1130-0108/2008/100/3/139-145
REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS

REV ESP ENFERM DIG (Madrid)
Vol. 100. N.° 3, pp. 139-145, 2008

Synchronous neoplastic lesions in colorectal cancer. An analysis of possible risk factors favouring presentation

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RESUMEN

Objetivo: en el cáncer colorrectal son poco conocidas las causas del frecuente desarrollo de lesiones neoplásicas sincrónicas. Pretendemos identificar posibles factores que pudieran influir en la multicentricidad lesional. Su conocimiento sería útil para, tras el tratamiento de las lesiones iniciales, optimizar el seguimiento en los pacientes que los presentaran.

Pacientes y métodos: estudiamos retrospectivamente 382 cánceres colorrectales diagnosticados mediante colonoscopia completa y estudio de la pieza quirúrgica. Comparamos una serie de parámetros referentes a los antecedentes personales y familiares, hábitos, datos clínicos y del tumor entre los grupos con y sin lesiones neoplásicas sincrónicas, mediante análisis estadístico univariable y multivariable.

Resultados: doscientos ocho (54,5%) pacientes presentaron adenomas sincrónicos y 28 (7,3%) carcinoma sincrónico. En el análisis multivariable el sexo masculino: OR = 1,97; IC = 1,13-3,45, p = 0,017; la edad superior a 59 años: OR = 2,57; IC = 1,54-4,29, p < 0,001; el antecedente personal de pólipo colónico: OR = 3,04, IC = 1,04-8,85, p = 0,042 y el carácter obstructivo del cáncer: OR = 0,48; IC = 0,27-0,85, p = 0,012 se asocian significativamente con la multicentricidad lesional.

Conclusión: en los enfermos con cáncer colorrectal, nuestro estudio muestra una serie de parámetros, de fácil determinación, que podrían comportarse como factores de riesgo para el desarrollo de multicentricidad lesional. Estos factores deberán confirmarse mediante un estudio de seguimiento, analizando su comportamiento entre los pacientes que presenten o no lesiones metacrónicas tras la limpieza quirúrgico-endoscópica inicial.

Palabras clave: Cáncer colorrectal. Lesiones sincrónicas. Factores de riesgo.

ABSTRACT

Aim: few data have been published regarding the causes of synchronous lesions in patients with colorectal cancer. The aim of our study was to identify potential factors that might be implicated in the development of multicentric lesions, since this knowledge could be useful for tailored follow-up once initial synchronous lesions have been removed.

Methods: we retrospectively reviewed 382 colorectal cancer cases diagnosed by total colonoscopy and histological study of surgical specimens. We divided our population into 2 groups, based on whether they had synchronous lesions or otherwise. Several data related to personal and family history, habits, symptoms, and tumor characteristics were assessed. Univariate and multivariate statistical analyses were performed.

Results: 208 (54.5%) patients had synchronous adenomas and 28 (7.3%) had synchronous cancer. A multivariate analysis showed that the following parameters were consistently related to the presence of multicentric lesions –male gender: OR = 1.97; CI = 1.13-3.45; p = 0.017; age ≥ 59 years: OR = 2.57; CI = 1.54-4.29; p < 0.001; personal history of colonic adenomas: OR = 3.04; CI = 1.04-8.85; p = 0.042; and obstructive tumors: OR = 0.48; CI = 0.27-0.85; p = 0.012.

Conclusion: our results show that several parameters that are easy to measure could be considered risk factors for the development of multicentric lesions. These factors need to be confirmed with follow-up studies analyzing their role in patients with and without metachronic lesions once all synchronous lesions have been removed.

Key words: Colorectal cancer. Synchronous lesions. Risk factors.

Borda A, Martínez-Peñuela JM, Muñoz-Navas M, Prieto C, Betés M, Borda F. Synchronous neoplastic lesions in colorectal cancer. An analysis of possible risk factors favouring presentation. Rev Esp Enferm Dig 2008; 100: 139-145.

Received: 27-08-07.
Accepted: 08-01-08.

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide (1). In Spain it is the second leading cause of death due to cancer (2). In our country it is estimated that

there are 25,000 new diagnoses and 12,500 deaths/year (2). A great majority of colorectal cancers develop from a pre-existing adenoma, following a multi-step adenoma-carcinoma sequence (1-13), and as a rule synchronous neoplastic lesions, adenomas, and less frequently carcinomas are present when the tumor is diagnosed (14-17). It has been postulated that tumoral multicentricity may be due to an interaction of numerous factors, which might include a particular predisposition, both personal and familiar, environmental causes, and/or tumor characteristics, which increase the likelihood of developing neoplasms in different colonic segments (18,19).

