Cancer Science
Japanese Cancer Association JCA
Open Access

Management strategies in Lynch syndrome and familial adenomatous polyposis: a national healthcare survey in Japan

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Key words

Disease management, familial adenomatous polyposis, Japanese, Lynch syndrome, screening

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Funding Information

Japan Society of Colorectal Cancer Research

Received August 16, 2016; Revised November 6, 2016; Accepted November 17, 2016

Cancer Sci **108** (2017) 243–249

doi: 10.1111/cas.13123

Lynch syndrome (LS) and familial adenomatous polyposis (FAP) are major sources of hereditary colorectal cancer (CRC) and are associated with other malignancies. There is some heterogeneity in management strategies in Japan. We undertook a survey of management of hereditary CRC in hospitals that are members of the Japan Society of Colorectal Cancer Research. One hundred and ninety departments responded, of which 127 were from designated cancer care hospitals (DCCHs) according to the Japanese government. There were 25 488 operations for CRC in these departments in 2015. The DCCHs performed better with regard to usage of Japan Society of Colorectal Cancer Research guidelines, referring new CRC patients for LS screening, and having in-house genetic counselors and knowledge of treatment for LS. There were 174 patients diagnosed with LS and 602 undergoing follow-up in 2011–2015, which is fewer than the number expected from CRC operations in 2015. These numbers were not affected by whether the institution was a DCCH. Universal screening for LS was carried out in 8% of the departments. In contrast, 541 patients were diagnosed with FAP and 273 received preventive proctocolectomy/colectomy in 2011–2015. The DCCH departments undertook more surgery than non-DCCH departments, although most of the management, including surgical procedures and use of non-steroidal anti-inflammatory drugs, was similar. Management of desmoid tumor in the abdominal cavity differed according to the number of patients treated. In conclusion, there was heterogeneity in management of LS but not FAP. Most patients with LS may be overlooked and universal screening for LS is not common in Japan.

Colorectal cancer is the second most common cancer in Japan, the third most common cancer in the USA, and one of the most common malignancies worldwide.[1–3] The hereditary forms of colorectal cancer (CRC) are considered to comprise 5% of all cases. Therefore, genetic testing and appropriate management are recommended.[4,5]

Lynch syndrome (LS), which is also known as hereditary non-polyposis CRC, is the most common form of hereditary CRC and is an autosomal dominant disorder caused by DNA MMR genes including *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[6,7] Most LS patients have MSI-H.[8] Lynch syndrome accounts for 2–4% of all CRCs in Western countries, although there are few data for LS in Japan.[4,5,9–12] The JSCCR published its guidelines in 2012 for the clinical management of hereditary CRC.[11] Diagnosis of LS is important because of the high risk of CRC and endometrial cancer, and increased risk of gastric, ovarian, urinary tract, and small bowel cancer in probands and their relatives because of chromosomal dominant heredity.[4,5,12] In the USA, the necessity of LS diagnosis has already been established and concern has shifted to THE cost-effectiveness of diagnosis.[13,14] At first, LS was screened by family history using the Amsterdam II and Revised Bethesda guidelines.[7,15] Then, many algorithms were proposed as screening methods to save time and money, although universal screening (MSI test and/or immunohistochemistry for MMR gene proteins) is considered the gold standard for diagnosis of LS.[16,17] Microsatellite instability is considered to be a useful biomarker for programmed death (PD)-1 antibody therapy in patients with advanced CRC and endometrial cancer.[18]

Familial adenomatous polyposis is a hereditary disease caused by mutations of *APC*.[4,5,10,18] All patients with FAP are considered to have had CRC at some point during their lifetime, unless they have received any treatment for adenomatous polyposis.[4,5,10,18] Therefore, follow-up by colonoscopy from the teenage years onwards and preventive proctocolectomy are recommended to patients and relatives with FAP.[4,5,11,19] The rare desmoid tumor is one of the common diseases that accompanies FAP.[5,19–22] Abdominal desmoid tumor is especially intractable because of its high recurrence rate after surgery.

