LYNCH-SYNDROME RELATED GYNECOLOGIC PATHOLOGY

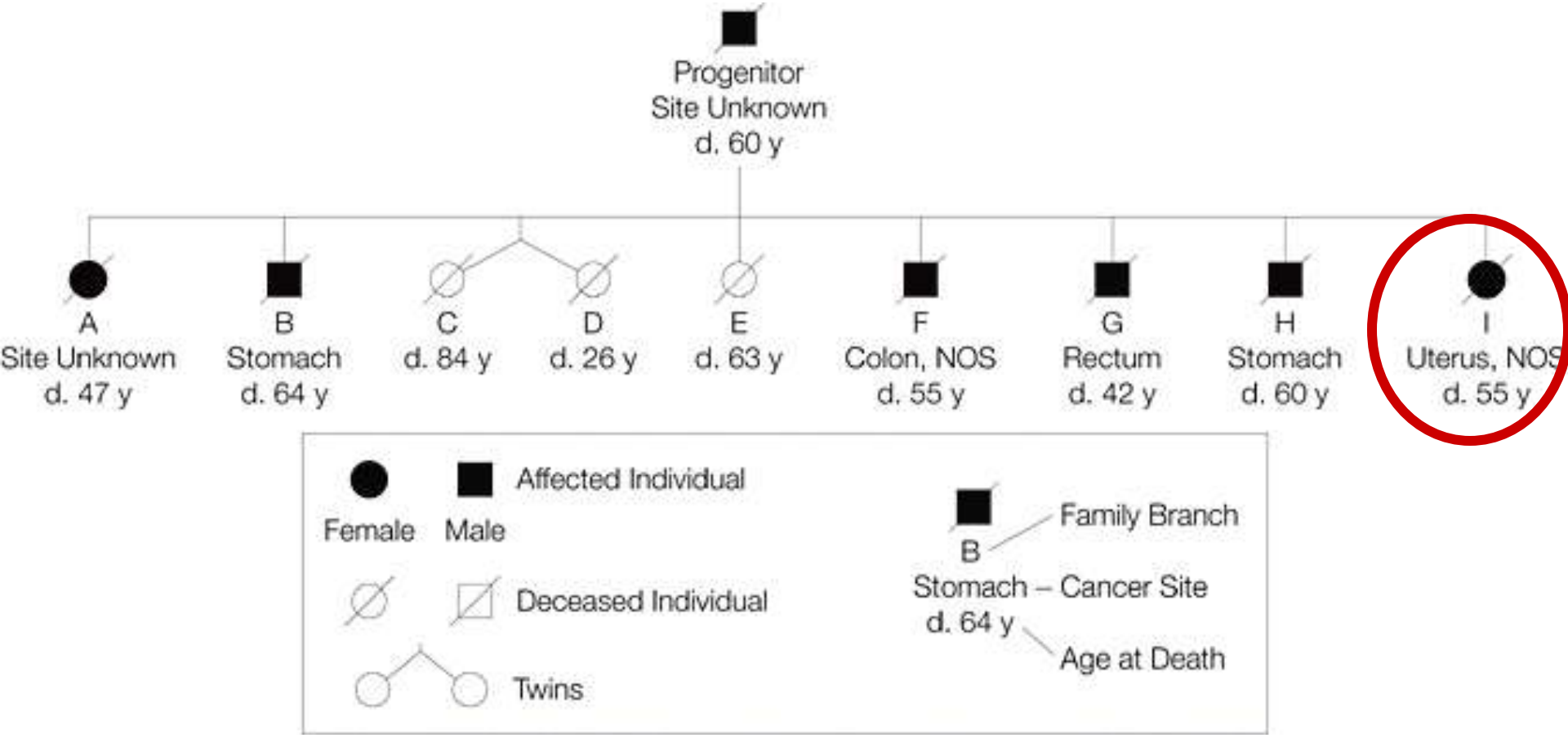
MARIA LUISA CARCANGIU M.D.

Aldred Scott Warthin

Warthin A. Heredity with reference to carcinoma. ***Arch Intern Med.*** **1913; 4:681– 696**

History

- **1913- Michigan pathologist Aldred Scott Warthin studied the family history of his seamstress who first developed colon cancer, and later died of endometrial cancer.**
- **She confided to him that one day she would die of cancer of the colon or of the female organs, "because everyone in my family died of these diseases."**
- **Her pedigree became known as “Family G” and illustrated a long line of colonic and endometrial cancer.**


Progenitor
Site Unknown
d. 60 y
A
Site Unknown
d. 47 y
B
Stomach
d. 64 y
C
d. 84 y
D
d. 26 y
E
d. 63 y
F
Colon, NOS
d. 55 y
G
Rectum
d. 42 y
H
Stomach
d. 60 y
I
Uterus, NOS
d. 55 y
Female
Male
Affected Individual
Deceased Individual
Twins
B
Family Branch
Stomach – Cancer Site
d. 64 y
Age at Death

COLORECTAL AND LS-ASSOCIATED CANCERS IN FAMILY G

Site	No. of Cases	Age at Diagnosis, Mean (SD) [Range]†	Generations
Colorectum	56	55 (16) [23-93]	II, III, IV, V
Endometrium	16	53 (12) [39-78]	II, III, IV, V
Stomach	8	62 (12) [44-76]	II, III, IV, V
Brain	4	44 (16) [23-59]	III, IV, V
Ovary	1	44	V
Total	**85***		

*Includes 74 individuals; 8 were diagnosed with multiple (2-5) primary cancers.
†Actual age is given for cancer of the ovary.

MEMBERS OF FAMILY G WITH MULTIPLE COLORECTAL AND LS-ASSOCIATED CANCERS

Generation	Branch	Sex	Cancer Sites	Ages at Diagnosis, y
IV	B	Female	Endometrium, colon (NOS)	75, 79
IV	B	Female	Colon (NOS), sigmoid	65, 75
V	D	Male	Ascending colon, sigmoid	41, 51
III	G	Female	Endometrium, cecum, sigmoid, stomach*	50, 60, 70, 72, 76
IV	I	Male	Cecum, descending colon	26, 27
III	I	Female	Endometrium, cecum	55, 57
IV	I	Female	Colon (NOS), colon (NOS)	43, 67
V	I	Female	Cecum, rectum	28, 45

Abbreviation: NOS, not otherwise specified.
*Cancer of the sigmoid was diagnosed twice at ages 60 and 72 years.

