Hindawi
Journal of Oncology
Volume 2020, Article ID 1807929, 17 pages
https://doi.org/10.1155/2020/1807929

Review Article

Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review

Maria Lorenzi,[1] **Mayur Amonkar**,[2] **Jacky Zhang**,[1] **Shivani Mehta**,[1] **and Kai-Li Liaw**[2]

[1]*Precision Xtract, Oakland, CA, USA*
[2]*Merck & Co, Inc., North Wales, PA, USA*

Correspondence should be addressed to Maria Lorenzi; maria.lorenzi@precisionxtract.com

Received 9 October 2019; Revised 23 January 2020; Accepted 28 January 2020; Published 9 March 2020

Academic Editor: Giandomenico Roviello

Background. Given limited data on the epidemiology of MSI-H and dMMR across solid tumors (except colorectal cancer (CRC)), the current study was designed to estimate their prevalence. *Materials and Methods*. A structured literature review identified English language publications that used immunohistochemistry (IHC) or polymerase chain replication (PCR) techniques. Publications were selected for all tumors except CRC using MEDLINE, EMBASE, and Cochrane databases and key congresses; CRC and pan-tumor genomic publications were selected through a targeted review. Meta-analysis was performed to estimate pooled prevalence of MSI-H/dMMR across all solid tumors and for selected tumor types. Where possible, prevalence within tumor types was estimated by disease stages. *Results*. Of 1,176 citations retrieved, 103 and 48 publications reported prevalence of MSI-H and dMMR, respectively. Five pan-tumor genomic studies supplemented the evidence base. Tumor types with at least 5 publications included gastric ($n = 39$), ovarian ($n = 23$), colorectal ($n = 20$), endometrial ($n = 53$), esophageal ($n = 6$), and renal cancer ($n = 8$). Overall MSI-H prevalence (with 95% CI) across 25 tumors was based on 90 papers (28,213 patients) and estimated at 14% (10%–19%). MSI-H prevalence among Stage 1/2 cancers was estimated at 15% (8%–23%); Stages 3 and 4 prevalence was estimated at 9% (3%–17%) and 3% (1%–7%), respectively. Overall, dMMR prevalence across 13 tumor types (based on 54 papers and 20,383 patients) was estimated at 16% (11%–22%). Endometrial cancer had the highest pooled MSI-H and dMMR prevalence (26% and 25% all stages, respectively). *Conclusions*. This is the first comprehensive attempt to report pooled prevalence estimates of MSI-H/dMMR across solid tumors based on published data. Prevalence determined by IHC and PCR was generally comparable, with some variations by cancer type. Late-stage prevalence was lower than that in earlier stages.

1. Introduction

DNA mismatch repair (MMR) is a process that plays a key role in maintaining genomic stability by recognizing and repairing base-base mismatches and insertion/deletion of DNA generated during replication and recombination. Defects in MMR are associated with genome-wide instability and the progressive accumulation of mutations, especially regions of simple repetitive DNA sequences known as microsatellites, resulting in MSI. MSI-high (MSI-H) is a hypermutable phenotype that allows mutations to be accumulated rapidly, resulting in tumor development via the selection of cancer-promoting mutations in pathways that are responsible for maintaining functional DNA repair, apoptosis, and cell growth.

To test for MSI-H and dMMR statuses in solid tumors, polymerase chain reaction (PCR) and immunohistochemistry (IHC) methods have been widely accepted as respective testing platforms for these biomarkers. The PCR method uses a panel of microsatellite markers to detect size shifts in different loci. The IHC method uses a more direct test to determine the presence of MMR proteins. A tumor is typically classified as MSI-H if shifts are detected in at least 2 of 5 loci using the PCR method and dMMR if at least one MMR protein is absent using the IHC method. The use of NCI (BAT-25, BAT-26, D2S123, D5S346, and D17S250) [1]

and Promega (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) [2] panels in PCR and the use of MLH1, MSH2, MSH6, and PMS2 proteins in IHC are considered the gold standard approaches [3, 4, 5].

Among patients diagnosed with metastatic cancer and MSI-H or dMMR, prognosis is generally poor [6]. Recently, evidence has mounted on the benefits of immunotherapy, especially with checkpoint inhibitors such as pembrolizumab on MSI-H/dMMR tumors [7, 8, 9]. Historically, most patients with a solid tumor diagnosis were not tested for MSI; a better understanding of MSI-H and dMMR prevalence can help estimate the size of the potential target population. To provide reliable estimates of MSI-H and dMMR prevalence, a comprehensive structured literature review was conducted to gather relevant and recent evidence on the epidemiology of MSI-H and dMMR across multiple tumors. When sufficient data were available, meta-analysis was performed to estimate the prevalence of MSI-H and dMMR tumors overall, across individual tumor types, and by stage of disease.

2. Methods

Study eligibility criteria outlined in Table 1 guided study identification and selection for the literature review.

2.1. Literature Review. Relevant studies were identified by searching the following through the Ovid platform: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (Embase), and Cochrane Central Register of Controlled Trials. Predefined search strategies were executed on October 26th, 2017. Study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN) were used. Population terms were adapted from published research [9]; no intervention or comparator terms were used.

Systematic reviews, meta-analyses, and key narrative reviews of interest were identified via hand searching. Targeted hand searches were conducted to identify colorectal cancer (CRC) studies and pan-tumor genomic studies reporting MSI-H/dMMR prevalence. Studies for all solid tumors except CRC were selected through database searches; CRC and pan-tumor genomic studies were selected through a targeted review. One reviewer reviewed all abstracts and proceedings identified through database searches and the targeted review according to the selection criteria. Studies identified as potentially eligible during abstract screening were screened in full-text by the same reviewer. The full-text studies identified at this stage were included for data extraction. The process of study identification and selection are summarized with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams [10].

One reviewer extracted data on study characteristics, interventions, patient characteristics, and outcomes from included studies. The second reviewer independently extracted data from a random 10% of the publications, reconciled the data, and determined the error rate and missing data rate of data extraction by the first reviewer. The error rate (number of cells with incorrect data/number of cells with text) was 2.9%, and the missing data rate (number of cells with missing data/number of blank cells) was 1.2% (an error rate greater than 5% would have triggered extraction of a further 10% of publications by the second reviewer). All errors discovered through this process were corrected. Potential publication biases were checked through funnel plots. Data were stored and managed in a Microsoft Excel workbook.

Only studies that used PCR or IHC methods were included in this review. To increase validity of the meta-analysis, only studies that used NCI (BAT-25, BAT-26, D2S123, D5S346, and D17S250) or Promega (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) panels in PCR and MLH1, MSH2, MSH6, and PMS2 proteins in IHC were included in the meta-analysis. The only exceptions were pan-tumor genomic studies, which used large-scale sequencing techniques to test for the presence of only the MLH1 gene. These genomic studies were included in sensitivity analyses to detect their potential effect on the meta-analysis.

Prevalence of MSI-H and/or dMMR was extracted overall, by tumor type, histology, stage, and country.

2.2. Meta-Analysis. Reported proportions were transformed according to the Freeman–Tukey variant of the arcsine square root (double arcsine) transformed proportion [11]. The pooled proportion was calculated by back-transforming the weighted mean of the transformed proportions, using the DerSimonian–Laird random effects model [12].

Meta-analysis was conducted using the *metafor* package version 1.9-9 in R 3.4.0. Weighting of each tumor type was based on cancer-specific prevalence estimates provided by the GLOBOCAN 2012 database from the World Health Organization [13]. For rare tumor types, when data were unavailable on the GLOBOCAN database, other databases and peer-reviewed publications were referenced [14–18]. Each tumor type was assigned a weight based on its general prevalence; in cases where two or more studies were included for a given tumor type, weight was split proportionally between studies based on the sample size.