Data about hereditary CRC in Japan are limited.[10,11] Our department has developed the surgical procedure of

proctocolectomy with hand-sewn ileal J-pouch anal anastomosis, and reported effective pharmacological management of advanced desmoid tumor using dacarbazine and doxorubicin.[23–25] Therefore, we undertook a questionnaire survey associated with hereditary CRC to establish the current situation for management of LS and FAP in Japan.

We also assessed the differences in management and knowledge of hereditary CRC by DCCHs and non-DCCHs to evaluate heterogeneity among the departments. Three hundred and ninety-nine DCCHs have been certified by the Japanese government in an attempt to eliminate cancer care disparities in Japan. Unlike university hospitals and cancer center hospitals located in big cities, DCCHs are distributed widely, even in local areas, and we considered them suitable to assess heterogeneity in the management of hereditary CRC in Japan.

Materials and Methods

Questionnaire. The questionnaire consisted of three sections. The first section was concerned with medical care systems for hereditary CRC (Table 1). The questions included: type of hospital, number of surgical procedures carried out for CRC in 2015, collection of family history details at first visit, the persons who collect the family history, presence of a genetic counselor in or near the hospital, and use of the JSCCR guidelines. The second section consisted of questions about LS (Table 2), including: consideration of new CRC patients to have LS, the number of LS patients undergoing follow-up, the number of LS patients with CRC undergoing follow-up, resection area (segmental or prophylactic colectomy/proctocolectomy),[26,27] simultaneous resection of uterus and bilateral ovaries and fallopian tubes during colorectal surgery in postmenopausal patients (preventive gynecological surgery),[28] use of 5-FU-based adjuvant chemotherapy,[29] prophylactic treatment with aspirin,[30] the number of patients with suspected LS in 2011–2015 who received counseling, MSI testing, or MMR gene sequencing, and were finally diagnosed with LS, knowledge about the usefulness of PD-1 antibody in clinical trials for treatment of advanced cancer in patients with MSI-H,[18] and practice of universal screening of new CRC patients. The last section consisted of questions regarding FAP (Table 3), including: number of FAP patients undergoing follow-up, number of FAP patients diagnosed in 2011–2015, number of patients receiving preventive surgery in 2011–2015 overall or by laparoscopic procedure,[31] whether the operation was carried out in their own hospital or elsewhere, surgical procedures, such as proctocolectomy or colectomy, proctocolectomy with hand-sewn or stapled ileal–anal anastomosis,[32,33] construction of pouch or not, type of pouch in case of pouch construction,[23,24,34] timing of operation, use of NSAIDs such as sulindac,[35] and number of patients with desmoid tumor in 2011–2015, type of desmoid tumor, and management.[20–22,36]

Data collection. We asked all departments that belonged to JSCCR to reply to the questionnaire from April 7 to May 13, 2016 using e-mail and letter. Questions could be answered using a website or by letter to the JSCCR office. Data submitted to the website were automatically recorded in Excel files and data received by post were inputted to the same files. One hundred and ninety departments (177 hospitals) out of 568 in JSCCR responded to the questionnaire. In detail, 184 of 418 surgical departments, six of 96 medical departments, and 0 of 39 pathology, seven radiology, and eight basic research departments responded.

Table 1. Medical care systems for patients with heriditary colorectal cancer in designated cancer care hospitals (DCCHs) and non-DCCHs in Japan

	Number of departments			*P*-value
	Total (%)	DCCH (n = 127)	Non-DCCH (n = 63)	
Type of hospital				
University hospital	88 (46)	73	15	**<0.0001**
Public hospital	69 (36)	46	23	
Private hospital	33 (17)	8	25	
Family history collection at first visit				
Yes	184 (97)	123	61	0.9900
No	6 (3)	4	2	
Who collects family history?				
Doctor	110 (58)	72	38	0.7100
Doctor and other staff	50 (26)	35	15	
Staff other than doctor	28 (15)	18	10	
Paper	2 (1)	2	0	
Existence of genetic counselor in hospital				
Yes	65 (34)	61	4	**<0.0001**
No	125 (66)	66	59	
Existence of genetic counselor near hospital				
Yes	136 (72)	94	42	0.2900
No	54 (28)	33	21	
Use of guidelines edited by JSCCR				
Yes	150 (79)	109	41	**0.0010**
No	40 (21)	18	22	

Bold values indicate significance. JSCCR, Japan Society of Colorectal Cancer Research.

