Prevalence of Synchronous Oligopolyposis in Incident Colorectal Cancer: A Population-Based Study

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Objective: Colorectal cancer (CRC) is a leading causes of cancer death among men and women. The purpose of this study was to determine the prevalence of oligopolyposis (≥20 synchronous colorectal adenomas) and its associated clinicopathological characteristics in Hispanics with incident CRC.

Methods: Pathology reports from individuals diagnosed with CRC (2007 to 2011) were obtained from the PR Central Cancer Registry. Colorectal polyp burden was calculated using pathology reports and the data was normalized to colon segment size. Comparisons of demographic and clinicopathological characteristics by synchronous oligopolyposis status (<20 vs. ≥20) were performed using the chi-square or Fisher's exact test. Multivariate logistic regression models were fitted to estimate the adjusted prevalence odds ratios (aPOR), with 95% confidence intervals (CI). All analyses were performed using Stata (v.12.0).

Results: Analyses of 1,573 colectomy specimens was performed. Oligopolyposis was observed in 9.47% (149 of 1,573) of the subjects with incident CRC. Increasing age ($aPOR_{50–64}$ = 1.72, 95% CI: 0.59–5.02; $aPOR_{65–74}$ = 1.83, 95% CI: 0.64–5.27; $aPOR_{\geq 75}$ = 2.67, 95% CI: 0.93–7.64) and proximal CRC tumor location (POR = 2.91, 95% CI: 1.98–4.30) were significantly associated with having oligopolyposis at CRC diagnosis. However, subjects diagnosed with CRC at a regional stage ($aPOR_{Regional}$ = 0.50, 95% CI: 0.32–0.79) or distant stage ($aPOR_{Distant}$ = 0.45, 95% CI: 0.29–0.69) were less likely to have synchronous oligopolyposis (p<0.05).

Conclusion: Our findings suggest that genetic syndromes associated with colorectal polyposis may be implicated in a higher than expected number of CRC cases. Individuals with CRC and synchronous oligopolyposis should receive genetic counseling. [*P R Health Sci J 2018;37:39-45*]

Key words: Colorectal cancer, Oligopolyposis, Polyposis, Hispanic

Hereditary colorectal cancer is believed to account for 10 to 15% of all colorectal cancer (CRC) cases (1, 2). Several types of hereditary polyposis syndromes have been described among hereditary CRC syndromes, including familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), familial juvenile polyposis, serrated polyposis, and Peutz–Jeghers syndrome (3, 4). These polyposis syndromes differ in terms of the number of colorectal polyps, ranging from the ten to the thousands (5–7). Individuals with hereditary polyposis syndromes have an increased risk of developing CRC, with individuals with FAP or MAP having close to a 100% or an 80% increased lifetime risk, respectively (4, 7, 8). In addition, patients with hereditary polyposis syndromes have an increased risk of developing CRC at a younger age. For instance, individuals with FAP typically present with CRC from the ages of 34 through 43 years, whereas the mean age at diagnosis for sporadic (non-hereditary) CRC in the general population is 68 years (9).

Colorectal adenomatous polyps are precursor lesions of most colorectal tumors. However, there is limited information regarding polyp burden among patients diagnosed with incident CRC. Furthermore, very little is known about the prevalence of hereditary polyposis syndromes among Hispanics, a population with a high CRC burden. A better understanding of the prevalence of polyposis is needed in order to establish clinical practices that may help identify

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The authors has/have no conflict/s of interest to disclose.

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individuals with hereditary polyposis syndromes, and to implement patient management protocols that will result in decreased morbidity and mortality in this population. The primary goal of this study was to determine the prevalence of colorectal adenomatous oligopolyposis, defined here as the presence of 20 or more synchronous adenomatous polyps, in Hispanics with incident CRC. We hypothesized that the synchronous adenomatous polyp burden among Hispanic individuals diagnosed with CRC would be high, which may suggest that a higher percentage of CRC cases can be attributed to hereditary predisposition in this population.