3. Results

The study selection process for identification of studies reporting MSI-H or dMMR prevalence in the structured literature review is outlined in Figure 1. Overall, 1,176 publications were assessed for eligibility; a total of 156 full-text publications were included based on the structured and targeted literature review.

3.1. Feasibility Assessment of Meta-Analysis. References for included studies can be found in Tables 2–4. Of the 156 included full-text publications, 103 studies reported prevalence of any MSI status, which included MSI-H, MSI-L (microsatellite instability-low), and MSS (microsatellite stable). Forty-eight studies reported prevalence of dMMR

Table 1: Eligibility criteria.

Criteria	Description
Population	Patients with solid tumors
Outcomes	(i) Assessment of prevalence of MSI-H (using NCI marker panel: BAT25, BAT26, D2S123, D5S346, and D17S250) or Promega marker panel: BAT25, BAT26, NR21, NR24, and MONO27) and/or dMMR (by immunohistochemistry for all four MMR proteins: MLH1, MSH2, MSH6, and PMS2) overall, by tumor type, by histology subtype, by stage, by treatment, by region, by country, and by gender (a) Proportion of MSI as defined in study (e.g., MSI-H, MSI-L, and MSI-S) (b) Proportion of dMMR and pMMR as defined in study (ii) Survival rates by MSI-H/dMMR status overall, by stage and by tumor type (a) Overall survival (OS) and progression-free survival (PFS) (1) Hazard ratios along with 95% confidence interval (CI) (2) Median (in months) and 95% CI (iii) Objective response rate (ORR), defined as complete response (CR) or partial response (PR) (iv) Disease control rate, defined as CR, PR, or stable disease
Study design	(i) Prospective and retrospective cohort studies (ii) Randomized controlled trials (iii) Case-control studies (iv) Cross-sectional studies (v) Controlled and uncontrolled longitudinal studies (cohorts or case series)
Language	Only studies published in English will be included
Time	No time limit

Abbreviations: dMMR, deficient mismatch repair; MLH1, MutL homolog 1; MSH2, MutS protein homolog 2; MSH6, MutS homolog 6; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; MSI-S/MSS, microsatellite stable; NCI, National Cancer Institute; pMMR, proficient mismatch repair; PMS2, postmeiotic segregation increased 2.

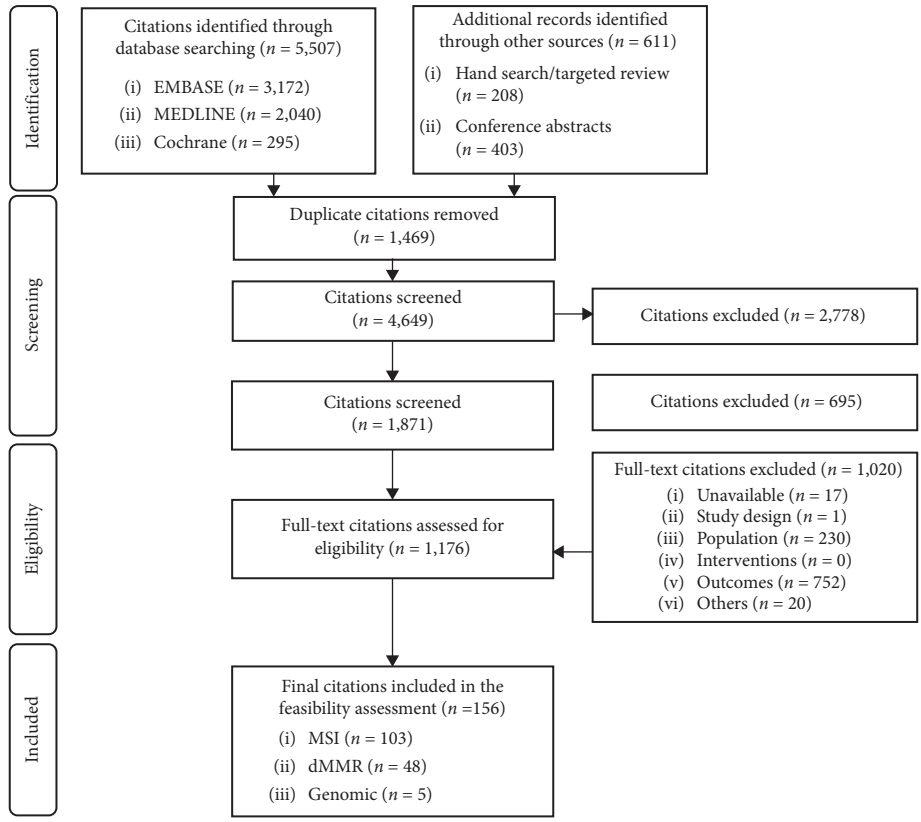

Figure 1: PRISMA study flow diagram of included studies for the structured literature review.

according to the eligibility criteria. Five large pan-tumor genomic studies reported MSI-H status across multiple solid tumors.

3.2. Study Characteristics. The most common tumor types (excluding CRC) identified were endometrial (53 studies), gastric (39 studies), ovarian (23 studies), renal (9 studies),

Table 2: References—MSI studies.

Author	Year	Title	Journal	Tumor type
Abraham	2002	Microsatellite instability in intraductal papillary neoplasms of the biliary tract	Nature	Pancreatic
Adduri	2014	P53 nuclear stabilization is associated with FHIT loss and younger age of onset in squamous cell carcinoma of oral tongue	BMC Clinical Pathology	Oral cavity
Akbari	2017	Correlation between germline mutations in MMR genes and microsatellite instability in ovarian cancer specimens	Familial Cancer	Ovarian
Alldinger	2007	Microsatellite instability in Ewing tumor is not associated with loss of mismatch repair protein expression	Journal of Cancer Research and Clinical Oncology	Ewing sarcoma
Altavilla	2010	Microsatellite instability and hMLH1 and hMSH2 expression in renal tumors	Oncology Reports	Renal
Amaki-Takao	2016	Colorectal cancer with BRAF D594G mutation is not associated with microsatellite instability or poor prognosis	Oncology (Switzerland)	Colorectal
An	2005	Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma	Clinical Cancer Research	Gastric
An	2012	Microsatellite instability in sporadic gastric cancer: its prognostic role and guidance for 5-fu based chemotherapy after r0 resection	International Journal of Cancer	Gastric
Aparicio	2013	Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study	British Journal of Cancer	Small bowel
Aysal	2012	Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability	The American Journal of Surgical Pathology	Ovarian
Bacani	2005	Tumor microsatellite instability in early onset gastric cancer	Journal of Molecular Diagnostics	Gastric
Bae	2015	Usefulness of immunohistochemistry for microsatellite instability screening in gastric cancer	Gut and Liver	Gastric
Basil	2000	Clinical significance of microsatellite instability in endometrial carcinoma	Cancer	Endometrial
Bataille	2003	Alterations in p53 predict response to preoperative high dose chemotherapy in patients with gastric cancer	Journal of Clinical Pathology-Molecular Pathology	Gastric
Billingsley	2015	Polymerase e (pole) mutations in endometrial cancer: clinical outcomes and implications for Lynch syndrome testing	Cancer	Endometrial
Black	2006	Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma	Journal of Clinical Oncology	Endometrial
Buller	2001	p53 mutations and microsatellite instability in ovarian cancer: Yin and Yang	American Journal of Obstetrics & Gynecology	Ovarian
Buttin	2006	Increased risk for abnormalities on perioperative colon screening in patients with microsatellite instability-positive endometrial carcinoma	International Journal of Gynecological Cancer	Endometrial
Cai	2004	Microsatellite instability and alteration of the expression of hMLH1 and hMSH2 in ovarian clear cell carcinoma	Human Pathology	Ovarian
Catasus	2004	Molecular genetic alterations in endometrioid carcinomas of the ovary: similar frequency of beta-catenin abnormalities but lower rate of microsatellite instability and PTEN alterations than in uterine endometrioid carcinomas	Human Pathology	Ovarian

Table 2: Continued.

