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Prognostic relevance of *MLH1* and *MSH2* mutations in hereditary non-polyposis colorectal cancer patients

Antonio Russo[1], Paola Sala[2], Paola Alberici[3], Isabella Gazzoli[3], Paolo Radice[3], Claudia Montefusco[3], Margherita Torrini[4], Cristina Mareni[4], Mara Fornasarig[5], Manuela Santarosa[6], Alessandra Viel[6], Piero Benatti[7], Monica Pedroni[7], Maurizio Ponz de Leon[7], Emanuela Lucci-Cordisco[8], Maurizio Genuardi[9], Luca Messerini[10], Vittoria Stigliano[11], Alessandro Cama[12], Maria Cristina Curia[12], Laura de Lellis[12], Stefano Signoroni[2], Marco A Pierotti[13], and Lucio Bertario[2]

[1]Epidemiology Unit, San Carlo Hospital, Milan; [2]Department of Preventive-Predictive Medicine, and [3]Department of Experimental Oncology and Molecular Medicine, IRCCS Istituto Nazionale Tumori Foundation, Milan; [4]Department of Internal Medicine, University of Genoa, Genoa; [5]Gastroenterology Unit, and [6]Experimental Oncology 1, National Cancer Institute, Aviano (PN); [7]First Medical Division, Department of Medicine and Medical Specialties, University of Modena and Reggio Emilia, Modena; [8]Center for Cancer Study and Prevention (CSPO), Florence; [9]Genetics Unit, Department of Clinical Pathophysiology, and [10]Department of Clinical Pathology, University of Florence, Florence; [11]Gastroenterology and Digestive Endoscopy Unit, Regina Elena Cancer Institute, Rome; [12]Department of Oncology and Neurosciences, University "G. D'Annunzio", and Center of Excellence on Aging "G. D'Annunzio", Chieti; [13]Scientific Directorate, IRCCS Istituto Nazionale Tumori Foundation, Milan, and Molecular Genetics of Cancer, FIRC Institute of Molecular Oncology Foundation, Milan, Italy.

ABSTRACT

Aims and background. Colorectal carcinoma patients from hereditary non-polyposis colorectal cancer families are suggested to have a better prognosis than sporadic colorectal carcinoma cases. Since the majority of hereditary non-polyposis colorectal cancer-related colorectal carcinomas are characterized by microsatellite instability due to germline mutations in DNA mismatch repair genes, this is consistent with the prolonged survival observed in sporadic microsatellite instability-positive colorectal carcinoma compared to microsatellite stable cases. However, a fraction of colorectal carcinoma cases belongs to families that, despite fulfilling the clinical criteria for hereditary non-polyposis colorectal cancer, do not carry mismatch repair gene mutations. Our aim was to verify to what extent the genotypic heterogeneity influences the prognosis of hereditary non-polyposis colorectal cancer patients.

Methods. A survival analysis was performed on 526 colorectal carcinoma cases from 204 Amsterdam Criteria-positive hereditary non-polyposis colorectal cancer families. Enrolled cases were classified as *MLH1*-positive, *MSH2*-positive and mutation-negative, according to the results of genetic testing in each family.

Results. Five-year survival rates were 0.73 (95% CI, 0.66-0.80), 0.75 (95% CI, 0.66-0.84) and 0.62 (95% CI, 0.55-0.68) for *MLH1*-positive, *MSH2*-positive and mutation-negative groups, respectively (logrank test, $P = 0.01$). Hazard ratio, computed using Cox regression analysis and adjusted for age, sex, tumor site and stage, was 0.71 (95% CI, 0.51-0.98) for the mutation-positive compared to the mutation-negative group. Moreover, in the latter group, patients with microsatellite instability-positive colorectal carcinomas showed a better outcome than microsatellite stable cases (5-year survival rates, 0.81 and 0.60, respectively; logrank test, $P = 0.006$).

Conclusions. Our results suggest that the prognosis of hereditary non-polyposis colorectal cancer-related colorectal carcinoma patients depends on the associated constitutional mismatch repair genotype.

Key words: hereditary non-polyposis colorectal cancer, *MLH1*, *MSH2*, survival.

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Correspondence to: Lucio Bertario, Department Preventive-Predictive Medicine, IRCCS Istituto Nazionale Tumori Foundation, Milan, Italy, Via Venezian 1, 20133 Milan, Italy.
E-mail
lucio.bertario@istitutotumori.mi.it

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