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EDITORIAL

Identification of Lynch syndrome: How should we proceed in the 21st century?

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Abstract

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer. Although great advances in the understanding of its molecular basis have taken place in the last decade, optimal selection of individuals for HNPCC genetic testing remains controversial. This is especially relevant since colonoscopy has been proven effective for reducing colorectal cancer incidence and mortality in individuals at-risk for this disorder. In this manuscript, we summarize the most significant contributions to this important issue that have appeared in the last few years.

Key words: Hereditary non-polyposis colorectal cancer; Screening; Prevention; Microsatellite instability; Genetics

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INTRODUCTION

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer (CRC), accounting for 2%-5% of all colorectal malignancies[1]. It is characterized by early onset of CRC and other related neoplasms including endometrial, ovarian, gastric and urinary tract cancer. This syndrome is inherited in a non-fully penetrant autosomal dominant pattern, and occurs as a result of germline mutations in mismatch repair genes, predominantly *MLH1* and *MSH2* (> 90% of cases), but also *MSH6* and *PMS2*. The abnormal function of these genes leads to the accumulation of errors during DNA replication, especially in repetitive sequences (microsatellites). As a result, tumors in patients with Lynch syndrome characteristically demonstrate microsatellite instability (MSI), as well as loss of expression of the affected protein[1].

Although great advances in the understanding of its molecular basis have taken place in the last decade, optimal selection of individuals for HNPCC genetic testing remains controversial[2]. This is especially relevant since colonoscopy has been proven effective for reducing CRC incidence and mortality in individuals at-risk for this disorder[3]. In 1991, the International Collaborative Group on HNPCC established clinical criteria, known as the Amsterdam criteria, which provided a pivotal definition of this syndrome and were critical in identifying its molecular basis[4]. In response to criticism that the Amsterdam criteria were too stringent, the extended Amsterdam Ⅱ criteria were developed to include extracolonic HNPCC-associated cancers[5].

The use of the Amsterdam criteria achieved the original purpose of classifying a family as having HNPCC, but their limited sensitivity hampered decisions about which patients should undergo genetic testing[2]. In 1996, an international workshop on HNPCC hosted by the National Cancer Institute outlined a set of recommendations, known as the Bethesda guidelines, for the identification of individuals with HNPCC who should be tested for MSI and/or genetic testing[6]. More recently, a second HNPCC workshop revised these criteria and proposed a new set of recommendations, the revised Bethesda guidelines[7].

As it was previously mentioned, tumor MSI is a phenotypic indicator of defective DNA mismatch repair[8]. The fact that more than 90% of HNPCC-related cancers exhibit MSI suggests that screening of tumors for MSI may be an efficient way of selecting individuals for HNPCC genetic testing[9-12]. On the other hand, most mutations in either *MSH2* or *MLH1* genes result in abnormal MSH2 or MLH1 protein expression[13,14]. As a consequence, immunostaining for these two proteins is associated with MSI[15,16], but this association is not without exceptions[17]. Indeed, a mutant protein product can be expressed and detected by immunostaining[18],

whereas germline mutations may occur in patients with MSI-negative tumors[19]. These conflicting results have precluded the establishment of a unique method for primary screening of mismatch repair deficiency.

Recently, the Epicolon study, a prospective, multicenter, nation-wide survey aimed at assessing the incidence and characteristics of hereditary and familial CRC in Spain[20], has demonstrated that the revised Bethesda guidelines constitute a very useful approach to select patients at risk for HNPCC[21]. Moreover, in patients fulfilling these criteria, both MSI testing and protein immunostaining were equivalent and highly cost-effective strategies to further select those patients who should be tested for *MSH2/MLH1* germline mutations. Considering this equivalence and the fact that immunostaining is more available than DNA analysis in a clinical setting, the use of immunohistochemistry may contribute to identify a larger proportion of patients with Lynch syndrome[21,22].