Author	Year	Title	Journal	Tumor type
Cesinaro	2007	Mismatch repair proteins expression and microsatellite instability in skin lesions with sebaceous differentiation: a study in different clinical subgroups with and without extracutaneous cancer	The American Journal of Dermatopathology	Sebaceous
Chiaravalli	2001	Immunohistochemical pattern of hMSH2/ hMLH1 in familial and sporadic colorectal, gastric, endometrial and ovarian carcinomas with instability in microsatellite sequences	Virchows Archiv	Gastric, endometrial, ovarian, and colorectal
Choe	2005	High frequency of microsatellite instability in intestinal-type gastric cancer in Korean patients	The Korean Journal of Internal Medicine	Gastric
Choi	2015	Correlation between microsatellite instability-high phenotype and occult lymph node metastasis in gastric carcinoma	APMIS	Gastric
Chong	2013	The genomic landscape of oesophagogastric junctional adenocarcinoma	Journal of Pathology	Oesophagogastric junctional
Choy	2004	Microsatellite instability and MLH1 promoter methylation in human retinoblastoma	Investigative Ophthalmology and Visual science	Retinoblastoma
Cook	2013	Endometrial cancer and a family history of cancer	Gynecologic Oncology	Endometrial and other unspecified tumors
Cullinane	2004	Microsatellite instability is a rare finding in tumors of patients with both primary renal and rectal neoplasms	Cancer Genetics & Cytogenetics	Rectal and renal
Dewdney	2012	Uterine serous carcinoma: increased familial risk for Lynch-associated malignancies	Cancer Prevention Research	Endometrial
Evans	2004	Microsatellite instability in esophageal adenocarcinoma	Cancer Letters	Esophageal
Fu	2012	Cpg island methylator phenotype-positive tumors in the absence of mlh1 methylation constitute a distinct subset of duodenal adenocarcinomas and are associated with poor prognosis	Clinical Cancer Research	Small bowel
Garcia	2006	Mismatch repair protein expression and microsatellite instability: a comparison of clear cell sarcoma of soft parts and metastatic melanoma	Modern Pathology	Clear Cell Sarcoma and Melanoma
Gargano	2007	Aberrant methylation within RUNX3 CpG island associated with the nuclear and mitochondrial microsatellite instability in sporadic gastric cancers. Results of a GOIM (gruppo oncologico dell'italia meridionale) prospective study	Annals of Oncology	Gastric
Geiseler	2003	Mismatch repair gene expression defects contribute to microsatellite instability in ovarian carcinoma	Cancer	Ovarian
Glavac	2003	Low microsatellite instability and high loss of heterozygosity rates indicate dominant role of the suppressor pathway in squamous cell carcinoma of head and neck and loss of heterozygosity of 11q14.3 correlates with tumor grade	Cancer Genetics & Cytogenetics	Head and neck
Goodfellow	2003	Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers	Proceedings of the National Academy of Sciences of the United States of America	Endometrial
Gras	2001	Microsatellite instability, MLH-1 promoter hypermethylation, and frameshift mutations at coding mononucleotide repeat microsatellites in ovarian tumors	Cancer	Ovarian

Table 2: Continued.

Author	Year	Title	Journal	Tumor type
Grogg	2003	Lymphocyte-rich gastric cancer: associations with Epstein-Barr virus, microsatellite instability, histology, and survival	Modern Pathology	Gastric
Gu	2009	Analysis of microsatellite instability, protein expression and methylation status of hmlh1 and hmsh2 genes in gastric carcinomas	Hepato-Gastroenterology	Gastric
Hampel	2005	Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer)	The New England Journal of Medicine	Colorectal
Hasuo	2007	Assessment of microsatellite instability status for the prediction of metachronous recurrence after initial endoscopic submucosal dissection for early gastric cancer	British Journal of Cancer	Gastric
Hermsen	2009	Genome-wide analysis of genetic changes in intestinal-type sinonasal adenocarcinoma	Head & neck	Nasopharynx
Honecker	2009	Microsatellite instability, mismatch repair deficiency, and BRAF mutation in treatment-resistant germ cell tumors	Journal of Clinical Oncology	Testis
Hong	2012	The differential impact of microsatellite instability as a marker of prognosis and tumour response between colon cancer and rectal cancer	European Journal of Cancer	Colorectal
Huang	2010	Comparative features of colorectal and gastric cancers with microsatellite instability in Chinese patients	Journal of Zhejiang University Science	Gastric and colorectal
Jahng	2012	Endoscopic and clinicopathologic characteristics of early gastric cancer with high microsatellite instability	World Journal of Gastroenterology	Gastric
Jensen	2008	Microsatellite instability and mismatch repair protein defects in ovarian epithelial neoplasms in patients 50 years of age and younger	American Journal of surgical Pathology	Ovarian
Jung	2016a	Prognostic impact of microsatellite instability in colorectal cancer presenting with mucinous, signet-ring, and poorly differentiated cells	Annals of Coloproctology	Colorectal
Jung	2016b	Observational study: familial relevance and oncological significance of revised bethesda guidelines in colorectal patients that have undergone curative resection	Medicine (United States)	Colorectal
Kanopiene	2014	Impact of microsatellite instability on survival of endometrial cancer patients	Medicina	Endometrial
Karpińska-Kaczmarczyk	2016	Expression of mismatch repair proteins in early and advanced gastric cancer in Poland	Medical Science Monitor	Gastric
Kawaguchi	2009	Analysis of candidate target genes for mononucleotide repeat mutation in microsatellite instability-high (MSI-H) endometrial cancer	International Journal of Oncology	Endometrial
Kawanaka	2016	Effects of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic treatment: analysis of molecular alterations by a randomised controlled trial	British Journal of Cancer	Gastric
Kim	1999	Accumulated frameshift mutations at coding nucleotide repeats during the progression of gastric carcinoma with microsatellite instability	Laboratory Investigation	Gastric
Kim	2013a	Microsatellite instability status in gastric cancer: a reappraisal of its clinical significance and relationship with mucin phenotypes	Korean Journal of Pathology	Gastric
Kim	2013b	Differential clinicopathologic features in microsatellite-unstable gastric cancers with and without MLH1 methylation	Human Pathology	Gastric

Table 2: Continued.

