Causes of Cancer Death Among First-Degree Relatives in Japanese Families with Lynch Syndrome

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Abstract. *Aim: To elucidate the causes of cancer death in Japanese families with Lynch syndrome (LS). Methods: The distributions of cancer deaths in 485 individuals from 67 families with LS (35, 30, and two families with MutL homologue 1 (MLH1), MSH2, and MSH6 gene mutations, respectively), obtained from the Registry of the Japanese Society for Cancer of the Colon and Rectum were analyzed. Results: Among 98 cancer deaths of first-degree relatives of unknown mutation status, 53%, 19%, 13% (among females), 7% (among females) and 5% were due to colorectal, gastric, uterine, ovarian, and hepatobiliary cancer, respectively. The proportion of deaths from extra-colonic cancer was significantly higher in families with MSH2 mutation than in those with MLH1 mutation (p=0.003). Conclusion: In addition to colonic and uterine cancer, management and surveillance targeting gastric, ovarian and hepatobiliary cancer are considered important for Japanese families with LS. Extra-colonic cancer in families with MSH2 mutation might require for more intensive surveillance.*

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Lynch syndrome (LS) is an autosomal dominant inherited disease caused by a germline mutation in one of the mismatch repair genes, namely MutL homologue 1 (*MLH1*), *MSH2, MSH6*, or *PMS2* (1), and is the most common

Table I. *Clinical background of the family members of Japanese patients with Lynch syndrome.*

	Probands	First-degree relatives[a]	Total
Number of individuals	67 (31:36)	418 (221:197)	485 (252:233)
Median age (range) at last follow-up, years	55 (26-84)	52 (0-93)	53 (0-93)
Mutation of the family			
MLH1	35 (17:18)	229 (131:98)	264 (148:11)
MSH2	30 (14:16)	175 (84:91)	205 (98:107)
MSH6	2 (0:2)	14 (6:8)	16 (6:10)
Cancer development			
Yes	67 (31:36)	135 (80:55)	202 (111:91)
No	0	283 (141:142)	283 (141:142)
Cancer death			
Yes	4 (2:2)	98 (54:44)	102 (56:46)
No	63 (29:34)	320 (167:153)	383 (196:187)

Unless otherwise specified, the data are presented as n (males:females). *MLH1*: MutL homologue 1; *MSH2*/*MSH6*: MutS protein homolog 2/MutS protein homolog 6. [a]Mutation status unknown.

hereditary colorectal cancer (CRC) syndrome, accounting for approximately 2-4% of all CRC cases (2). The lifetime risk of CRC has been estimated to range from 25% to 70% (2, 3), and the main clinical features of hereditary CRC include an early age of onset and the occurrence of multiple cancers. Moreover, patients with LS have also been reported to have increased risk for extra-colonic cancer such as endometrial, gastric, ovarian, small bowel, urinary tract, hepatobiliary tract, pancreatic and brain cancer, as well as sebaceous gland adenomas/carcinomas and keratoacanthomas (4).

While several studies have demonstrated the lifesaving benefits of endoscopic surveillance in patients with LS with regards to CRC risk (5), the benefits of surveillance for extra-colonic cancer have not yet been determined, and there is currently no consensus on the optimal surveillance recommendations for such cancer. Since cancer morbidity and mortality depend on various factors such as the cancer type, geographic location, ethnicity, lifestyle (6), stage at diagnosis, treatment, and the surveillance strategy employed (7), information on cancer deaths in each geographic region is essential for the management of families with LS. The vast majority of previous reports on LS have been derived from data of Caucasian patients in Western countries (7, 8), whereas very few studies on cancer deaths in LS to date have been reported from Japan or other Asian countries. Accordingly, the aim of this study was to elucidate the distributions of cancer deaths by body site among individuals from Japanese families with LS.

