Review Article

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

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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 29% 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 arc sine square root (double arc sine) 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
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),
| Author          | Year | Title                                                                 | Journal                                      | Tumor type       |
|-----------------|------|----------------------------------------------------------------------|----------------------------------------------|------------------|
| Abraham         | 2002 | Microsatellite instability in intraductal papillary neoplasms of the biliary tract P53 nuclear stabilization is associated with FHIT loss and younger age of onset in squamous cell carcinoma of oral tongue Correlation between germline mutations in MMR genes and microsatellite instability in ovarian cancer specimens Microsatellite instability in Ewing tumor is not associated with loss of mismatch repair protein expression | Nature                                      | Pancreatic       |
| Adduri          | 2014 | P53 nuclear stabilization is associated with FHIT loss and younger age of onset in squamous cell carcinoma of oral tongue Correlation between germline mutations in MMR genes and microsatellite instability in ovarian cancer specimens | BMC Clinical Pathology                        | Oral cavity      |
| Akbari          | 2017 | MMR genes and microsatellite instability in ovarian cancer specimens Microsatellite instability in Ewing tumor is not associated with loss of mismatch repair protein expression | 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 Colorectal cancer with BRAF D594G mutation Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma Microsatellite instability in sporadic gastric cancer; its prognostic role and guidance for 5-fluorouracil-based chemotherapy after resection Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability | Oncology Reports | Renal            |
| Amaki-Takao     | 2016 | Microsatellite instability in Ewing tumor is not associated with loss of mismatch repair protein expression | Oncology (Switzerland)                       | Colorectal       |
| An              | 2005 | Microsatellite instability and hMLH1 and hMSH2 expression in renal tumors Colorectal cancer with BRAF D594G mutation Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma Microsatellite instability in sporadic gastric cancer; its prognostic role and guidance for 5-fluorouracil-based chemotherapy after resection Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability | Clinical Cancer Research                      | Gastric          |
| An              | 2012 | Microsatellite instability and hMLH1 and hMSH2 expression in renal tumors Colorectal cancer with BRAF D594G mutation Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma Microsatellite instability in sporadic gastric cancer; its prognostic role and guidance for 5-fluorouracil-based chemotherapy after resection Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability | International Journal of Cancer              | Gastric          |
| Aparicio        | 2013 | Microsatellite instability and hMLH1 and hMSH2 expression in renal tumors Colorectal cancer with BRAF D594G mutation Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma Microsatellite instability in sporadic gastric cancer; its prognostic role and guidance for 5-fluorouracil-based chemotherapy after resection Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability | British Journal of Cancer                     | Small bowel      |
| Aysal           | 2012 | Microsatellite instability and hMLH1 and hMSH2 expression in renal tumors Colorectal cancer with BRAF D594G mutation Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma Microsatellite instability in sporadic gastric cancer; its prognostic role and guidance for 5-fluorouracil-based chemotherapy after resection 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 | Oncology Reports                                      | Clinical Cancer Research                      | Gastric          |
| Bae             | 2015 | Oncology Reports                                      | International Journal of Cancer              | Gastric          |
| Basil           | 2000 | Oncology Reports                                      | British Journal of Cancer                     | Small bowel      |
| Bataille        | 2003 | Oncology Reports                                      | The American Journal of Surgical Pathology    | Ovarian          |
| Billingsley     | 2015 | Oncology Reports                                      | Journal of Molecular Diagnostics            | Gastric          |
| Black           | 2006 | Oncology Reports                                      | Gut and Liver                                | Gastric          |
| Buller          | 2001 | Oncology Reports                                      | American Journal of Obstetrics & Gynecology  | Endometrial      |
| Buttin          | 2006 | Oncology Reports                                      | International Journal of Gynecological Cancer| Endometrial      |
| Cai             | 2004 | Oncology Reports                                      | Human Pathology                              | Ovarian          |
| Catasus         | 2004 | Oncology Reports                                      | 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 | Microsatellite instability 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                         |