There are currently several publications concerning the risk of synchronous lesions developing in patients with colorectal adenoma (15,16,20-23), but we were only able to find one study referring to the identification of possible risk factors for the development of synchronous neoplastic lesions in colorectal cancer (14). Identifying differences amongst colorectal cancer series, both with and without synchronous lesions, could define some possible risk factors for tumoral multicentricity. Colorectal cancer surveillance is currently a matter of debate (3,24-31). The identification of possible multicentricity factors could facilitate a more rational monitorization for the screening of metachronous lesions following initial endoscopic-surgical cleansing procedures. Finally, it would facilitate a practical approach to the theoretical possibility of selecting patient subgroups, which in the future could benefit from chemoprevention treatments, with the aim of avoiding lesion recurrence (32-35).

MATERIAL AND METHODS

Colorectal cancers diagnosed between 1999 and 2003 at *Clínica Universitaria de Navarra* and *Hospital de Navarra* by total preoperative colonoscopy or total colonoscopy within 3 months after surgery were included. In all cases tumors were removed and confirmed histologically. All pathological studies were reviewed by a single pathologist in order to ensure that the same criteria were used, and to avoid inter-observer differences. Colorectal cancers occurring in the context of multiple familial polyposis or inflammatory intestinal disease were excluded.

The presence of a second colorectal carcinoma, adenomatous polyps, tubular and/or villous polyps, and serrated adenomas was considered a synchronous neoplastic lesion, and hyperplastic polyps were not included in our study.

In patients with two or more tumors the lesion with a lower tumoral stage was labeled as synchronous cancer. We also considered malignized polyps with any areas of *in situ* carcinoma as synchronous cancer.

Our series was divided into two groups depending on whether they presented synchronous neoplastic lesions when colorectal cancer was diagnosed. We studied the possible differences between both groups with respect to the following parameters: a) *Age:* We analyzed this variable using continuous values and in patients over and under 60 years of age; b) *Gender*; c) *Regular place of residence:* In Navarre or any other Spanish Autonomous Community; d) *Body mass index* (BMI), using the WHO classification system (36) to classify patients as underweight: BMI < 21; normal weight: 21-24.9; overweight: 25-29.9; and obese: > 30. We compared the incidence of cases with and without synchronous lesions for the following BMI cut-off points: < 21, < 25 and ≥ 30; e) *Tobacco:* Like other authors (37-39), we considered patients who had smoked 7 or more cigarettes weekly for at least a year prior to the diagnosis as smokers, and ex-smokers were patients who had not smoked for at least one year. Both groups were analyzed as to whether patients were smokers or nonsmokers, and number of cigarettes smoked, establishing cut-off points as ≥ 20, ≥ 15, ≥ 10 and ≥ 5 cigarettes/day; f) *Alcohol:* Non-drinkers, drinkers who consumed less than 40 grams and over 40 grams of ethanol/day, evaluating patients overall and according to their gender; g) *Patient medical history of:* Colorectal cancer or cancer of any organ, previous history of adenomatous colon polyps; h) *History of cancer in first-degree family members*. All these medical history factors were considered dichotomously: Yes/no responses, in accordance with clinical record data and/or a posted questionnaire; i) *Revised Bethesda criteria* (40), with cases fulfilling at least 1 of all 5 criteria being considered positive; j) *Predominant clinical symptom*, based on the reason for diagnostic colonoscopy and using the following classification system: i) *Personal or family history of polyps or colorectal cancer*; ii) *Check-up of asymptomatic patient*; iii) *Rectal bleeding*; iv) *Abdominal pain*; v) *Altered bowel movements, constipation or diarrhea*; vi) *Anemia*; vii) *Other*; k) *Cleaning achieved during the diagnostic colonoscopy*: i) *Good:* Correct visualization of the mucosa; ii) *Acceptable:* Aspirable liquid contents permitting adequate examination of the mucosa; and iii) *Poor:* Colon contents are solid or liquid but cannot be aspirated, making an adequate examination of the mucosa difficult or not feasible; l) *Location of colorectal cancer:* Rectum, sigmoid, descending, transverse, and ascending-cecum colon; m) *Obstructive nature of the colorectal cancer:* Cancer which blocks the passage of the endoscope, avoiding cecum intubation; n) *Histological classification of the cancer:* To facilitate the statistical study cancers were grouped into adenocarcinomas and other tumors; o) *Grade of tumor differentiation* (41): Well differentiated, moderately differentiated, and undifferentiated; and p) *Tumor staging using the American Joint Comittee on Cancer pTNM classification* (5th edition) (42). For this statistical study stages 0 and I were placed in the same group.