CARDINAL CLINICAL FEATURES OF LYNCH SYNDROME (HNPCC)

- Dominant inheritance; high penetrance
- Main cancers:colorectal, endometrial
- Other frequent cancers: gastric, ovarian
- Other infrequent cancers: small bowel, pancreas ureter, renal pelvis, biliary tract, brain tumors in the Turcot syndrome variant of HNPCC, cutaneous stigmata (sebaceous adenomas, sebaceous carcinomas, and multiple keratoacanthomas) in the Muir–Torre syndrome variant of HNPCC

- **Before molecular genetic diagnostics came of age in the 1990s, a comprehensive family history was the only basis on which familial risk of colorectal cancer could be estimated**

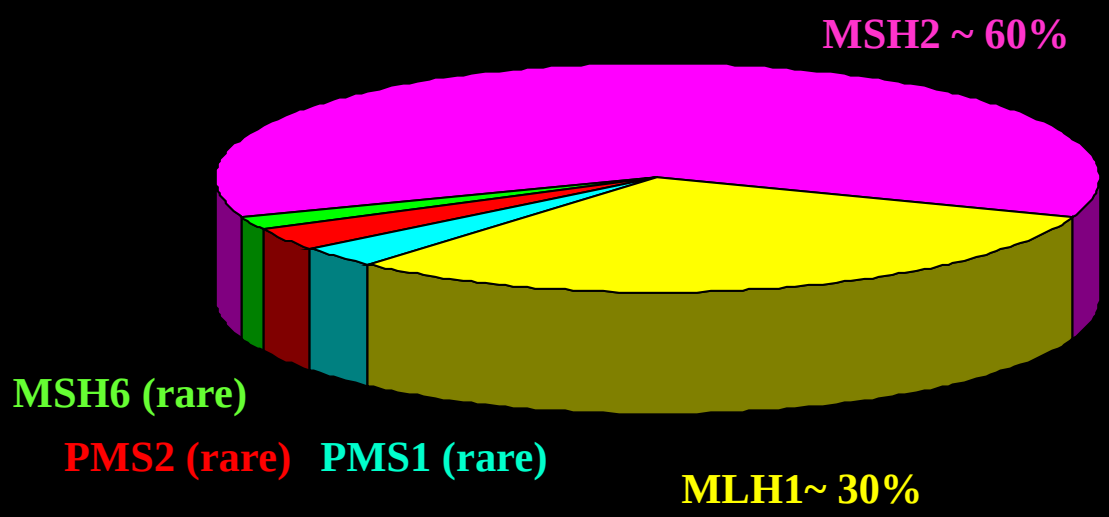
- **Amsterdam Criteria (Classic ICP-HNPCC Criteria), 1990 †**
  Clinical HNPCC identification requires at least three relatives with CRC plus the following:
  1) One affected patient is a first-degree relative of the other two
  2) Two or more succesive generations affected
  3) One or more affected relative received CRC diagnosis at age <50
  4) Familial adenomatous polyposos excluded
  5) Tumours verified by pathological examination

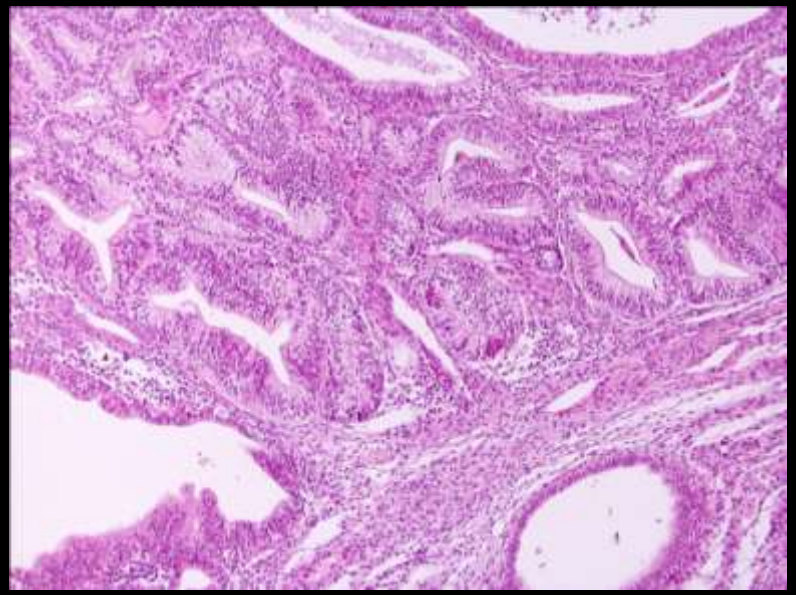
- **Amsterdam II Criteria (revised ICG-HNPCC Criteria) 1998 ‡**
  Clinical HNPCC identification requires three or more relatives with HNPCC associated cancer (CRC, or cancer of the endometrium, small bowel, ureter, or renal pelvis) plus all of the following:
  1) One affected patient is a first-degree relative of the other two
  2) Two or more succesive generations affected
  3) One or more affected relative received diagnosed at age <50 y
  4) Familial adenomatous polyposos excluded in any cases of CRC
  5) Tumours verified by pathological examination

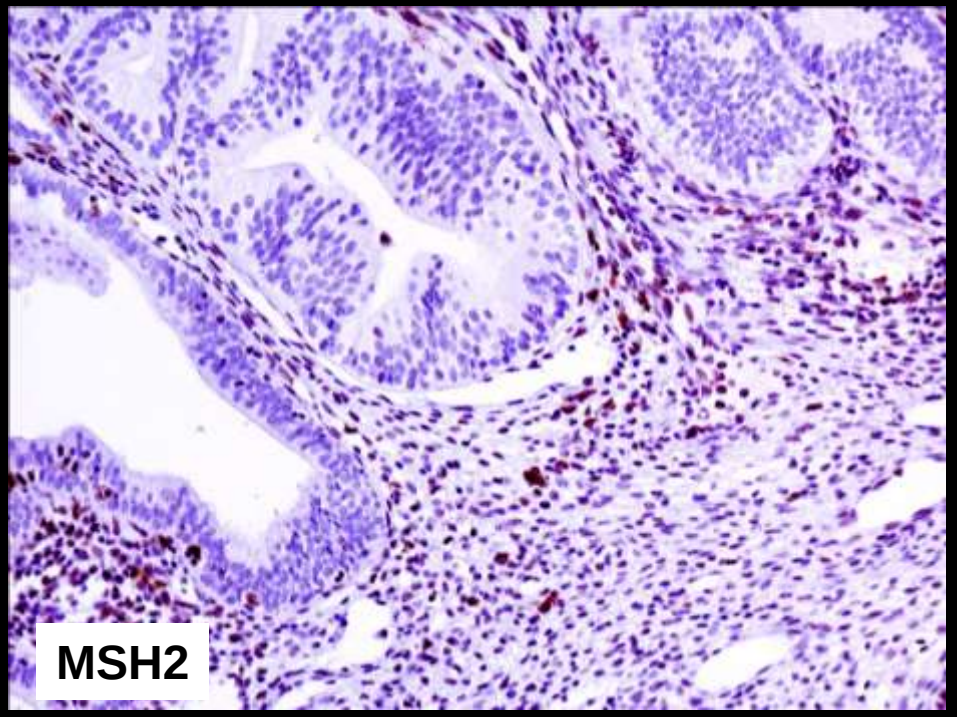
- **Bethesda Guidelines 1996 #**
  Guidelines for identification of patients with colorectal tumors who should undergo testing for microsatellite instability:
  1) Cancer in families that meet the Amsterdam Criteria
  2) Two HNPCC-related tumors, including synchromois and metachronous CRC or associated extracolonic cancer (endometrium, ovarian, gastric, hepatobillary, or samll bowel cancer or transitional-cell carcinoma of the renal pelvis or ureter)
  3) CRC and a first degree relative with CRC or HNPCC-related extracolonic cancer or a colorectal adenoma; one of the cancers diagnosed at the age < 50 y, and the adenoma diagnosed at the age < 40 y
  4) CRC or endometriumcarcinoma < 50 y
  5) Right-sided CRC with an undifferentiated pattern (solid, cibriform) on histopathology < 45 y
  6) Signet ring cell type CRC < 50 y
  7) Adenoma < 40 y

