performed for defined time intervals before and after colonoscopy date (actual day of examination or assigned reference virtual date of colonoscopy for colonoscopy group and control group, respectively). The start of monitored period is defined on the basis of an invitation letter that was sent to the screenees 6 weeks (42 days) before colonoscopy date. End of monitored period was censored on 30 days to assess 30-day mortality rates and 30-day hospitalization rates commonly used in the literature.

### Data Management

Study data were collected, stored, and analyzed by the PCSP investigators. Demographic and personal data of screenees were obtained from the Ministry of Interior of Poland and NFZ. Access to the database was password-protected from unauthorized users at different levels: administrative, and endoscopic at sites according to Guidelines of the General Inspector for Personal Data in Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw.

**What You Need to Know**

**Background**

It is difficult to quantify the adverse events associated with screening colonoscopies. We compared rates of death and unplanned hospitalizations among subjects who underwent screening colonoscopy within the Polish Colonoscopy Screening Program vs unscreened matched controls in Poland.

**Findings**

We found high-quality evidence that screening colonoscopies do not increase mortality before or after colonoscopy. However, screening colonoscopies are associated with a small but significant increase in unplanned hospitalizations, especially after the colonoscopy is completed.

**Implications for patient care**

Screening colonoscopies have low rates of death and complications.

### Ethics Approval

This information is available in the Supplementary Material.

### Statistical Methods

Continuous data were described by using means, standard deviations, medians, and interquartile ranges and compared by using *t* test or Wilcoxon rank-sum test. Categorical data were described by using frequencies and compared by using $\chi^2$ test or Fisher exact test. All tests were two-sided. $P$ value $<.05$ was considered to denote statistically significant differences. All analyses were performed by STATA 13.1 (StataCorp LLC, College Station, TX).

### Power Analysis

This information is available in the Supplementary Material.

## Results

A total of 341,900 and 342,027 individuals were assigned to colonoscopy and control group, respectively. Of those, 3423 and 3470 were excluded from the analysis for the reasons presented in Figure 1. A total of

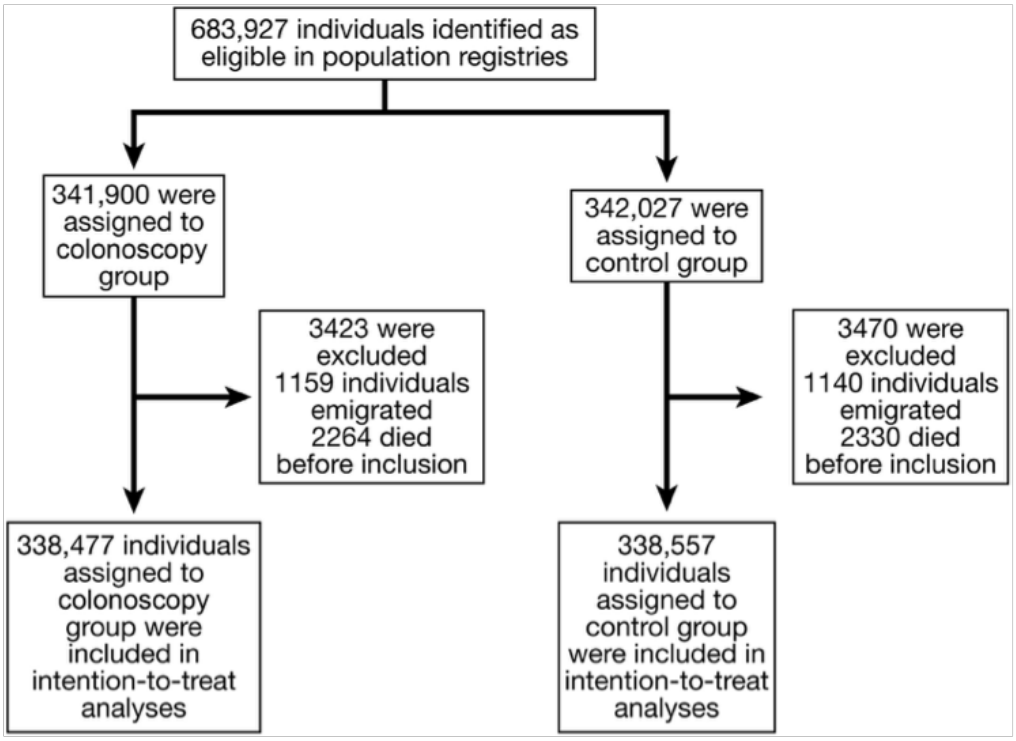


**Figure 1.** Study design with inclusion and exclusion protocol.

338,477 individuals in the colonoscopy group and 338,557 individuals in the control group were left and included in the ITT analysis. Mean age was 59.3 years (standard deviation, 2.8), and proportion of male individuals was 46.5% in both groups. Of the 338,477 individuals assigned to the colonoscopy group, 55,390 (16.4%) were screened and were analyzed in per-protocol (PP) analysis, which is described in Supplementary Material. This article presents results of ITT analysis in detail. Results of PP analysis are discussed in a limited capacity. Full PP results are to be found in Supplementary Material.

### *Mortality Rates*

Summary of findings on mortality is presented in Table 1. Analysis of mortality was stratified by time of death into 3 time frames: (1) before and after: death recorded in whole observation period, 42 days before colonoscopy to 30 days after; (2) before: 42 days before colonoscopy to the day before the colonoscopy; and (3) after: day of the colonoscopy to 30 days after the colonoscopy.

Overall there were no significant differences in mortality rates between control group and screening group in ITT. Mortality rates did not differ significantly in any time frame: before or after (0.22% vs 0.22%; $P = .913$), before (0.12% vs 0.12%; $P = .704$), and at day of colonoscopy or 30 days after (0.09% vs 0.10%; $P = .551$), respectively, for control and screening groups.

### *Hospitalization Rates*

Summary of findings on hospitalizations is presented in Table 2, and graphical illustration of hospitalization

**Table 1.** Mortality Reported Before and After Actual Colonoscopy Date in Screening Group and Reference Colonoscopy Date in Matched Control Group (Virtual Colonoscopy Group)

| | Intention-to-treat | | | | | Per-protocol | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | Invited | | | Control | | Screened | | |
| | N | % | N | % | *P* value | N | % | N | % | *P* value |
| Total | 338,557 | | 338,477 | | | 54,743 | | 55,390 | | |
| Screened | | | 55,390 | 16.36 | | N/R | | N/R | | |
| Death (−42 days/+30 days) | 730 | 0.22 | 734 | 0.22 | .913 | 115 | 0.21 | 11 | 0.02 | <.001 |
| Death before | 418 | 0.12 | 407 | 0.12 | .704 | 66 | 0.12 | 0 | 0.00 | NA |
| Death at day 0 or after | 312 | 0.09 | 327 | 0.10 | .551 | 49 | 0.09 | 11 | 0.02 | <.001 |

NA, not available; N/R, not reported.

**Table 2.** Hospitalizations Stratified by Relevance Reported Before and After Actual Colonoscopy Date in Screening Group and Reference Colonoscopy Date in Matched Control Group (Virtual Colonoscopy Group)