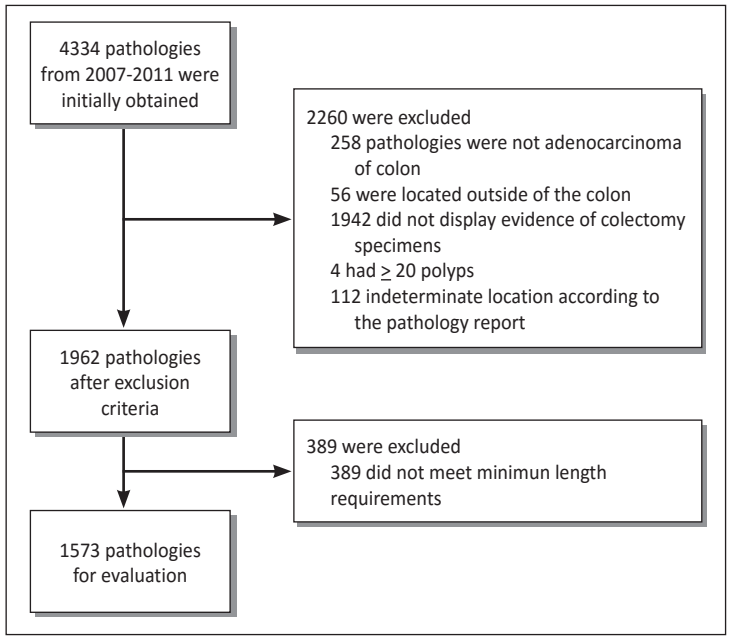

Figure 1. Selection of study population.

Methods

Study design and Study population

To determine the prevalence of synchronous colorectal adenomatous oligopolyposis, we performed a retrospective review of pathology reports entered into the database of the Puerto Rico Cancer Central Registry (PRCCR) from January 1, 2007 to December 31, 2011. The PRCCR is one of the oldest population-based registries in the Americas (9). This registry collects data on all newly diagnosed cancer cases in PR from individuals visiting public and private hospitals, as well as outpatient clinics. For each case, the PRCCR collects demographic characteristics, date of cancer diagnosis, anatomical cancer type, histological cancer type and grade, method of CRC diagnosis, stage at diagnosis, treatment status, and follow-up status. The PRCCR database uses the International Classification of Diseases for Oncology (ICD-O) for the classification of malignant tumors (1). This study was performed as a secondary analysis of the pathology reports available in the PRCCR database.

The study population included all of the CRC pathology cases identified by the PRCCR January 1, 2007 through December 31, 2011. Abstracted data were obtained only from the contents of the pathology report provided by the PRCCR; the data included sex, age, stage, histology, tumor differentiation (low, intermediate, high), location in the colon (cecum, ascending, transverse, descending, sigmoid, rectum), tumor size, length of specimen (centimeters), and number/histology of colorectal polyps. A total of 4,334 pathology reports were initially obtained; 2,256 were excluded because they did not meet the eligibility criteria (Figure 1). Among the excluded cases, 4 were excluded because the colectomy specimens had 20 or more polyps prior to the normalization of data, suggesting a genetic polyposis syndrome; 112 were excluded because the location of the primary tumor was not specified; and 389 were excluded due to the colectomy size (<12cm). The 1,573 pathology reports included in the analysis were from patients who were 21 years of age or older and who had been diagnosed with adenocarcinomas in the colon or rectum. The study was evaluated and authorized by the University of Puerto Rico Medical Sciences Campus Institutional Review Board (protocol number A2210114).