Statistical analysis

The results are expressed as mean ± standard deviation when variables displayed a normal distribution pattern

using the Kolmogorov-Smirnoff test, and as the median value and range in the remaining cases. Categorical variables are expressed as frequencies and percentages.

The quantitative variables showing normal distribution patterns were compared using Student's t-test. Otherwise the Mann-Whitney U test was employed. Qualitative variables were compared by means of the Chi square and Fisher's exact tests, with odds ratio (OR) and 95% confidence interval (CI) determination. Values of $p < 0.05$ were regarded statistically significant.

Multivariate analysis

A multivariate analysis was performed using a multiple logistic regression analysis, the dependent variable being the presence or absence of synchronous lesions, and independent variables being those which exhibited a $p < 0.20$ value in the univariate study. Interactions were tested by introducing the sum of variables into the model.

RESULTS

In all 382 patients with colorectal cancer were analyzed, 65.2% of which were males and 34.8% females. Median age was 65 years (range = 20-88). The presence of synchronous tumors was confirmed in 28 patients (7.3% of the entire population), all of them with synchronous adenomas. At least one synchronous adenoma was diagnosed in 208 patients (54.5% of total). No significant differences were identified with regard to colon cleansing between groups with and without synchronous neoplastic lesions in the diagnostic endoscopy: Good preparation = 68.6 *vs*. 70.5%, acceptable preparation = 17.3 *vs*. 22.3%, and poor preparation = 14.1 *vs*. 7.25% ($p = 0.46$).

Median age in the group with synchronous lesions (67, range 30-83) was significantly higher than in patients without polyps (60, range 20-88; $p < 0.001$). Table I shows the differences between colorectal cancers, with and without synchronous neoplastic lesions, with respect to patient age (under or over 60 years), gender, regular place of residence, medical history of colon polyps, colorectal or any other type of cancer, medical history of cancer in first-degree family members, and revised Bethesda criteria. A higher frequency of synchronous adenomas in the ≥ 60-year group was confirmed: 64 *vs*. 37%, OR = 3.02; 95% CI: 1.91-4.78; $p < 0.000001$. Synchronous lesions were significantly more frequent in males (62.7%) compared to females (39.1%), OR = 2.61; CI = 1.66-4.12; $p < 0.0001$. Patients with a medical history of colon polyps had a greater tendency to have synchronous lesions (68 *vs*. 48.8%), but this difference was not statistically significant ($p = 0.10$).

The links between tobacco consumption, alcohol consumption, and body mass index and synchronous lesion frequency are shown in table II. Toxic habits mainly affected males, 80.8% of whom were smokers, 88.5% drinkers, and 84.4% both smokers and drinkers. We recorded a higher proportion of synchronous lesions in cases of patients who actively smoked and/or had smoked, and this difference was almost statistically significant (smokers *vs*. non-smokers: $p = 0.07$); smokers and ex-smokers *vs*. non-smokers: $p = 0.098$. Patients with synchronous lesions more often consumed 10 or more cigarettes/day: 29/207 (14%) *vs*. 14/175 (8%), $p = 0.064$. The other cut-off points studied showed smaller differences between these two groups: ≥ 20 cigarettes/day: $p = 0.15$; ≥ 15: $p = 0.17$; and ≥ 5 cigarettes/day: $p = 0.094$.

Forty-seven percent of patients consumed alcohol, but only 4% of cancer patients consumed over 40 grams of ethanol/day, so our statistical analysis made a distinction between drinkers and non-drinkers, without specifying cut-off points for alcohol consumption. A significantly higher incidence of drinkers was observed in the series with synchronous lesions: $p = 0.006$; OR = 1.86; CI 95%: 1.16-2.99. When groups were divided on the basis of gender, differences were reduced in males: $p = 0.058$; and

Table I. Personal and familial factors, and synchronous lesion rate

	No synchronous lesions		*Synchronous lesions*		*p*
	n	%	*n*	%	
Age					
≥ 60 years	89/247	36	158/247	34	< 0.000001
< 60 years	85/135	65.4	50/135	34.6	
Gender					
Male	93/249	37.3	156/249	62.7	< 0.001
Female	81/133	60.9	52/133	39.1	
Place of residence					
Navarre	92/174	52.9	109/208	52.4	0.93
Other	82/174	47.1	99/208	47.6	
History of adenomatous polyps	144/295	48.8	17/25	68	0.10
Personal history of CRC	4/173	2.3	7/208	3.4	0.46
Personal history of other tumors	10/173	5.8	17/207	8.2	0.57
History of cancer in first-degree family members	82/146	56.2	83/170	48.8	0.53
Revised Bethesda criteria (at least one criteria)	64/131	48.9	86/195	44.1	0.40