Patients and Methods

Families, samples, and data collection. This nationwide Japanese study was conducted by the Hereditary Non-Polyposis Colorectal Cancer Registry and Genetic Testing Project of the Japanese Society for Cancer of the Colon and Rectum between September 2002 and July 2010. To determine patient eligibility, a modified version of the Amsterdam II criteria was used, in which gastric cancer was included as an extra-colonic cancer. All probands provided written informed consent to participate in the study. Clinical information of LS families, which included mutation-positive probands and first-degree relatives (FDRs) of proven mutation carriers with unknown mutation status, was collected either from medical records or directly from probands who were provided genetic counseling. These clinical data included the cancer site, age at cancer diagnosis, and cancer-specific death. The distributions of cancer deaths by site among the individuals of families with LS were analyzed.

Germline mutation analysis. DNA extraction and mutation analysis were conducted as previously described (9). Briefly, genomic DNA was extracted from peripheral blood samples using the standard phenol extraction/purification procedure. Germline mutation analyses were performed with direct sequencing of the entire coding regions in the *MLH1, MSH2*, and *MSH6* genes. Large deletions/duplications in the *MLH1* and *MSH2* genes were also investigated by multiplex ligation-dependent probe amplification and long-range polymerase chain reaction.

Statistical analysis. Data are presented as the total values or medians (range). The FDRs were divided into three groups according to the mismatch repair mutations in the family. The proportions of extra-colonic cancer deaths were compared between families with *MLH1* and those with *MSH2* mutations. The differences were analyzed using the Chi-square test. All statistical analyses were carried out using JMP 10.0.2 (SAS Institute, Cary, NC, USA), with p-values less than 0.05 considered statistically significant.

Results

A total of 125 probands with CRC were eligible for inclusion in the study, of whom 67 were identified to have LS (35, 30, and two probands with *MLH1, MSH2*, and *MSH6* mutations, respectively). The median age of the 67 probands at the last

Table II. *Cancer distributions in Japanese families with Lynch syndrome*.

Cancer site	Probands				First-degree relatives[a]			
	MLH1	*MSH2*	*MSH6*	Total (%)	*MLH1*	*MSH2*	*MSH6*	Total (%)
Colorectal	35	30	2	67 (69%)	63	36	6	105 (54%)
Gastric	6	2	-	8 (8%)	17	18	1	36 (18%)
Uterine[b]	4	2	1	7 (14%)[c]	13	9	2	24 (22%)[c]
Ovary	1	-	-	1 (2%)[c]	2	1	-	3 (3%)[c]
Hepatobiliary	1	-	-	1 (1%)	2	2	1	5 (3%)
Brain	-	-	-	-	1	3	-	4 (2%)
Breast	1	1	-	2 (2%)	1	2	-	3 (2%)
Ureter	-	3	-	3 (3%)	-	2	-	2 (1%)
Urinary bladder	-	2	-	2 (2%)	1	1	-	2 (1%)
Pancreas	-	-	-	-	2	1	-	3 (2%)
Thymus	-	-	-	-	1	1	-	2 (1%)
Lung	-	1	-	1 (1%)	1	1	-	2 (1%)
Skin	-	-	-	-	-	2	-	2 (1%)
Small intestine	-	2	-	2 (2%)	-	1	-	1 (0.5%)
Maxillary	-	-	-	-	1	-	-	1 (0.5%)
Prostate	-	1	-	1 (2%)[d]	-	-	-	-
Kidney	1	-	-	1 (1%)	-	-	-	-
Thigh[e]	-	1	-	1 (1%)	-	-	-	-
Unknown	-	-	-	-	-	1	-	1 (0.5%)
Total	49	45	3	97	105	81	10	196

MLH1: MutL homologue 1; *MSH2*/*MSH6*: MutS protein homolog 2/MutS protein homolog 6. [a]Mutation status unknown; [b]Developed seven cases of endometrial cancer, whereas the first-degree relatives developed two, seven, and 15 cases of cervical, endometrial, and non-specified uterine cancer, respectively; [c]among females; [d]among males; [e]liposarcoma.