| 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 | 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) Assessment of microsatellite instability status | The New England Journal of Medicine          | Colorectal  |
| Hasuo           | 2007 | 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 Microsatellite instability, mismatch repair deficiency, and BRAF mutation in treatment-resistant germ cell tumors The differential impact of microsatellite instability as a marker of prognosis and tumour response between colon cancer and rectal cancer | Head & neck                                  | Nasopharynx |
| Honecker        | 2009 | Study                                                                 | Journal of Clinical Oncology                 | Testis      |
| Hong            | 2012 | Comparative features of colorectal and gastric cancers with microsatellite instability in Chinese patients | European Journal of Cancer                   | Colorectal  |
| Huang           | 2010 | Journal of Zhejiang University Science                                 |                                               | Gastric and colorectal |
| Jahng           | 2012 | 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| Observational study; familial relevance and oncological significance of revised Bethesda guidelines in colorectal patients that have undergone curative resection | Annals of Coloproctology                    | Colorectal  |
| Jung            | 2016b| Medicina                                                               |                                               | Colorectal  |
| Kanopiene       | 2014 | Impact of microsatellite instability on survival of endometrial cancer patients | Medicina                                     | Endometrial |
| Karpinska-      | 2016 | Expression of mismatch repair proteins in early and advanced gastric cancer in Poland Analysis of candidate target genes for mononucleotide repeat mutation in microsatellite instability-high (MSI-H) endometrial cancer | Medical Science Monitor                      | Gastric     |
| Kaczmarsczyk    |      |                                                                        |                                               |             |
| Kawaguchi       | 2009 | Effects of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic treatment: analysis of molecular alterations by a randomised controlled trial Accumulated frameshift mutations at coding nucleotide repeats during the progression of gastric carcinoma with microsatellite instability Microsatellite instability status in gastric cancer: a reappraisal of its clinical significance and relationship with mucin phenotypes Differential clinicopathologic features in microsatellite-unstable gastric cancers with and without MLH1 methylation | International Journal of Oncology           | Endometrial |
| Kawanaka        | 2016 | British Journal of Cancer                                             |                                               | Gastric     |
| Kim             | 1999 | Laboratory Investigation                                             |                                               | Gastric     |
| Kim             | 2013a| Korean Journal of Pathology                                           |                                               | Gastric     |
| Kim             | 2013b| Human Pathology                                                       |                                               | Gastric     |
| 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 Frequent microsatellite instability in primary esophageal carcinoma associated with extraesophageal primary carcinoma | British Journal of Cancer                | Colorectal                      |
| Kubo   | 2005 | Frequent microsatellite instability in primary esophageal carcinoma                                                                                                                                       | International Journal of Cancer         | Esophageal                      |
| Koopman| 2009 | Deficient mismatch repair system in patients with sporadic advanced colorectal cancer Frequent microsatellite instability in primary esophageal carcinoma associated with extraesophageal primary carcinoma | British Journal of Cancer                | Colorectal                      |
| Leenen | 2012 | MSI phenotype and MMR alterations in familial and sporadic gastric cancer Microsatellite instability and expression of hMLH1 and hMSH2 proteins in ovarian endometrioid cancer | Gynecologic Oncology                     | Endometrial                     |
| Leite  | 2011 | MSI phenotype and MMR alterations in familial and sporadic gastric cancer Microsatellite instability and expression of hMLH1 and hMSH2 proteins in ovarian endometrioid 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 Clinicoopathologic characteristics of microsatellite instable gastric carcinomas revisited: urgent need for standardization | Journal of Cancer Research and Clinical Oncology | Brain                           |
| Mathiak| 2015 | Microsatellite instability and clinopathological features in esophageal squamous cell cancer                                                                                                                                 | Applied Immunohistochemistry and Molecular Morphology | Gastric                         |
| Matsumoto| 2007| Prognostic utility of molecular factors by age at diagnosis of colorectal cancer Detection of DNA mismatch repair (mmr) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (msi) phenotype in endometrial carcinomas | Oncology Reports                         | Endometrial                     |
