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A Review of the Clinical Relevance of Mismatch-Repair Deficiency in Ovarian Cancer

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Abstract

Ovarian cancer ranks fifth in both cancer incidence and mortality among women in the United States. Defects in the mismatch-repair (MMR) pathway that arise through genetic and/or epigenetic mechanisms may be important etiologically in a reasonable proportion of ovarian cancers. Genetic mechanisms of MMR dys-function include germline and somatic mutations in the MMR proteins. Germline mutations cause hereditary nonpolyposis colorectal cancer (HNPCC), which is the third most common cause of inherited ovarian cancer after *BRCA1* and *BRCA2* mutations. An epigenetic mechanism known to cause inactivation of the MMR system is promoter hypermethylation of 1 of the MMR genes, mutL homolog 1 (*MLH1*). Various laboratory methods, in addition to clinical and histopathologic criteria, can be used to identify MMR-deficient ovarian cancers. Such methods include microsatellite instability analysis, immunohistochemistry, *MLH1* promoter hypermethylation testing, and germline mutation analysis. In this review, the authors describe the existing literature regarding the molecular, clinical, and histologic characteristics of MMR-deficient ovarian cancers along with the possible effect on survival and treatment response. By further defining the profile of MMR-deficient ovarian cancers and their associated etiologic mechanisms, there may be a greater potential to distinguish between those of hereditary and sporadic etiology. The ability to make such distinctions may be of diagnostic, prognostic, and therapeutic utility.

Keywords

mismatch repair; ovarian cancer; microsatellite instability; immunohistochemistry; hereditary nonpolyposis colorectal cancer; mutL homolog 1; mutS homolog 2; *MMR* genes

Ovarian cancer ranks fifth in both cancer incidence and cancer mortality among women in the United States.[1] An estimated 22,430 women in the United States will be newly diagnosed, and 15,280 deaths will be attributed to this disease during the year 2007.[1] Ovarian cancer has the highest mortality rate among gynecologic cancers: Greater than 66% of patients present with late-stage, metastatic disease at initial diagnosis, and the 5-year survival rate is only 20% to 30%.[1] Conversely, at early stages, the long-term survival rate approaches 90%.[2]

Overall, it is estimated that 5% to 12% of invasive ovarian cancers are caused by hereditary susceptibility.[3] On the basis of epidemiologic studies, hereditary breast ovarian cancer syndrome, because of gene mutations in *BRCA1* or *BRCA2*, accounts for 65% to 75% of all cases of hereditary ovarian cancer.[4] Hereditary nonpolyposis colorectal cancer (HNPCC) is the third major cause of hereditary ovarian cancer and is believed to account for an additional 10% to 15% of all inherited cases.[4] HNPCC is caused by mutations in genes involved in DNA

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mismatch repair (MMR), which is 1 of the best-defined molecular pathways involved in both inherited[5-10] and sporadic[11-13] cancer pathogenesis.

One of the consequences of deficient MMR is microsatellite instability (MSI) in tumors.[14] MSI is a hallmark feature of HNPCC-associated tumors. Although MSI is a useful molecular marker in colorectal cancer and has etiologic significance,[15] its utility in ovarian cancer is an area of active investigation. The objectives of this review were to examine the available literature investigating the molecular and histopathologic characteristics of ovarian cancers caused by genetic defects in the MMR pathway and to highlight the clinical significance of the findings.

The Molecular Basis of MMR Defects

The intact MMR system has been reviewed extensively.[16] Briefly, this system of enzymes coordinately works in sequential steps to repair DNA mismatch mutations. To date, it has been demonstrated that 7 MMR proteins, mutL homolog 1 (MLH1),[6,10] mutS homolog 2 (MSH2),[7] MSH6,[5,8] postmeiotic segregation increased 1 (PMS1),[9] PMS2,[9] MSH3,[17] and MLH3,[18] are involved in human MMR function. The steps consist of the recognition of the mismatch/insertion/deletion and protein-complex formation to correct the error (Fig. 1). Specifically, the heterodimer between MSH2 and MSH6 recognizes the mismatch, although a heterodimer between MSH2 and MSH3 also can start the process. The formation of the MSH2-MSH6 heterodimer accommodates a second heterodimer of MLH1 and PMS2, although a heterodimer between MLH1 and either PMS3 or MLH3 can substitute for PMS2. This protein complex formed between the 2 sets of heterodimers enables repair of the defect. Thus, decreased expression of certain MMR proteins can be observed together as a consequence of errors in this repair process.[19] Furthermore, the redundancy in this pathway results in variable degrees of MSI associated with MSH6 defects, because the MSH2-MSH3 complex can compensate for this activity.