| | Intention-to-treat | | | | | Per-protocol | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | Invited | | | Control | | Screened[a] | | |
| | N | % | N | % | *P* value | N | % | N | % | *P* value |
| Total | 338,557 | | 338,477 | | | 54,743 | | 55,390 | | |
| Screened | | | 55,390 | 16.36 | | | | 55,390 | | |
| Total | | | | | | | | | | |
| Before and after | 7820 | 2.31 | 8095 | 2.39 | **.026** | 1023 | 1.87 | 1052 | 1.90 | .709 |
| Before | 4672 | 1.38 | 4681 | 1.38 | .916 | 671 | 1.23 | 482 | 0.87 | **<.001** |
| After | 3436 | 1.01 | 3735 | 1.10 | **<.001** | 383 | 0.70 | 595 | 1.07 | **<.001** |
| Related | | | | | | | | | | |
| Before and after | 1054 | 0.31 | 1113 | 0.33 | .202 | 117 | 0.21 | 208 | 0.38 | **<.001** |
| Before related | 314 | 0.09 | 299 | 0.09 | .546 | 41 | 0.07 | 36 | 0.06 | .534 |
| After related | 748 | 0.22 | 827 | 0.24 | **.046** | 76 | 0.14 | 172 | 0.31 | **<.001** |
| Total | | | | | | | | | | |
| No. of hospitalizations before and after | 7820 | | 8095 | | .85 | | | | | **.032** |
| 1 | 6920 | 88.49 | 7159 | 88.44 | | 911 | 89.05 | 971 | 92.30 | |
| 2 | 750 | 9.59 | 789 | 9.75 | | 90 | 8.80 | 68 | 6.46 | |
| ≥3 | 150 | 1.92 | 147 | 1.82 | | 22 | 2.15 | 13 | 1.24 | |
| Related | | | | | | | | | | |
| No. of hospitalizations before and after related, median (IQR) | | | | | .449 | | | | | .419 |
| 1 | 1008 | 95.64 | 1073 | 96.41 | | 113 | 96.58 | 204 | 98.08 | |
| 2 | 40 | 3.80 | 37 | 12.37 | | 3 | 2.56 | 4 | 11.11 | |
| ≥3 | 6 | 0.57 | 3 | 0.36 | | 1 | 0.85 | 0 | 0.00 | |
| Time to hospitalization before, median (IQR) | –21 (–32 to -11) | | –21 (–31 to-10) | | .704 | –21 (–32 to -11) | | –25 (–33 to –15) | | **<.001** |
| Time to hospitalization after, median (IQR) | 14 (7–22) | | 14 (7–22) | | .416 | 12 (6-20) | | 13 (6–22) | | .766 |
| No. of hospitalization days | 3 (1–7) | | 3 (1–7) | | .716 | 3 (1-7) | | 2 (1–5) | | **<.001** |
| No. of related hospitalization days | 3 (1–7) | | 3 (1–6) | | .821 | 4 (2-7) | | 3 (1–5) | | **.02** |

NOTE. Statistically significant differences are indicated with bold.
IQR, interquartile range.
[a]Screened individuals actually underwent screening colonoscopy.

rates over time is presented in Figure 2. Analysis of hospitalizations was stratified by time of hospitalization into 3 time frames as described in mortality subsection. Furthermore, it was stratified by relevance to the colonoscopy procedure into 2 categories, related and not related. Subanalyses of number of hospitalizations per patient and total number of hospitalization days were performed.

Overall rate of all hospitalizations was lower for control group when compared with colonoscopy group (2.31% vs 2.39%; $P = .026$). This was especially noticeable in all hospitalizations after colonoscopy (1.01% vs 1.10%; $P < .001$). Analysis of all hospitalizations before colonoscopy did not reveal statistically significant differences.

### *Related Hospitalizations*

Overall rate of related hospitalizations did not differ significantly between control and screening groups (0.31% vs 0.33%; $P = .202$). Similarly, there were no differences before colonoscopy (0.09% vs 0.09%, $P = .546$). However, related hospitalizations after colonoscopy alone did differ with statistical significance (0.22% vs 0.24%; $P = .046$). In an analysis of number of events (hospitalizations) per patient and duration of

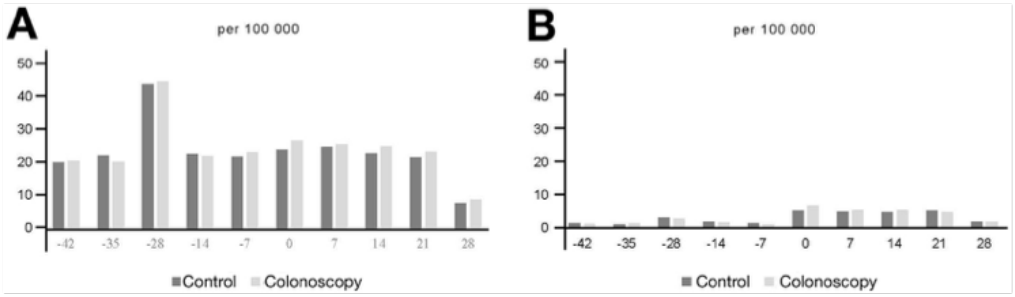


**Figure 2.** Comparison of hospitalization rates (per 100,000 individuals). All hospitalizations (*A*) ($P = .026$); related hospitalizations (*B*) ($P = .202$). Time axis presents days from colonoscopy. Last period is 3 days long (days 28–30).

hospitalizations, no statistically significant differences were found (Supplementary Table 2).

### *Per-Protocol*

Full results of PP are to be found in Tables 1 and 2 and are explained in Supplementary Material. In PP, 55,390 individuals who actually underwent screening colonoscopy were compared with matched controls. Mortality was significantly higher for matched control group when compared with screening group: overall (0.21% vs 0.02%; $P < .001$) and after colonoscopy period (0.09% vs 0.02%; $P < .001$). Overall rate of hospitalizations did not differ significantly between control and screening colonoscopy groups (1.87% vs 1.90%; $P = .709$). There were no differences in rates of related hospitalizations before the screening between control and screening groups (0.07% vs 0.06%; $P = .534$). However, screening colonoscopy did increase rates of related hospitalizations after the date of screening more than 2-fold (0.14% vs 0.31%; $P < .001$).

## Discussion

In the current study we provide high-quality evidence that screening colonoscopy as a public health policy is a safe procedure. It did not significantly increase periprocedural mortality or unplanned hospital admissions related to colonoscopy in the entire observation period ($P = .913$ and $P = .202$, respectively). However, an increase was observed in postprocedural unplanned hospitalizations related to colonoscopy. Thus, colonoscopy screening can be offered as a public health policy without significant burden of serious AEs. Nevertheless, the financial burden of additional hospitalizations should be taken into account when performing cost-effectiveness analyses.

In our study postprocedural 30-day mortality was 0.10% and 0.09% for screening and control group, respectively, and there was no statistically significant difference between the groups ($P = .55$). Similar percentages were reported in other screening programs. In a study assessing the feasibility of national screening programs in the United Kingdom, 10 deaths (0.10%) were reported within 30 days after the procedure; colonoscopy was considered a possible factor in 6 patients (0.07%).[15] On the other hand, in a summary of cancer screening program in Germany of 2,821,392 screening colonoscopies performed between 2003 and 2008, a total of 7 deaths had been recorded (0.245/100,000 colonoscopies); however, observation period is hard to determine from the original manuscript.[1] Studies reporting rates of AEs and mortality of colonoscopy as a diagnostic rather than screening tool can be expected to report higher rates of events. A Swedish registry-based study on AEs of colonoscopies reported 30-day mortality at level of 0.68%.[16] However, some other nonscreening colonoscopy studies report lower 30-day mortality rates. Levin et al[17] reported rate of 0.06% (10 deaths), and Rabeneck et al[18] reported rate of 0.08% (51 deaths). This may be due to loss to follow-up, because providers' databases were used. This is in contrast to our study, which facilitated country-wide government-maintained database containing demographic data. Moreover, one study by Mäklin et al[19] was designed in a similar manner to the present study, as a randomized health service study. However, it analyzed effects of fecal occult blood test as a screening tool; therefore, results are not directly comparable.

In ITT analysis unplanned hospitalization rates were significantly higher in the whole observation period and in period after the colonoscopy for the colonoscopy group ($P = .026$ and $P < .001$, respectively). However, in period before the colonoscopy there were no significant differences in hospitalization rates ($P = .916$). Therefore, it may be assumed that the discovered difference in total rates of hospitalizations is an effect of the increased rates of hospitalizations after colonoscopy date. Furthermore, it has to be considered that out of 338,557 individuals per arm of the study, the increase in absolute number of cases is 299 in invited group (0.09%) per 30 days of observation. This result should be considered as the true burden of screening colonoscopy as a healthcare policy.

In ITT analysis of unplanned hospitalization rates that were related to colonoscopy as assigned according to National Cancer Institute Adverse Event Reporting Requirements, a significant increase was observed in the invited group only in the 30-day postprocedural observation period ($P = .046$).[14] This increase translates to an absolute number of 79 patients with at least 1 unplanned hospitalization (827 vs 748 patients). In PP analysis a substantially significant increase of postprocedural hospitalization rates that were related to colonoscopy was observed. The absolute value of the increase was 96 (172 vs 76 patients). Therefore, it may be concluded that the increase in hospitalization rates in ITT analysis is an effect of increased hospitalization rates of patients who have actually undergone screening colonoscopy. These results should be considered as a measure of burden of colonoscopy as a diagnostic tool rather than as a screening intervention.

