Editorial

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Prediction of New Cancer in Patients with Lynch Syndrome Based on Mutation Patterns

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Editorial

Lynch syndrome (LS), previously referred to as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant disorder caused by a defect in one of the DNA mismatch repair (MMR) genes-MSH2, MLH1, PMS2 or MSH6. Patients with LS suffer from early onsets of cancer, including colorectal cancer, endometrial cancer, and others. With improvements to screening and surveillance, the life expectancy of LS patients has been greatly prolonged. However, this has created a new situation since the long-term prevalence of a second cancer in aged LS patient remains unclear. In a recent report [1], the European Hereditary Tumor Group (Mallorca Group) published data on the cumulative lifetime incidence of cancer in LS patients with long-term follow-up. A total of 3119 patients (1723 females and 1396 males) were included, and a total of 24,475 cumulative years were analyzed. The authors calculated the cumulative lifetime incidence of various cancer types in patients from 25 to 75 years old. We have adapted and summarized the cumulative incidence in **Table 1**.

Table 1 Cumulative incidence of cancers up to 75-year-old patients with LS.

	Cumulative incidence (% (95% CI))			
Organ	**MLH1**	**MSH2**	**MSH6**	**PMS2**
Any cancer	75.8 (68.5 to 83.2)	80.4 (69.8 to 90.9)	60.9 (42.7 to 79.0)	52.1 (0.1 to 100.0)
Colorectal cancer	45.8 (37.8 to 53.9)	43.0 (33.2 to 52.8)	15.0 (3.3 to 26.6)	0
Gynecologic cancer	49.8 (40.5 to 59.0)	65.7 (52.2 to 79.1)	54.0 (34.6 to 73.4)	26.4 (0.8 to 51.9)
Upper gastrointestinal tract cancer	21.4 (15.6 to 27.1)	10.2 (4.1 to 16.3)	6.6 (0 to 14.8)	0
Urinary tract	8.0 (4.3 to 11.7)	24.9 (16.6 to 33.2)	11.0 (1.7 to 20.3)	0

As LS has been increasingly acknowledged by practitioners and researchers, the disease prognosis has been greatly improved, and many patients with LS survive to their old age. As such, LS patients may develop a second cancer over time. This study helps to predict new cancer development in LS patients, which can facilitate the implementation of an appropriate follow-up and screening plan based on the specific gene mutation. The number of patients with a PMS2 mutation was low, as PMS2 mutations account for only up to 6% of LS families [2]. Therefore, the calculated 95% CI for these patients was unusually wide (for instance, 0.1 to 100). The authors had also calculated the survival rates after the occurrence of a second cancer in LS patients. However, the cohort size for prognosis data was relatively small, and should therefore be carefully interpreted.

As cancer is a consequence of an interaction between genetic and environmental factors, environmental elements should be considered in an epidemiology study. This report did not include the effects of the environment. If researchers can identify risk factors from the environment, LS patients would then be able to avoid those factors to reduce their cancer risk, which could be a future direction to study the epidemiology of LS. For instance, the CAPP2 randomized control trial [3] indicated that aspirin (600 mg per day for a mean of 25 months) reduced cancer incidence in LS gene carriers, highlighting that chemical interventions have the potential to prevent or postpone the onset of cancer in LS patients or

carriers. However, it still remains unclear if chemoprevention is feasible for secondary cancers in LS patients. It would be useful to build a guideline for cancer prevention after the first cancer is cured in LS patients, if a similar trial can be run in this unique population.

It has been suggested that carriers of mutated MMR genes should be routinely screened for colon, uterine, ovarian, and other cancers. For instance, it is recommended that LS patients should receive a screening colonoscopy at least every 2 years beginning between 20 and 25 years old [4]. It is unknown how to schedule a screening plan for LS survivors based on the specific gene mutation, or how to predict the location of a metachronous tumor. Meanwhile, cost-effectiveness and risk-benefit should be considered and leveraged for each individual patient. It would be impactful if future studies could be performed to design a follow-up plan for LS survivors.

A retrospective analysis of 315 females with MMR mutations [5] indicated that woman with prophylactic gynecologic surgery did not subsequently develop cancer, whereas woman without surgery had a 33% and 5.5% incidence of uterine and ovarian cancer, respectively. A cost-effectiveness model [6] comparing gynecologic screening and prophylactic gynecologic surgery in 30-year-old female LS patients indicated that prophylactic surgical treatments had a lower cost and lead to a higher quality of life. These data highlight the value of prophylactic surgery to prevent gynecologic cancers in female LS patients. However, whether prophylactic gynecologic surgery is also valuable for a second incidence of cancer in LS patients who survive the first cancer still requires further trials. According to the significance of the previous studies, it is worthy to investigate the value of prophylactic surgery in female LS patients who survive the first cancer based on the MMR mutation type.

LS results from a total loss of DNA MMR function in alleles inherited from unaffected parents. Thus, LS falls into a Mendelian dominant inheritance profile. Therefore, a question emerges: can we prevent LS through preconception care? Carrier screening is a valuable tool to identify prospective parents who are carriers. Another procedure for parents who are both carriers of MMR mutations is preimplantation genetic diagnosis, which detects the embryonic genotype in order to select mutation-free embryos. Therefore, it is possible that the medical community can stop the inheritance of mutated MMR genes.

In brief, work form the Mallorca Group extends our understanding for LS patients who have a long survival following a cure of the first cancer. However, in order to provide better care to this unique population, further investigations are warranted.

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