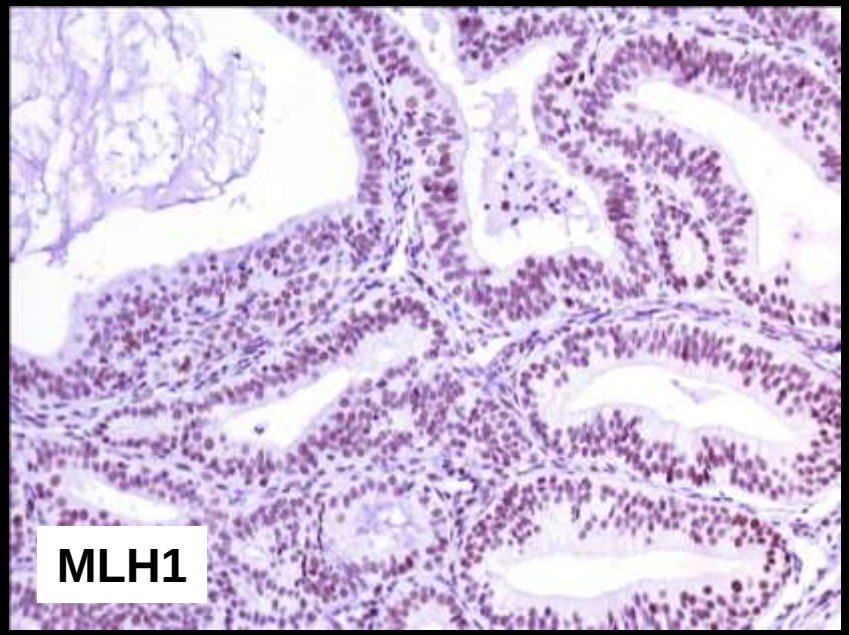
* CRC = colorectal cancer; HNPCC = hereditary nonpolyposis colorectal cancer; ICG = International Collaborative Group, † reference

Contribution of Gene Mutations to LS Families






MSH2


MLH1

ENDOMETRIAL CARCINOMA IN WOMEN WITH LYNCH SYNDROME

PREVALENCE OF GERM-LINE (INHERITED) DNA MISMATCH REPAIR GENE MUTATION IN THE GENERAL POPULATION:

1:2000-1:600

de la Chapelle A, Fam.Cancer 2005; 4:233

ATTRIBUTABLE TO MMR MUTATIONS:

~ 1-3% OF ALL ENDOMETRIAL CANCERS

~ 5% OF ENDOMETRIAL CANCERS IN WOMEN <55 YEARS OF AGE

de la Chapelle A, Fam.Cancer 2005; 4:233

Frequency of germline DNA MMR

- **Mutations among unselected patients with EC has been found to be 1.8% to 2.3%**
- **In patients younger than 50 years , the incidence of mutation is increased up to 9%**

LIFETIME RISK OF CANCER REPORTED IN FAMILIES WITH AN IDENTIFIED MISMATCH REPAIR MUTATION

- Colorectal cancer (men): 28–75%
- Colorectal cancer (women): 24–52%
- Endometrial cancer: 27–71% [2.3%]
- Ovarian cancer: 3.6 –13% [1.8%]
- Gastric cancer: 2–13%
- Urinary tract cancer: 1–12%
- Brain tumour: 1–4%
- Bile duct/gallbladder cancer: 2%
- Small-bowel cancer: 4–7%

Vasen, H F A et al. J Med Genet 2007;44:353-362

Endometrial Cancer Risk Assessment

Hendriks et al.2006

MMR Gene	Cumulative Endometrial Carcinoma Risk (at Age 70)	Mean Age of Diagnosis of Endometrial Carcinoma
MLH1	27%	48 years
MSH2	40%	49 years
MSH6	71%	54 years

General population: 2.3%

Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome.

Lu KH, et al.Obstet Gynecol. 2005;105:569-74.

117 WOMEN WITH DUAL PRIMARY CANCERS FROM 223 AMSTERDAM FAMILIES

First primary	n.	Median age
Colon	*49 (49%)*	40ys
Endometrium	*46 (45.5%)*	45ys
Ovary	*6 (5.9%)*	39.5ys

16 cases diagnosed simultaneously

CRC/endometrial ca. :11 cases
CRC/ovarian ca. :4 cases
CRC/endometrial/ovarian ca. :1case

Bethesda Criteria.

1. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter)

2. Individuals with colorectal cancer and a first degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or colorectal adenoma; one of the cancers diagnosed at age <45 y, and the adenoma diagnosed at age <40 y

3. Individuals with colorectal cancer or endometrial cancer diagnosed at age <45 y

4. Individuals with right-sided colorectal cancer with an undifferentiated pattern on histopathology diagnosed at age <45 y

5. Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <45 y

6. Individuals with adenomas diagnosed at age <40

Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening.

Walsh CS, Blum A, Walts A, Alsabeh R, Tran H, Koeffler HP, Karlan BY.

Gynecol Oncol. 2010;116:516-21.

72 eligible patients:

50 with early-onset endometrial cancer

22 with synchronous endometrial and ovarian primary cancers

molecular findings consistent with LS:

6/50 (12%)

3/22 (14%)

Walsh CS, 2010

Journal of Clinical Oncology, Vol 23, No 36 (December 20), 2005: pp. 9344-9350

Women With Synchronous Primary Cancers of the Endometrium and Ovary: Do They Have Lynch Syndrome?