Data analysis. The responses to the questions were counted or categorized depending on the type of questions. The results were further analyzed by χ^2-test or t-test to evaluate if the type of hospital (DCCH or not) influenced the answers. Responses related to desmoid tumor treatment were analyzed by logistic test to evaluate whether the number of patients influenced the answers. Statistical analysis was carried out using JMP version 11 (SAS Japan, Tokyo, Japan). $P < 0.05$ was considered significantly different.

Results

Medical care systems for hereditary CRC. The results of questions about medical care systems are listed in Table 1. Eighty-eight departments (46%) belonged to university hospitals and 127 (67%) departments were categorized as belonging to DCCHs. There were 25 488 surgical procedures for CRC in 2015 (Table 4). Family history details were collected at the first visit by most departments (97%) and collected by doctors alone (58%), doctors and other staff (26%), or staff other than doctors (15%). A counselor was present in only 34% of the hospitals. However, 72% of departments could consult genetic counselors near the hospital if necessary. Seventy-nine percent of departments used the JSCCR guidelines.

We analyzed the differences in medical care systems in DCCHs or non-DCCHs to evaluate the heterogeneity among the departments. There were significant differences between DCCHs and non-DCCHs for type of hospital ($P < 0.0001$), number of operations carried out in 2015 ($P < 0.0001$),

Table 2. Management associated with patients with Lynch syndrome (LS) in designated cancer care hospitals (DCCHs) and non-DCCHs in Japan

Questions about LS	Number of departments			*P*-value
	Total (%)	DCCH (n = 127)	Non-DCCH (n = 63)	
Consideration of LS to new CRC patients				
Yes	164 (86)	116	48	**0.004**
No	26 (14)	11	15	
Surgical procedure				
Same as sporadic CRC	108 (58)	74	34	0.790
Preventive proctocolectomy or colectomy	19 (9)	13	6	
No comment	63 (33)	40	23	
Recommendation of preventive gynecological surgery				
Yes	35 (18)	19	16	**0.007**
No	109 (57)	83	26	
No comment	46 (24)	25	21	
Adjuvant setting by 5-fluorouracil				
Yes	125 (66)	91	34	**0.009**
No	21 (11)	15	6	
No comment	44 (23)	21	23	
Chemical prevention by aspirin				
Yes	6 (3)	4	2	**0.030**
No	140 (74)	101	39	
No comment	44 (23)	22	22	
Practice of universal screening for LS				
Yes	15 (8)	14	1	**0.020**
No	175 (92)	113	62	
Usefulness of PD-1 antibody				
Known	127 (67)	91	36	**0.046**
Not known	63 (33)	36	27	

Bold values indicate significance. CRC, colorectal cancer; PD-1, programmed death-1.

Table 3. Management associated with patients with familial adenomatous polyposis (FAP) in designated cancer care hospitals (DCCHs) and non-DCCHs in Japan

Questions about FAP	Number of departments			*P*-value
	Total (%)	DCCH (n = 127)	Non-DCCH (n = 63)	
Place of surgery				
Own hospital	164 (86)	117	47	**0.0009**
Another hospital	26 (14)	10	16	
Resection area				
Proctocolectomy	136 (72)	97	39	0.0600
Colectomy	27 (14)	17	10	
No reply	27 (14)	13	14	
Anastomosis in case of proctocolectomy				
Handsewn ileal–anal anastomosis	95 (50)	63	32	0.1900
Stapled ileal–anal anastomosis	64 (34)	47	17	
No reply	31 (16)	17	14	
Pouch construction in case of proctocolectomy				
Yes	152 (80)	106	46	0.1700
No	9 (5)	6	3	
No reply	29 (15)	15	14	
Type of pouch in case of pouch construction				
J	150 (99)	104	46	0.6400
J or W	1 (1)	1	0	
W	1 (1)	1	0	
Recommendation of operation at diagnosis				
Yes	44 (23)	29	15	0.8800
No	146 (77)	98	48	
Timing of operation depending on patient's lifestyle				
Yes	184 (97)	123	61	0.9900
No	6 (3)	4	2	
Use of NSAID as chemoprevention drug				
Yes	81 (43)	58	23	0.2000
No	108 (57)	69	39	
No reply	1 (1)	0	1	
Main treatment for desmoid in abdominal wall				
Resection	125 (66)	91	34	**0.0460**
No resection, drug	27 (14)	16	11	
Introduction to the other hospitals	17 (9)	7	10	
No reply	21 (11)	13	8	
Main treatment for desmoid in abdominal cavity				
Resection	118 (62)	82	36	**0.0300**
No resection, drug	33 (17)	25	8	
Introduction to other hospitals	16 (8)	6	10	
No reply	23 (12)	14	9	