Mutations in each of the 7 genes encoding the 7 MMR enzymes have been discovered. The *MLH1* and *MSH2* genes are the most common susceptibility genes for HNPCC and account for 80% to 90% of observed mutations[10,20] followed by *MSH6*[5,8,21] and, more recently, *PMS2*,[22-24] and have been observed primarily in HNPCC families, which do not meet clinical diagnostic criteria. The remaining 3 genes are seldom (*PMS1*9) or never (*MSH3*17,[25,26] and *MLH3*[25,27]) reported to be mutated in the germline.

Impaired MMR gene function leads to MSI, a hallmark feature of tumors associated with HNPCC.[28] Microsatellites are short, polymorphic sequences of DNA between 1 and 5 base pairs in length that are repeated from 15 to 30 times and are distributed across the genome.[29] Inactivation of the MMR system leads to the accumulation of mutations, particularly in these highly repeated sequences (microsatellites), leading to MSI.[30]

Initial studies that sought to estimate the frequency of MSI in ovarian cancer used various definitions, making it difficult to compare results across studies. In 1997, the National Cancer Institute (NCI) developed uniform criteria to classify MSI.[28] Five specific markers for microsatellite analysis in colorectal cancer were recommended, including 2 mononucleotide repeats (Bat25 and Bat26) and 3 dinucleotide repeats (D2S123, D5S346, and D17S250). Tumors are classified as having high-level MSI (MSI-H) if ≥2 of the 5 markers exhibit variations in microsatellite sequence length.

Clinical Characteristics of MMR Defects

HNPCC was described first by Warthin in 1913 in a report based on his observations and review of pathology records in cancer-prone families,[31] although it took over half a century before

Lynch and coworkers collected data that accurately led to the description of such families.[32] In 1991, the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer developed the initial criteria, called the 'Amsterdam Criteria,' to provide a basis for uniformity of diagnosis in multicenter studies.[33,34] However, because those criteria were too stringent to identify all HNPCC families,[35] they were broadened over time to include extracolonic cancers (the Modified Amsterdam Criteria[36] and the Amsterdam II Criteria[34]) and tumor characteristics (the Bethesda Guidelines[37] and the Revised Bethesda Guidelines[36]).

HNPCC is characterized by autosomal-dominant inheritance of susceptibility to predominantly right-sided colon cancer, endometrial cancer, ovarian cancer, and other extracolonic cancers (including cancer of the renal pelvis, ureter, small bowel, and pancreas), multiple primary cancers, and a young age at onset of cancer.[38] The estimated population incidence is between 1:2000 and 1:660.[39]

The estimated lifetime risk for ovarian carcinoma in women with HNPCC is up to 12%, and the reported relative risk of ovarian cancer has ranged from 3.6 to 13 based on families ascertained from high risk-clinics with known or suspected HNPCC (Table 1).[40-45] In those studies, the majority of individuals with known HNPCC had a germline mutation in *MLH1* or *MSH2*. HNPCC-associated ovarian tumors often develop at a younger age, with a mean age at diagnosis that ranges from 41 years 49 years, compared with sporadic tumors, with a mean age at diagnosis that ranges from 60 years to 65 years.[40,46,47]

Although ovarian cancer risk in *MSH6* carriers has not been studied specifically in an unselected series of HNPCC families, ovarian cancer is in the *MSH6* tumor spectrum, as evidenced by several case reports in which ovarian cancer has been observed in MSH6 family pedigrees.[8,48-50] Cederquist et al[51] reported a particularly high frequency of ovarian cancers in women members of HNPCC families with mutations in *MSH6*, with a lifetime risk of 33% observed in the 2 large Swedish pedigrees that were studied.

Taken together, the evidence to date suggests that women with germline deleterious mutations in the MMR genes have an elevated risk for ovarian cancer. However, the magnitude of this risk is not well known, and studies to date are severely limited by sample size and varied ascertainment strategies. Larger scale studies involving known HNPCC cases are needed to explore this issue further.