In ITT analysis mortality rates were not significantly different during the entire observation period as well as periods before and after colonoscopy analyzed separately. However, in PP analysis a significantly lower number of deaths were observed in the screened population, when compared with their matched controls (Supplementary Material). This may be due to selection bias of screenees (ie, healthy screenee bias), which seems to be typical for all screening settings.[20] A similar phenomenon was observed in a study by Stock et al.[21] It may be explained by a less healthy control group. Individuals who respond to the screening invitation tend to be in better general health compared with their peers. These

results of lower mortality in PP colonoscopy group when compared with ITT colonoscopy group could be interpreted as proof that colonoscopy has a protective effect toward risk of death. However, this is a logical fallacy. Therefore, these results should be rather interpreted as proof that from a healthcare provider viewpoint, PP analysis of effect of colonoscopy on population is flawed because of biases and therefore may bear falsified findings. However, ITT analysis is free from those biases and should bear more trustworthy results.

The observed discrepancies between hospitalization rates are derivatives of screening compliance rates. Compliance in our study was 16.4%, which is suboptimal. An increase in screening program compliance would result in a proportional increase in hospitalization rates toward values from PP analysis (Supplementary Material).

Taking into account presented results, it may be concluded that screening colonoscopy is a safe intervention on a populational level. This finding is especially of interest because colonoscopy is not the only available screening intervention for CRC, with fecal occult blood test and fecal immunochemical test in play. Main concern regarding colonoscopy in comparison with other screening methods is the invasiveness, which may create burden for the patients. Nevertheless, current study proves that this concern is not relevant on a populational level. On the other hand, colonoscopy offers significant advantages because it is both a diagnostic and a curative modality at the same time.

Main strength of our study is the design. The randomized health services study includes multicenter randomized control group and allows performing an ITT analysis. On the contrary, majority of available studies report only a crude mortality or complication rates, which attest only to the burden of colonoscopy.[22,23] Similar study design was previously used to assess the use of hospital resources in fecal occult blood test–based screening and to compare colonoscopy versus fecal immunochemical testing for CRC screening.[19,24] Along with a wide observation time span including both post-colonoscopy and, what has not been reported to date, precolonoscopy events, the present study provides novel insight into screening colonoscopy burden. The latter enables detection of possible AEs occurring before colonoscopy after receiving the invitation letter. This may be the result of the bowel preparation itself, diet and medication modification, or the stress generated by undergoing cancer screening. As mentioned, ITT analysis enabled by the unique design of the present study allows analysis of the burden of screening colonoscopy as a healthcare policy rather than colonoscopy as diagnostic or treatment procedure. Compliance to screening policies is inherently less than 100%; therefore, PP analyses or analyses of crude AE rates do not provide accurate results on the risks of the policy.

One of the most important concerns regarding analysis of complications detected during or after any colonoscopy is underreporting. This could be due to several reasons including endoscopists' unwillingness to report intraprocedural complications or lack of feedback in cases emerging outside of endoscopy suite. Current study data are based on the registry of Ministry of Interior of Poland (death certificates) and healthcare provider billing data of NFZ. Therefore, the study is free from biases of subjective judgment and reporting of endoscopists. In addition, there is a market of private insurance health services; however, the market share is less than 1%, mainly focusing on outpatient services, with negligible number of unplanned hospitalizations. Another possible limitation is the system of determining whether a specific AE was associated with colonoscopy. This was based on ICD coding and experience of physicians making the assessment, which has obvious limitations. However, we have used categories proposed by National Cancer Institute guidelines to ensure quality of results. ICD coding is another issue, because its quality is varying.[25] Moreover, even though coding in the study sample may have not always been accurate, this should be a systematic error and should not impact the validity of the analysis. Furthermore, we have taken into account only unplanned hospitalizations. This was intentional because it is possible that some patients experiencing mild complications of colonoscopy were referred to a hospital in "planned" hospitalization code and therefore were not included in the analysis. Finally, although the results of the ITT analysis show a statistically significant increase in unplanned hospitalizations, the effect size is quite small and may be due to the very large sample size (notably 2.39% vs 2.31%). This should be taken into consideration when interpreting the results.

## Conclusions

In summary, current study provides high-quality evidence that colonoscopy as a healthcare intervention does not increase mortality either before or after colonoscopy. However, colonoscopy may be associated with a very small increase in unplanned hospitalizations after the colonoscopy is completed, but this requires further study. Therefore, colonoscopy screening programs should not be considered as a substantial burden for both populations and healthcare providers. Nevertheless, the financial consequences of additional hospitalizations should be taken into account when performing cost-effectiveness analyses.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.09.010.

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**Conflicts of interest**
This author discloses the following: M. F. Kaminski has received honoraria for consultancy and speaker fees from Olympus and reports receiving equipment from FujiFilm. The remaining authors disclose no conflicts.

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## Supplementary Material

In the main study we have reported an ITT analysis in which we compared patients who were randomized for colonoscopy with paired controls. In this supplementary material we also present findings from PP analysis in which we compared patients who actually underwent colonoscopy with matched controls (ie, virtual colonoscopy group). Supplementary Table 1 presents number of individuals included into analysis in specific years of study. We present findings from PP analysis, and data from ITT will be shown for reference. Supplementary Figure 1 presents comparison of mortality in PP and ITT analyses. Supplementary Figure 2 presents comparison of hospitalization rates in PP and ITT analyses.

### *Mortality: Per-Protocol Analysis*

In PP analysis, mortality was significantly higher for control group when compared with colonoscopy group: before and after period (0.21% vs 0.02%; $P < .001$) and after colonoscopy period (0.09% vs 0.02%; $P < .001$). Patients who died before screening were excluded from analysis; therefore, no deaths were recorded before actual colonoscopy.

### *Hospitalizations: Per-Protocol Analysis*

Overall rate of hospitalizations did not differ significantly between control and colonoscopy groups (1.87% vs 1.90%; $P = .709$). Colonoscopy did not increase rates of related hospitalizations before the date of screening (0.07% vs 0.06%; $P = .534$). However, it did increase rates of related hospitalizations after the date of screening more than 2-fold (0.14% vs 0.31%; $P < .001$). Number of hospitalizations did differ significantly between groups ($P = .032$); a greater share of individuals from control groups had more than 1 hospitalization in comparison with colonoscopy group. Furthermore, individuals in control group had longer hospital stays, both overall and related (3 days vs 2 days; $P < .001$ and 4 days vs 3 days; $P = .02$, respectively).

### *Additional Information on Methodology*

**Definitions of attribution categories.**

- Unrelated: The hospitalization is clearly not related to the intervention.
- Unlikely: The hospitalization is doubtfully related to the intervention.
- Possible: The hospitalization may be related to the intervention.
- Probable: The hospitalization is likely related to the intervention.
- Definite: The hospitalization is clearly related to the intervention.

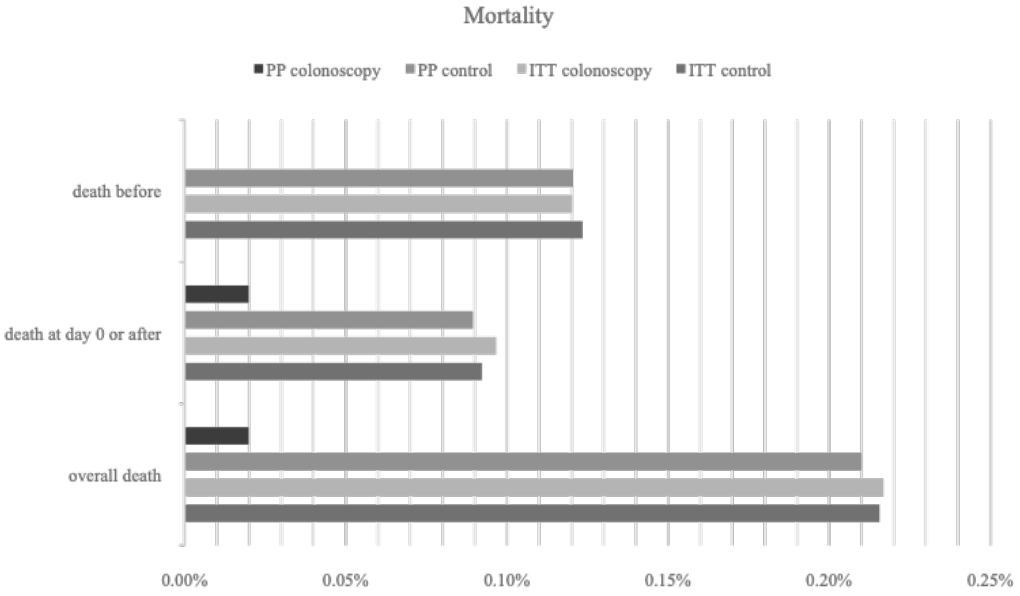
Attribution was performed by a panel of 3 experienced clinicians. The determination into a category was made on the discretion of the individual experienced clinician. On completion of determination, all discrepancies were solved by a discussion within the panel and voting.