| McCleary| 2016| Prognostic utility of molecular factors by age at diagnosis of colorectal cancer Detection of DNA mismatch repair (mmr) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (msi) phenotype in endometrial carcinomas | Clinical Cancer Research                 | Colorectal                      |
| McConchy| 2015| Body mass index: relationship to clinical, pathologic and features of microsatellite instability in endometrial cancer                                                                                                                                               | Gynecologic Oncology                     | Endometrial                     |
| McCourt| 2007| Microsatellite instability in gallbladder carcinoma Genetic changes of p53, Kras, and microsatellite instability in gallbladder carcinoma in high-incidence areas of Japan and Hungary | Gynecologic Oncology                     | Endometrial                     |
| Moy    | 2015 | Microsatellite instability in gallbladder carcinoma Genetic changes of p53, Kras, and microsatellite instability in gallbladder carcinoma in high-incidence areas of Japan and Hungary | Virchows Archiv                          | Gallbladder                     |
| Nagahashi| 2008| The profile of hMLH1 methylation and microsatellite instability in colorectal and non-small cell lung cancer DNA mismatch repair defects 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 DNA mismatch repair defects and microsatellite instability in gallbladder carcinoma in high-incidence areas of Japan and Hungary | International Journal of Molecular Medicine | Colorectal, NSCLC              |
| Rajan  | 2014 | Microsatellite instability in periocular sebaceous carcinoma                                                                                                                                             | American Journal of Ophthalmology      | Sebaceous                       |
| Roa    | 2005 | Microsatellite instability in prineoplastic and neoplastic lesions of the gallbladder                                                                                                                                         | Journal of Gastroenterology             | Gallbladder                     |
| 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 | Implications of mismatch repair genes hmlh1 and hmsh2 in patients with sporadic renal cell carcinoma | BJU international                            | Renal               |
| Seo                         | 2009 | Clinicopathologic characterization 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 | Microsatellite instability, promoter methylation, and protein expression of the DNA mismatch repair genes in epithelial ovarian cancer | International Journal of Cancer              | Gastric and endometrial |
| 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 gastric and endometrial adenocarcinomas | 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? Application of the National Cancer Institute international criteria for determination of microsatellite instability in ovarian cancer Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts | Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology | Endometrial and ovarian |
| Sood                        | 2001 | Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts | Cancer Research                               | Ovarian             |
| Stello                      | 2016 | Mismatch repair proteins hMLH1 and hMSH2 are differently expressed in the three main subtypes of sporadic renal cell carcinoma Intratumoral cd8+ lymphocyte infiltration as a prognostic factor and its relationship with cyclooxygenase 2 expression and microsatellite instability in endometrial cancer Genetic differences stratified by PCR-based microsatellite analysis in gastric intramucosal neoplasia | Clinical Cancer Research                      | Endometrial         |
| Stoehr                      | 2012 | Effect of eradication of Helicobacter pylori on genetic instabilities in gastric intestinal metaplasia | Pathobiology                                  | Renal               |
| Suemori                     | 2015 | Genetic differences stratified by PCR-based microsatellite analysis in gastric intramucosal neoplasia | International Journal of Gynecological Cancer | Endometrial         |
| Sugai                       | 2017 | Effect of eradication of Helicobacter pylori on genetic instabilities in gastric intestinal metaplasia | 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             |
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 tumorspecific 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
| 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-11 in low and high grade endometrial tumors | Gynecologic Oncology                         | Endometrial        |
| Bruegl        | 2014 | 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: Tumor mismatch repair immunohistochemistry and DNA mhl1 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 | Cancer Prevention Research                   | Endometrial        |
| Buchanan      | 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 |
| Carleton      | 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: Association of distinct mutational signatures with correlates of increased immune activity in pancreatic ductal adenocarcinoma | The American Journal of Surgical pathology   | Endometrial        |
| Connor        | 2017 | Relationship between PTEN, DNA mismatch repair, and tumor histotype in endometrial carcinoma: retained positive expression of PTEN preferentially identifies sporadic non-endometrioid carcinomas | JAMA Oncology                                | Pancreatic         |