Molecular and Histologic Classification of MMR-deficient Ovarian Tumors

The reported prevalence of MSI-H status (as defined by instability in ≥2 markers studied) in unselected ovarian cancers has ranged from 0% to 37% (Table 2). This wide variation reflects differences in several factors, including study design, sample size, number and type of microsatellite markers used, and criteria used to define MSI phenotype. On the basis of studies of unselected ovarian cancer patients, the true range of MSI probably is between 12% and 20% [11,52-56] (Table 2). Furthermore, of the 18 studies of unselected ovarian cancer cases cited in Table 2, 11 studies had a sample size of <60 patients, and 8 studies were performed before 1997. Of the 7 studies with a sample size >60 patients, 1 was a Japanese study of 68 patietns[57] and had an MSI-H frequency of 3%. Because of the paucity of data regarding the prevalence of MSI-H frequency in the Japanese population, it is unclear whether this low estimate may reflect ethnic variation in the particular alleles that influence MSI in this population. Another United States-based study had a sample size of 95 patients[58] and reported an MSI-H frequency of 6%. Because that report was published before the development of the 5 NCI-standardized markers, that frequency may be an underestimate. All of the remaining 5 studies[11,52,56,59,60] were from the United States and included 4 studies that were based at the same center,[11,52,56,59] had samples sizes between 66 and 116 patients, and reported MSI frequencies between 12% and 37%. In addition, several studies have investigated MSI in

specific histologic subtypes (ie, endometrioid,[61-63] serous,[64-66] clear cell,[67,68] and mucinous[65]). Those studies suggested higher frequencies of MSI-H phenotype in ovarian cancers of nonserous histology (Table 2).

Impaired MMR gene function arising from germline or somatic mutations also results in reduced protein expression.[69,70] Immunohistochemistry (IHC) provides a means to measure protein expression in various tumors. Furthermore, large-scale studies have demonstrated clearly that IHC of MSI-H tumors is an accurate screening test for the identification of the specific MMR gene involved in HNPCC-associated tumors.[19,70-72] Data on MMR protein expression in ovarian cancer are beginning to emerge (Table 3) through studies investigating IHC in ovarian cancer series.[11,73-75] To date, a single published study has comprehensively evaluated the relation between MSI and protein expression in an unselected series of 107 invasive epithelial ovarian cancers by performing both MSI and MMR protein expression analyses,[11] and the results indicated loss of MLH1 expression in 10 of 21 tumors with MSI-H. Eight of 10 tumors that lacked MLH1 expression also failed to express MSH2 and various other MMR proteins. The remaining MSI-H tumors expressed all MMR proteins and, upon subsequent protein truncation testing in snap-frozen tumors, none demonstrated a truncating defect in the *MLH1* or *MSH2* genes. Tumors without the MSI-H phenotype expressed all MMR proteins.

To date, 3 studies have evaluated loss of protein expression in unselected invasive epithelial ovarian carcinomas.[47,73,75] Malander et al[47] observed loss of expression in 2.3% of tumors (n = 3). Loss of expression of MLH1/PMS2 was observed in 2 tumors: One produced a normal result from sequencing and multiplex ligation-dependent probe amplification (MLPA), and the other had deletion of exons 4 through 6 in *MLH1* that was detected by MLPA but not by sequencing. The third tumor had loss of expression of MSH6, and the sequencing results indicated that it had a truncating mutation in the *MSH6* gene. Rosen et al[75] reported loss of expression in 2.2% of unselected ovarian cancers, including 5 tumors with loss of MLH1 expression and 2 tumors with loss of MSH2 expression. The underlying genetic etiology (either somatic or germline) was not investigated in any of those cases. Finally, Domanska et al[73] reported loss of expression in 6.1% of patients aged ≤40 years at diagnosis, including 2 patients who had loss of MLH1/PMS2, 1 patient who had loss of MSH2/MLH6, and 3 patients who had loss of MSH6 only. That study did not systematically study the underlying genetic etiology of the loss of MMR protein expression, although 1 patient with loss of protein expression of MSH6 was diagnosed with an *MSH6* truncating mutation. Those 3 studies[47,73,75] all performed MSI analyses in tumors lacking MMR expression, and the results suggest that the majority of tumors lacking expression of MMR proteins have an MSI-H phenotype (Table 3).