Bold values indicate significance. NSAID, non-steroidal anti-inflammatory drug.

presence of a genetic counselor ($P < 0.0001$), and use of JSCCR guidelines ($P = 0.001$). However, there was no significant difference in collection of family history details and presence of a genetic counselor near the hospital. These results indicated that most of the departments could consult a genetic counselor if necessary.

Management of patients with LS. The results of questions about LS are listed in Tables 2,4. New CRC patients were considered to have LS in 86% of the departments. There were 602 LS patients undergoing follow-up, 464 LS patients with CRC undergoing follow-up, 1443 suspected LS cases in 2011–2015, and 174 patients diagnosed with LS in 2011–2015 (Table 4). The medians of these numbers were 0, except for suspected LS patients, for which the median was 1 (Table 4). These numbers seemed low compared with the number of surgical procedures for CRC. Nine percent of departments undertook preventive proctocolectomy/colectomy and 18% of departments recommended preventive gynecological surgery with CRC surgery to postmenopausal women.[26–28] Eleven percent of departments did not use 5-FU-based adjuvant chemotherapy, which implies knowledge about the ineffectiveness of 5-FU-based adjuvant chemotherapy for CRC in patients with MSI-H.[29] Three percent of departments used aspirin for prevention of CRC, which implies knowledge of the report by Burn *et al.*,[30] although the recommendation for chemoprophylaxis has not been certified yet. Universal screening was carried out in only 8% of the departments. The usefulness of PD-1 antibody in clinical trials against CRC in patients with MSI-H, including LS, was known to 67% of departments.[18]

We analyzed the difference in management and knowledge of LS between DCCHs and non-DCCHs. There was a significant difference between DCCHs and non-DCCHs in considering that new CRC patients had LS ($P = 0.004$). However,

Table 4. Number of patients assessed in this study

	Number of patients			*P*-value
	Total	DCCH	Non-DCCH	
CRC surgery in 2015				
Median (range)	120	135 (2–663)	90 (0–229)	**<0.0001**
Total	25 488	19 362	6126	
LS				
Under follow-up				
Median (range)	0	0 (0–114)	0 (0–20)	0.1900
Total	601	493	108	
With CRC under follow-up				
Median (range)	0	0 (0–89)	0 (0–18)	0.2100
Total	464	382	82	
Suspected in 2011–2015				
Median (range)	1	1 (0–465)	0 (0–44)	0.1400
Total	1634	1443	191	
Receiving genetic counselling				
Median (range)	0	0 (0–459)	0 (0–18)	0.2500
Total	925	880	45	
Receiving MSI test				
Median (range)	0	0 (0–278)	0 (0–17)	0.1900
Total	732	676	56	
Receiving sequencing				
Median (range)	0	0 (0–48)	0 (0–4)	**0.0260**
Total	326	302	24	
Diagnosed in 2011–2015				
Median (range)	0	0 (0–30)	0 (0–7)	0.4300
Total	174	138	36	
FAP				
Under follow-up				
Median (range)	2	3 (0–118)	0 (0–150)	0.0900
Total	1232	968	264	
Diagnosed in 2011–2015				
Median (range)	1	2 (0–46)	0 (0–14)	**0.0030**
Total	541	462	79	
Diagnosed by sequencing				
Median (range)	0	0 (0–22)	0 (0–5)	**0.0390**
Total	152	131	21	
Preventive surgery in 2011–2015				
Median (range)	0	1 (0–16)	0 (0–9)	**0.0090**
Total	273	223	50	
By laparoscopic surgery				
Median (range)	0	0 (0–12)	0 (0–5)	**0.0020**
Total	215	184	31	
Desmoid in all areas				
Median (range)	0	0 (0–7)	0 (0–5)	0.1400
Total	129	99	30	
Desmoid in abdominal wall				
Median (range)	0	0 (0–4)	0 (0–3)	0.3500
Total	46	11	35	
Desmoid in abdominal cavity				
Median (range)	0	0 (0–7)	0 (0–4)	**0.0380**
Total	104	83	21	