Pamela T. Soliman, Russell R. Broaddus, Kathleen M. Schmeler, Molly S. Daniels, Delia Gonzalez, Brian M. Slomovitz, David M. Gershenson, Karen H. Lu

102 women with synchronous endometrial and ovarian cancers (1989-2004)

Median age 50 years

- **59 patients had tumor blocks available for analysis**

- **7% of women met either clinical or molecular criteria for Lynch syndrome. All of these women had a prior history or a first-degree relative with an HNPCC-associated cancer**

Incidence of Microsatellite Instability in Synchronous Tumors of the Ovary and Endometrium

Catherine Shannon, Judy Kirk, Rebecca Barnetson, Justin Evans, Margaret Schnitzler, Michael Quinn, Neville Hacker, Alex Crandon and Paul Harnett

Clin Cancer Res. 2003 ;9:1387-92

45 patients with a median age at diagnosis of 53 years.

Of a total of 134 samples analyzed, only three samples (3.3%) were MSI-H

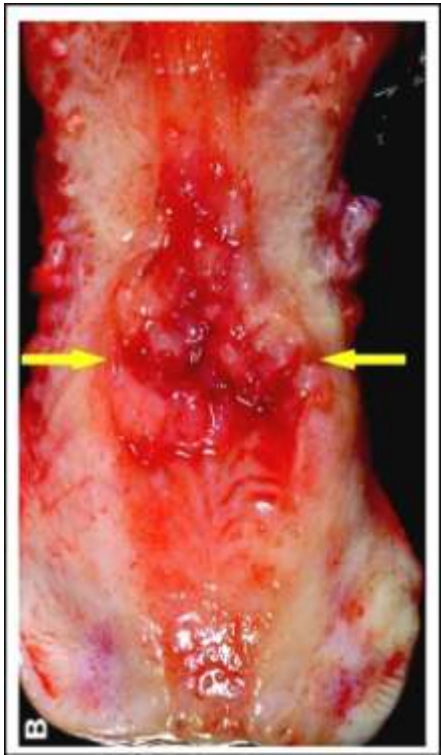
Carcinoma of the Lower Uterine Segment: A Newly Described Association With Lynch Syndrome

Westin, S. N. et al.

Journal of Clinical Oncology, 26, 2008:5965-5971

- **35 (3.5%) of 1,009 women with endometrial cancer had endometrial carcinoma of the LUS.**
- **LUS patients were younger, had higher stage tumors, and had more invasive tumors**

10 (29%) of the 35 women with LUS tumors were confirmed to have Lynch syndrome or were strongly suspected to have Lynch syndrome on the basis of tissue-based molecular assays



KNOWN FACTS ABOUT ENDOMETRIAL CARCINOMA IN WOMEN WITH LYNCH SYNDROME

- **IS THE MOST COMMONLY OCCURRING TUMOR IN HNPCC FEMALE MUTATION CARRIERS**
- **IN ABOUT 50% OF WOMEN WITH HNPCC IS THE FIRST CANCER TO DEVELOP**
- **HAS AN EARLIER AGE OF ONSET WHEN COMPARED WITH SPORADIC ENDOMETRIAL CARCINOMA**
- **IS FREQUENTLY CENTERED IN THE LOWER UTERINE SEGMENT**
- **MAY SHOW A SYNCHRONOUS OVARIAN CARCINOMA**
- **ITS HISTOLOGIC FEATURES AND BEHAVIOUR ARE NOT AS WELL KNOWN AS THOSE OF HNPCC-RELATED COLORECTAL CARCINOMA**

Lynch Syndrome-Related Endometrial Carcinomas Show a High Frequency of Nonendometrioid Types and of High FIGO Grade Endometrioid Types.

Carcangiu ML, Radice P, Casalini P, Bertario L, Merola M, Sala P.

Int J Surg Pathol. 2010; 18:21

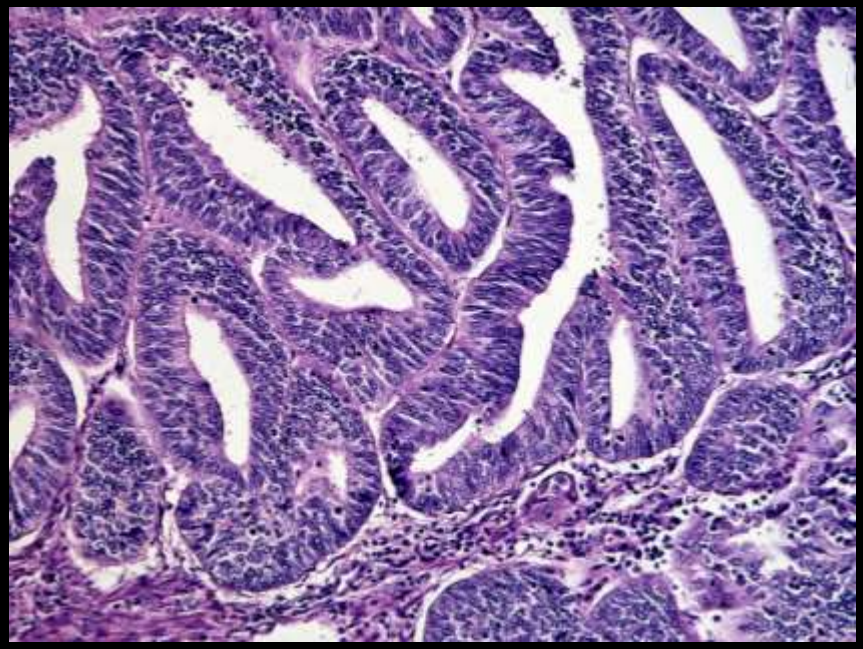
LS-RELATED ENDOMETRIAL CARCINOMA

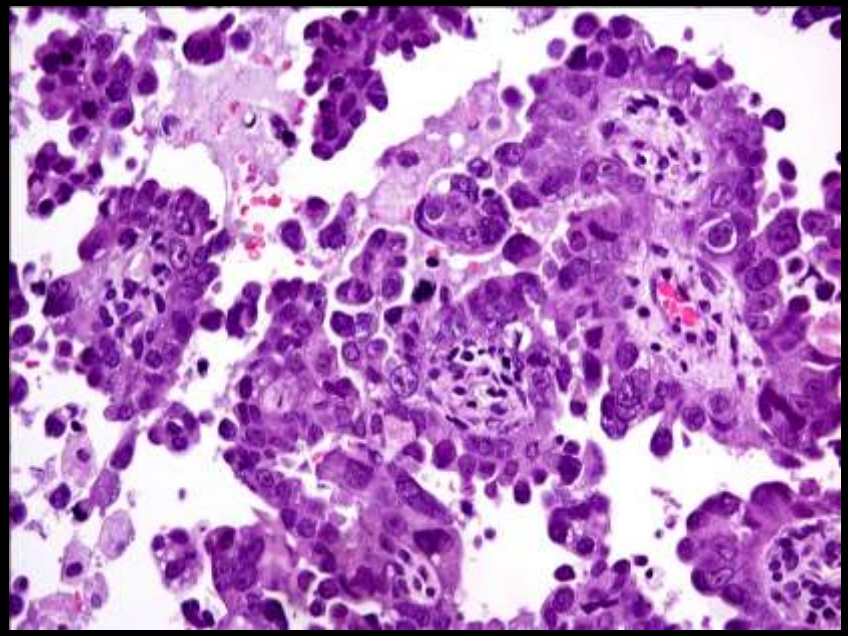
Endometrial carcinoma in 23 patients with proved MMR mutation (mean age 42.6 ys)