Normalization

A surgical pathology report was made at the time of each patient's colectomy; the report included the number of synchronous polyps found as well as their histological features. Due to the general assumption that CRC develops from a pre-existing polyp, we adjusted the number of polyps for each specimen by adding 1 to the total polyp count. Colorectal polyp data for each colectomy specimen was normalized using the following parameters: (a) the length of the colectomy specimen extracted during surgery and (b) the number of polyps in the colectomy segment. Based on the literature, we assumed that the colon length would be approximately 5 feet (152.4 cm) long for patients of either sex (10). Pendergrass et al. reported that the polyp ration of proximal vs distal colon is 0.81 (11), similar to the proximal to distal length ratio (0.83) as determined by data reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (10). Based on this assumption, the polyp burden was calculated as follows:

$$\hat{x}_i = \frac{n_i * c}{l_i * d} \times L$$

where n_i is the number of polyps recorded per individual; c is the right/left ratio of the number of polyps in older adults (0.81), as determined by Pendergrass et al.; l_i is the length of the given colectomy specimen; d is the ratio of the lengths of the right and left sides of the colon (0.83), as suggested by SEER (10); and L is the average length of the colon (152.4 cm).

Statistical analysis

The current clinical guidelines for the testing and management of hereditary GI cancers from the American College of Gastroenterology (2015) recommend genetic testing in individuals with more than 10 cumulative colorectal adenomatous polyps (12). However, we were strict in our definition of synchronous polyposis, thus increasing specificity to our definition of polyposis. In this study, synchronous polyposis was defined as having at least 20 polyps after normalization, as stated by 2013 revision of the *Local Coverage Determination for Genetic Testing of Medicare and Medicaid Service*, the American Gastroenterology Association, and the American College of Gastroenterology practice guidelines, all which specify that individuals with 20 or more colorectal adenomatous polyps in their lifetimes are considered at risk for hereditary CRC and should be referred for genetic counseling (13). Frequency distributions for categorical variables and summary measures for continuous variables were used to describe the cohort. The prevalence of synchronous oligopolyposis was analyzed according to age, sex, tumor stage at CRC diagnosis, and CRC location. Age was analyzed according to the following subgroups: <50 years, 50–64 years, 65–75 years, and >75 years (14). Tumor stage was categorized as local (carcinoma in situ/stage I), regional (stage II), or distant (stage III and stage IV), according to the tumor–node–metastases (TNM) staging system of the American Joint Committee on Cancer/Union for International Cancer Control (15). Tumor location was categorized as being in the proximal colon (cecum, ascending, and transverse colon) or the distal colon (descending, sigmoid and rectum).

Descriptions of the demographic and clinicopathological characteristics according to oligopolyposis status (<20 vs. ≥20) were generated using either the chi-square or Fisher's exact test if the expected frequency in a given cell was less than 5. Logistic regression models were fitted to estimate the prevalence odds ratios (POR), with 95% confidence intervals (CI) for the association of risk factors for oligopolyposis among subjects with incident CRC with all independent covariates. Variables significantly associated with oligopolyposis in the simple logistic regression models were included in the multivariable model. For the interpretation of results, p values below 0.05 were considered statistically significant. Statistical analyses were performed using Stata (v. 12.0) (Stata Corporation, College Station, Texas).

Results

Descriptive analysis of Study population

A total of 1,573 pathology reports of individuals with incident CRC were evaluated. The clinical characteristics of the study population are described in Table 1. Most of the study subjects were from 50 to 75 years old (65.9%); only 6.4% (n = 101) of the subjects were under 50 years of age. The mean age at CRC diagnosis was 68.1 years (SD ± 11.8). A comparable sex distribution was observed, with a slightly higher percentage of male (53.5%) than female subjects (46.5%). No statistical difference was observed between the excluded pathology reports and those that were analyzed in terms of the age and sex distribution. Most of the subjects presented with tumors at distant stages (stage III/IV: 45.5%). Distal tumors were present in 53.6% of the subjects, and the vast majority of these tumors were intermediate-grade adenocarcinomas (72.9%). The mean polyp number in the study population was 11.07 (SD ± 9.6). The length of the colectomy specimens (comprising the distal and proximal colon) did not differ significantly between patients (p>0.50). Of the pathology reports included in the analysis, 530 (33.6%) described synchronous polyps; of these, 89% were adenomatous polyps (tubular adenomas, tubulovillous adenomas, and sessile serrated adenomas).