Bold values indicate significance. CRC, colorectal cancer; DCCH, designated cancer care hospital; FAP, familial adenomatous polyposis; LS, Lynch syndrome; MSI, microsatellite instability.

there was no significant difference between DCCHs and non-DCCHs in the number of patients assessed for LS, except for the number receiving MMR gene sequencing (Table 4). There were significant differences between DCCHs and non-DCCHs in recommendation of preventive gynecological surgery ($P = 0.007$), knowledge of 5-FU-based adjuvant chemotherapy ($P = 0.009$), aspirin chemoprophylaxis ($P = 0.03$), and usefulness of PD-1 antibody for MSI-H patients, including those with LS ($P = 0.046$), and universal screening ($P = 0.02$). In 2011–2015, only 174 of 1635 suspected patients were diagnosed with LS, although the method of diagnosis of LS differed between DCCHs and non-DCCHs (Fig. 1a). In DCCHs, 126 of 138 patients were diagnosed with LS by sequencing of MMR genes. However, in non-DCCHs, 26 of 36 patients were diagnosed with LS by methods other than sequencing of MMR genes.

FAP management. The results of questions about FAP are listed in Tables 3,4. A total of 1232 FAP patients were followed up, 541 were newly diagnosed as FAP, and 273 received preventive proctocolectomy/colectomy in 2011–2015. Medians of these patients were 2, 1, and 0, respectively. However, 86% of departments replied that they carried out preventive surgery in their own hospitals. The responses to questions about surgical procedures were as follows: proctocolectomy (72%) or colectomy (14%), proctocolectomy with hand-sewn (50%) or stapled (34%) ileal–anal anastomosis, ileal pouch construction (80%) or not (5%) in case of proctocolectomy, and J-pouch construction in cases of pouch construction (99%). Lack of response to questions about these surgical procedures indicated departments where the surgery was undertaken elsewhere. Although 23% of departments recommended proctocolectomy soon after diagnosis of FAP, the operation was usually postponed to meet the patients' requirements. Non-steroidal anti-inflammatory drugs were used for chemoprophylaxis in 43% of departments.

One hundred and twenty-nine FAP patients had desmoid tumors. Forty-six patients had desmoid tumors in the abdominal wall and 104 had desmoid tumors in the abdominal cavity. Seventy-four percent and 71% of departments managed desmoid tumor by resection, with or without other treatment in cases involving the abdominal wall and abdominal cavity, respectively.

We analyzed the difference in management of FAP between DCCHs and non-DCCHs. There were significant differences between DCCHs and non-DCCHs for the numbers of patients who were diagnosed with FAP ($P = 0.003$), received preventive surgery ($P = 0.009$), received preventive laparoscopic surgery ($P = 0.002$), and were diagnosed by sequencing of the *APC* gene in 2011–2015 ($P = 0.039$; Table 4). There was a significant difference between DCCHs and non-DCCHs in terms of performing surgeries in their own hospital or elsewhere (Table 3; $P < 0.0009$). However, there was no significant difference between the hospitals for surgical procedures, including proctocolectomy or colectomy, proctocolectomy with hand-sewn or stapled ileal–anal anastomosis, and pouch construction, or chemoprophylactic use of NSAIDs. There was no significant difference in the number of desmoid tumors, regardless of the location, although there was a significant difference in the treatment of desmoid tumors ($P = 0.046$ in abdominal wall, $P = 0.03$ in abdominal cavity) (Table 3). We further analyzed the treatment selection according to the number of patients (Fig. 2). Although there was no significant difference in the treatment of abdominal wall desmoid tumors (Fig. 2a,b), there was a significant association between the number of patients and treatment of abdominal cavity desmoid tumors (Fig. 2c,d). This difference was shown in DCCHs ($P < 0.0001$) but not in non-DCCHs ($P = 0.36$) (Fig. 2c,d).