EVALUATED FOR :

- **HISTOLOGIC TYPE**
- **HISTOLOGIC GRADE**
- **VASCULAR INVASION**
- **NON NEOPLASTIC ENDOMETRIUM**
- **STAGE**
- **SURVIVAL**

Carcangiu ML, Radice P, Casalini P
Int J Surg Pathol. 2009





ENDOMETRIOID: 13 (56.5%)

NON-ENDOMETRIOID: 10 (43.4%)

COMPARISON OF THE FREQUENCY OF HISTOLOGIC TYPES AND FIGO GRADES OF ENDOMETRIAL CANCERS IN LYNCH SYNDROME PATIENTS AND CONTROLS

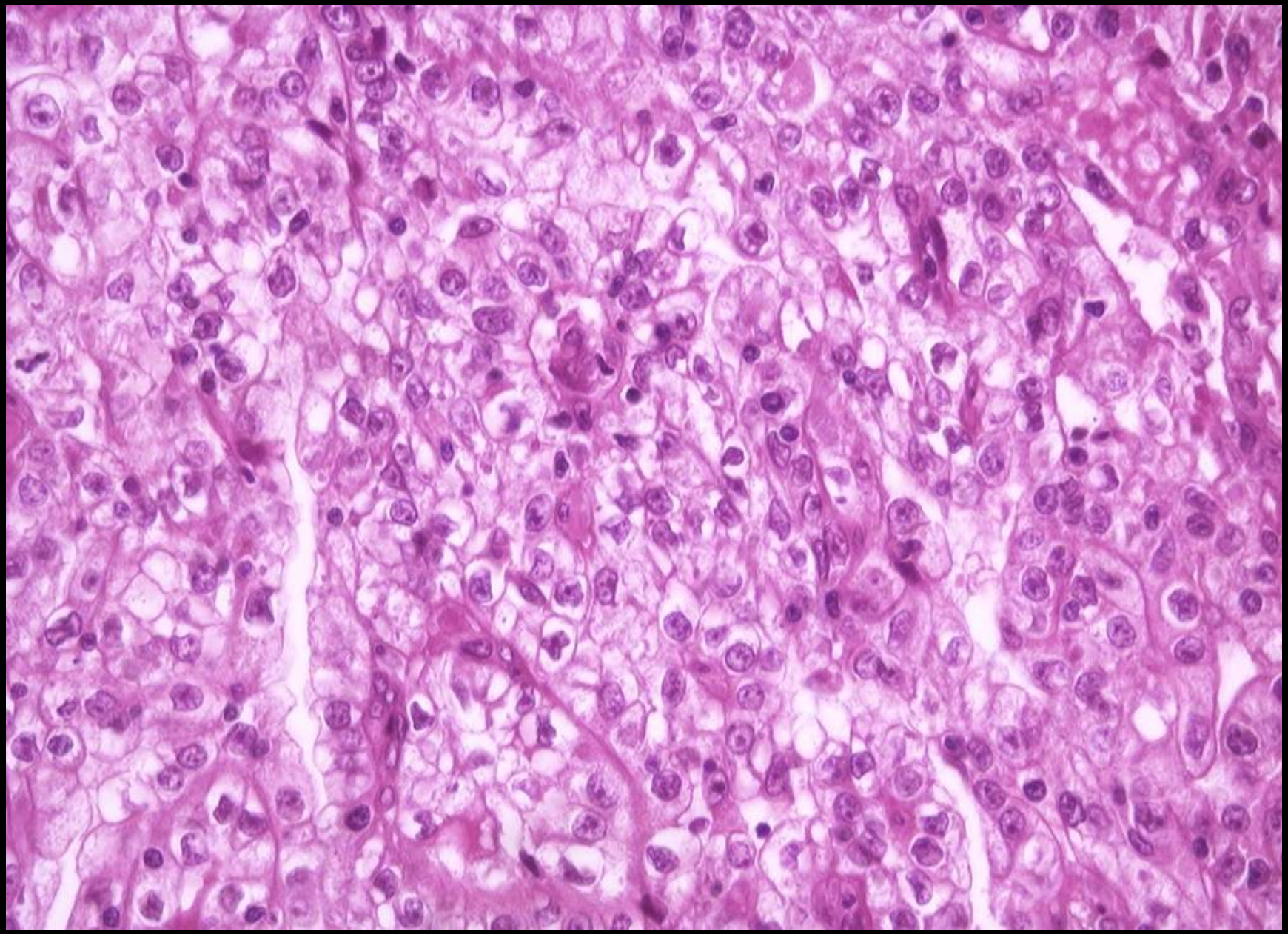
	LYNCH SYNDROME-RELATED EC (23)	CONTROLS (46)
ENDOMETRIOID	13 (56.5%)[1]	44 (95.6%)[1]
FIGO GRADE I	3 (23.0%)[2]	20 (45.4%)[2]
FIGO GRADE II	4 (30.7%)[2]	19 (43.1%)[2]
FIGO GRADE III	6 (46.1%)[2]	5 (11.3%)[2]
NON -ENDOMETRIOID	10 (43.4%)[1]	2 (4.3%)[1]
CLEAR CELL	5 (50.0%)	0
SEROUS	2 (20.0%)	1
MMMT	2 (20.0%)	0
NEUROENDOCRINE	1(10.0%)	1