| Everett       | 2014 | Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm: The significance of DNA mismatch repair genes in the diagnosis and management of perirectal sebaceous cell carcinoma and Muir-Torre syndrome: Microcystic, elongated, and fragmented pattern invasion in ovarian endometrioid carcinoma: immunohistochemical profile and prognostic implications | JAMA Dermatology                             | Sebaceous          |
| Gaskin        | 2011 | 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        |
| Goldberg      | 2017 | Clinical and pathologic features of young endometrial cancer patients with loss of mismatch repair expression Mismatch repair protein expression in 1049 endometrial carcinomas, associations with body mass index, and other clinicopathologic variables | Gynecologic Oncology                         | Endometrial        |
| Grzankowski   | 2017 | DNA mismatch repair-related protein loss as a prognostic factor in endometrial cancers: Clinopathological 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 | Journal of Gynecologic Oncology              | Endometrial        |
| Kawazoe       | 2017 | Frequent mismatch repair protein deficiency in mixed endometrioid and clear cell carcinoma of the endometrium | 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 pericellular sebaceous carcinoma and is associated with younger patient age DNA mismatch repair abnormalities in acinar cell carcinoma. The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories | Human Pathology                  | Sebaceous                      |
| Liu        | 2014 | DNA mismatch repair abnormalities in acinar cell carcinoma of the pancreas frequency and clinical significance | Pancreas                         | Pancreatic                     |
| Milione    | 2016 | 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: a correlative study assessing microsatellite instability, mlh1 hypermethylation, DNA mismatch repair protein expression, and pten, pik3ca, kras, and braf mutation analysis | Journal of Gynecologic Oncology   | Endometrial                    |
| Peterson   | 2012 | Lack of association between deficient mismatch repair expression and outcome in endometrial carcinomas of the endometrioid type | International Journal of Gynecological Pathology | Endometrial                    |
| Ramos      | 2017 | Lymphoepithelioma-like gastric carcinoma: Clinicopathological characteristics and infection status Women 50 years or younger with endometrial cancer the argument for universal mismatch repair screening and potential for targeted therapeutics | Journal of surgical Research      | Gastric                        |
| Ring       | 2013 | Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms | International Journal of Gynecological Cancer | Endometrial                    |
| Roberts    | 2013 | Molecular genetic heterogeneity in undifferentiated endometrial carcinomas Lack of association between deficient mismatch repair expression and outcome in endometrial carcinomas of the endometrioid type | Journal of Genetic Counseling     | Sebaceous                      |
| Rosa-Rosa  | 2016 | Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger Invasion pattern and histologic features of tumor aggressiveness correlate with MMR protein expression, but are independent of activating kras and braf mutations in CRC Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: earlier prognostic information to guide treatment | Modern Pathology                 | Endometrial                    |
| Ruiz       | 2014 | Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms | Gynecologic Oncology              | Endometrial                    |
| Sahnane    | 2015 | Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome | European Journal of Neurology     | Brain                          |
| Shih       | 2011 | A clinically applicable molecular-based classification for endometrial cancers | British Journal of Cancer         | Endometrial                    |
| Steinestel | 2014 | Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome | Virchows Archiv                   | Colorectal                     |
| Talhous    | 2016 | Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome | Gynecologic Oncology              | Endometrial                    |
| Talhous    | 2015 | Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome | Cancer                           | Endometrial                    |
| Talhous    | 2017 | Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome | British Journal of Cancer         | Endometrial                    |
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 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 | 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.
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 patients) 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

| Subgroup | Status | N study | N  | n  | Prevalence | 95% CI | All tumors, random effects |
|----------|--------|---------|----|----|------------|--------|----------------------------|
| 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.
### Table

| 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        | Histology-clear cell            | MSI-H  | 2       | 4    | 1     | 0.27         | 0.00–0.77  |
| Endometrial        | Histology-serous                | MSI-H  | 3       | 29   | 4     | 0.14         | 0.04–0.29  |
| Endometrial        | Histology-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            | Stages 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.

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.

### 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.

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.
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.

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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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