Received: 21 September 2020 | Revised: 7 January 2021 | Accepted: 7 January 2021

DOI: 10.1111/cas.14798

ORIGINAL ARTICLE

Cancer Science WILEY

Real-world data on microsatellite instability status in various unresectable or metastatic solid tumors

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Funding information
Japan Agency for Medical Research and Development (AMED), Grant/Award Number: JP18kk0205004; JSPS KAKENHI, Grant/Award Number: JP18K07339; National Cancer Center Research and Development Fund, Grant/Award Number: 31-A-2.

Abstract

Microsatellite instability-high (MSI-H) is an important biomarker for predicting the effect of immune checkpoint inhibitors (ICIs) on advanced solid tumors. Microsatellite instability-high is detected in various cancers, but its frequency varies by cancer type and stage. Therefore, precise frequency is required to plan ICI therapy. In this study, the results of MSI tests actually carried out in clinical practice were investigated. In total, 26 469 samples of various cancers were examined between December 2018 and November 2019 to determine whether programmed cell death-1 blockade was indicated. The results of MSI tests were obtained for 26 237 (99.1%) of these samples. The male : female ratio was 51:49 and mean age was 64.3 years. In all samples, the overall frequency of MSI-H was 3.72%. By gender, the frequency of MSI-H was higher in female patients (4.75%) than in male patients (2.62%; $P < .001$). A comparison by age revealed that the frequency of MSI-H was significantly higher in patients younger than 40 years of age (6.12%) and 80 years or older (5.77%) than in patients aged between 60 and 79 years (3.09%; $P < .001$). Microsatellite instability-high was detected in 30 cancer types. Common cancer types were: endometrial cancer, 16.85%; small intestinal cancer, 8.63%; gastric cancer, 6.74%; duodenal cancer, 5.60%; and colorectal cancer, 3.78%. Microsatellite instability-high was detected in cancer derived from a wide variety of organs. The frequency of MSI-H varied by cancer type and onset age. These data should prove especially useful when considering ICI treatment.

KEYWORDS

advanced solid tumor, immune checkpoint inhibitor, microsatellite instability, mismatch repair, PD-1 blockade

Correction added on 16 Jan 2021, after initial online publication. A duplicate of this article was published under the DOI 10.1111/cas.14804. This duplicate has now been deleted and its DOI redirected to this version of the article.

Abbreviations: dMMR, deficiency in mismatch repair function; ICI, immune checkpoint inhibitor; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; QMVR, quasimonomorphic variation range.

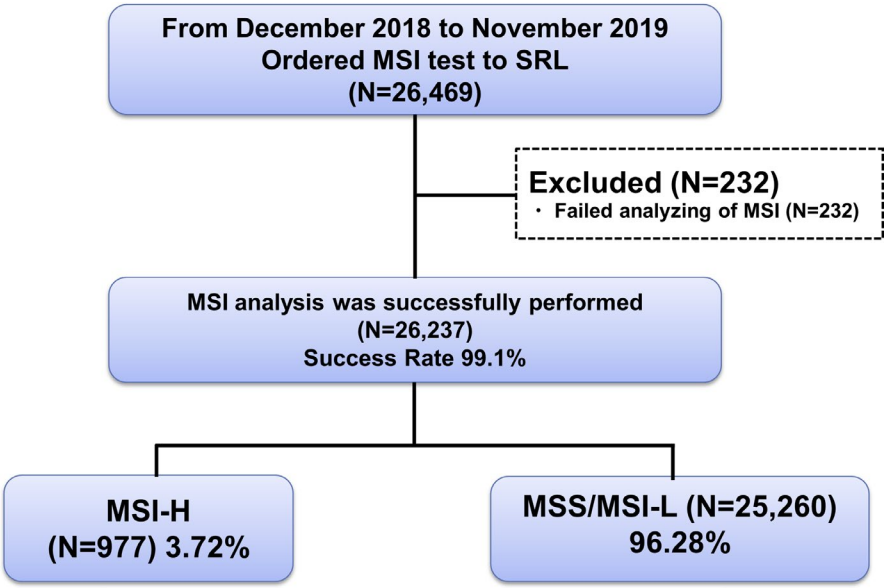


FIGURE 1 CONSORT flow diagram of this study. Of the 26 469 samples, 232 were excluded due to poor or insufficient sample conditions. Microsatellite instability (MSI) testing results were obtained from the remaining 26 237 samples. Success rate of tumor-agnostic MSI testing was 99.1% and 3.72% of all tumor showed MSI-high (MSI-H) status. MSI-L, microsatellite instability-low; MSS, microsatellite stable.