Author	Year	Title	Journal	Tumor type
Kim	2016a	Clinicopathologic features of gastric cancer with synchronous and metachronous colorectal cancer in Korea: are microsatellite instability and p53 overexpression useful markers for predicting colorectal cancer in gastric cancer patients?	Gastric Cancer	Gastric and colorectal
Kim	2016b	Microsatellite instability of gastric and colorectal cancers as a predictor of synchronous gastric or colorectal neoplasms	Gut and Liver	Gastric and colorectal
Koopman	2009	Deficient mismatch repair system in patients with sporadic advanced colorectal cancer	British Journal of Cancer	Colorectal
Kubo	2005	Frequent microsatellite instability in primary esophageal carcinoma associated with extraesophageal primary carcinoma	International Journal of Cancer	Esophageal
Kumagai	2015	Mucinous phenotype and cd10 expression of primary adenocarcinoma of the small intestine	World Journal of Gastroenterology	Small bowel
Leenen	2012	Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer ≤70 years	Gynecologic Oncology	Endometrial
Leite	2011	MSI phenotype and MMR alterations in familial and sporadic gastric cancer	International Journal of Cancer	Gastric
Liu	2004	Microsatellite instability and expression of hMLH1 and hMSH2 proteins in ovarian endometrioid cancer	Modern Pathology	Ovarian
Lu	2007	Prospective determination of prevalence of Lynch syndrome in young women with endometrial cancer	Journal of Clinical Oncology	Endometrial
Martinez	2005	Low-level microsatellite instability phenotype in sporadic glioblastoma multiforme	Journal of Cancer Research and Clinical Oncology	Brain
Mathiak	2017	Clinicopathologic characteristics of microsatellite instable gastric carcinomas revisited: urgent need for standardization	Applied Immunohistochemistry and Molecular Morphology	Gastric
Matsumoto	2007	Microsatellite instability and clinicopathological features in esophageal squamous cell cancer	Oncology Reports	Esophageal
McCleary	2016	Prognostic utility of molecular factors by age at diagnosis of colorectal cancer	Clinical Cancer Research	Colorectal
McConechy	2015	Detection of DNA mismatch repair (mmr) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (msi) phenotype in endometrial carcinomas	Gynecologic Oncology	Endometrial
McCourt	2007	Body mass index: relationship to clinical, pathologic and features of microsatellite instability in endometrial cancer	Gynecologic Oncology	Endometrial
Moy	2015	Microsatellite instability in gallbladder carcinoma	Virchows Archiv	Gallbladder
Nagahashi	2008	Genetic changes of p53, Kras, and microsatellite instability in gallbladder carcinoma in high-incidence areas of Japan and Hungary	World Journal of Gastroenterology	Gallbladder
Okuda	2005	The profile of hMLH1 methylation and microsatellite instability in colorectal and non-small cell lung cancer	International Journal of Molecular Medicine	Colorectal, NSCLC
Rajan	2014	DNA mismatch repair defects and microsatellite instability status in periocular sebaceous carcinoma	American Journal of Ophthalmology	Sebaceous
Roa	2005	Microsatellite instability in preneoplastic and neoplastic lesions of the gallbladder	Journal of Gastroenterology	Gallbladder

Table 2: Continued.

Author	Year	Title	Journal	Tumor type
Rodriguez-Hernandez	2013	Integrated analysis of mismatch repair system in malignant astrocytomas	PLoS One (electronic resource)	Brain
Rubio	2016	Analysis of Lynch syndrome mismatch repair genes in women with endometrial cancer	Oncology	Endometrial
Rubio-Del-Campo	2008	Implications of mismatch repair genes hmlh1 and hmsh2 in patients with sporadic renal cell carcinoma	BJU international	Renal
Ruemmele	2009	Histopathologic features and microsatellite instability of cancers of the papilla of vater and their precursor lesions	The American Journal of Survival Pathology	Pancreatic
Saetta	2004	Mononucleotide markers of microsatellite instability in carcinomas of the urinary bladder	European Journal of Surgical Oncology	Bladder
Schneider	2000	Microsatellite instability, prognosis and metastasis in gastric cancers from a low-risk population	International Journal of Cancer	Gastric
Seo	2009	Clinicopathologic characteristics and outcomes of gastric cancers with the MSI-H phenotype	Journal of Surgical Oncology	Gastric
Seo	2015	Clinicopathologic and molecular features associated with patient age in gastric cancer	World Journal of Gastroenterology	Gastric
Shibata	2006	RAB32 hypermethylation and microsatellite instability in gastric and endometrial adenocarcinomas	International Journal of Cancer	Gastric and endometrial
Shilpa	2014	Microsatellite instability, promoter methylation and protein expression of the DNA mismatch repair genes in epithelial ovarian cancer	Genomics	Ovarian
Shirai	2006	Interleukin-8 gene polymorphism associated with susceptibility to non-cardia gastric carcinoma with microsatellite instability	Journal of Gastroenterology and Hepatology (Australia)	Gastric
Singer	2004	Different types of microsatellite instability in ovarian carcinoma	International Journal of Cancer	Ovarian
Skenderi	2017	Warthin-like papillary renal cell carcinoma: Clinicopathologic, morphologic, immunohistochemical and molecular genetic analysis of 11 cases	Annals of Diagnostic Pathology	Renal
Soliman	2005	Women with synchronous primary cancers of the endometrium and ovary: do they have Lynch syndrome?	Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology	Endometrial and ovarian
Sood	2001	Application of the National Cancer Institute international criteria for determination of microsatellite instability in ovarian cancer	Cancer Research	Ovarian
Stello	2016	Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts	Clinical Cancer Research	Endometrial
Stoehr	2012	Mismatch repair proteins hMLH1 and hMSH2 are differently expressed in the three main subtypes of sporadic renal cell carcinoma	Pathobiology	Renal
Suemori	2015	Intratumoral cd8+ lymphocyte infiltration as a prognostic factor and its relationship with cyclooxygenase 2 expression and microsatellite instability in endometrial cancer	International Journal of Gynecological Cancer	Endometrial
Sugai	2017	Genetic differences stratified by PCR-based microsatellite analysis in gastric intramucosal neoplasia	Gastric Cancer	Gastric
Tanaka	2006	Effect of eradication of Helicobacter pylori on genetic instabilities in gastric intestinal metaplasia	Alimentary Pharmacology and Therapeutics Symposium Series	Gastric

Table 2: Continued.

Author	Year	Title	Journal	Tumor type
Tay	2003	A combined comparative genomic hybridization and expression microarray analysis of gastric cancer reveals novel molecular subtypes	Cancer Research	Gastric
Vladimirova	2008	Low level of microsatellite instability in paediatric malignant astrocytomas	Neuropathology and Applied Neurobiology	Brain
Wen	2012	DNA mismatch repair deficiency in breast carcinoma a pilot study of triple-negative and non-triple-negative tumors	The American Journal of Survival Pathology	Breast
Wong	2003	The role of microsatellite instability in cervical intraepithelial neoplasia and squamous cell carcinoma of the cervix	Gynecologic Oncology	Cervical
Yan	2016	Prediction of biological behavior and prognosis of colorectal cancer patients by tumor msi/mmr in the Chinese population	OncoTargets and Therapy	Colorectal
Yoon	2008	Clinical significance of microsatellite instability in sporadic epithelial ovarian tumors	Yonsei Medical Journal	Ovarian
Zighelboim	2007	Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type	Journal of Clinical Oncology	Endometrial

and esophageal (6 studies). Twenty CRC studies were identified from the targeted review. Overall, 54 studies were conducted in the United States, 18 in Korea, 12 in Japan, 12 in multiple countries, and 60 in other countries. Most studies provided an MSI-H cut-off between 30 and 40%, inclusive, translating into a change in loci size of greater than or equal to 2 of 5 loci tested; however, there were two prominent outliers at 9% (Glavac 2003) and 66% (Wen 2012). Fifty-four studies used all four MMR proteins to detect MMR status, 3 studies used three proteins, 6 studies used two proteins, and 3 studies did not specify number of proteins used. Included studies reported different study designs: case control, cross-sectional, prospective cohort, and retrospective cohort.

3.3. Patient Characteristics. Across studies, the mean/median age ranged from 20.7 to 74 years. Percentage of patients by ethnicity ranged as follows: Caucasian (0–94.8%), African American (0–17.2%), Asian (0–100%), and other ethnic groups (0–13.8%). In studies where disease stage was reported, percentage of patients with stage 1 disease ranged from 0 to 80.7%, stage 2 disease ranged from 4.2 to 38.6%, stage 3 disease ranged from 8 to 73.5%, and stage 4 disease ranged from 0 to 97.7%.

3.4. MSI-H and dMMR Prevalence. The number of studies with available MSI-H and dMMR data is presented in Table 5. Of the 156 included studies, MSI-H prevalence as determined by NCI or Promega markers was reported in 90 studies, and MSS prevalence was reported in 79 studies. Sixty-six studies reported dMMR prevalence; 54 of those used all 4 MMR proteins in the IHC assay. Pooled MSI-H and dMMR prevalence estimates were reported in 140 studies.