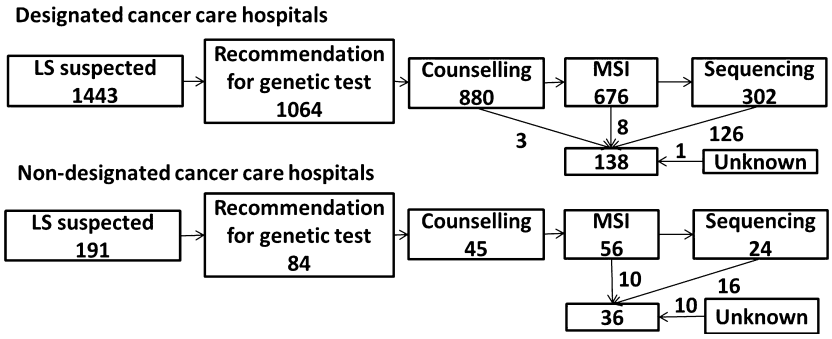

Fig. 1. Flow chart from suspected Lynch syndrome (LS) to diagnosis of LS in designated cancer care hospitals (DCCHs; upper chart) or non-DCCHs (lower chart) in Japan. Upper chart, 138 patients were diagnosed with LS in 2011–2015, mainly by mismatch repair gene sequencing in DCCHs. Lower chart, in non-DCCHs in 2011–2015, 36 patients were diagnosed with LS by methods other than sequencing. MSI, microsatellite instability.

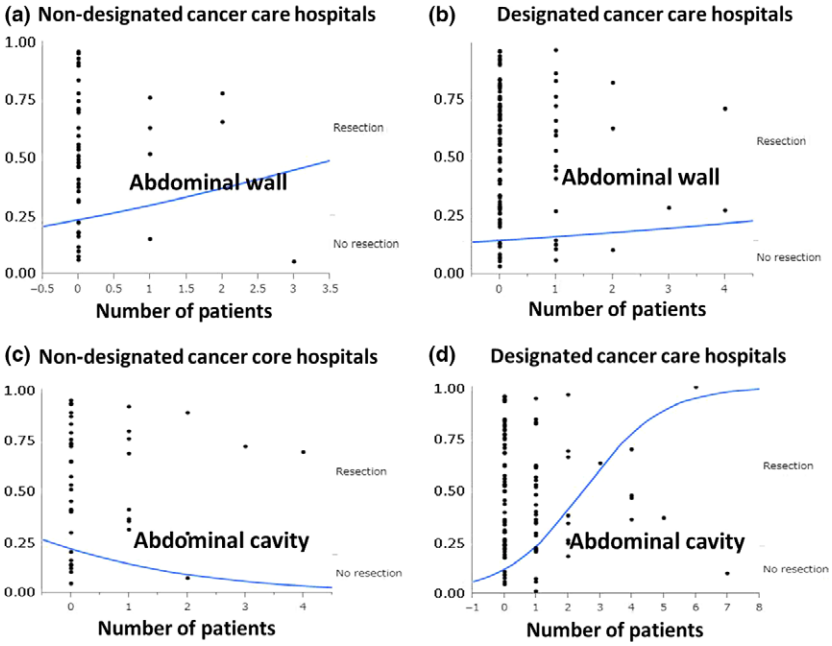

Fig. 2. Logistic analysis between desmoid tumor treatment (resection or no resection) and number of desmoid tumor patients with familial adenomatous polyposis treated at designated cancer care hospitals (DCCHs) or non-DCCHs in Japan. (a,b) Analysis of treatment decisions for abdominal wall desmoid tumor at non-DCCHs (a) and DCCHs (b). (c,d) Analysis of treatment decisions for abdominal cavity desmoid tumor at non-DCCHs (c) and DCCHs (d).

Discussion

To the best of our knowledge, this is the first report regarding the status of hereditary CRC management in Japanese hospitals. Although this was a retrospective study by questionnaire, our data indicate the problems of management of hereditary CRC in Japan.