1 | INTRODUCTION

Cancer drug therapy with ICIs has made remarkable progress but is not effective for all cancers. Therefore, it is necessary to narrow down those patients expected to respond to ICIs. Currently, biomarkers to predict therapeutic response, such as PD-L1 expression,[1] MSI-H, or loss of mismatch repair protein expression[2-4] and tumor mutation burden-high[5] are used. Microsatellite instability-high results from dMMR. Furthermore, dMMR causes hypermutation and results in the production of many neoantigens in tumor cells; thus, treatment with anti-PD-1/-L1 Abs appears to be an effective option. That is, dMMR tumor is one of the real targets for ICI treatment.

To identify dMMR tumors, simple tests such as MSI testing[6,7] and immunohistochemistry testing for MMR proteins[8,9] are frequently applied. Microsatellite instability testing is a method to assess changes in microsatellites, which are simple repetitive DNA sequences in genomes, using DNA from both normal and tumor tissue. In recent years, however, an MSI testing method that allows assessment only with tumor tissue by utilizing specific microsatellite markers (BAT25, BAT26, NR21, NR24, and MONO27), which have almost no individual differences, has been developed.[7] In Japan, this method was approved in December 2018 as a companion diagnostic technique to determine whether pembrolizumab is indicated for unresectable or metastatic solid tumors. Consequently, this test has been widely adopted in Japan.

Several recent large-scale investigations predicted the MSI-H frequency in each tumor type. However, as these results are based on unique MSI assessment methods (pipeline and algorithm) using NGS,[11-15] it is unclear whether they are equivalent to conventional MSI testing. In addition, the cohorts examined in those studies were different from the actual target patients for whom MSI testing is used to determine ICI therapy.

To plan ICI therapy for unresectable or metastatic solid tumors, the precise frequency of MSI-H in each tumor type needs to be determined.

In this study, the results of MSI testing undertaken as a companion diagnostic technique was used to elucidate the frequency of MSI-H in each cancer type. These results were obtained from the actual target patients and actually used in clinical practice; that is, these are real-world data on MSI status in each cancer type.

2 | MATERIALS AND METHODS

2.1 | Samples

The samples had been submitted by nationwide medical institutes to SRL Inc. (CLIA-certificated CAP-accredited central laboratory) for MSI testing as a companion diagnostic technique to determine whether pembrolizumab was indicated for unresectable or metastatic solid tumors. Analyses were undertaken between December 2018 and November 2019. All results were anonymized by SRL, and the aggregated results of MSI were analyzed in this study. The use of anonymized results was approved by the ethics review board of SRL (No. 20-69).

2.2 | DNA extraction

Thin slices of formalin-fixed paraffin-embedded tumor tissue specimens were used for the test after confirmation by pathologists.[10] DNA was isolated using QIAsymphony DNA Mini kit (Qiagen) according to the manufacturer's recommendations.

2.3 | Microsatellite instability test

As previously reported, MSI testing with an assessment method using the QMVR was generally carried out.[7] The MSI status was

classified as MSI-H with the presence of two or more unstable markers, as MSI-low with only one unstable marker, and as microsatellite stable with no unstable marker.[6]

2.4 | Statistical analyses

Patient characteristics were compared using *t* tests for continuous variables and χ^2 tests or Fisher's exact tests by SPSS for categorical variables.

3 | RESULTS

3.1 | Cohort of this study

Of the 26 469 samples, 232 samples were excluded due to poor or insufficient sample conditions. Microsatellite instability testing results were obtained from the remaining 26 237 samples and used for this study (Figure 1). The testing success rate was as high as 99.1%. Among cancer types tested, colorectal cancer was the most common, found in 10 226 samples and accounting for 39% of all samples, followed by pancreatic cancer in 2775 samples (10.6%), gastric cancer in 1929 samples (7.4%), and endometrial cancer in 1389 samples (5.3%) (Figure 2, Table S1).

3.2 | Patient characteristics and MSI-H frequency

The ratio of male to female patients who could be analyzed was 51:49. The mean age was 64.3 years. The frequency of MSI-H was higher in female patients (4.7%) than in male patients (2.6%, $P < .001$). The frequency of MSI-H in all the samples was 3.72% (Table 1).