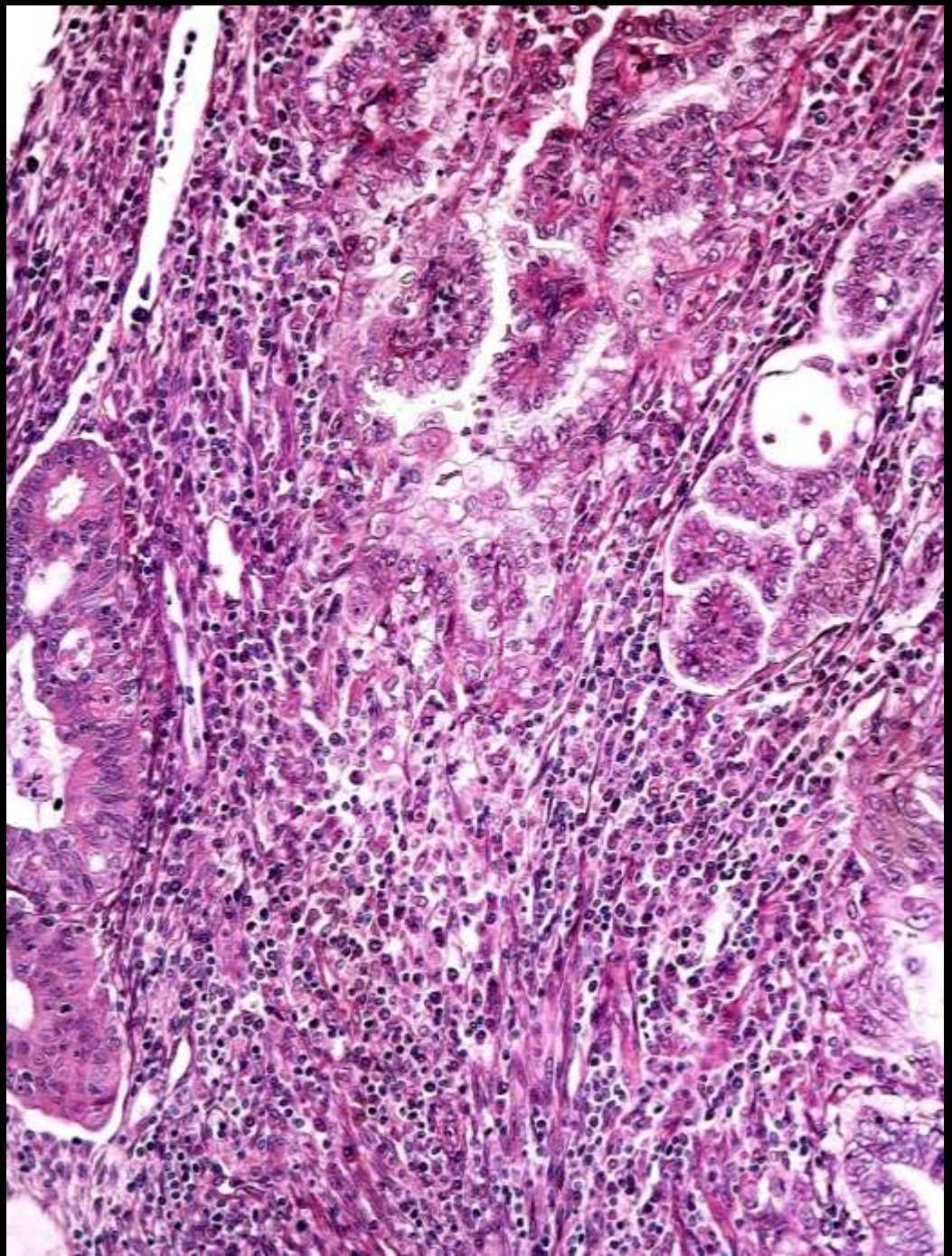
EC:endometrial cancer

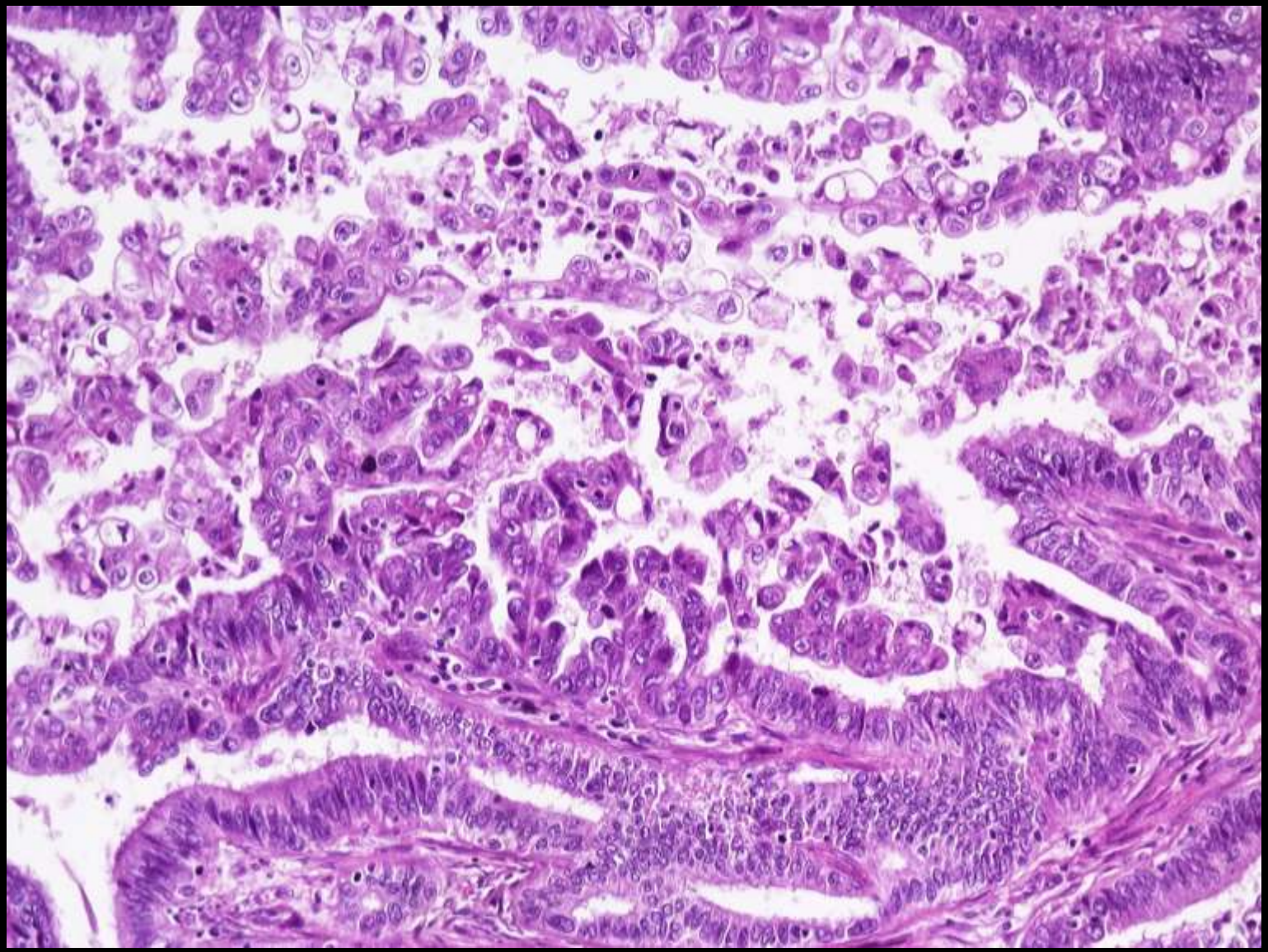
[1] : P<0.0001 by Fisher's exact test