When characterizing MMR-deficient ovarian cancers, molecular data may be supplemented by histologic data. There has been evidence to suggest an overrepresentation of the less common nonserous histologies, such as endometrioid and clear cell subtypes, in ovarian cancers with MMR defects (Table 4). Specifically, studies of HNPCC-associated ovarian cancers (based either on clinical criteria or on germline mutation analysis) generally have suggested an overrepresentation of nonserous histologies.[4,40,45,46,71,76] Likewise, most[12,53,54,72] (but not all[52,60]) studies of MMR-deficient ovarian cancers based on MSI or MMR protein expression analyses have produced similar findings. Investigations of MSI-H frequency in specific histologic subtypes, such as endometrioid,[61-63] mucinous,[65] and clear cell[67,68] carcinomas, generally have reported higher proportions of MMR defects than serous subtypes (Table 1). Furthermore, all studies of MMR protein expression that we identified[47,73,75] reported nonserous histologies in MMR-deficient tumors. However, those observations are based on very few studies, all with limited sample sizes, making it impractical to draw firm conclusions.

Taken together, data from previous United States-based studies of unselected ovarian cancers suggests that the MMR pathway is relevant etiologically in a reasonable proportion of ovarian tumors; however, more research is needed to refine the estimate. Furthermore, studies investigating expression of various numbers of proteins in unselected ovarian cancers have demonstrated that the majority of MSI-H tumors have loss of MLH1 and MSH2 expression. Loss of MSH6 expression also appears to be important, especially when early-onset cases are investigated. Far less is known regarding the relation between MSI and other MMR proteins, namely, PMS2. There is a suggestion that MMR-deficient ovarian cancers may be characterized by an overrepresentation of nonserous histologic subtypes. However, additional research is needed to resolve this question because of the limited numbers of studies and sample sizes. It is possible that the clarification of histologic associations may aid in distinguishing between MMR-associated and non-MMR-associated ovarian cancers.

MLH1 Promoter Hypermethylation Leads to MSI-H Tumors

Mismatch-repair dysfunction can arise through epigenetic and genetic mechanisms (Fig. 2). An epigenetic mechanism known to cause inactivation of the MMR system is DNA methylation.[77] DNA methylation occurs on cytosine bases linked to guanine bases, forming CpG dinucleotide pairs known as islands.[77] Localized methylation of CpG islands within the promoter of genes involved in the control of cell proliferation results in their inactivation, leading to carcinogenesis.[78] Although the underlying etiology of methylation and epigenetic silencing is uncertain, a recent study involving the *MLH1* gene demonstrated that inherited polymorphisms in the promoter region may contribute to this phenomenon.[79]

In HNPCC, as discussed above, MMR inactivation is caused by a heterozygous germline mutation in 1 of the MMR genes, primarily *MLH1* and *MSH2*. Consistent with the Knudson '2-hit' hypothesis,[80] in HNPCC tumors, loss of the remaining wild-type allele has been attributed to deletions and somatic mutations.[81] Recent evidence also suggests that promoter hypermethylation of *MLH1* may occur as a second 'hit' in hereditary cases.[82] Consequently, the detection of promoter hypermethylation does not exclude the possibility of HNPCC. In an effort to differentiate between the clinicopathologic characteristics of hereditary and sporadic MSI-H ovarian cancers, it may be important to investigate the various patterns of inherited and somatic events that are the consequences of genetic and epigenetic mechanisms.

Promoter hypermethylation of the *MLH1* gene has been observed in sporadic MSI-H cancers, including colorectal and endometrial cancers.[83] Studies in ovarian cancer[11-13,84] have had sample sizes from 6 patients to 93 patients and have reported a frequency of MLH1 promoter hypermethylation that ranges between 10% and 50%, with the higher estimates reported in MSI-H tumors.[12] Those studies suggest that *MLH1* promoter hypermethylation is observed in a significant proportion of ovarian cancers, especially those with MSI-H.

Survival and Treatment Implications Associated With Ovarian Cancers With MMR Deficiency

In addition to providing insight into the pathogenesis of ovarian cancer, the MMR-deficiency pathway also may influence treatment and survival. Numerous studies performed in patients with colorectal cancer suggest that women with HNPCC-associated and/or MSI-H tumors may have improved survival.[29,85,86] It has been suggested that the intrinsic tumor biology that leads to the extensive genetic instability associated with microsatellite alterations ultimately may compromise tumor progression,[87] accounting for the improved survival.