By age, the frequency of MSI-H was significantly higher in patients aged less than 40 years (6.1%) and 80 years or older (5.8%) than in patients aged 50-59 years (3.8%, $P = .002$, $P = .001$), 60-69 years (3.1%, $P < .0001$, $P < .0001$), and 70-79 years (3.1%, $P < .0001$, $P < .0001$) (Table 2, Figure 3).

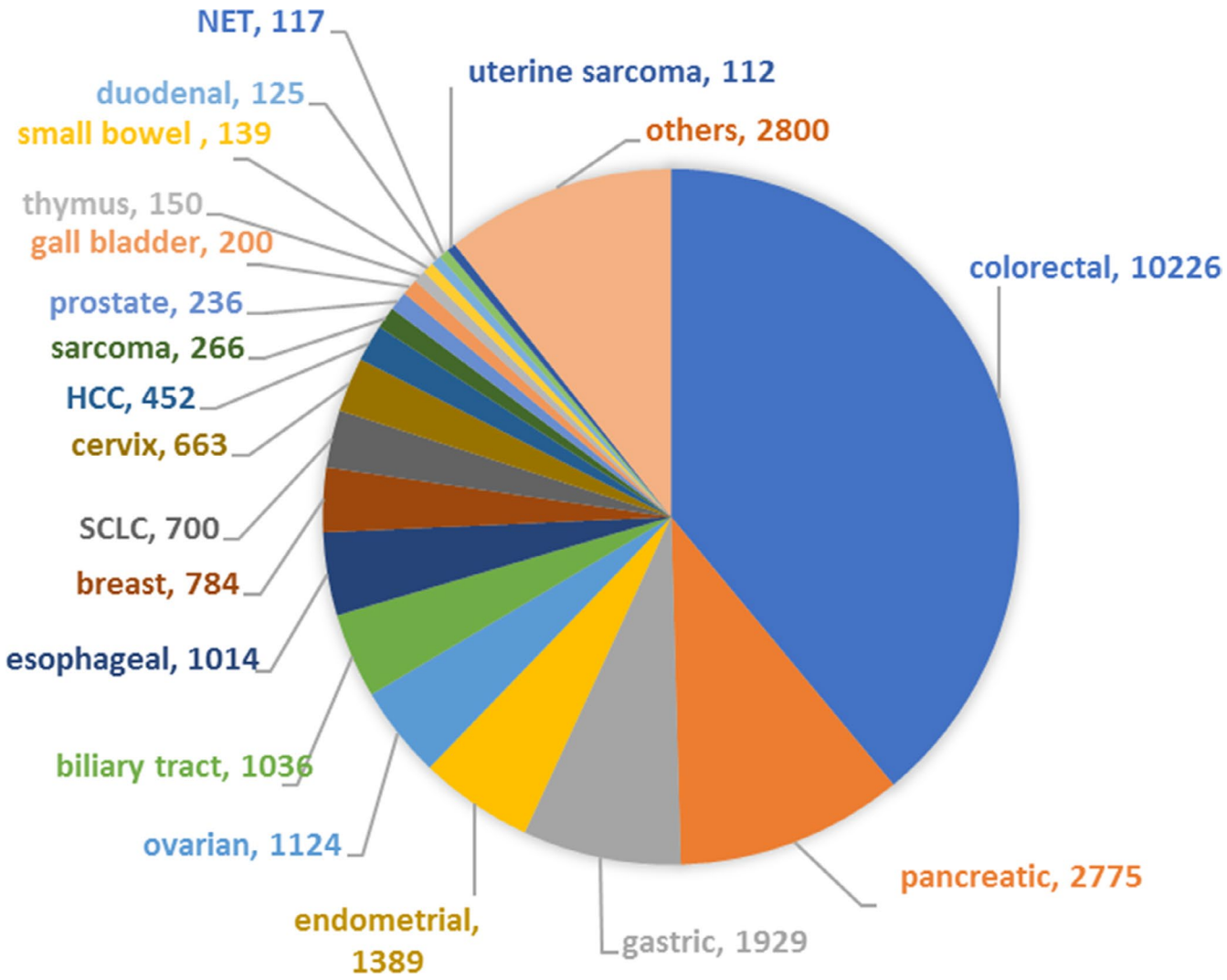


FIGURE 2 Number and proportion for each tumor sample from patients with unresectable or metastatic solid tumors examined with the microsatellite instability test. HCC, hepatocellular carcinoma; NET, neuroendocrine tumor; SCLC, small-cell lung carcinoma

3.3 | Frequency of MSI-H in each cancer type

In this analysis, MSI-H was detected in 30 cancer types (Table S1). Among cancer types for which the number of analyzable samples was 100 or more, MSI-H was frequently detected in the following: endometrial cancer, 16.9%; small intestinal cancer, 8.6%; gastric cancer, 6.7%; duodenal cancer, 5.6%; and colorectal cancer, 3. 8% (Figure 4A, Table 3). Among cancer types for which the number of analyzable samples was <100, MSI-H was frequently detected in the following: upper urinary tract cancer, 16.7% (3/18); adrenal cancer, 11.5% (3/26); and testicular cancer, 9.1% (2/22; Figure 4B, Table 4).