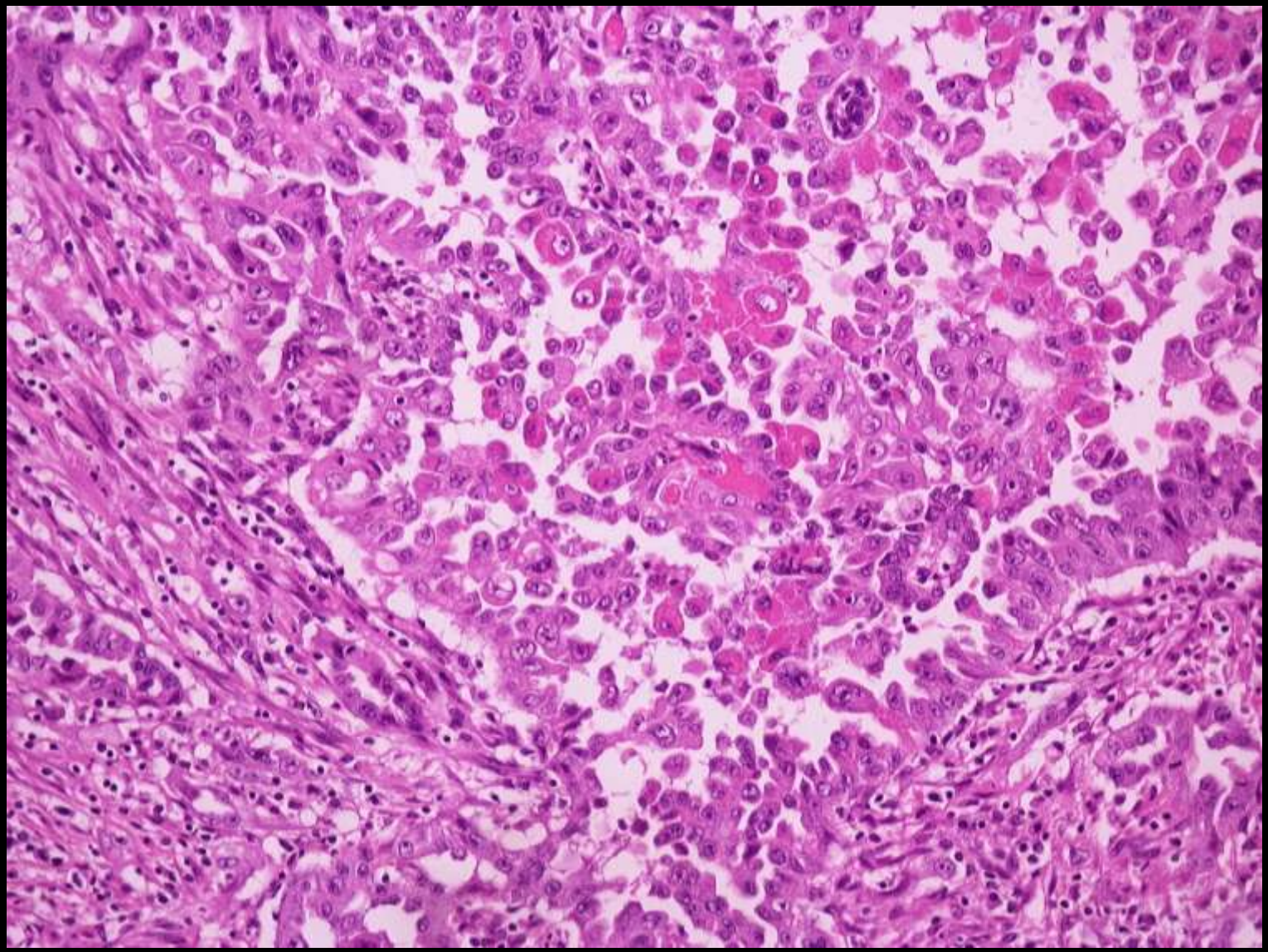
[2] : P= 0.0368 by Chi-square test

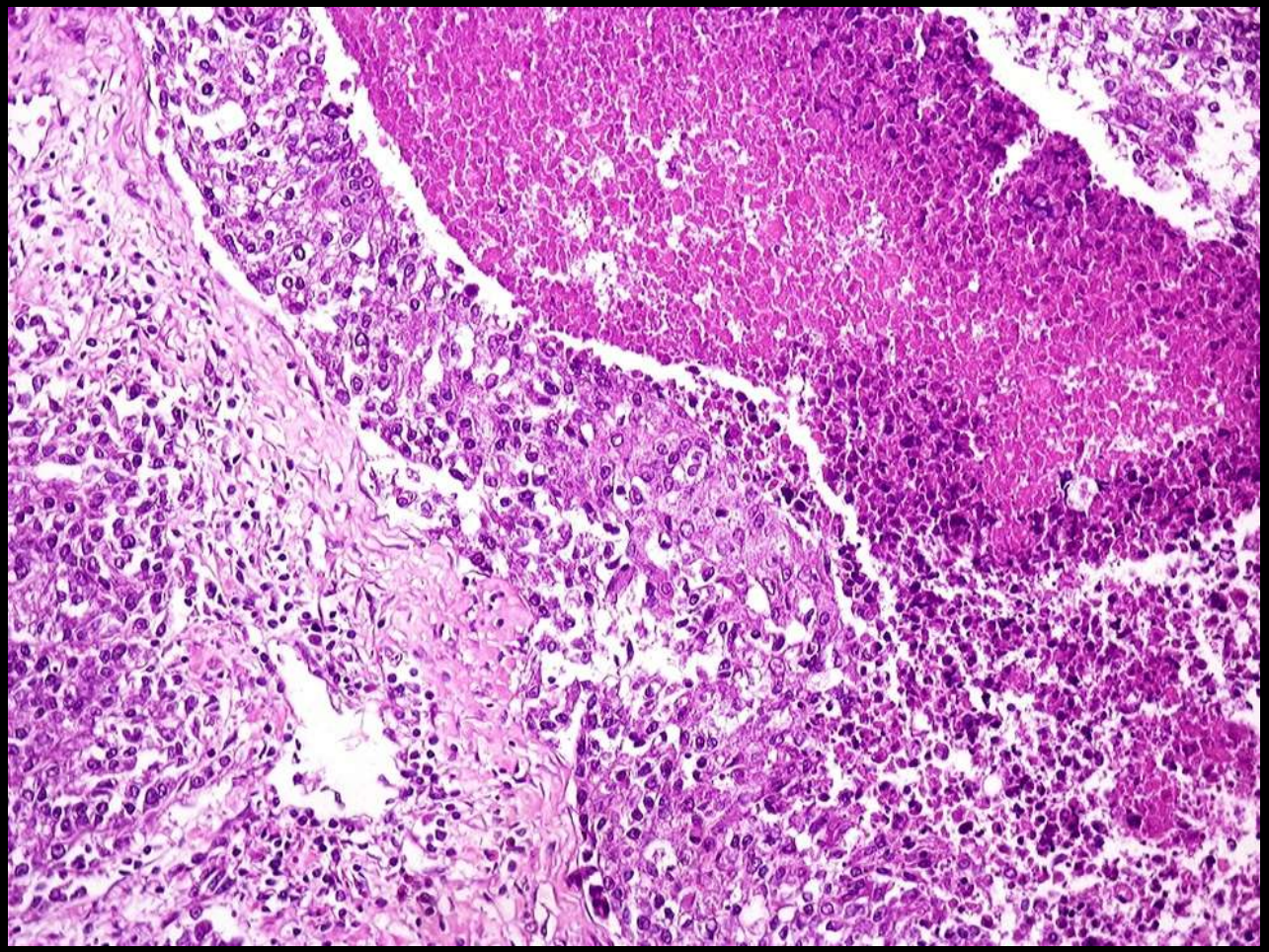
Carcangiu ML, et al.
Int J Surg Pathol. 2010