### *Ethics Approval*

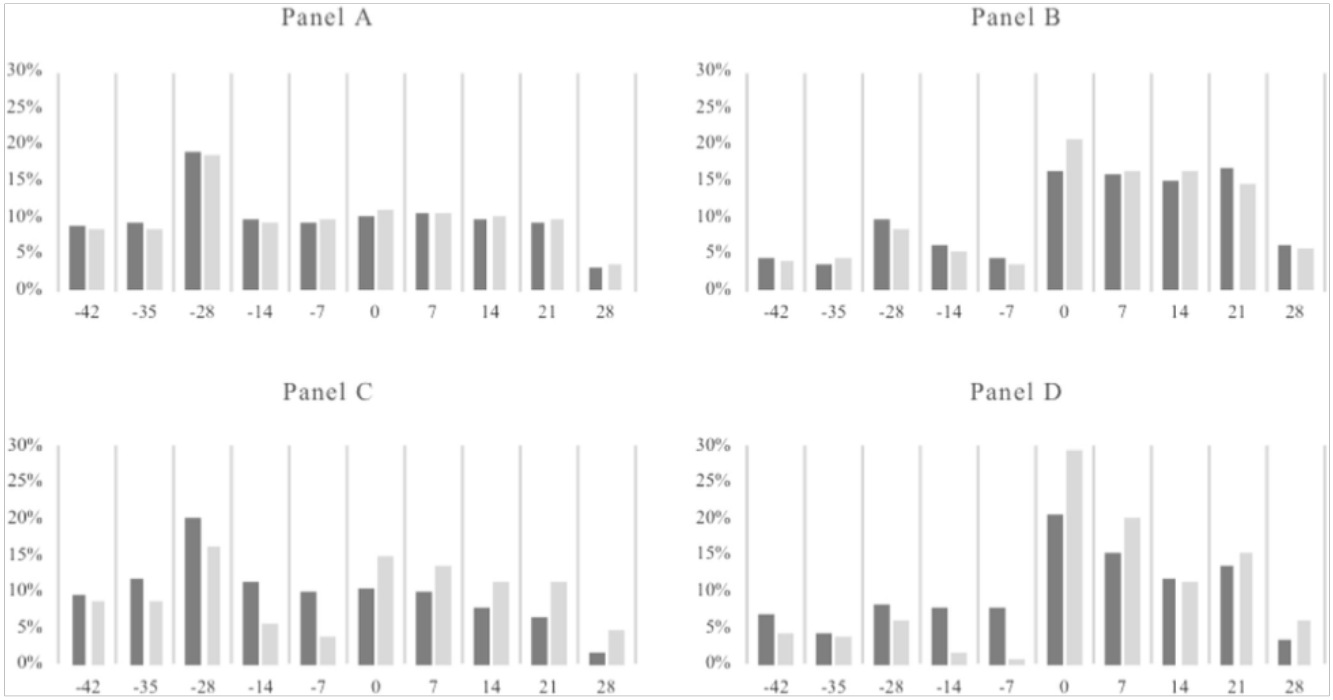
The research proposal of this RHS was reviewed by the Bioethical Committee at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology on October 3, 2014 and was judged to be exempt from oversight, because data were de-identified and could not be linked to specific subject. Study protocol conforms to the 1975 Declaration of Helsinki, as reflected by above-mentioned exemption by Bioethical Committee. Written informed consent was obtained from all participants entering the National Colorectal Cancer Screening Program.

### *Power Analysis*

With 338,477 individuals in the colonoscopy group and 338,557 in the control group, 80% power and rates in the control group as observed, we were powered to detect statistically significant difference at .05 significance level as follows: mortality (reference 0.22%), 0.03%; hospitalizations (reference 2.31%), 0.1%; hospitalizations related to colonoscopy (reference 0.31%), 0.04%.




**Supplementary Figure 1.** Comparison of mortality stratified by time (before or after colonoscopy) in ITT and PP analyses. ITT, intention-to-treat; PP, per-protocol.




**Supplementary Figure 2.** Control on *left (dark)*, colonoscopy on *right (light) side* of graphs. (*A*) All hospitalizations in ITT analysis. (*B*) Related hospitalizations in ITT analysis. (*C*) All hospitalizations in PP analysis. (*D*) Related hospitalizations in PP analysis. Values present share of hospitalizations in certain time frame in relation to all hospitalizations. ITT, intention-to-treat; PP, per-protocol.

**Supplementary Table 1.** Number of Individuals Enrolled in the Study in Individual Years

| | Colonoscopy group | Control group |
|---|---|---|
| 2012 | 21,662 | 21,656 |
| 2013 | 52,942 | 52,931 |
| 2014 | 87,918 | 88,083 |
| 2015 | 175,955 | 175,887 |
| Total | 338,477 | 338,557 |

**Supplementary Table 2.** Mortality Reported Before and After Actual Colonoscopy Date in Screening Group and Reference Colonoscopy Date in Matched Control Group (Virtual Colonoscopy Group)

| | Intention-to-treat | | | | | Per-protocol | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | Invited | | | Control | | Screened | | |
| | N | % | N | % | *P* value | N | % | N | % | *P* value |
| Total | 338,557 | | 338,477 | | | 54,743 | | 55,390 | | |
| Screened | | | 55,390 | 16.36 | | N/R | | N/R | | |
| Death (–42 days/+30 days) | 730 | 0.22 | 734 | 0.22 | .913 | 115 | 0.21 | 11 | 0.02 | **<.001** |
| Death before | 418 | 0.12 | 407 | 0.12 | .704 | 66 | 0.12 | 0 | 0.00 | NA |
| Death at day 0 or after | 312 | 0.09 | 327 | 0.10 | .551 | 49 | 0.09 | 11 | 0.02 | **<.001** |

NOTE. Statistically significant differences are indicated with bold.
NA, not available; N/R, not reported.

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# Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in the Polish Colonoscopy Screening Program

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## Abstract

**Background:** Obesity is a known risk factor of colorectal cancer (CRC). However, precise interconnections between excessive body fat and CRC are still vague. Therefore, the aim of this study was to assess whether stage of CRC detected in overweight and obese individuals differs from individuals with normal body mass index (BMI). A secondary aim of this study was to elucidate whether overweight and obesity influence the overall survival in CRC.

**Methods:** This study was a cross-sectional analysis of 163,129 individuals who underwent screening colonoscopy performed on data from a prospectively maintained database of the Polish Colonoscopy Screening Program.

**Results:** Overweight and obese individuals present with a less advanced CRC in screening setting ($p = 0.014$). This trend is the most pronounced in males ($p = 0.001$). Univariable and multivariable analyses revealed that obesity was a negative predictor of detection of advanced CRC with odds ratio 0.72 (95% confidence interval 0.52–1.00; $p = 0.047$). Furthermore, overweight and obesity were not statistically significant predictors of risk of death ($p = 0.614$ and $p = 0.446$, respectively).

**Conclusions:** Obese screenees present with a less advanced disease in comparison to non-obese. Moreover, survival stratified by clinical stage seems to not be influenced by BMI category. Therefore, a higher proportion of early diagnosed cancers can potentially create a survival benefit in this group.

## Keywords

Colorectal cancer, colonoscopy, screening, obesity, colorectal cancer epidemiology

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## Introduction

With colorectal cancer (CRC) being one of the most common and most deadly cancers, national screening programs have been established in many countries. However, only relatively recently it has been proven that screening lowers the incidence of CRC and improves survival.[1] In Poland, asymptomatic citizens between 50 and 66 years old are eligible for participation in the Polish Colonoscopy Screening Program (PCSP) – a CRC screening program utilizing colonoscopy as primary diagnostic tool. Non-symptomatic individuals participate in opportunistic or letter-invited screening. Data available from this program create unique opportunities to perform cross-sectional population-based analyses.