4 | DISCUSSION

In this study, we presented real-world data on MSI status based on data from MSI testing undertaken on patients with unresectable or metastatic solid tumors to determine whether pembrolizumab was indicated. To the best of our knowledge, this was the first time this has been done using the largest MSI dataset in Asia. The data and results obtained from this nationwide large-scale investigation should prove very useful when ICI treatment is being considered.

In our study, the frequency of MSI-H in all the cases was 3.72%. In previous studies, Latham et al[11] reported that MSI-H was detected in 2.1% of all samples based on NGS analysis data from 15 045 samples of various cancer types. Le et al[12] carried out an NGS analysis using 12 019 samples consisting of 32 cancer subtypes and reported that the frequency of MMR-deficient cancer in stage IV patients was 4%. In these cohorts, cancers at different stages were included, and they did not confine themselves to collecting only those patients who might be candidates for treatment with ICIs. The frequency of MSI-H varies by cancer type[11-15] and stage[12,16]; thus, in actual clinical practice, when considering whether ICIs are indicated, the frequency by tumor type is more useful than the frequency for all samples. In our study, MSI-H was most frequently detected in endometrial cancer (16.9% of all cases) followed by, in descending order of frequency, cancer of the small intestine (8.6%), gastric cancer (6.7%), duodenal cancer (5.6%) and colorectal cancer (3.8%). This order is generally consistent with the results reported by Le et al[12] and Trabucco et al.[15]

Among cancer types for which the number of analyzable samples was less than 100, and for which the frequency could not be determined with a high degree of accuracy, MSI-H was frequently detected in the following cancer types: upper urinary tract cancer, 16.7% (3/18); adrenal cancer, 11.5% (3/26); and testicular cancer, 9.1% (2/22).

In this study, MSI-H was detected in 30 of 43 cancer types. For the 13 cancer subtypes in which MSI-H was not detected, the number of cases tested was as few as 97 or less. If the number of cases could be increased, it might be possible to identify MSI-H cases for these cancer types as well. More cases are needed to obtain an accurate estimation of frequency for these cancer types.

In addition, the classification of cancer type could also affect the frequency of MSI-H. For example, MSI-H was not detected among 97 thyroid carcinoma cases in this study, whereas Le reported that 2% of thyroid carcinoma showed MSI-H.[12] A recent study reported that MSI-H was observed in 2.5% of follicular thyroid carcinoma, but was either entirely absent or rare in other histology subtypes of thyroid carcinoma.[17] Thus, the classification of cancer type might also affect the frequency of MSI-H.

The frequency of MSI-H by gender was approximately 1.8-fold higher for female patients (4.75%) than male patients (2.62%). This

TABLE 1 Characteristics of patients with unresectable or metastatic solid tumors and frequency of microsatellite instability-high (MSI-H) tumors

	All cases N = 26 237	MSI-L/MSS N = 25 260	MSI-H N = 977	Frequency of MSI-H 3.72*
Gender				
Male	12 803	12 468	335	2.62
Female	12 277	11 694	583	4.75
Unknown	1157	1098	59	5.1
Mean age (y)				
All	64.3 (±12.0)	64.3 (±11.99)	63.4 (±13.98)	NA
	range, 2-96	range, 2-96	range, 13-93	
Male	66.0 (±11.26)	66.1 (±11.11)	63.5 (±15.42)	NA
	range, 5-96	range, 5-96	range, 13-91	
Female	62.5 (±12.61)	62.4 (±12.59)	63.2 (±13.06)	NA
	range, 2-96	range, 2-96	range, 18-93	
Stage				
I-III	5464	5137	327	5.98
IV	17 970	17 427	543	3.02
Unknown	2803	2696	107	3.82

MSI-L, microsatellite instability-low; MSS, microsatellite stable; NA, not applicable.
*The frequency of MSI-H in all the samples.