Table II. Tobacco, alcohol, body mass index, symptoms, and synchronous lesion rate

	No synchronous lesions		*Synchronous lesions*		*p*
	n	*%*	*n*	*%*	
Tobacco					
No smoker	91/164	55.5	91/197	46.2	0.14
Ex-smoker	47/174	28.7	61/197	31	
Smoker	26/164	15.8	45/197	22.8	
Alcohol (global)					
Non-drinkers	89/145	61.4	81/176	46	0.006
Drinkers	56/145	38.6	95/176	54	
Alcohol (males)					
Non-drinkers	36/81	44.4	41/131	31.3	0.058
Drinkers	45/81	55.6	90/131	68.7	
Alcohol (females)					
Non-drinkers	55/69	79.7	41/48	85.4	0.43
Drinkers	14/69	20.3	7/48	14.6	
Body mass index					
< 21	9/174	5.2	3/208	1.4	0.036
< 25	52/174	29.9	47/208	22.6	0.094
≥ 30	29/129	22.5	29/143	20.3	0.66
Predominant symptom					
Rectal bleeding	92/173	53.2	113/207	54.6	0.99
Anemia	27/173	15.6	29/207	14	
Change bowel movements	20/173	11.6	24/207	11.6	
Abdominal pain	16/173	9.2	18/207	6.7	
Check-up	8/173	4.6	10/207	4.8	
History of colonic lesion	5/173	2.9	8/207	3.9	
Others	5/173	2.9	5/207	2.4	

these differences were statistically eliminated in females: p = 0.43.

A BMI < 21 was recorded in 3.9%, and 58.3% of these patients were female. The group with synchronous lesions showed a lower incidence of patients with BMI < 21: 1.9% as opposed to 6.2%, p = 0.09, with no significant differences between BMI cut-off points ≥ 30 and < 25.

The clinical symptoms which prompted the diagnostic colonoscopy were very similar for the series with and without synchronous lesions (p = 0.99) (Table II).

Table III. Location, histological classification, differentiation grade, and synchronous lesion rate

	No synchronous lesions		*Synchronous lesions*		*p*
	n	*%*	*n*	*%*	
Location					0.21
Rectum	79	48.2	77	37	
Sigma	35	21.3	62	29.8	
Descending	8	4.9	12	5.8	
Transverse	13	7.9	17	8.2	
Ascending-cecum	39	23.7	40	19.2	
Histological classification					0.31
Adenocarcinoma	151	87.8	173	83.6	
Other	21	12.2	34	16.4	
Differentation grade					0.44
Well	26	26.8	37	19.3	
Moderately	102	65.8	132	68.7	
Undifferentiated	27	17.4	23	12	

Regarding cancer-dependent factors, we noted that in cases with obstructive carcinoma the incidence of adenomas was 34/88 (38.6%), which was significantly lower than in cases of non-obstructive cancer: 173/293 (59%); p < 0.001; OR = 0.44; CI: 0.26-0.73.

We did not detect significant differences (p = 0.21) in cancer-involved anatomical colonic segment and presence or absence of synchronous lesions, or histological type of tumor and grade of differentiation (Table III).

Tumor staging (pTNM) was similar for groups with and without synchronous lesions (p = 0.79) (Fig. 1).

Multivariate statistical analysis

The results for the multivariate logistic regression analysis model are shown in table IV. Being over 59 years of age, being male, and having a medical history of colon polyps are factors associated with a higher frequency of synchronous lesions, and obstructive cancer is associated with a lower risk of associated adenomas. BMI and tobacco consumption do not show significant differences between groups with and without synchronous lesions. Alcohol, although having no significant association with synchronous lesions (p = 0.19), adjusts the effect of sex on the frequency of these lesions.

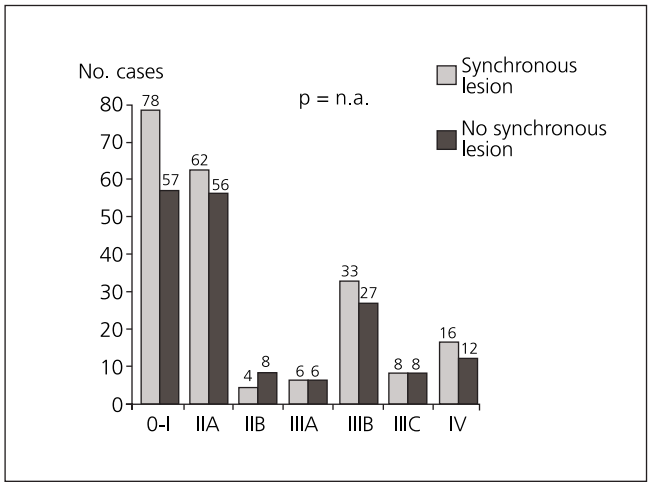

Fig. 1. CRC staging and synchronous lesions.