Table III. *Causes of cancer death among first-degree relatives in Japanese families with Lynch syndrome*.

Cancer site	*MLH1*[a] n=51	*MSH2*[a] n=39	*p*-Value	*MSH6*[a] n=8	Total n=98	Median age (range) at cancer death, years
Colorectal	33 (65%)	13 (33%)		6 (75%)	52 (53%)	48 (22-74)
Extra-colonic	18 (36%)	26 (67%)	0.003[b]	2 (25%)	46 (47%)	
Gastric	8 (16%)	11 (28%)		-	19 (19%)	51.5 (36-83)
Uterine	1 (5%)	4 (20%)[c]		1 (25%)[c]	6 (13%)[c]	50 (35-62)
Ovary	2 (10%)[c]	1 (5%)[c]		-	3 (7%)[c]	44 (41-46)
Hepatobiliary	2 (4%)	2 (5%)		1 (25%)	5 (5%)	65 (53-88)
Brain	1 (2%)	3 (8%)		-	4 (4%)	44 (17-76)
Lung	1 (2%)	1 (3%)		-	2 (2%)	77 (70-84)
Pancreatic	1 (2%)	1 (3%)		-	2 (2%)	68
Maxillary	1 (2%)	-		-	1 (1%)	57
Breast	-	1 (3%)		-	1 (1%)	80
Small intestinal	-	1 (3%)		-	1 (1%)	54
Urinary bladder	1 (2%)	-		-	1 (1%)	44
Unknown[d]	-	1 (3%)		-	1 (1%)	-

MLH1: MutL homologue 1; *MSH2*/*MSH6*: MutS protein homolog 2/MutS protein homolog 6. [a]First-degree relatives of unknown mutation status; [b]comparison of the proportions of extra-colonic cancer deaths between families with *MLH1* and *MSH2* mutations; [c]among females; [d]not colorectal cancer.

follow-up was 55 years (range=26-84 years). Among the 67 families with LS, 418 FDRs of unknown mutation status were noted (median age at the last follow-up=52 years). All 67 probands developed cancer, while four died of cancer during the study period; of the 418 FDRs, 135 and 98 developed and died of cancer, respectively (Table I).

Table II shows the cancer distribution in the probands and FDRs in the families with LS. All 67 probands developed

one or more carcinomas, with a total of 97 individual carcinomas noted. Among the 97 carcinomas in the probands, 69%, 8%, and 14% (among females) were colorectal, gastric, and uterine, respectively. Among the 418 FDRs, 135 individuals developed one or more carcinomas, with a total of 196 recorded. Among the 196 carcinomas in the FDRs, 54%, 18%, 22% (among females), 3% (among females), and 3% were colorectal, gastric, uterine, ovarian, and hepatobiliary cancer, respectively. With regard to uterine cancer, the probands developed seven cases of endometrial cancer, whereas the FDRs developed two, seven, and 15 cases of cervical, endometrial, and non-specified uterine cancer, respectively.

Next, the probands and FDRs were analyzed for the causes of cancer death. Among the four probands who died, two, one, and one died due to colorectal, hepatobiliary, and lung cancer, respectively. Since cancer deaths among the probands were rare during the study period, we instead focused on the cancer deaths among the FDRs. Among the 98 FDRs who died, 53%, 19%, 13% (among females), 7% (among females) and 5% of deaths were due to colorectal, gastric, uterine, ovarian, and hepatobiliary cancer, respectively. The proportion of extra-colonic cancer deaths in the FDRs was significantly higher in families with the *MSH2* mutation than in those with the *MLH1* mutation (p=0.003). The median age at the times of cancer death was 48 years (range=22-74) for CRC, 51.5 years (range, 36-83) for those with gastric cancer, and 50 years (range=35-62) for those with uterine cancer (Table III).