TABLE 2 Age of disease onset and microsatellite stability status in patients with unresectable or metastatic solid tumors

Age (y)	All cases N = 23 379	MSI-L/MSS N = 22 530	MSI-H N = 849	Frequency of MSI-H 3.72*
<10 (n = 13)	13	13	0	0
10s (n = 44)	44	41	3	6.82
20s (n = 131)	131	121	10	7.63
30s (n = 695)	695	654	41	5.90
40s (n = 2098)	2098	2004	94	4.48
50s (n = 4038)	4038	3885	153	3.79
60s (n = 7374)	7374	7146	228	3.09
70s (n = 7407)	7408	7179	229	3.09
80s (n = 1526)	1526	1442	84	5.51
90s (n = 52)	52	45	7	13.46

MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable.

*The frequency of MSI-H in all the samples.

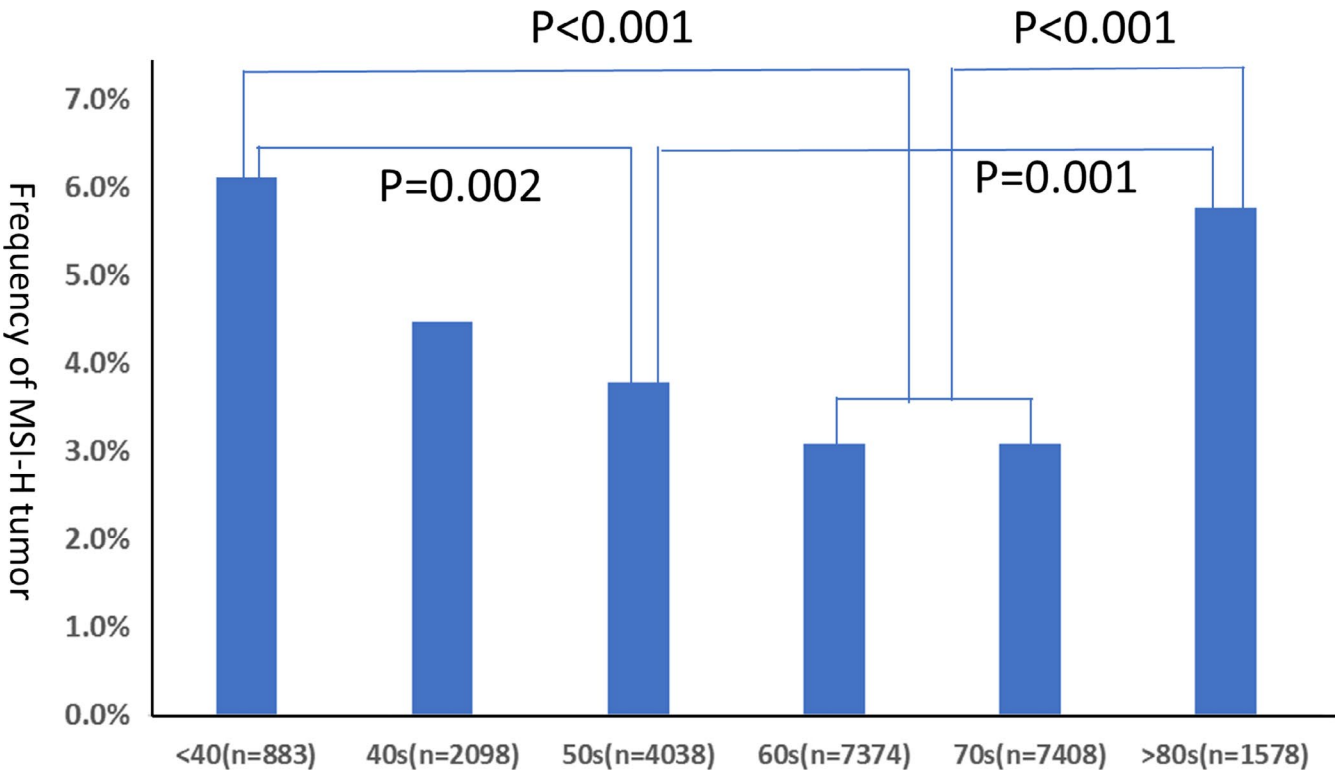


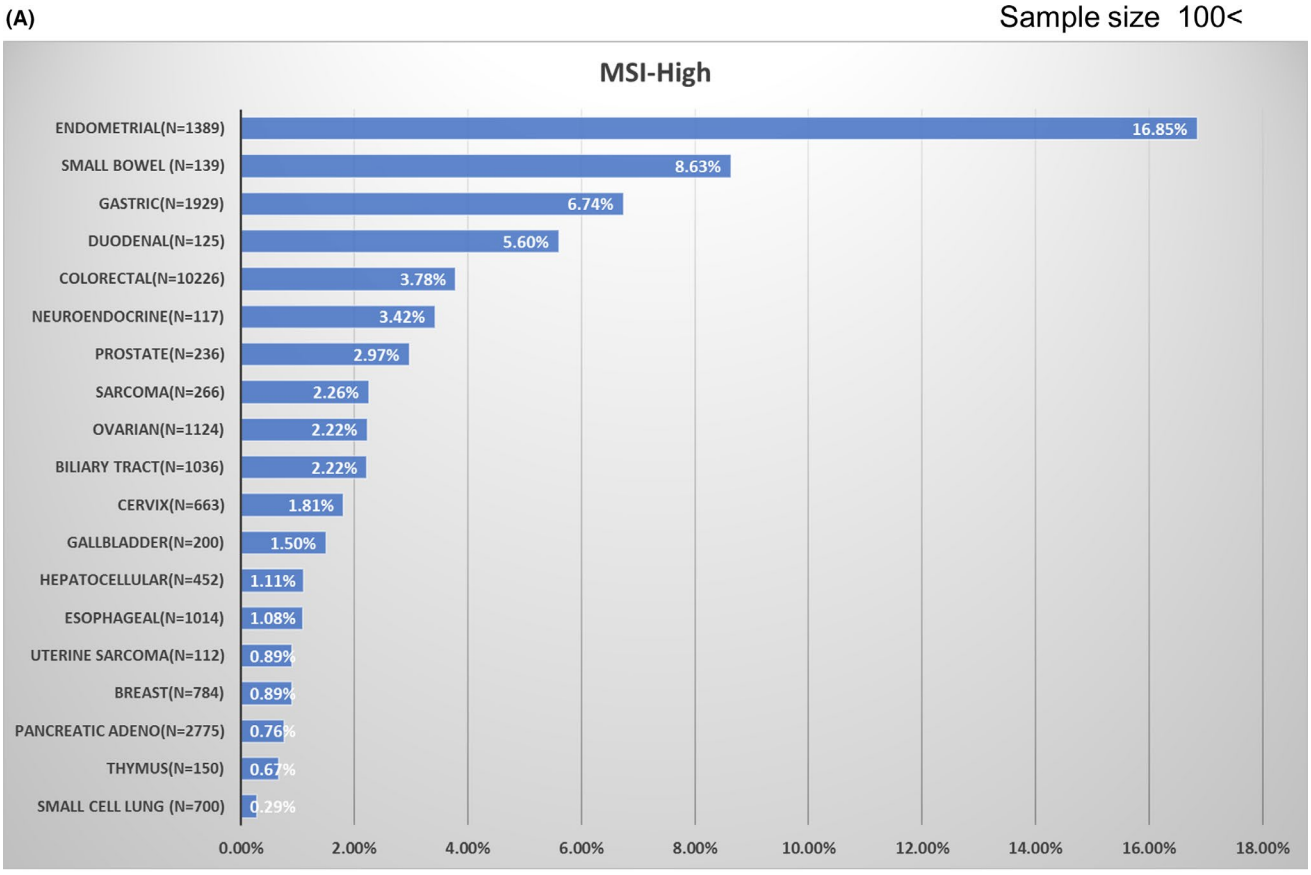
FIGURE 3 Frequency of microsatellite instability-high (MSI-H) tumor in each generation of patients with unresectable or metastatic solid tumors. The frequency of MSI-H was significantly higher in patients aged <40 y (6%) and 80 y or older (5.77%) compared with patients aged between 60 and 79 y (3.09%; $P < .001$)

could be attributable to the effect of the high MSI-H frequency in endometrial cancer, unique to female patients. Actually, when frequency was calculated excluding endometrial cancer, it was 3.2%, similar to the frequency seen in male patients.

The frequency of MSI-H by age was higher in the young and elderly patients than in other age groups. In younger patients, MSI-H was likely attributable to a genetic background that makes these patients susceptible to the development of cancer. It was assumed that Lynch syndrome[18,19] and constitutional mismatch repair deficiency syndrome[20,21] were included among these predisposing conditions.