Table 1. Demographic and clinical characteristics of the incident CRC cases reported to the Puerto Rico Central Cancer Registry from 2007 to 2011 (n = 1,573).

Characteristics	n (%)
Age in years*	
<50	101 (6.4)
50–64	478 (30.4)
65–75	558 (35.5)
≥75	434 (27.6)
Mean age (± SD)	68.07 ± 11.82
Sex*	
Female	732 (46.5)
Male	841 (53.5)
Mean number of polyps (±SD)	11.22 ± 9.80
CRC Stage*	
Local	339 (22.3)
Regional	489 (32.2)
Distant	693 (45.5)
Grade*	
Low	312 (21.7)
Intermediate	1044 (72.9)
High	77 (3.4)
CRC Location*	
Distal	842 (53.6)
Proximal	729 (46.4)

*The number of cases may vary between categories due to missing information.

Prevalence and Clinicopathological characteristics associated with Oligopolyposis

A total of 149 of 1,573 incident CRC subjects had synchronous oligopolyposis (9.47%; 95% CI: 8.02–10.92). Clinical characteristics according to oligopolyposis status are presented in Table 2. Significant differences were observed in the age at CRC diagnosis, tumor stage, and tumor location according to oligopolyposis status (p<0.05). The majority of subjects with synchronous oligopolyposis were 50 years old or older, with a higher proportion of subjects in the 75 years and older subgroup (36.2%; p = 0.03). The mean age of subjects with synchronous oligopolyposis was significantly higher (70 ± 11 years) compared to those without synchronous oligopolyposis (68.8 ± 12 years). In addition, subjects with synchronous oligopolyposis were more likely to present with

Table 2. Characteristics of incident CRC reported to the Puerto Rico Central Cancer Registry, by number of polyps, from 2007 to 2011.

Characteristics	Number of polyps <20 n (%)	Number of polyps ≥20 n (%)	p-value*
Age in years^			0.03
<50	97 (6.8)	4 (2.7)	
50–64	439 (30.9)	39 (26.2)	
65–74	506 (35.6)	52 (34.9)	
≥75	380 (26.7)	54 (36.2)	
Mean age (± SD)	67.8 ± 11.9	70.0 ± 11.6	0.02
Gender^			0.39
Female	668 (46.9)	64 (43.0)	
Male	756 (53.1)	85 (57.0)	
CRC Stage^			<0.01
Local	291 (21.1)	48 (34.5)	
Regional	447 (32.3)	42 (30.2)	
Distant	644 (46.6)	49 (35.3)	
CRC Grade^			0.62
Low	282 (21.6)	30 (23.4)	
Intermediate/High	1,026 (78.4)	98 (76.6)	
CRC Location^			<0.01
Distal	792 (55.7)	50 (33.6)	
Proximal	630 (44.3)	99 (66.4)	

*p-value from the Pearson chi-square or Fisher's exact test. ^The number of cases may vary between categories due to missing information.

Table 3. Prevalence odds ratio (POR) estimation for the association of risk factors for synchronous oligopolyposis in incident CRC cases reported to the Puerto Rico Central Cancer Registry from 2007 to 2011.