Table IV. Results for the multivariate analysis model

Parameters	*p*	*Odds ratio*	*95% CI*
Male gender	0.017	1.97	(1.13-3.45)
Age ≤ 60 years	< 0.01	2.57	(1.54-4.29)
Alcohol	0.196	1.42	(0.84-2.41)
History of adenomatous polyps	0.042	3.04	(1.04-8.85)
Obstructive colorectal cancer	0.012	0.48	(0.27-0.85)

DISCUSSION

The lack of bibliographical references concerning factors which could produce lesional multicentricity in patients with colorectal cancer was mentioned above (14). The identification of readily accessible factors (clinical, personal or familial factors, or specific tumor characteristics) which might influence the multiplicity of lesions would be an important step to permit the identification of a subgroup of patients who would require closer monitorization after tumor resection and endoscopic polyp cleansing procedures (14). Hypothetically, this subgroup of patients with a greater tendency to present lesional multicentricity could even constitute a target population for chemoprevention therapies such as acetylsalicylic acid or COX-2 inhibitors, which are currently under investigation (32-35), in order to avoid or reduce the risk of continuing to present new colon neoplastic lesions. Our study aims to identify possible risk factors for the development of synchronous lesions by analyzing the frequency of these possible risk factors in two colorectal cancer groups, with and without synchronous neoplastic lesions.

As this is a retrospective study, we have had to contend with the limitations imposed by a lack of certain data, which are insufficiently detailed in the clinical records and essentially refer to the familial and personal medical history of cancer patients and their toxic habits. We have tried to make up for this by sending patients a questionnaire. Nevertheless, as this limitation affects both groups, with and without synchronous lesions, in our opinion this has not caused any significant bias in our evaluation of results.

As in the only bibliographical reference we came across (14), in patients with colorectal cancer being male and having a history of colon adenomas is associated with a significantly higher incidence of synchronous neoplastic lesions, which appears to indicate that this is a risk factor for their occurrence. These factors have already been postulated to favor multicentricity in patients with colon adenomas who have not developed cancer (15,16,20,43). On the other hand, in our study we were unable to confirm the possible influence of other parameters such as a family history of gastric cancer or specific characteristics of the tumor, for example proximal localization, mucinous histological type, or T II staging, which, in the series by Piñol are described as linked to lesional multicentricity (14).

As would be expected, greater age is associated with a higher incidence of synchronous lesions, which has already been reported in series of patients with adenomas (15,16).

It has been reported that both tobacco and alcohol dependency increase the risk of developing neoplastic lesions of the colon (44-52), even at a very young age (44), and the possible effect of alcohol and tobacco on the stability system of microsatellites is a matter of debate (53-57). Similarly, it has been demonstrated that patients who smoke have a higher risk of new adenomas after endoscopic polypectomy (58). In the univariate analysis tobacco and alcohol consumption were more common in patients with synchronous lesions, but both habits were associated with the male sex. In the multivariate analysis neither tobacco nor alcohol showed any significant association with synchronous lesions. When alcohol is introduced into the model, the effect of gender on the frequency of synchronous lesions is adjusted, which confirms that alcohol is a confounding factor and that the male gender is a risk factor for the development of synchronous lesions.

It has been postulated that an increase in BMI may favor the development of colorectal adenomas and carcinomas (59-63). In the univariate analysis thinness, expressed as BMI < 21, appears to act as a protective factor against the presence of synchronous lesions. In the multivariate analysis no significant differences were observed, possibly owing to the small number of underweight patients and an association with the female sex.

Finally, our cases of colorectal cancer with an obstructive pattern showed a lower incidence of synchronous lesions. We can provide no logical explanation for this finding, given that in our bibliographical search the incidence of synchronous lesions in this type of neoplasm ranges from 36 to 58% (64,65), which is no less than for other cancers (64).

In summary, in patients with colorectal cancer our study has shown a series of variables very easy to obtain: Male gender, advanced age, medical history of colon polyps, and non-obstructive nature of the tumor, which could act as risk factors for the development of lesional

multicentricity, defining a subgroup of patients who will require closer post-surgical monitoring. These possible risk factors should be confirmed in a follow-up study after surgical-endoscopic cleansing of initial lesions, analyzing their behavior in patients who present or fail to present with metachronous lesions. This research is currently underway.

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