The JSCCR consists of doctors who specialize in CRC, including surgeons, physicians, pathologists, radiologists, and basic researchers. We found that 25 488 CRC patients underwent surgery in 2015. This corresponded to ~20% of the total number of CRC patients in Japan, which is estimated at 130 000.

The presence of a genetic counselor was not common, even in DCCHs (Table 1). However, if necessary, the patients could be introduced to a counselor near the hospital and the JSCCR guidelines seemed to be used.

The number of CRC patients with LS seemed to be lower than would have been expected if the ratio in Japan were similar to that in Western countries.[4,5,9,12] One hundred and seventy-four CRC patients were diagnosed with LS in 2011–2015, which corresponded to only 0.17% if the hospitals that responded to the questionnaire were considered to treat 100 000 CRC patients in 2011–2015. This incidence is lower than that reported by Kumamoto *et al.*[10] The diagnosis of LS depended on MSI-H alone or methods other than genetic testing in some cases, especially in non-DCCHs. These results suggest a lower incidence of LS in Japan than in Western countries, or that many LS patients were overlooked in the clinic. Universal screening for LS was carried out in only 8% of departments in the present study, although most hospitals perform universal screening in the USA.[37] Data about the incidence of LS in Japan will soon be available from the departments that perform universal screening. The differences in management and knowledge of LS between DCCHs and non-DCCHs seem reasonable because insufficient data about LS have been collected to show any advantage in LS diagnosis in CRC patients in Japan.

The numbers of FAP patients diagnosed and undergoing follow-up in 2011–2015 were higher than the corresponding numbers of LS patients. The incidence of FAP should be lower than that of LS, even if the number of cases of LS is lower in Japan than in Western countries. This difference should be related to the method of diagnosis. Familial adenomatous polyposis was diagnosed from the clinical features of colon polyposis and family history. Unlike for LS, genetic testing (sequencing) is not indispensable for diagnosis of FAP in most cases. The number of patients diagnosed with FAP and the number who received preventive surgery in 2011–2015 differed significantly between DCCHs and non-DCCHs. However, there was no difference in the surgical procedures and timing

or use of NSAIDs for chemoprophylaxis between DCCHs and non-DCCHs. These results indicate that most management of FAP was undertaken similarly in departments belonging to JSCCR, although the number of patients differed according to the size of the hospitals.

Treatment for desmoid tumor in the abdominal cavity, but not in the abdominal wall, differed significantly when data were analyzed by the number of patients. Patients with desmoid tumors were rare in most departments. There were differences in follow-up after preventive surgery depending on the number of patients.

The present study had several limitations. We investigated the issues associated with management of LS and FAP in Japan; however, we did not collect data about patient sex, age, economic status, details of follow-up, or other malignancies, except for desmoid tumor. We focused on the departments belonging to JSCCR and DCCHs and non-DCCHs to evaluate the heterogeneity of management for LS and FAP. Therefore, our results do not strictly reflect the heterogeneity in Japan because we collected data from specialized hospitals for CRC management. Further studies about treatment and care of patients with LS and FAP in Japan are required to resolve the limitations in this study.

In conclusion, there were differences in the management of LS and FAP in Japan. The low incidence of LS in this study indicated that many patients were overlooked, or that there really was a low incidence of LS in Japan. Therefore, the ratio of LS in newly diagnosed CRC patients should be investigated as soon as possible before the introduction of universal screening in Japan. Compared with LS, surgical management of FAP patients seemed appropriate both in the DCCHs and non-DCCHs.

Acknowledgments

This study was supported by the Japan Society of Colorectal Cancer Research (JSCCR). We are grateful to the members of JSCCR for replying to the questionnaire. We also thank the staff of JSCCR for data collection and Edanz for editing the manuscript.

Disclosure Statement

The authors have no conflict of interest.

Abbreviations

5-FU	5-fluorouracil
CRC	colorectal cancer
DCCH	designated cancer care hospital
FAP	familial adenomatous polyposis
JSCCR	Japan Society of Colorectal Cancer Research
LS	Lynch syndrome
MMR	mismatch repair
MSI-H	high-frequency microsatellite instability
NSAID	nonsteroidal anti-inflammatory drug
PD-1	programmed death-1

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