Obesity is a known risk factor for higher incidence of colorectal adenomas, advanced colorectal adenomas, and CRC.[2,3] Most studies assessing the influence of obesity on CRC, as well as on other diseases, employ body mass index (BMI) as an indicator of body fat and obesity. However, precise interconnections between BMI and CRC are still vague. Studies have shown that obese individuals have higher incidence of

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adenomas, higher incidence of CRC, and lower compliance to screening programs.[4] Moreover, quality of bowel preparation in obese individuals is inferior to that in non-obese.[5] On the other hand, adenoma detection rates (ADR) and advanced adenoma detection rates (AADR) are higher in this group, which can be both due to screening performance and mentioned changes in the incidence.[6,7] Survival seems to be influenced by body weight as well – with some studies reporting inferior results in obese individuals.[8] Thus, evidence is accumulating to support the hypothesis that people with obesity are a distinct subgroup of CRC patients. This distinction includes incidence, progression rates, as well as screening and treatment characteristics. An especially interesting observation, originating from a case-control study by Choe et al.,[9] is that obesity enhances the rate of normal to adenoma sequence but not adenoma to early carcinoma sequence. It is possible that dynamics of CRC formation and CRC progression are both influenced by obesity, but do not follow the same pattern of change. This could lead to an altered distribution of CRC stages in obese individuals. Therefore, the aim of this study is to assess whether the stage of CRC detected in overweight and obese individuals in a screening setting differs from individuals with normal body weight. A secondary aim of this study is to elucidate whether overweight and obesity influence the overall survival (OS) of patients diagnosed with CRC.

## Material and methods

### Study design

We performed a cross-sectional analysis of database records of individuals who entered the national colonoscopy screening program for CRC in Poland, from January 2007 through December 2011. The database contained demographic data, colonoscopy results, self-reported data on weight and height, and colorectal findings from 114 screening centers throughout Poland. Patients diagnosed with CRC were identified and followed for OS through the National Cancer Registry. Follow-up time was censored on December 31, 2015.

The research proposal was reviewed by the Bioethical Committee at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology on October 3, 2014 and was judged to be exempt from oversight, as data was de-identified and could not be linked to specific subject. Study protocol conforms to the 1975 Declaration of Helsinki, as reflected by above-mentioned exemption by Bioethical Committee. Written informed consent was obtained from all participants entering the National Colorectal Cancer Screening Program.

### Study procedures and definitions

Study procedures were in line with Polish Screening Colonoscopy Program and have been previously described in detail.[10] Patients between the ages of 50 and 66 years (40 and 66 years in the case of positive family history of cancer of any type) were offered screening. Exclusion criteria were clinical suspicion of CRC, characteristics that met the criteria for Lynch syndrome, familial adenomatous polyposis, or inflammatory bowel disease, and colonoscopy within the preceding 10 years, according to PCSP regulations.[10–12] On the day of colonoscopy (before the procedure) all participants were asked to fill in an epidemiological questionnaire including data on self-reported weight and height. Screening colonoscopy procedures were previously described in detail.[10–12]

Cancer stage was assessed using the American Joint Committee on Cancer (AJCC) TNM scoring system after histopathological examination of specimens.[13] Thereafter, for the purpose of some of the univariable and multivariable analyses, Stage 1 and Stage 2 were pooled together as early CRC. Stage 3 and Stage 4 were consequently pooled together as advanced CRC.

BMI was calculated using weight (kg(/(height (m))$^2$ and stratified according to the World Health Organization (WHO) classification.[14] First, second, and third class of obesity were pooled together to achieve appropriate power of analysis. For the clarity of the manuscript, individuals within the range of normal BMI (18.5–24.99) will be referred to as "normal," individuals with overweight (BMI 25–29.99) will be referred to as "overweight," and individuals with class I, II, or III obesity (BMI > 30) will be referred to as "obese."

### Study population

Between January 2007 and December 2011, 163,129 participants who met eligibility criteria were screened within the program. Of those, 48,176 had normal BMI, 70,173 were overweight, and 34,891 were obese; 1561 were diagnosed with CRC. Of those, 76 had missing data on BMI and were excluded and 295 had missing data on TNM and were excluded. An additional seven patients had BMI below 18.5 (BMI 16.65–18.37; stage 1–2) and were excluded from analysis. Finally, 1183 patients remained and were stratified into BMI, according to WHO guidelines. Procedures for achieving study populations are presented as a flowchart in Figure 1.

### Statistical methods

Descriptive statistics were prepared with the use of contingency tables, means, and standard deviations depending on variables type. Categorical variables were compared with the use of chi-squared test and

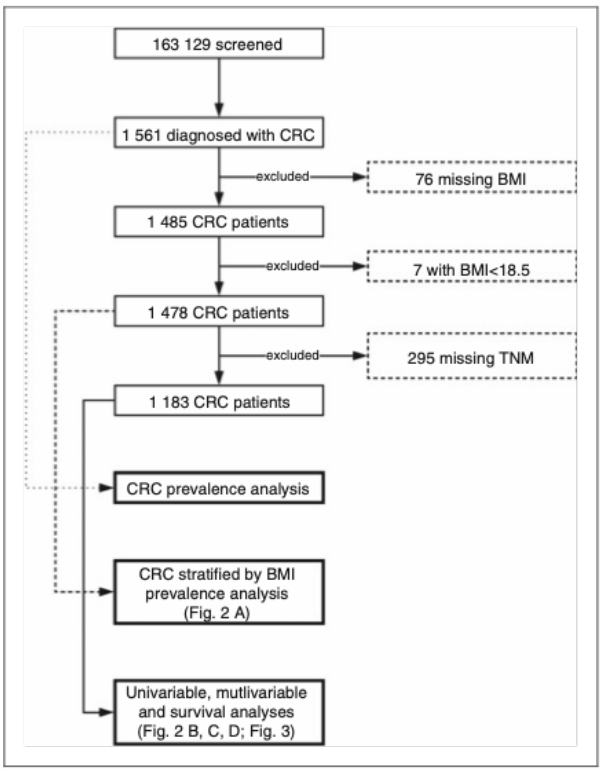


**Figure 1.** Flowchart of patients' inclusion into analyses.

test for trend. Tests for trend were used to investigate differences between stage distribution stratified by BMI and by BMI and gender. Univariable and multivariable logistic regression models were used to investigate the associations between advanced CRC and patient's BMI, gender, age, and family history of CRC. Probability of OS stratified by stages and BMI was estimated using the Kaplan–Meier method. Survival curves were compared using log-rank test. Univariable and multivariable Cox proportional hazard models were used to estimate hazard ratios of death according to CRC stage, patient's BMI, gender, age, and family history of CRC. Forward stepwise selection at the 0.1 significance level was used for variable selection in multivariable models. BMI was included in all multivariable models regardless of its significance. All reported $p$-values are two-sided. A $p$-value $< 0.05$ was considered to denote statistically significant difference. All statistical analysis was performed using Stata Statistical Software, v. 13.1 (Stata Corporation, College Station, TX, USA).

## Results

Between January 2007 and December 2011, 163,129 participants who met eligibility criteria were screened within the program. Of those, in 1561 (0.96%) CRC was diagnosed. Prevalence of CRC in the whole screened population was almost twofold higher in males than in females (855 (1.36%) vs 706 (0.70%), respectively, $p < 0.001$). In analysis of the 1478 patients with reported BMI patients, CRC prevalence was highest in obese: 429 (0.89%) vs 670 (0.95%) vs 379 (1.08%), respectively, for normal, overweight, and obese ($p = 0.017$). Specific $p$-values are presented in Figure 2(a). After exclusions, 1183 patients entered final analyses (Figure 1). Table 1 presents general characteristics of the final sample group.

### BMI and CRC stage

Figure 2(a) presents distribution of CRC prevalence with sub-analysis of stages in each BMI category. Significant $p$-values are marked indicating that overweight and obese individuals have higher prevalence of CRC. Analysis of stage of diagnosed CRC in subgroups stratified by BMI revealed a negative trend between stage and BMI group ($p = 0.014$), i.e. with higher BMI subgroup, stage was lower. Figure 2(b) presents the distribution of stage stratified by BMI.

### Gender subgroups analysis

There were no significant differences in the distribution of stages between genders ($p = 0.394$).

*Females.* Furthermore, in the female subgroup there were no differences in stage distribution when stratified by BMI categories with $p$-value for trend $= 0.752$ (Figure 2(c)).

*Males.* In the male subgroup, analysis of trend for stage stratified by BMI categories revealed significant differences in distribution with higher frequency of Stage 1 CRC in group of patients with obesity, as shown on Figure 2(d) ($p = 0.001$).