The reason why the frequency was high in more elderly patients might be because their MSI-H status occurs through *MLH1* promoter methylation.[22] In fact, MSI-H was frequently detected in elderly female patients with colorectal cancer[23] and endometrial cancer.[24]

The MSI test kit (FALCO) used in this study is an MSI assessment method using the QMVR and only requires tumor tissue.[7] This



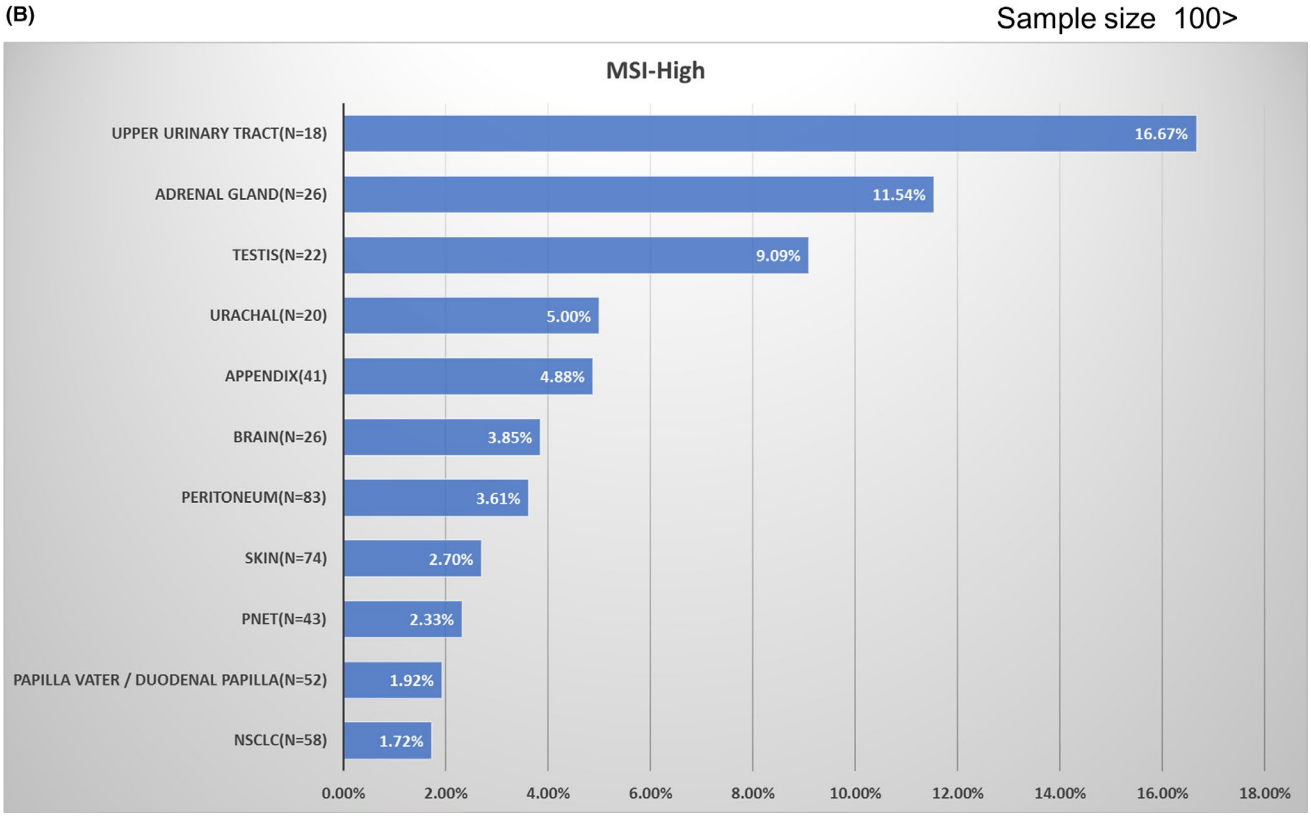


FIGURE 4 Frequency of microsatellite instability-high (MSI-H) in each tumor type among patients with unresectable or metastatic solid tumors. A, Tumors for which the number of analyzable samples was 100 or more. B, Tumors for which the number of analyzable samples was less than 100. adeno, adenocarcinoma; NSCLC, non-small-cell lung carcinoma; PNET, pancreatic neuroendocrine tumor

TABLE 3 Microsatellite stability status in each tumor type classified by anatomical site or histology