MSI-H prevalence was available in 25 studies conducted in the United States, 17 studies conducted in Korea, and 8 studies conducted in Japan. dMMR prevalence data were available in 27 conducted in the United States and 2 studies conducted in Japan. MSI-H prevalence was reported by stages 1 (18 studies), 2 (18 studies), 3 (17 studies), 4 (16 studies), 1 or 2 (24 studies), and 3 or 4 (23 studies).

Beyond the 6 main tumor types feasible for tumor-specific meta-analyses, 19 other tumor types were included in the meta-analysis of overall MSI-H prevalence. Overall, MSI-H prevalence differed considerably across tumor types. A low prevalence of 2% (95% CI, 0%–8%) was observed in Ewing sarcoma [19], while a much higher prevalence of 35% (95% CI, 15%–57%) was reported in sebaceous tumors [20]. Small bowel [21] and cervical tumors [22] had prevalence of 12% each, which were very close to the all-tumor estimate.

3.5. Meta-Analysis Results: Random Effects. Overall meta-analysis results is presented in Figure 2. Prevalence estimates, 95% confidence intervals, and number of studies included in each analysis are shown. Meta-analysis results obtained from the random effects model in all tumor types are presented as forest plots in the Supplementary information (Appendix Figures 1–Figure 26). Funnel plots obtained from each meta-analysis are also presented in the Supplementary information (Appendix Figure 27–Figure 44).

The weighted prevalence of MSI-H without genomic studies was estimated to be 14% (95% CI, 10%–19%) across all tumor types and stages. The prevalence was 10% (95% CI, 7%–14%) when four of the five large pan-tumor genomic studies were included (one genomic study was excluded as it did not report the total number of patients or the number of patients with MSI-H). Overall weighted dMMR prevalence was estimated to be 16% (95% CI, 11%–22%) across all

Table 3: References—MMR studies.

Author	Year	Title	Journal	Tumor type
Backes	2009	Prospective evaluation of DNA mismatch repair protein expression in primary endometrial cancer	Gynecologic Oncology	Endometrial
Bennett	2016	Mismatch repair protein expression in clear cell carcinoma of the ovary: incidence and morphologic associations in 109 cases	The American Journal of Surgical Pathology	Ovarian
Bhosale	2017	Can reduced field-of-view diffusion sequence help assess microsatellite instability in FIGO stage 1 endometrial cancer?	Journal of Magnetic Resonance Imaging	Endometrial
Brady	2017	Sebaceous carcinoma treated with Mohs micrographic surgery	Dermatologic Surgery	Sebaceous
Bregar	2017	Characterization of immune regulatory molecules b7-h4 and pd-l1 in low and high grade endometrial tumors	Gynecologic Oncology	Endometrial
Bruegl	2014	Evaluation of clinical criteria for the identification of Lynch syndrome among unselected patients with endometrial cancer	Cancer Prevention Research	Endometrial
Bruegl	2017	Clinical challenges associated with universal screening for Lynch syndrome-associated endometrial cancer	Cancer Prevention Research	Endometrial
Buchanan	2014	Tumor mismatch repair immunohistochemistry and DNA mlh1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing	Journal of Clinical Oncology	Endometrial
Carleton	2016	A detailed immunohistochemical analysis of a large series of cervical and vaginal gastric-type adenocarcinomas	The American Journal of Surgical pathology	Cervical and vaginal
Chen	2017	Immunohistochemical profiling of endometrial serous carcinoma	International Journal of Gynecological Pathology	Endometrial
Clay	2014	Risk of secondary malignancy (including breast) in patients with mismatch-repair protein deficiency	The American Journal of Surgical pathology	Endometrial
Connor	2017	Association of distinct mutational signatures with correlates of increased immune activity in pancreatic ductal adenocarcinoma	JAMA Oncology	Pancreatic
Djordjevic	2013	Relationship between PTEN, DNA mismatch repair, and tumor histotype in endometrial carcinoma: retained positive expression of PTEN preferentially identifies sporadic non-endometrioid carcinomas	Modern Pathology	Endometrial
Everett	2014	Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm	JAMA Dermatology	Sebaceous
Gaskin	2011	The significance of DNA mismatch repair genes in the diagnosis and management of periocular sebaceous cell carcinoma and Muir-Torre syndrome	British Journal of Ophthalmology	Sebaceous
Goldberg	2017	Microcystic, elongated, and fragmented pattern invasion in ovarian endometrioid carcinoma: immunohistochemical profile and prognostic implications	International Journal of Gynecological Pathology	Ovarian
Grzankowski	2012	Clinical and pathologic features of young endometrial cancer patients with loss of mismatch repair expression	Gynecologic Oncology	Endometrial
Joehlin-Price	2014	Mismatch repair protein expression in 1049 endometrial carcinomas, associations with body mass index, and other clinicopathologic variables	Gynecologic Oncology	Endometrial
Kato	2015	DNA mismatch repair-related protein loss as a prognostic factor in endometrial cancers	Journal of Gynecologic Oncology	Endometrial
Kawazoe	2017	Clinicopathological features of programmed death ligand 1 expression with tumor-infiltrating lymphocyte, mismatch repair, and Epstein-Barr virus status in a large cohort of gastric cancer patients	Gastric Cancer	Gastric
Kobel	2017	Frequent mismatch repair protein deficiency in mixed endometrioid and clear cell carcinoma of the endometrium	International Journal of Gynecological Pathology	Endometrial

Table 3: Continued.

Author	Year	Title	Journal	Tumor type
Liau	2014	Hypermethylation of the cdkn2a gene promoter is a frequent epigenetic change in periocular sebaceous carcinoma and is associated with younger patient age	Human Pathology	Sebaceous
Liu	2014	DNA mismatch repair abnormalities in acinar cell carcinoma of the pancreas frequency and clinical significance	Pancreas	Pancreatic
Milione	2016	The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories	Neuroendocrinology	Gastroenteropancreatic
Moreira	2012	Identification of Lynch syndrome among patients with colorectal cancer	JAMA	Colorectal
Okoye	2016	Defective DNA mismatch repair influences expression of endometrial carcinoma biomarkers	International Journal of Gynecological Pathology	Endometrial
Park	2016	Epstein-Barr virus positivity, not mismatch repair-deficiency, is a favorable risk factor for lymph node metastasis in submucosa-invasive early gastric cancer	Gastric Cancer	Gastric
Pecorino	2017	Genetic screening in young women diagnosed with endometrial cancer	Journal of Gynecologic Oncology	Endometrial
Peterson	2012	Molecular characterization of endometrial cancer: a correlative study assessing microsatellite instability, mlh1 hypermethylation, DNA mismatch repair protein expression, and pten, pik3ca, kras, and braf mutation analysis	International Journal of Gynecological Pathology	Endometrial
Ramos	2017	Lymphoepithelioma-like gastric carcinoma: Clinicopathological characteristics and infection status	Journal of surgical Research	Gastric
Ring	2013	Women 50 years or younger with endometrial cancer the argument for universal mismatch repair screening and potential for targeted therapeutics	International Journal of Gynecological Cancer	Endometrial
Roberts	2013	Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms	Journal of Genetic Counseling	Sebaceous
Rosa-Rosa	2016	Molecular genetic heterogeneity in undifferentiated endometrial carcinomas	Modern Pathology	Endometrial
Ruiz	2014	Lack of association between deficient mismatch repair expression and outcome in endometrial carcinomas of the endometrioid type	Gynecologic Oncology	Endometrial
Sahnane	2015	Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity	Endocrine-Related Cancer	Gastroenteropancreatic
Shih	2011	Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger	Gynecologic Oncology	Endometrial
Steinestel	2014	Invasion pattern and histologic features of tumor aggressiveness correlate with MMR protein expression, but are independent of activating kras and braf mutations in CRC	Virchows Archiv	Colorectal
Talhouk	2016	Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: earlier prognostic information to guide treatment	Gynecologic Oncology	Endometrial
Talhouk	2015	A clinically applicable molecular-based classification for endometrial cancers	British Journal of Cancer	Endometrial
Talhouk	2017	Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer	Cancer	Endometrial
Therkildsen	2015	Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome	European Journal of Neurology	Brain

Table 3: Continued.