Characteristics	POR unadjusted (95% CI)	POR adjusted (95% CI)*
Age in years		
<50	1.0	1.0
50–64	2.15 (0.75–6.17)	1.72 (0.59–5.02)
65–74	2.49 (0.88–7.05)	1.83 (0.64–5.27)
≥75	3.44 (1.22–9.75)	2.67 (0.93–7.64)
Sex		
Female	1.0	1.0
Male	1.17 (0.83–1.64)	1.39 (0.97–2.01)
CRC Stage		
Local	1.0	1.0
Regional	0.57 (0.37–0.88)	0.50 (0.32–0.79)
Distant	0.46 (0.30–0.70)	0.45 (0.29–0.69)
CRC Location		
Distal	1.0	1.0
Proximal	2.49 (1.74–3.55)	2.91 (1.98–4.30)

*Adjusted by all the variables in the model simultaneously.

localized-stage disease (p<0.01) and proximal colonic location (p<0.01) than were those subjects without oligopolyposis. No statistically significant differences were observed when comparing sex and tumor grade according to oligopolyposis status (p>0.05).

Table 3 shows the estimation of the unadjusted and adjusted POR (95% CI) for individuals with synchronous oligopolyposis. The multivariable-adjusted model showed that increasing age ($POR_{50–64}$ = 1.72, 95% CI: 0.59–5.02; $POR_{65–74}$ = 1.83, 95% CI: 0.64–5.27; $POR_{\geq 75}$ = 2.67, 95% CI: 0.93–7.64) and the CRC having a proximal location (POR = 2.91, 95% CI: 1.98–4.30) were significantly associated with the possibility of having oligopolyposis at the moment of tumor presentation. However, subjects diagnosed with CRC at regional stages ($aPOR_{Regional}$ = 0.50, 95% CI: 0.32–0.79) or distant stages ($aPOR_{Distant}$ = 0.45, 95% CI: 0.29–0.69) were less likely to have oligopolyposis (p<0.05). Sex was not associated with synchronous oligopolyposis in the bivariate and multivariate analysis (p>0.05).

Discussion

Hereditary polyposis accounts for approximately 1% of all CRC cases (5). However, there is limited information regarding the contribution of synchronous oligopolyposis to the overall burden of CRC. This study is the first to report the prevalence of oligopolyposis (≥20 synchronous adenomatous polyps) in a large cohort of Hispanics with incident CRC. In our cohort, CRC was associated with synchronous oligopolyposis in approximately 1 of every 10 cases, which is 10 times higher than the expected contribution of hereditary polyposis (~1% of all CRC) (5). In addition, subjects with CRC and synchronous oligopolyposis presented with an earlier tumor stage at diagnosis, were relatively older, and tended to have tumors that were proximally located.

An average normal range of colonic adenomatous polyps among individuals without known hereditary polyposis syndrome has not been clearly defined (5). Our group previously reported that of the 745 Hispanic individuals who had undergone screening colonoscopies, 25.1% had colonic adenomatous polyps (16). Similarly, Alecu et al. reported that out of 1,368 screening colonoscopies, 18% were of patients who had at least one but no more than 5 colonic adenomatous polyps and, 9.9% were of patients who had multiple polyps (defined as having >5 polyps) (17). Pendergrass et al. reported that among individuals younger than 50 years old, having 2 or more polyps was considered beyond 2 standard deviations from the mean, suggesting a genetic syndrome. Revealed by the same article, in individuals who were over 50 years old, having 5 or more polyps represented such a threshold (11).

In the present study, we determined that 93.7% of the subjects with 20 or more polyps were 50 years old or older, indicating that the prevalence of oligopolyposis increases with age. This presentation markedly contrasts with hereditary polyposis syndromes such as FAP, attenuated FAP, and MYH-polyposis syndrome (MAP), in which the average age at onset is less than 50 years (5, 18–20). CRC is usually diagnosed in individuals with FAP who are from 30 to 40 years old (4, 19), whereas patients with MAP and AFAP are usually diagnosed when they are from 40 to 50 years old (21–23). Individuals with serrated polyposis syndrome (SPS), characterized by the presence of

Table 4. Comparison between phenotypic characteristics of hereditary polyposis syndrome and subjects with synchronous oligopolyposis.