To date, a single study has investigated survival systematically in HNPCC-associated ovarian cancers[46] and demonstrated that the survival rate was not significantly different between

HNPCC-associated cases and registry-based controls. Results of that study should be interpreted with caution because of the limited sample size and sampling strategy of the control group. Future studies are warranted in this area, because a survival advantage for MMR-deficient ovarian cancers seems plausible based on data demonstrating 1) an overrepresentation of nonserous histologies compared with the more aggressive serous subtype[4,12,40,45,46,53,54,71,72,76] and 2) an overrepresentation of early stage at presentation.[53,88,89]

Regarding treatment implications for women with MMR-deficient ovarian tumors, there are in vitro data[84,90-94] to suggest that MMR deficiency may be a predictor of tumor response to clinical therapy. Platinum-based therapy (such as cisplatin and carboplatin), in combination with taxanes, is the main chemotherapeutic treatment for ovarian cancer.[95] However, clinical observations from ovarian cancer have produced conflicting results regarding survival and treatment response. Although Scartozzi et al[96] reported that acquired loss of *MLH1* expression caused by treatment was correlated with improved survival, others reported that intrinsic MMR deficiency was not highly predictive of survival.[97] Marcelis et al[98] described chemotherapy resistance in 2 patients from the same family with inactivating germline mutations in *MSH2*; however, others reported no association between treatment response and MMR status.[97,99]

Overall, the data suggest that, despite the finding that acquired loss of expression of *MLH1* may be associated with improved survival,[96] in vitro evidence[84,90-94] suggests that MMR-deficient cells may be more resistant to platinum-based treatment, but there are conflicting results from in vivo studies.[97-99] Furthermore, although MSI may be a useful genetic marker for predicting prognosis and may be an influential factor in deciding between treatment options, its significance in ovarian cancer remains unclear, and further evaluation is required. Once the associations between drug resistance, treatment response, and survival are determined, the basis for the improved survival despite drug resistance of MMR-deficient tumors may be dissected out and potentially may lead to the development of targeted therapies for MSI-H tumors.

Conclusion and Future Directions

Of all the common cancers in women, ovarian cancer is the site with the highest hereditary proportion. Although at least 10% of tumors are caused by mutations in the *BRCA1* and *BRCA2* genes, the proportion of hereditary ovarian cancers caused by MMR genes remains poorly defined.[43] The MMR pathway may be impaired in a reasonable proportion of ovarian cancers as a consequence of genetic and epigenetic mechanisms. Various laboratory methods and clinical and histologic criteria can be used to help identify MMR-deficient ovarian cancers. The identification of this subtype of ovarian cancer has clinical utility with regard to the assessment of etiology and diagnosis. Furthermore, specific chemotherapeutic regimens capable of improving treatment efficacy and reducing drug toxicity may exist specifically for MMR-deficient ovarian cancers. Further clarification of genetic-epigenetic-environmental interactions in a large-scale study of ovarian cancers may stimulate the development of novel chemotherapy agents.

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FIGURE 1.

Schematic representation of the human mismatch-repair system. T indicates thymine; G, guanine; MLH1, mutL homolog 1; PMS2, postmeiotic segregation increased 2; MLH3, mutL homolog 3; MSH2, mutS homolog 2; MSH3, mutS homolog 3; MSH6, mutS homolog 6; C, cytosine. (Adapted from Polato F, Broggini M. Microsatellite instability and genetic alterations in ovarian cancer. Minerva Ginecol. *2003;55:129−138*.)