### Risk factors of advanced CRC

Results of univariable and multivariable analyses are presented in Table 2. As mentioned in methods, CRC was dichotomized into early and advanced CRC. Obesity was a negative predictor of detection of advanced CRC with odds ratio 0.72 (95% confidence interval (CI) 0.52–1.00; $p = 0.047$). Overweight, gender, age, family history, and preparation for colonoscopy were not statistically significant predictors of diagnosis of advanced stage CRC.

*Survival analysis.* Patients were observed for a median of 5.66 years (interquartile range 4.29–7.53) from the examination date. OS ratios were calculated for groups stratified by BMI. Five-year survival

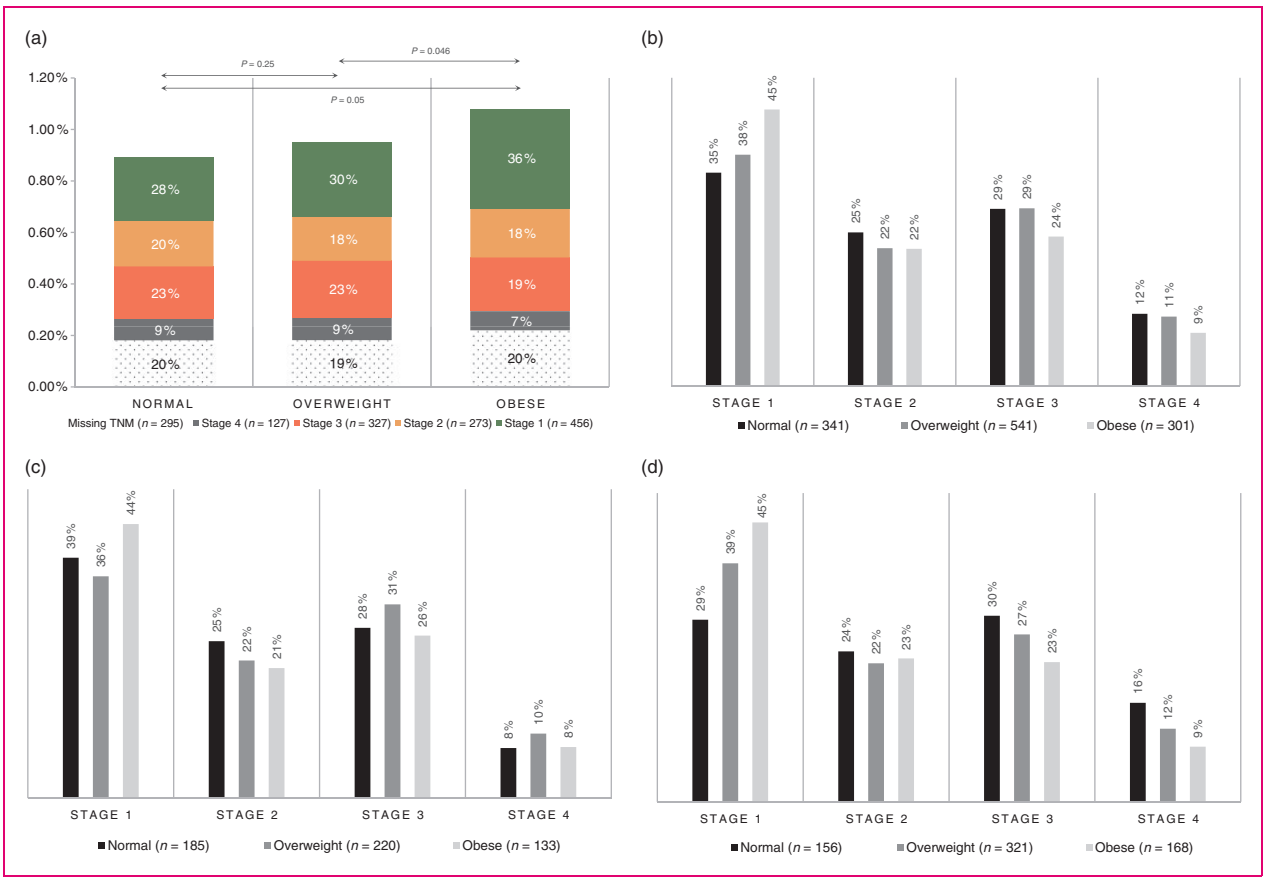


**Figure 2.** (a) Prevalence of CRC stratified by BMI categories with representation of distribution of stages. Stage 1 on the top, Stage 4 on the bottom. Significant *p*-values for comparisons of prevalence between BMI groups are marked. Percentages in (a) are calculated with a following formula: (no. of cases with Stage X and BMI category Y)/(no. of cases with BMI category Y)*(prevalence of CRC in BMI category Y) to correct for the different prevalence in the BMI categories. (b) Distribution of BMI categories in stage subgroups; *p*-value for trend of the distribution = 0.014. (c) Distribution of BMI categories in stage subgroups in females; *p*-value for trend of the distribution = 0.752. (d) Distribution of BMI categories in stage subgroups in males; *p*-value for trend of the distribution = 0.001. Percentages in (b–d) are calculated without correction for prevalence as follows: (no. of cases in Stage X with BMI category Y)/(no. of cases with BMI category Y).

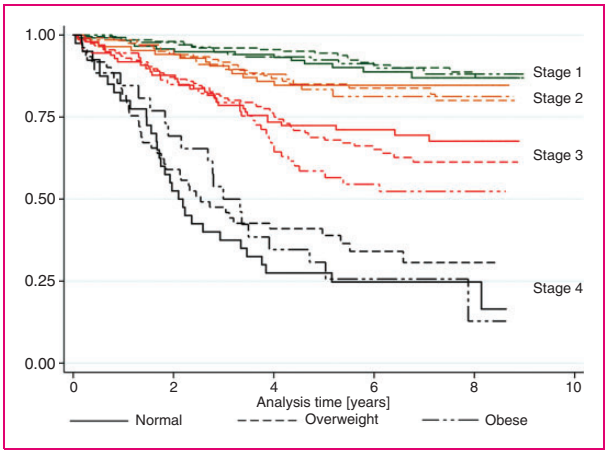


**Figure 3.** Kaplan–Meier survival curve stratified by BMI and stage.

probabilities were calculated for groups stratified by BMI and stage. OS between normal, overweight, and obese individuals did not differ significantly: Stage 1 ($p = 0.852$); Stage 2 ($p = 0.931$); Stage 3 ($p = 0.165$); Stage 4 ($p = 0.578$). Probabilities of 5-year survivals are presented in Table 3. Kaplan-Meier survival curves were plotted and are presented in Figure 3.

Univariable and multivariable analyses of OS are presented in Table 4. Overweight and obesity were not statistically significant predictors of risk of death with HR (hazard ratio) of 0.93 (95% CI 0.71–1.22; $p = 0.614$) for the overweight group and HR 1.13 (95% CI 0.83–1.53; $p = 0.446$) for the obese group.

## Discussion

To our knowledge this is the first study reporting increase of early stage CRC (Stage 1 and 2) in obese

**Table 1.** Baseline characteristics stratified by BMI categories. Underweight BMI category is excluded from the table. Obesity class I, II, and III categories are pooled into "Obese pooled."

| | Normal $N=341$ | Overweight $N=541$ | Obese pooled N = 301 | All $N=1183$ |
|---|---|---|---|---|
| Age, mean (SD) | 57.80 (5.20) | 58.33 (4.50) | 58.53 (4.55) | 58.23 (4.73) |
| Male gender, *n* (%) | 156 (45.75%) | 321 (59.33%) | 168 (55.81%) | 645 (54.52%) |
| Positive family history, *n* (%) | 55 (16.13%) | 67 (12.38%) | 41 (13.62%) | 163 (13.78%) |
| Distal localization,[a] *n* (%) | 268 (78.59%) | 424 (78.37%) | 234 (77.74%) | 926 (78.28%) |

[a]Left colon and rectum.

**Table 2.** Odds ratio (OR) for diagnosis of advanced CRC: univariable and multivariable model.

| Variable | Univariable models OR (95% CI) | *p* | Multivariable model OR (95% CI) | *p* |
|---|---|---|---|---|
| Normal | | | | |
| Overweight | 0.99 (0.75–1.30) | 0.916 | 0.99 (0.75–1.30) | 0.916 |
| Obese | **0.72 (0.52–1.00)** | **0.047** | **0.72 (0.52–1.00)** | **0.047** |
| Male gender | 1.04 (0.82–1.31) | 0.767 | # | # |
| Age[a] | 1.00 (0.98–1.03) | 0.996 | # | # |
| Family history | 1.08 (0.77–1.51) | 0.671 | # | # |

#: these variables were not found statistically significant in forward stepwise regression.
[a]Continuous variable.