Author	Year	Title	Journal	Tumor type
Thoury	2014	Evidence for different expression profiles for c-Met, EGFR, PTEN and the mTOR pathway in low and high grade endometrial carcinomas in a cohort of consecutive women. Occurrence of pik3ca and k-ras mutations and microsatellite instability	Histology and Histopathology	Endometrial
Vierkoetter	2014	Lynch syndrome in patients with clear cell and endometrioid cancers of the ovary	Gynecologic Oncology	Ovarian
Vierkoetter	2016	Loss of mismatch repair protein expression in unselected endometrial adenocarcinoma precursor lesions	International Journal of Gynecological Cancer	Endometrial
Watkins	2016	Universal screening for mismatch-repair deficiency in endometrial cancers to identify patients with Lynch syndrome and Lynch-like syndrome	International Journal of Gynecological Pathology	Endometrial
Wiegand	2014	Arid1a/baf250a as a prognostic marker for gastric carcinoma: a study of 2 cohorts	Human Pathology	Gastric
Woo	2014	The immunohistochemistry signature of mismatch repair (MMR) proteins in a multiethnic Asian cohort with endometrial carcinoma	International Journal of Gynecological Pathology	Endometrial
Zakhour	2017	Abnormal mismatch repair and other clinicopathologic predictors of poor response to progestin treatment in young women with endometrial complex atypical hyperplasia and well-differentiated endometrial adenocarcinoma: a consecutive case series	BJOG: An International Journal of Obstetrics and Gynecology	Endometrial

Table 4: References–genomic studies.

Author	Year	Title	Journal	Tumor type
Bonneville	2017	Landscape of microsatellite instability across 39 cancer types	JCO Precision Oncology	Many (genomic)
Chalmers	2017	Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden	Genome Medicine	Many (genomic)
Cortes-Ciriano	2017	A molecular portrait of microsatellite instability across multiple cancers	Nature Communications	Many (genomic)
Hause	2016	Classification and characterization of microsatellite instability across 18 cancer types	Nature Medicine	Many (genomic)
Le	2017	Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade	Science	Many (genomic)

Table 5: Availability of prevalence data.

Subset	Any (with and without results)	Reported MSI-H data	Reported dMMR (any IHC)	Reported dMMR (4 MMR proteins)	Reported MSS	Reported MSI-H/dMMR
Total number of studies included	156	94	66	54	79	140
Studies in gastric cancer	39	32	6	4	23	35
Studies in endometrial cancer	53	27	28	26	16	49
Studies in ovarian cancer	23	17	8	5	13	20
Studies in colorectal cancer	20	14	8	4	6	17
Studies in esophageal cancer	6	6	0	0	3	6
Studies in renal cancer	9	7	3	1	3	8
Studies in other cancers	36	18	16	13	21	31

Abbreviations: MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; MSS, microsatellite stable.

Subgroup	Status	*N* study	*N*	*n*	Prevalence	95% CI
Overall	dMMR	54	20383	3279	0.16	0.11–0.22
Overall (sens.)	dMMR	52	20216	3190	0.16	0.12–0.21
Country-United States	dMMR	27	5416	1066	0.14	0.06–0.23
Country-United States (sens.)	dMMR	25	2594	977	0.14	0.07–0.22
Country-Japan	dMMR	2	678	101	0.20	0.00–0.63
Overall (without genomic studies)	MSI-H	90	28213	3494	0.14	0.10–0.19
Overall (with genomic studies)	MSI-H	94	66669	4843	0.10	0.07–0.14
Country-United States	MSI-H	25	5654	1127	0.20	0.16–0.24
Country-Korea	MSI-H	17	14630	1192	0.09	0.06–0.12
Country-Japan	MSI-H	8	1681	198	0.16	0.09–0.26
Stage 1	MSI-H	18	3305	409	0.10	0.04–0.17
Stage 2	MSI-H	18	1535	258	0.19	0.11–0.27
Stage 3	MSI-H	17	1636	157	0.09	0.03–0.17
Stage 4	MSI-H	18	665	36	0.03	0.01–0.07
Stages 1-2	MSI-H	24	5827	915	0.15	0.08–0.23
Stages 3-4	MSI-H	23	2514	246	0.09	0.04–0.16
Overall (without genomic studies)	MSI-H/dMMR	136	47218	6560	0.15	0.11–0.18
Overall (with genomic studies)	MSI-H/dMMR	140	85674	7909	0.11	0.08–0.15
Overall	MSS	79	17613	14056	0.79	0.72–0.85

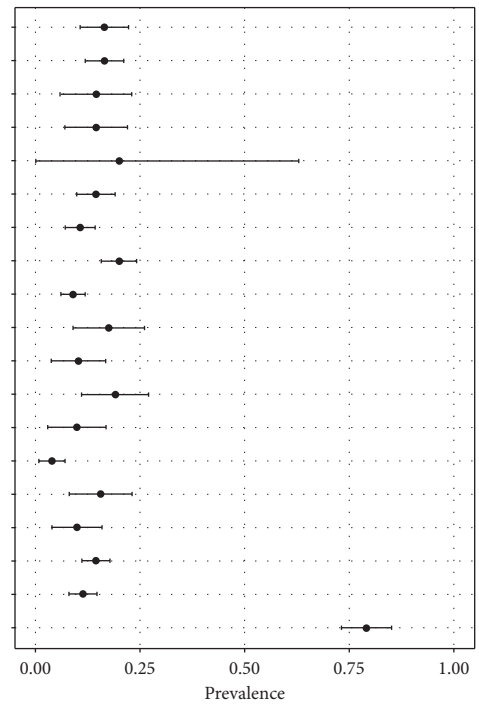

Figure 2: Summary of meta-analysis results, all tumor types, random effects. Abbreviations: *N*, total number of subjects; *n*, number of subjects with mutation status of interest.

tumor types and stages. This estimate remained unchanged (16% (95% CI, 12%–21%)) in the sensitivity analysis, in which two studies (Everett 2014 and Roberts 2013) that possibly screened patients based on their Lynch syndrome status were excluded. Overall, MSS prevalence was found to be 79% (95% CI, 72%–85%) across tumor types and stages. Estimated pooled MSI-H and dMMR prevalence without genomic studies was 15% (95% CI, 11%–18%) and dropped to 11% (95% CI, 8%–15%) when genomic studies were included.

Country-specific MSI-H prevalence was estimated only in the United States, Korea, and Japan, for which at least 2 publications were included. The weighted prevalence of MSI-H for the United States, Korea, and Japan was estimated at 20% (95% CI, 16%–24%), 9% (95% CI, 6%–12%), and 16% (95% CI, 9%–26%), respectively, across all cancers and stages. dMMR all-stage prevalence for the United States was estimated at 14% (95% CI, 6%–23%) and for Japan was estimated at 20% (95% CI, 0%–63%). Stages 1-2 MSI-H prevalence was 15% (8–23%), while stage 3 and stage 4 prevalence was estimated at 9% (3%–17%) and 3% (1%–7%), respectively.