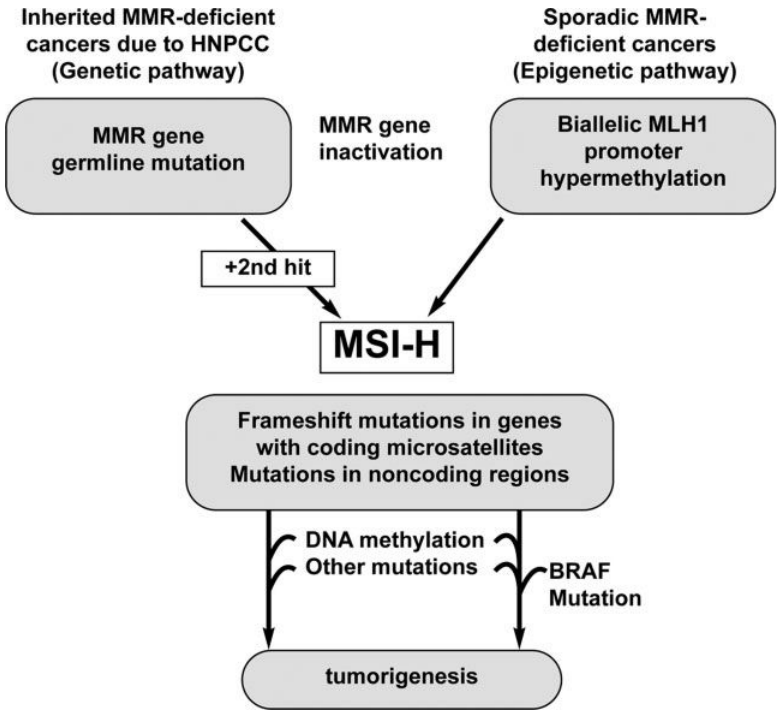

FIGURE 2.

Genetic versus epigenetic pathways leading to the high-level microsatellite instability (MSI-H) phenotype and subsequent tumorigenesis. The epigenetic type of MSI-H cancers frequently are accompanied by the B-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutation. MMR indicates mismatch repair; HNPCC, hereditary nonpolyposis colorectal cancer; MLH1, mutL homolog 1. (Adapted from Imai K, Yamamoto H. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. *2007 Oct 17;[Epub ahead of print]*.)

TABLE 1

Ovarian Cancer Risk in Hereditary Nonpolyposis Colorectal Cancer

Reference	Ascertainment Source	Location	Sample Size	Relative Risk	Cumulative Incidence, %
Watson & Lynch 1993[43]	1300 High-risk members from 23 HNPCC kindreds	Nebraska	13	3.5	-
Aarnio 1995[42]	293 Putative HNPCC gene carriers from 40 families	Finland	14	-	9
Vasen 1996[41]	382 Relatives from 19 families with HNPCC mutations	Netherlands	2	8	-
Aarnio 1999[45]	1763 High-risk members from 50 HNPCC families	Finland	13	13	12
Brown 2001[44]	120 HNPCC families	Australia	24	5 (by age 40 y)	-

HNPCC indicates hereditary nonpolyposis colorectal cancer.

TABLE 2

Frequency of Ovarian Cancers With High-level Microsatellite Instability Phenotype

Reference	No. of Markers	Sample Size	No. With MSI-H (%)
Unselected ovarian cancers			
Allen 2000[100]	4	26	1 (4)
Alvi 2001[101]	5	43	3 (7)
Buller 2001[56]	6	116	24 (20)
Codegoni 1999[102]	8	31	8 (26)
Dellas 2004[60]	5	66	20 (30)
Fujita 1995[54]	4	47	8 (17)
Geisler 2003[11]	6	107	21 (20)
Gras 2001[12]	5	42	2 (5)
Han 1993[69]	4	19	1 (5)
Iwabuchi 1995[58]	66	95	6 (6)
King 1995[53]	2	41	7 (17)
Kobayashi 1995[57]	5	68	2 (3)
Krajinovic 1998[55]	8	12	2 (17)
Osborne&Leech 1994[103]	9	25	2 (8)
Shih 1998[104]	69	31	0 (0)
Sood&Buller 1996[59]	10	68	25 (37)
Sood 2001[52]	14	109	13 (12)
Tangir 1996[105]	13	31	0 (0)
Specific histologic subtypes of ovarian cancer			
Cai 2004[67]	5	42*	6 (14)
Haas 1999[64]	6	14†	0 (0)
Liu 2004[63]	4	74‡	15 (20)
Moreno-Bueno 2001[62]	2	26‡	5 (19)
Ohwada 2000[65]	5	61§	15 (25)
Shenson 1995[61]	28	17‡	2 (12)
Singer 2004[66]	5	75//	6 (8)
Ueda 2005[68]	5	24*	6 (25)

MSI-H indicates high-level microsatellite instability.