Condition	Mean Number of Adenomatous Polyps	Age at CRC Presentation	Stage	Location
Familial Adenomatous Polyposis (19, 22)	>100	<40 y/o	Local/Regional	Distal
Attenuated Adenomatous Polyposis (22, 23)	10–100	56	-	Proximal
MUTYH-Associated Polyposis (21, 26)	10–100	48	Local/Regional	Proximal
Serrated Polyposis Syndrome (24)	≥20	50–60	-	Distal
General Population (9, 11)	>5	68–69	Distant	Distal
Cohort of subjects with synchronous oligopolyposis	≥20	70	Local	Proximal

multiple serrated and/or large-sized hyperplastic polyps in the colon, usually present with CRC when they are from age 50 to 60 years old (24). Cruz-Correa et al. reported that the mean ages at diagnosis for Puerto Rican Hispanic patients with FAP and MAP were 27.6 and 53.1 years, respectively (25). Even though some of the hereditary polyposis syndromes present with polyposis/cancer around the 5th or 6th decade of life, the mean age at diagnosis for patients with oligopolyposis in our cohort was higher (70 ± 11 years), compared to that of the above-mentioned hereditary syndromes. The most likely explanation for this is that our population was composed of patients who already had developed CRC.

As has been the case with other polyposis syndromes, the subjects in our population with synchronous oligopolyposis were more likely to have local tumors (12, 21, 22, 24). This phenomenon has also been described in patients with FAP in which said patients are diagnosed after presenting with symptoms caused by the increased colorectal polyp burden, which symptoms include rectal bleeding and changes in bowel movements (8, 18, 19). Individuals with MAP were also reported to usually present with local/regional stage CRC tumors (21). Gastrointestinal symptoms, such as rectal bleeding, may have caused the patients in our cohort with oligopolyposis to seek medical evaluation earlier, resulting in their receiving diagnoses at local stages.

The clinical presentation of subjects with oligopolyposis observed in this Hispanic cohort differs from what was previously described for the known hereditary polyposis syndromes. Compared to those with FAP, subjects with oligopolyposis presented with CRC at an older age. Another key finding in our study was the proximal location of CRC seen in subjects with synchronous oligopolyposis. In contrast to FAP and serrated polyposis syndrome, in which CRC tumors usually present in the distal colon (4, 8, 18, 22, 24, 25), subjects in our cohort with oligopolyposis predominantly had tumors located in the proximal colon. Tumor location in subjects with oligopolyposis was similar to what has been reported for patients with AFAP and MAP, both of which present predominantly with right-sided neoplastic tumors (8, 14, 20, 26). Similar to subjects with AFAP and MAP, subjects with oligopolyposis presented with local/regional tumors, had proximal colonic tumors, and had similar polyp burdens, suggesting an underlying genetic etiology. As previously reported, patients with AFAP and MAP can be misdiagnosed since their colonic polyp burdens are similar—with tumors usually located in the right colon—and are markedly less, compared to the polyp burdens associated with classic FAP (22). However, genetic testing is needed to definitively determine whether the synchronous oligopolyposis cases observed were due to hereditary polyposis syndromes. The observed high prevalence of individuals with oligopolyposis among the current CRC Hispanic cohort highlights the importance of genetic counseling and testing for patients with incident CRC and the presence of synchronous colonic adenomas or with a cumulative history of at least 20 adenomas.

To our knowledge, this is the first population-based study in Puerto Rico that comprehensively reviews all of the pathology reports of incident CRC deposited in the PRCCR database over a 3-year period to determine the prevalence of synchronous oligopolyposis and its associated clinicopathological characteristics in Hispanics with incident CRC. However, the study, being retrospective in nature, is not without limitations. The data evaluated was limited to what was available within the pathology reports; thus, details about other important covariates, such as CRC family history, medical co-morbidities, extra-colonic manifestations, environmental factors, and germline genetic information, were not available. In addition, polyp burden was determined by a normalization equation that inferred the polyp burden by the number of polyps examined within a given colectomy specimen. However, although synchronous oligopolyposis has been previously described as having a polyp burden from 10 to 100 (18), we limited the classification of oligopolyposis to those subjects who had 20 or more polyps after the normalization of the data, thus strengthening our estimation of synchronous oligopolyposis prevalence in our study population.