Tumor-specific meta-analysis was feasible for 3 key gastrointestinal tumors (gastric, colorectal, and esophageal), 2 gynecological tumors (endometrial and ovarian), and 1 genitourinary tumor (renal) with results presented in Figures 3–5. Among the gastrointestinal tumors, gastric cancer MSI-H pooled prevalence (with 95% CI) from 32 studies (16,308 patients) was estimated at 11% (9–12%) and dMMR pooled prevalence from 4 studies (854 patients) was estimated at 8% (2–17%); Based on stages across gastrointestinal tumors, the prevalence was 13% (10%–16%; 10 studies; 3,194 patients) for stages 1-2, and the prevalence was 10% (7–13%; 10 studies; 1,319 patients) in stages 3-4 cancer. The highest MSI-H pooled prevalence was observed for the intestinal histological subtype with 13% (10–17%) based on 14 studies (2,652 patients). In CRC, MSI-H pooled prevalence from 14 studies (8,156 patients) was estimated at 13% (10–16%) and dMMR pooled prevalence from 4 studies (11,434 patients) was estimated at 10% (5–15%). For stages 1-2 CRC, the prevalence was 20% (10%–32%; 4 studies; 888 patients), and for stages 3-4, the prevalence was 9% (3–16%; 4 studies; 873 patients). Based on histology, the highest MSI-H pooled prevalence was observed for the poorly differentiated CRC subtype with 32% (25–40%) based on 6 studies (1,204 patients). Among esophageal cancers, MSI-H pooled prevalence from 3 studies (147 patients) was estimated at 4% (0–11%). For stages 3-4 esophageal cancers, the prevalence was 18% (4%–39%; 2 studies; 62 patients). Based on histology, the highest MSI-H pooled prevalence was observed for well-differentiated and poorly differentiated esophageal subtypes with 16% (3–35%) and 16% (0%–45%), respectively. dMMR analysis was not feasible for esophageal tumors. For the gynecological tumors, endometrial cancer MSI-H pooled prevalence from 27 studies (6,813 patents) was estimated at 26% (23–29%) and dMMR pooled prevalence from 26 studies (5,248 patients) was estimated at 25% (22–28%). In ovarian cancers, MSI-H pooled prevalence from 17 studies (4,150 patients) was estimated at 11% (6–18%) and dMMR pooled prevalence from 5 studies (356

Cancer	Subgroup	Status	*N* study	*N*	*n*	Prevalence	95% CI
Endometrial	Overall	dMMR	26	5248	1302	0.25	0.22–0.28
Endometrial	Country-United States	dMMR	15	3311	770	0.21	0.18–0.25
Endometrial	overall	MSI-H	27	6813	1773	0.26	0.23–0.29
Endometrial	Country-United States	MSI-H	14	4396	1127	0.25	0.22–0.30
Endometrial	Country-Japan	MSI-H	2	192	65	0.34	0.27–0.41
Endometrial	Stages 1-2	MSI-H	4	1360	374	0.27	0.21–0.33
Endometrial	Stages 3-4	MSI-H	3	109	32	0.26	0.14–0.41
Endometrial	Histology-endometrioid	MSI-H	6	1204	368	0.30	0.25–0.35
Endometrial	Histrology-clear cell	MSI-H	2	4	1	0.27	0.00–0.77
Endometrial	Histrology-serous	MSI-H	3	29	4	0.14	0.04–0.29
Endometrial	Histrology-mixed	MSI-H	2	11	2	0.20	0.01–0.48
Ovarian	Overall	dMMR	5	356	28	0.08	0.06–0.11
Ovarian	Country-United States	dMMR	5	356	28	0.08	0.06–0.11
Ovarian	Overall	MSI-H	17	4150	299	0.11	0.06–0.18
Ovarian	Country-United States	MSI-H	11	2832	125	0.09	0.04–0.16
Ovarian	Satges 1-2	MSI-H	2	68	12	0.17	0.07–0.30
Ovarian	Stages 3-4	MSI-H	2	47	9	0.20	0.09–0.32
Ovarian	Histology-endometrioid	MSI-H	3	211	34	0.17	0.09–0.27
Ovarian	Histology-clear cell	MSI-H	3	103	10	0.10	0.05–0.17
Ovarian	Histology-serous	MSI-H	3	529	76	0.14	0.12–0.18
Ovarian	Histology-mucinous	MSI-H	2	43	7	0.17	0.07–0.30

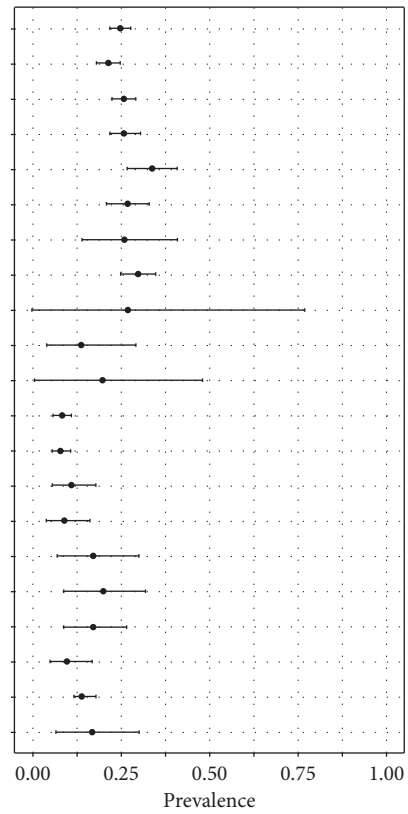

Figure 3: Summary of meta-analysis results, gynecological tumors, random effects. Abbreviations: *N*, total number of subjects; *n*, number of subjects with mutation status of interest.

patients) was estimated at 8% (6–11%). Based on histology, the highest MSI-H pooled prevalence was observed for endometrioid subtype for each tumor with 30% (25–35%) based on 6 studies (1,204 patients) for endometrial cancers and 17% (25–35%) based on 3 studies (211 patients) for ovarian cancers. Among renal tumors, MSI-H all-stage prevalence was estimated to be 1% (95% CI, 0%–2%) based on 7 studies (2,231 patients); dMMR analysis was not feasible for renal tumors.

4. Discussion

This structured literature review and meta-analysis investigated MSI-H and dMMR prevalence across tumor types and compared prevalence estimates by tumor type, tumor stage, and country subgroups. Analysis results estimated the prevalence of MSI-H across all tumor types as 14% (95% CI, 10%–19%). dMMR prevalence was comparable at 16% (95% CI, 11%–22%).

Pooled dMMR prevalence estimates by tumor type were similar to those for MSI-H. It has been suggested that, for Lynch syndrome testing, PCR testing may be less sensitive than IHC due to the fact that mutations in MSH6 may present as MSI-L [23]. The results of this review, however, suggest that MSI-H and dMMR IHC testing results are generally comparable.

The United States had higher MSI-H prevalence than Korea and Japan, but this result is possibly biased due to the lack of weighting for country-specific tumor prevalence.

Subgroup analysis indicated that early stage diseases (stage 1 and 2) tended to have a higher MSI-H prevalence than later stages (stages 3 and 4). Numerous studies have established the value of MSI status as a prognostic factor [24–26]. Results of a meta-analysis including 7642 patients indicated that MSI (MSI-H + MSI-L) tumors corresponded with significantly improved prognosis compared to MSS CRCs (overall survival HR 0.65 (95% CI, 0.59–0.71) [27]. This may partially explain the lower MSI-H prevalence in the later stages of cancers.

Some tumor types had noticeably higher MSI-H prevalence than others. Endometrial tumors had MSI-H prevalence of 26% (95% CI, 23%–29%), whereas renal tumors only had MSI-H prevalence of 1% (95% CI, 0%–2%). This observation corroborates findings from recent genomic studies, which revealed that the frequency of MSI-H events is highly variable across tumor types [13, 28]. One study noted that MSI-H prevalence was highest in Lynch syndrome-associated tumor types (endometrial, colon, gastric, and rectal) [13] which is well-aligned with findings from the current study.