Discussion

For the management of patients with LS, determination of the risk of cancer mortality of LS is crucial. The present study showed that colorectal, uterine, and gastric cancer are the most common types of cancer in these families, representing approximately 80% of all cancer deaths in Japanese families with LS. Our results of high morbidity and mortality of colorectal and uterine cancer in Japanese LS are consistent with previous reports from Western countries (7, 8). Colon surveillance for LS is recommended and is backed-up by robust evidence (3, 5, 10). Colonoscopic surveillance starts between 20-25 years of age and is repeated at 1- to 2-year intervals (3, 10). While the usefulness of endometrial surveillance for LS lacks solid evidence, nevertheless, regular endometrial sampling and transvaginal ultrasound are also recommended for women with LS for the prevention or early diagnosis of cancer (3, 10).

Conversely, there are currently few recommendations or guidelines for upper gastrointestinal surveillance in this population, owing to the limited evidence supporting the effectiveness of such surveillance. The cancer spectrum in LS has been reported to depend on the background incidence of each cancer type (11), and there are significant differences in the incidence of gastric cancer in different geographic regions. In the general population, gastric cancer is more common in East Asia, South America, and Southern Europe compared to in North America, Northern Europe, and Northern Africa (12). In Western countries, individuals with LS are reported to have a 2-13% lifetime risk of gastric cancer (2), whereas in Japan and Korea, the lifetime risk of gastric cancer in LS is estimated at approximately 30% (9, 11). In Japan, in the general population, a case–control study and a cohort study reported that endoscopic screening for gastric cancer reduced the mortality (30-65%) (13, 14); endoscopic screening every 2 years has also been reported to increase the detection rate of early-stage gastric cancer (15). Hence, given the fact that surveillance for gastric cancer might be effective even in the general population, we believe that endoscopic screening for gastric cancer is likely even more effective in patients with LS, especially in the above-mentioned countries or regions with high prevalence of gastric cancer. Since the present study showed that the median age of gastric cancer death was 51.5 years (range=36-83 years), lifelong endoscopic surveillance for gastric cancer should be performed in families with LS.

The present study has several limitations which may affect the estimation of the impact of cancer mortality. Firstly, its retrospective design and small sample size: in particular for the FDRs, the number of patients with cancer with *MSH6* mutations was only eight and no data were available on *PMS2* mutations. Accordingly, owing to the low frequency as well as the high number of pseudogenes thereof, we did not analyze *PMS2* mutations in the present study. Secondly, there is a possibility of self-selection bias. We used a modified version of the Amsterdam II criteria to identify patients eligible for our study, in which gastric cancer was included as an extra-colonic cancer. The use of the modified criteria may lead to an overestimation of gastric cancer deaths in this case. Thirdly, FDRs are at 50% risk of being mutation carriers. Hence, our results might include data of cancer originating from both LS-related and sporadic cases. However, the median age at cancer death in the FDRs was ≥10 years younger than those for the general population. Specifically, the age at death from gastric cancer in the LS families was ≥20 years younger than those for the general population (73 years) (13), indicating that these cases were likely mainly LS-related rather than of sporadic origin. Nevertheless, further studies are needed to estimate the distribution of cancer deaths by site among individuals from LS families in Japan.

Despite these limitations, an advantage of this study was that our database included only LS families with proven mutations. Data of cancer deaths in LS families with proven mutations are very limited (8), and, to the best of our knowledge, this is the first study to investigate the causes of

cancer death in LS families from Asia. Hence, we believe that our results reflect the actual cancer spectrum of LS in the Japanese population and hope that our findings may help researchers and physicians better plan the management of patients with LS.

Conclusion

Based on our results, in addition to colonic and uterine cancer, management and surveillance targeting gastric, ovarian, and hepatobiliary cancer are considered important for families with LS in Japan. Extra-colonic cancer in families with *MSH2* mutation might require more intensive surveillance than in those with *MLH1* mutation.

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