**Table 3.** Five-year survival rates for groups stratified by BMI and stage.

| BMI | Stage 1 % (95% CI) | Stage 2 % (95% CI) | Stage 3 % (95% CI) | Stage 4 % (95% CI) |
|---|---|---|---|---|
| Normal | 91.28 (84.37–95.22) | 84.71 (75.12–90.82) | 72.43 (62.44–80.19) | 27.50 (14.86–41.72) |
| Overweight | 94.48 (90.25–96.91) | 85.05 (77.32–90.31) | 68.80 (60.08–75.49) | 38.93 (26.69–50.98) |
| Obese | 92.43 (86.34–95.86) | 83.42 (72.06–90.46) | 58.58 (46.35–68.94) | 30.77 (14.63–48.55) |

**Table 4.** Univariable and multivariable analysis of overall survival (OS).

| | Univariable models | | Multivariable model | |
|---|---|---|---|---|
| Variable | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Normal | | | | |
| Overweight | 0.96 (0.73–1.25) | 0.753 | 0.93 (0.71–1.22) | 0.614 |
| Obese | 1.00 (0.74–1.36) | 0.997 | 1.13 (0.83–1.53) | 0.446 |
| Stage 1 (ref.) | | | | |
| Stage 2 | **1.80 (1.19–2.71)** | **0.005** | **1.81 (1.20–2.73)** | **0.005** |
| Stage 3 | **4.28 (3.04–6.04)** | **<0.001** | **4.38 (3.10–6.17)** | **<0.001** |
| Stage 4 | **12.87 (8.98–18.43)** | **<0.001** | **12.75 (8.89–18.28)** | **<0.001** |
| Male gender | **1.36 (1.08–1.72)** | **0.009** | **1.29 (1.02–1.64)** | **0.032** |
| Age[a] | **1.00 (0.97–1.02)** | **0.603** | # | |
| Positive family history | **0.94 (0.68–1.31)** | **0.725** | # | |

#: these variables were not found statistically significant in forward stepwise regression.
[a]Continuous variable.

individuals in a screening setting. This finding is especially observed in the male subgroup. Below we will explore potential explanations of the detected phenomenon as well as limiting factors that have to be considered while interpreting the results of our study.

It is proven that obese individuals have higher risk of colorectal adenoma, advanced adenoma, and CRC.[2,15,16] However, it is not fully understood whether this is due to acceleration of adenoma formation only (i.e. acceleration of normal to adenoma sequence) or acceleration of the whole carcinogenesis and progression process. The higher proportion of Stage 1 CRC observed in a screening setting could be explained by increased rate of adenoma formation without a proportional increase in CRC progression rate. Some authors observed a similar phenomenon, describing that only the rate of normal to adenoma sequence is accelerated but not the adenoma to carcinoma sequence.[9] However, enhanced formation of adenomas solely may not be a sufficient explanation for the observed phenomenon. In such a situation, we would see a higher proportion of adenoma prevalence to CRC prevalence in obese individuals. Nevertheless, there is no data demonstrating whether this proportion differs between BMI categories. The missing piece of the explanation could be a change in dynamics of CRC progression. It is possible that while obesity is a risk factor for the formation of adenomas and CRC, it does not influence the progression in the same way. This may be due to metabolic factors explored below.

The first explanation of potentially decreased progression rates may be that lymph nodes and liver in obese individuals are distinct, unfavorable microenvironments for CRC cells. Park et al. observed that in individuals with CRC visceral obesity was associated with lower rates of lymph node involvement and improved OS.[17] The same study did not demonstrate such association for BMI. This suggests that it is visceral obesity and not the BMI that actually influences epidemiology and clinical presentation of CRC. Furthermore, Murono et al. observed that hepatic steatosis is associated with lower incidence of liver metastases of CRC.[18] The authors of this study propose that fat deposition in the liver results in an unfavorable microenvironment for the invasion and growth of metastatic tumor cells and suppresses seeding and growth of cancer cells. While this was demonstrated only for the liver, and not for other organs, it has to be remembered that liver metastases contribute to almost 70% of all CRC metastases.[19] Therefore, this mechanism may substantially influence proportions of advanced CRC observed in obese patients. These explanations are in accordance with results presented in this study. In Figure 2(b) and (d) it can be noticed that overweight and obese individuals have higher proportion of Stage 1 CRC and lower proportions of Stage 3 and Stage 4 disease with significant *p*-values for trend.

Another possible metabolic explanation is insulin resistance that is often caused by obesity. Yamaji et al. found that, even after adjustment for BMI, higher C-peptide serum concentration is associated with increased risk of colorectal adenoma and this effect is most potent in males.[20] These observations are in accordance with results from the present study, where discrepancies between stages of CRC were observed in males. This may be due to factors influencing the CRC carcinogenesis particularly concerning females, such as estrogen concentrations, which may exert a protective effect on CRC risk.[20]

Lastly, the observed phenomenon may be elucidated by pre-diagnosis changes in body mass. Development of neoplastic disease is very energy consuming and causes loss of body mass, and finally cachexia. It is possible that observed higher frequency of Stage 1 CRC in our group, is due to the fact that individuals with higher stages of CRC lost enough weight before screening to be classified in lower BMI group. This would mean that only the least affected by the disease individuals remain in higher BMI categories. This last notion may be a part of a phenomenon called the obesity paradox, which has been previously described in numerous diseases, including cancer.[21] According to the obesity paradox, observation that obese individuals present with a less advanced cancer maybe altogether false due to a logical fallacy known as *cum hoc ergo propter hoc* (with this, therefore because of this) or *false cause*. This means, that it is possible that cancer changes BMI and therefore patients move between BMI categories, and thus BMI stratification becomes flawed. There are several other possible explanations of obesity paradox which can be found elsewhere,[21] as discussing this in detail is not in the scope of this article.

Analysis of survival in our study did not reveal statistically significant differences between groups stratified by BMI. This suggests that BMI does not influence survival of CRC detected in screening setting. Some authors have reported that survival in obese individuals is inferior, available studies vary in methods of BMI acquisition (pre versus post diagnosis).[8] On the other hand, Aparicio et al. reported that survival in overweight men was superior in comparison to normal BMI patients. This study however acquired BMI prior to palliative chemotherapy.[22] In our group, BMI was acquired before CRC diagnosis, and therefore was less susceptible to change occurring due to cancer. This may explain why survival in our cohort was not influenced by BMI. In the present study the only factors that were predictors of inferior survival were: higher stage of the disease and male gender.

The main strength of our study is a prospectively maintained database that was used to perform analysis. It contains data on every screening colonoscopy performed in Poland between 2007 and 2011. This enabled us to gather a substantial group of 163,129 individuals. Furthermore, screening setting of diagnosis creates unique opportunities. Firstly, it enabled gathering data on BMI that was possibly the least biased by obesity paradox. Secondly, only asymptomatic individuals are eligible for screening, and therefore analysis of a homogeneous group was possible. It has been reported that obese individuals tend to not attend screening,[23] which may cause underrepresentation of obese in study sample. However, comparison of data from epidemiological study WOBASZ II on BMI structure of polish society to data from our study confirms good compliance of obese individuals in the study sample. In our study 46% of diagnosed patients were overweight and 26% were obese, while in WOBASZ II overweight rates were between 34–45% and obesity rates were 26–37%.[24]

There are several limiting factors that have to be considered when analyzing results of our study. Those especially include selection bias (healthy screenee bias), response bias (BMI was based on a self-reported survey), as well as missing data on BMI and CRC stage. To explore impact of those limitations we have performed post-hoc analyses which are described and discussed in detail in appendix. These analyses shown that despite mentioned limitations conclusions can be drawn and our study adds to the current state of knowledge.

## Conclusions

Our study provides new insight into the relationship between obesity and CRC – that screenees, especially males, present with a less advanced disease. Moreover, survival stratified by clinical stage seems to not be influenced by BMI category. More studies are warranted to explore possible causes of this phenomenon. Especially studies exploring dynamics of CRC development and progression are needed. However, regardless of origin of the present observation it is already clear that obese individuals especially benefit from CRC screening. Higher proportion of early diagnosed cancers can potentially create a survival benefit in this group. This should be taken into consideration when planning public health campaigns.

### Declaration of Conflicting Interests

The authors have no conflicts of interest to declare.

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### Ethics approval

Waived from ethics board oversight.