*Clear cell.

†Serous.

‡Endometrioid.

§Serous, 32; mucinous, 29.

//Serous, 53; nonserous, 22.

TABLE 3

Immunohistochemistry for Mismatch-Repair Protein Expression in Unselected Ovarian Cancers

Reference	Location	Study Design	Sample Size	No. With MMR Loss (%)	Proteins Investigated	Method	Comments
Geisler 2003[11]	Holden Comprehensive Cancer Center (Iowa)	Hospital-based	107	10 (9.3)	MLH1, MSH2, MSH3, MSH6, PMS1, PMS2	RT-PCR	No tumors without MSI-H had loss of MMR protein expression
Malander 2006[47]	Lund University Hospital (Sweden)	Hospital-based	128	3 (2.3)	MLH1, MSH2, MSH6, PMS2	IHC on TMAs	All tumors with loss of MMR protein expression had MSI-H
Rosen 2006[75]	M. D. Anderson Cancer Center (Tex)	Hospital-based	322	7 (2.2)	MLH1, MSH2	IHC on TMAs	-
Domanska 2007[73]	Lund University Hospital/Swedish Cancer Registry (Sweden)	Population-based, age <40 y	98	6 (6.1)	MLH1, MSH2, MSH6, PMS2	IHC on full section	Five of 6 tumors with loss of MMR protein expression had MSI-H

MMR indicates mismatch-repair; MLH, mutL homolog; MSH, mutS homolog; PMS, postmeiotic segregation increased; RT-PCR, reverse transcriptase-polymerase chain reaction; MSI-H, high-level microsatellite instability; IHC, immunohistochemistry; TMAs, tissue microarrays.

TABLE 4

Histology of Ovarian Cancer Cases With Mismatch-Repair Defects

Reference	Sample Size	S	M	E	C	Ud	Us	Mi	NE*	NS (%)†
HNPCC-associated ovarian cancers										
Aarnio 1999[45]	13	4	2	1	2	0	4	0	0	5/9 (56)
Bewtra 1992[4]	4	1	0	1	2	0	0	0	0	3/4 (75)
Crijnen 2005[46]	26	12	1	4	1	1	1	0	4	7/19 (37)‡
Ichikawa 1999[71]	4	2	1	1	0	0	0	0	0	2/4 (50)
Stratton 1999[76]	2	0	1	1	0	0	0	0	N/A	2/2 (100)
Watson&Lynch 2001[40]	79	17	7	13	7	0	26	4	5	31/48 (65)
MSI-H ovarian cancers										
Chiaravalli 2001[72]	4	0	3	1	0	0	0	0	0	4/4 (100)
Dellas 2004[60]	20	11	3	3	1	0	2	0	N/A	7/18 (39)
Fujita 1995[54]	8	2	1	5	0	0	0	0	N/A	6/8 (75)
Geisler 2003[11]	21	12	2	6	0	0	1	0	0	8/20 (40)
Gras 2001[12]	2	0	0	1	1	0	0	0	0	2/2 (100)
King 1995[53]	7	2	0	2	1	0	0	1	1	4/6 (67)
Sood 2001[52]	13	7	—	—	—	—	—	—	N/A	6/13 (46)§
Ovarian cancers with loss of MMR protein expression										
Domanska 2007[73]	6	0	1	3	2	0	0	0	N/A	6/6 (100)
Malander 2006[47]	3	0	1	0	1	0	0	1	N/A	3/3 (100)
Rosen 2006[75]	7	0	0	1	2	0	0	3	1	6/6 (100)

S indicates serous; M, mucinous; E, endometrioid; C, clear cell; Ud, undifferentiated; Us, unspecified; Mi, mixed; NE, nonepithelial; NS, nonserous; HNPCC, hereditary nonpolyposis colorectal cancer; N/A, not applicable; MSI-H, high-level microsatellite instability; MMR, mismatch repair.

*Studies in which only epithelial ovarian cancers were included; N/A is indicated in this column, because nonepithelial ovarian cancers were not included in these studies.

†Unspecified adenocarcinomas and nonepithelial cancers were not included within the denominator.

‡Two histologic subtypes were unknown and, thus, were not included in the percentage.

§Details about specific histopathologic subtypes of nonserous tumors were not provided.