Tumor type	All cases N = 26 237	MSI-L/MSS N = 25 260	MSI-H N = 977	Frequency of MSI-H 3.72*
Endometrial	1389	1155	234	16.85
Small bowel	139	127	12	8.63
Gastric	1929	1799	130	6.74
Duodenal	125	118	7	5.60
Colorectal	10 226	9839	387	3.78
Neuroendocrine carcinoma[a]	117	113	4	3.42
Prostate	236	229	7	2.97
Biliary tract	1036	1013	23	2.22
Ovarian	1124	1099	25	2.22
Sarcoma	266	260	6	2.26
Cervix	663	651	12	1.81
Gallbladder	200	197	3	1.50
Hepatocellular	452	447	5	1.11
Esophageal	1014	1003	11	1.08
Breast	784	777	7	0.89
Uterine sarcoma	112	111	1	0.89
Pancreatic adenocarcinoma	2775	2754	21	0.76
Thymus	150	149	1	0.67
Small cell lung	700	698	2	0.29

MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable.

[a]Excluding pancreatic neuroendocrine tumor.

*The frequency of MSI-H in all the samples.

TABLE 4 Microsatellite stability status in each tumor type classified by anatomical site or histology

Tumor type	All cases N = 26 237	MSI-L/MSS N = 25 260	MSI-H N = 977	Frequency of MSI-H 3.72*
Upper urinary tract	18	15	3	16.67
Adrenal gland	26	23	3	11.54
Testis	22	20	2	9.09
Urachus	20	19	1	5.00
Appendix	41	39	2	4.88
Brain	26	25	1	3.85
Peritoneum	83	80	3	3.61
Skin	74	72	2	2.70
Pancreatic neuroendocrine tumor	43	42	1	2.33
Papilla vater/duodenal papilla	52	51	1	1.92
Non-small-cell lung cancer	58	57	1	1.72

MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable.

*The frequency of MSI-H in all the samples.

testing method was developed based mainly on the use of colorectal cancer. Consequently, sufficient data had not been obtained from cancer types other than colorectal cancer. In this study, however, MSI testing with various solid tumors was successfully carried out and the success rate for this method was as high as 99.1%. In addition, MSI-H was detected in various cancer types. This indicated

that the five microsatellite markers (BAT25, BAT26, NR21, NR24, and MONO27) showed their utility in a tumor-agnostic manner.

Although MSI testing is used for the purpose of cancer treatment, it is anticipated that patients with Lynch syndrome will be found among MSI-H patients at a certain level of frequency[11]; a medical management system that includes genetic counseling, genetic diagnosis, and surveillance in patients and their blood relatives needs to be organized.

In this study, we presented real-world data using the results of MSI testing undertaken for determining whether pembrolizumab treatment was indicated for patients with unresectable or metastatic solid tumors. The data and results were obtained from nationwide large-scale investigations. Such real-world data on MSI status in unresectable or metastatic solid tumors have not been reported previously and should therefore prove highly useful when devising strategies for cancer treatment with ICIs.

ACKNOWLEDGMENT

We thank SRL Inc. for providing anonymized MSI data. This research was supported by the Japan Agency for Medical Research and Development (AMED) under grant JP18kk0205004, JSPS KAKENHI Grant Number JP18K07339, and National Cancer Center Research and Development Fund Grant Number 31-A-2.

DISCLOSURE

K. Akagi reports research funding received from Ono and Falco Biosystems and lecture fees received from MSD. E. Oki reports lecture fees received from Bayer, Chugai, Eli Lilly, Merck, Ono, Taiho, Takeda, and Yakult Honsha. H. Taniguchi reports honoraria received from Bayer, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, MBL, Merck Serono, Mitsubishi Tanabe Pharma, MSD, Nippon Kayaku, Novartis, Sanofi, Taiho, Takeda, and Yakult Honsha and research funding received from Array Bio Pharma, Daiichi Sankyo, Dainippon Sumitomo Pharma, MSD, Novartis, Ono, Sysmex, and Takeda. D. Aoki reports research funding received from Chugai and Takada and honoraria received from Astra Zeneka, Chugai, and MSD. T. Kuwata reports research funding from Ono and Daiichi Sankyo and honoraria from MSD, Astra Zeneca, and Taiho. T. Yoshino reports research funding received from Chugai, Daiichi Sankyo, Dainippon Sumitomo Pharma, GSK, MSD, Novartis, Ono, Parexel, and Sanofi. The other authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Akagi K, Oki E, Taniguchi H, et al. Real-world data on microsatellite instability status in various unresectable or metastatic solid tumors. *Cancer Sci*. 2021;112:1105–1113. https://doi.org/10.1111/cas.14798