The combination of revised Bethesda guidelines with tumor molecular analysis, however, is not fully accepted since some gene mutation carriers do not fulfill these clinical criteria[23]. To overcome this limitation, a massive, universal tumor mismatch repair screening by MSI analysis and/or immunostaining in any given CRC patient has been proposed[23,24]. Nevertheless, this approach is much less efficient[21], a critical issue that could be somehow solved by improving tumor molecular analysis. In that sense, it has been recently demonstrated that the use of two microsatellite markers (combination of BAT25 or BAT26 with NR21 or NR24) performed as well as the entire pentaplex of mononucleotide repeats (BAT26, BAT25, NR21, NR22, and NR24 markers) and better than the recommended panel by the National Cancer Institute (BAT26, BAT25, D5S346, D2S123, and D17S250 markers) in identifying mismatch repair deficient tumors[25]. Similarly, the introduction of BRAF V600E mutation analysis as a step prior to germline gene testing in patients with mismatch repair deficiency improves the cost-effectiveness of this approach, especially in those with incomplete or unknown family history[26,27].

On the other hand, the revised Bethesda guidelines have also been criticized because of their broad and complex variables, their relatively low specificity, and their inability to establish the likelihood of carrying a mutation in a given patient[24,28]. In addition, the need of performing tumor molecular analyses in patients fulfilling these criteria by some means constitutes a restriction since tissue samples are not always available. In that sense, as in hereditary breast-ovarian cancer syndrome in the past, identification of Lynch syndrome is moving toward complex algorithms and multivariable models combining personal and family history[28-31].

The first approach to this goal was the Leiden model[29], a regression logistic model derived from CRC patients attended in a high-risk clinic and designed to identify *MLH1/MSH2* mutation carriers, which has represented the only predictive model for years. Variables included in this model were fulfillment of the Amsterdam criteria, mean age of CRC diagnoses, and presence of any endometrial cancer in the family. However, it still included rather complex variables, it was developed using a relatively small population in a high-risk setting, and it did not take into account tumor molecular.

More recently, a second model was developed in the United Kingdom in a large population-based cohort of early onset (< 55 years) CRC patients[30] and consists of two consecutive stages: stage 1, based exclusively on clinical variables (age, sex, tumor location, presence of synchronous or metachronous CRC, family history of colorectal and endometrial cancer, and age of the youngest relative with CRC) and available on the web[32]; and stage 2, based on tumor MSI or immunostaining data. The area under the ROC curve of this model, which predicts MLH1, MSH2 and MSH6 germline mutations, was 0.82 (95% CI, 0.72-0.91). However, its applicability to CRC patients older than 55 years or those with other Lynch syndrome-associated tumors has not been assessed yet[30].

The third approach is a Mendelian model for determining *MLH1*, *MSH2* and *MSH6* carrier probabilities based on published estimates of mutation frequencies and cancer penetrances in both mutation and non-mutation carriers, and including MSI data[31]. This Bayesian model uses the CancerGene software[33] and provides the likelihood of finding a mutation in both probands and relatives on the basis of clinical and molecular information (age at diagnoses of colorectal and endometrial cancer, age of healthy relatives, MSI analysis and genetic testing). The area under its ROC curve was 0.83 (95% CI, 0.78-0.88). The performance of this model on clinical practice and different population settings is still unknown[31].

Finally, the PREMM1,2 model (accessible at the Dana-Farber Cancer Institute web site[34]) has demonstrated an excellent ability to discriminate between risk groups (area under the ROC curve of 0.80; 95% CI, 0.76-0.84), categorized by the estimated risk for probability of a mutation[28]. This study provides a new model based on a logistic regression analysis from one of the largest cohorts published so far of patients at-risk for hereditary CRC with proved mutation in the *MSH2/MLH1* genes. The authors recommend using their model as an initial assessment for individuals at risk for this disorder, before molecular information is available to the clinician. Based on the risk estimate generated from the model and other factors (accessibility to genetic services, timelines of genetic information, insurance coverage, and availability of tumor block), the clinician may choose whether genetic evaluation should be pursued as well as the approach to testing (MSI analysis and/or immunostaining, versus direct germline testing)[28]. The model does not include tumor molecular data to further refine the estimated probability nor takes into account *MSH6* gene mutations, although updates of the model are planned.

In summary, at the beginning of the 21st century, there is no unique, universally accepted strategy for the identification of Lynch syndrome. However, the tremendous advanced experiences in recent years allow us to be optimistic. Indeed, besides the fact that ongoing investigations may eventually elucidate the most effective and efficient approach to select individuals for HNPCC gene testing, the attention paid by the whole medical

community to this disease in the last decade will definitely contribute to make Lynch syndrome recognition more widely accessible.

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