### Informed consent

Not applicable.

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**Appendix**

This is supplementary material to manuscript entitled: ***Clinical stages of colorectal cancer diagnosed in obese and overweight individuals in Polish Screening Colonoscopy Program.*** In the study we analyse CRC stage distribution stratified by BMI.

Appendix Table 1. Supplements Manuscript Table 1 and presents data for BMI categories that were excluded or pooled (underweight and obese I, II and III classes). Appendix Table 2. And Table 3. present crude numbers for screenees divided by age, gender and family history. Table 2. contains all screenees, while table 3. contains only screenees that had TNM record present in the database.

| | **UNDERWEIGHT N=7** *(EXCLUDED)* | **NORMAL N=341** | **OVERWEIGHT N=541** | **OBESE I N=244** *(POOLED)* | **OBESE II N=43** *(POOLED)* | **OBESE III N=14** *(POOLED)* | **OBESE POOLED N=301** | **ALL N=1183** |
|---|---|---|---|---|---|---|---|---|
| **AGE MEAN (SD)** | 57.71 (7.63) | 57.80 (5.20) | 58.33 (4.50) | 58.70 (4.55) | 58.02 (4.46) | 57.00 (4.66) | 58.53 (4.55) | 58.23 (4.73) |
| **MALE GENDER N (%)** | 2 (28.57%) | 156 (45.75%) | 321 (59.33%) | 138 (56.56%) | 23 (53.49%) | 7 (50.00%) | 168 (55.81%) | 645 (54.52%) |
| **POSITIVE FAMILY HISTORY (%)** | 2 (28.57%) | 55 (16.13%) | 67 (12.38%) | 32 (13.11%) | 7 (16.28%) | 2 (14.29%) | 41 (13.62%) | 163 (13.78%) |
| **DISTAL LOCALIZATION* (%)** | 5 (71.43%) | 268 (78.59%) | 424 (78.37%) | 192 (78.69%) | 33 (76.74%) | 9 (65.29%) | 234 (77.74%) | 926 (78.28%) |
| ***LEFT COLON AND RECTUM** | | | | | | | | |

**Appendix Table 1.** *Baseline characteristics stratified by BMI categories.*

| | **NORMAL N=48,176** | **OVERWEIGHT N=70,173** | **OBESE POOLED N=34,891** |
|---|---|---|---|
| **AGE <60 N=107,955** | 243 (0.67) | 366 (0.75) | 213 (0.92) |
| **AGE ≥60 N=45,285** | 185 (1.55) | 303 (1.40) | 165 (1.40) |
| **FEMALES N=94,189** | 233 (0.67) | 270 (0.70) | 164 (0.81) |
| **MALES N=59,051** | 195 (1.48) | 399 (1.27) | 214 (1.47) |
| **NEGATIVE FAMILY HISTORY N=124,970** | 364 (0.95) | 587 (1.02) | 324 (1.11) |
| **POSITIVE FAMILY HISTORY N=28,333** | 64 (0.64) | 82 (0.65) | 54 (0.93) |

**Appendix Table 2.** *Baseline characteristics stratified by BMI categories. The table includes screenees that did not have date on TNM*

| | NORMAL N=48,176 | OVERWEIGHT N=70,173 | OBESE POOLED N=34,891 |
|---|---|---|---|
| **AGE <60 N=107,955** | 194 (0.54) | 300 (0.61) | 168 (0.73) |
| **AGE ≥60 N=45,285** | 147 (1.24) | 241 (1.12) | 133 (1.14) |
| **FEMALES N=94,189** | 185 (0.53) | 220 (0.57) | 133 (0.65) |
| **MALES N=59,051** | 156 (1.19) | 321 (1.03) | 168 (1.16) |
| **NEGATIVE FAMILY HISTORY N=124,970** | 286 (0.75) | 474 (0.82) | 260 (0.90) |
| **POSITIVE FAMILY HISTORY N=28,333** | 55 (0.55) | 67 (0.54) | 41 (0.71) |

**Appendix Table 3.** *Baseline characteristics stratified by BMI categories. The table includes only screenees that did have date on TNM*

Below can be found additional considerations regarding the manuscript:

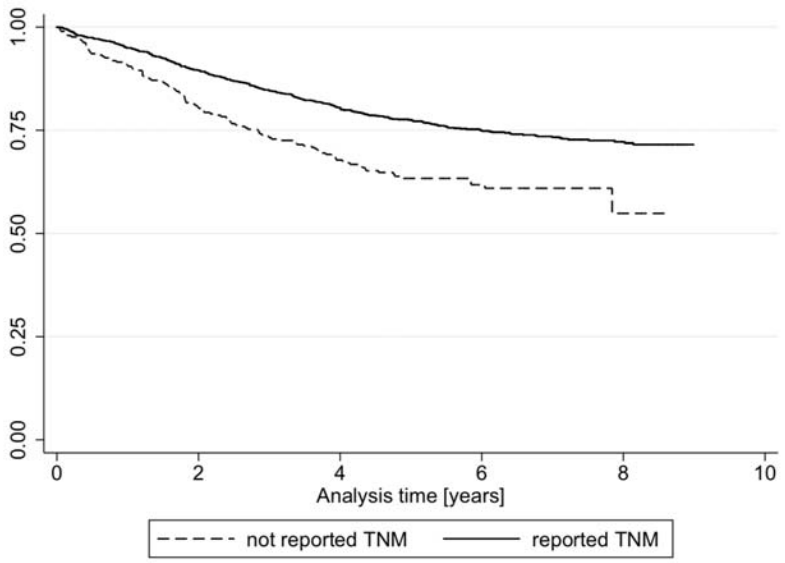
There are several limiting factors that have to be considered when analyzing results of our study. As mentioned, studies performed in screening setting bear very specific results, and therefore may not always be generalizable to the whole population. One of the particularities

that have to be considered is the selection bias. It has been named as the healthy screenee bias (described in detail elsewhere) and can lead to a more healthy study group when compared to the population [1]. This however should influence the whole study group in the same way and therefore stage distribution across BMI should not be biased. Another possible limitation is the self-reporting of BMI that was used in the study protocol. Potentially individuals with overweight and obesity may be more prone not to report BMI or to reduce reported values [2]. In analyzed group 76 individuals did not report BMI, what can potentially be a selection bias and response bias. To verify the influence of this limitation, we have tested the distribution of cancer stage among people with unreported BMI versus groups stratified by BMI. In this analysis we have shown that the 76 individuals with unreported BMI are resembling the group with obesity. Details of this post-hoc analysis can be found below. Nevertheless, patients that did not report BMI, constitute to only less then 5% of analyzed population. This suggests that impact of this bias should not be meaningful. Furthermore, in the present study we show that obese individuals are more likely to have lower stage of CRC. Therefore, reporting lower than actual weight should rather diminish the impact of performed analyses rather than inflate it. TNM was based on questionaries filled by physicians, therefore was susceptible to response bias. It is probable, that the majority of the missing TNM data was in patients with advanced disease. Those patients potentially were not eligible for surgery, changed center that they were treated in or died, and thus TNM was not reported in the database. To test this hypothesis, we have performed a post-hoc analysis and compared Kaplan-Meier survival functions in patients with unreported TNM versus those with reported, described in detail below. Statistically significant differences were found, suggesting an inferior survival in patients with missing TNM, as shown on Figure below. This limitation however should have not influenced the distribution of stages across groups stratified by BMI. Another factor that may limit the power of conclusions is lack of specific data on treatment and survival. This includes lack of data on

treatment modalities used as well as cancer-specific survival rates. Gathering such data was impossible due to cross-sectional design of the study. In summary, it is our belief that in spite of those limitations present study provides new information on details of CRC epidemiology.

In order to perform analysis, we used self-reported BMI scores and physician-reported Stage (TNM) scores. Substantial number of records was however missing from the database, what could have led to biased results. To test whether underreporting of BMI and TNM influenced results we have performed following analyses:

- To test whether underreporting of BMI influenced the results of the study we have tested the distribution of CRC stages among people with unreported BMI versus groups stratified. We found borderline significant difference (p=0.044). After analysis versus specific subgroups we found that people with unreported BMI may resemble people with obesity (p=0.810).
- To test whether underreporting of CRC stage influenced the results of the study we have tested Kaplan-Meier survival functions in patients with unreported TNM versus groups with reported TNM. Statistically significant difference was found (p<0.001), suggesting an inferior survival in patients missing TNM, as shown on Fig 1. below.



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