The identified evidence base included 156 articles reporting on the prevalence of MSI-H and/or dMMR

Cancer	Subgroup	Status	*N* study	*N*	*n*	Prevalence	95% CI
Gastric	Overall	dMMR	4	854	72	0.08	0.02–0.17
Gastric	Overall	MSI-H	32	16308	1441	0.11	0.09–0.12
Gastric	Country-United States	MSI-H	4	993	168	0.16	0.11–0.22
Gastric	Country-Korea	MSI-H	14	13122	1015	0.08	0.07–0.10
Gastric	Stages 1-2	MSI-H	10	3194	346	0.13	0.10–0.16
Gastric	Stages 3-4	MSI-H	10	1319	104	0.10	0.07–0.13
Gastric	Histology-intestinal	MSI-H	14	2652	348	0.13	0.10–0.17
Gastric	Histology-diffuse	MSI-H	14	2281	104	0.05	0.03–0.08
Gastric	Histology-mixed	MSI-H	8	368	35	0.10	0.07–0.13
Colorectal	Overall	dMMR	4	11434	1513	0.10	0.05–0.15
Colorectal	Overall	MSI-H	14	8156	937	0.13	0.10–0.16
Colorectal	Country-United States	MSI-H	5	4820	569	0.12	0.08–0.17
Colorectal	Country-Korea	MSI-H	4	1530	182	0.13	0.05–0.24
Colorectal	Stages 1-2	MSI-H	4	888	144	0.20	0.10–0.32
Colorectal	Stages 3-4	MSI-H	4	873	69	0.09	0.03–0.16
Colorectal	Histology-well-differentiated	MSI-H	2	149	12	0.08	0.04–0.13
Colorectal	Histology-poorly differentiated	MSI-H	3	147	47	0.32	0.25–0.40
Colorectal	Histology-mucinous	MSI-H	2	21	3	0.14	0.00–0.36
Esophageal	Overall	MSI-H	6	731	33	0.04	0.00–0.11
Esophageal	Country-United States	MSI-H	2	383	4	0.01	0.00–0.02
Esophageal	Country-Japan	MSI-H	2	138	26	0.15	0.01–0.39
Esophageal	Stages 3-4	MSI-H	2	62	13	0.18	0.04–0.93
Esophageal	Histology-well-differentiated	MSI-H	3	46	7	0.16	0.03–0.35
Esophageal	Histology-moderately differentiate	MSI-H	3	65	9	0.09	0.00–0.27
Esophageal	Histology-poorly differentiated	MSI-H	3	50	10	0.16	0.00–0.45

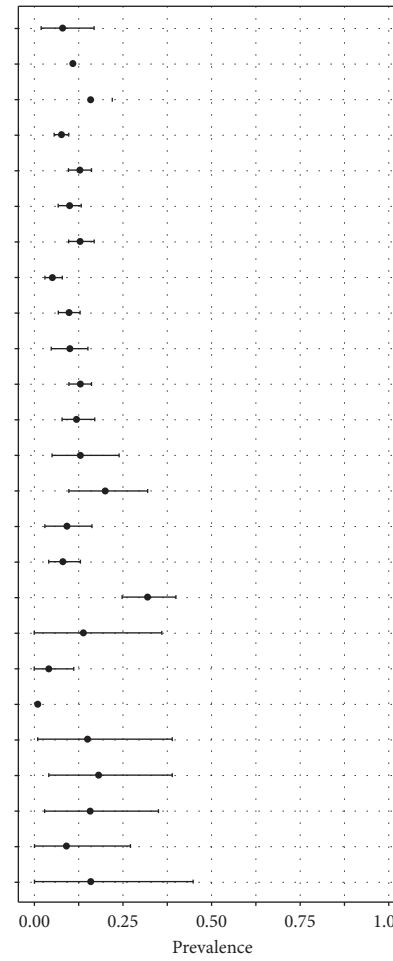

Figure 4: Summary of meta-analysis results, gastrointestinal tumors, random effects. Abbreviations: *N*, total number of subjects; *n*, number of subjects with mutation status of interest.

Cancer	Subgroup	Status	*N* study	*N*	*n*	Prevalence	95% CI
Renal	Overall	MSI-H	7	2231	21	0.01	0.01–0.02
Renal	Country-United States	MSI-H	3	1276	11	0.01	0.00–0.02

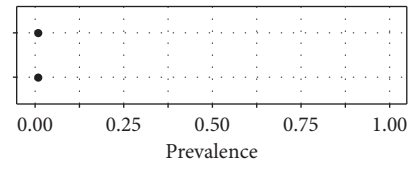

Figure 5: Summary of meta-analysis results, genitourinary tumors, random effects. Abbreviations: *N*, total number of subjects; *n*, number of subjects with mutation status of interest.

published between 1999 and 2017. This review includes the most cancer types of a published review to date. Of the other two known published meta-analyses that have quantified the prevalence of MSI-H for selective tumors, the first (including publications to 2007) reported an MSI-H prevalence of 12% (95% CI, 8%–17%) in ovarian tumors [29], the second (including publications to 2009) reported an MSI-H prevalence of 10% (95% CI, 6%–14%) in ovarian tumors [30], and the third (including studies published up to 2014) reported an MSI-H prevalence of 17% (95% CI, 15%–19%) in colorectal tumors [31]. The finding from the current meta-analysis suggests MSI-H prevalence of 11% (95% CI, 6%–18%) in ovarian cancer patients and 13% (95% CI, 10%–16%) in colorectal cancer patients, which are well-aligned with findings from previous meta-analyses.

This large-scale meta-analysis of the prevalence of MSI-H and dMMR used rigorous methodology in selection of testing methods, subgroup analyses, and incorporation of pan-tumor genomic studies in sensitivity analyses. First, this meta-analysis of MSI-H and dMMR prevalence included the

most number of studies (156) to date. Second, weighting techniques were used to adjust for overall tumor prevalence in order to prevent oversampling of commonly reported tumor types. Third, only studies that utilized the "gold standard" MSI-H and dMMR testing methods were included in the meta-analysis, so the results from these studies were more comparable. Fourth, the subgroup analyses, which were stratified by factors such as tumor type, country, and disease stage, indicated which factors had potential association with prevalence. Fifth, the inclusion of pan-tumor genomic studies in the sensitivity analyses offered an alternative scenario and suggested that the testing method used in large-scale genomic studies (sequencing) is significantly different from the widely accepted methods (PCR and IHC) used in other included studies.

This meta-analysis has some limitations. First, the literature review for CRC was a targeted hand search; some potentially relevant publications may not have been identified. Studies were reviewed by a single researcher, but a quality check was performed to validate the dataset. An additional limitation was the heterogeneity of included study designs included, which included case control, cross-sectional, prospective cohort, and retrospective cohort studies. However, because of scarcity of the numbers in most cancer types, studies with different designs were included to maximize the data sources. Symmetry was observed on most funnel plots, which suggest a lack of publication bias. To address heterogeneity in study designs included in the meta-analysis, data were analyzed using fixed- and random-effects models; however, this exploration did not provide evidence of any specific source of heterogeneity. Finally, given the lack of MSI/MMR publications on a few major cancer types, the "overall" prevalence estimate does not include all solid tumors.

Recent evidence [32, 33] supporting the role of MSI-H and dMMR, and associated immunogenicity as a mechanism for increased efficacy of PD-1/PD-L1 blockade in metastatic tumors with MSI-H or dMMR [8], demonstrates to the importance of increasing understanding [34] of prevalence across tumor type, stage, histology, and ethnicity.

Conflicts of Interest

M. Amonkar and K.-L. Liaw are employees of and own shares in Merck & Co, Inc. The other authors declare no conflicts of interests.

Acknowledgments

This work was financially supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Supplementary Materials

Meta-analysis results obtained from random effects model in all tumor types are presented as forest plots in the Supplementary information (Appendix Figures 1–Figure 26). Funnel plots obtained from each meta-analysis are also presented in the Supplementary information (Appendix Figure 27–Figure 44). (*Supplementary Materials*)

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