Conclusion

The newly published American College of Gastroenterology guidelines for the management of hereditary CRC establish the importance of genetic testing in individuals with a high polyp

burden. This study provides additional data on Hispanics, a growing population in the US with a high CRC burden, but under-represented in CRC studies. In conclusion, we found that the prevalence of synchronous oligopolyposis in subjects with incident CRC was higher than that of those with hereditary polyposis syndromes (9.47% and 1%, respectively). Based on this finding, we highlight the contribution of hereditary polyposis syndromes to the overall burden of CRC, which is perhaps much higher than previously reported. Genetic testing is recommended for at-risk individuals to exclude hereditary polyposis syndromes that present with less aggressive phenotypes, such as AFAP and MAP. Increasing CRC screening in individuals with synchronous oligopolyposis, a population with a high-risk of CRC, may help in the identification of those with hereditary polyposis syndromes and, thereby, lead to improvements in the management of these patients and a subsequent reduction in morbidity and mortality in this population.

Resumen

Objetivos: El cáncer colorrectal (CCR) es una de las principales causas de muerte por cáncer en hombres y mujeres. El propósito de este estudio fue determinar la prevalencia de oligopoliposis (definida como ≥20 adenomas colorrectales síncronos) y sus características clínico-patológicas asociadas entre los hispanos con CCR incidental. Métodos: Los informes de patología de las personas diagnosticadas con CCR entre los años 2007-2011 fueron recuperados del Registro Central De Cáncer de Puerto Rico. La carga de pólipos colorrectales en los sujetos se calculó utilizando informes de patología. La carga de pólipos colorrectales en los sujetos se calculó utilizando la normalización de datos basados en el tamaño de segmento del colon. Las comparaciones por estado oligopoliposis (<20 frente a ≥20) se realizaron mediante los análisis estadísticos de chi-cuadrado o las pruebas exactas de Fisher. Se ajustaron modelos de regresión logística para estimar la razón de momios de prevalencia (POR) con intervalos de confianza del 95% (IC). Todos los análisis estadísticos se realizaron utilizando Stata (v.12.0). Resultados: Se realizó un análisis de 1,573 muestras de colectomía. Se observó una prevalencia de oligopoliposis en el 9.47% (149 de 1,573) de los sujetos con CCR incidente. A mayor edad (POR_{50-64}=1.72, IC 95%: 0.59-5.02; POR_{65-74}=1.83, IC 95%: 0.64-5.27; $POR_{\geq 75}$=2.67, IC 95%: 0.93-7.64), y la localización del tumor CCR en el colon proximal (POR=2.91, IC 95%: 1.98-4.30) fueron significativamente asociados con oligopoliposis. Sin embargo, a etapas tempranas del tumor CCR, ($POR_{Regional}$=0.50, IC 95%: 0.32-0.79; $POR_{Avanzado}$=0.45, IC 95%: 0.29-0.69) tenían menos probabilidad de tener oligopoliposis. Conclusión: Nuestras observaciones sugieren que los síndromes genéticos asociados con la poliposis colorrectal pueden explicar un número más alto de lo esperado de casos de CCR. El asesoramiento genético debe ser considerado en individuos con CCR y oligopoliposis.

Acknowledgments

This project was supported by RCMI grant G12MD007600 (Center for Collaborative Research in Health Disparities) and grant U54MD007587 (Puerto Rico Clinical and Translational Research Consortium), both from the Institute on Minority Health and Health Disparities, National Institutes of Health and both awarded to the University of Puerto Rico, Medical Sciences Campus; and by grant U54CA096297/CA096300 (UPR/MDACC Partnership for Excellence in Cancer Research Program) from the National Cancer Institute of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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