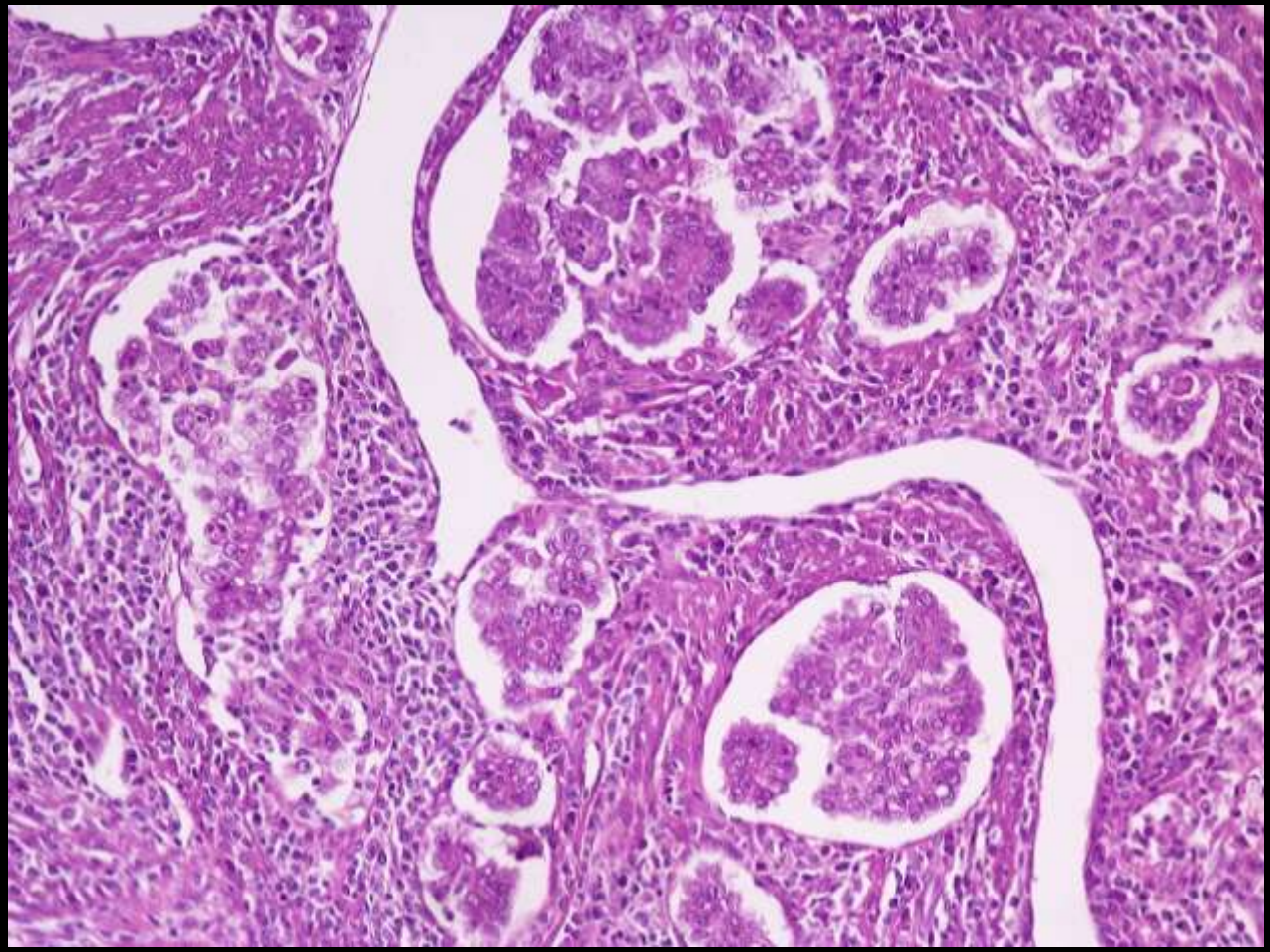




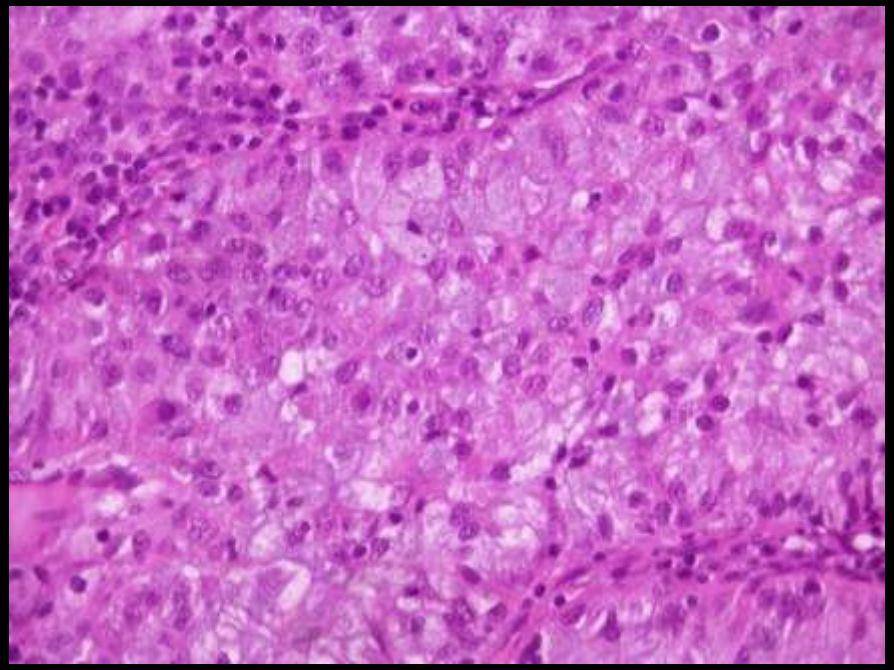


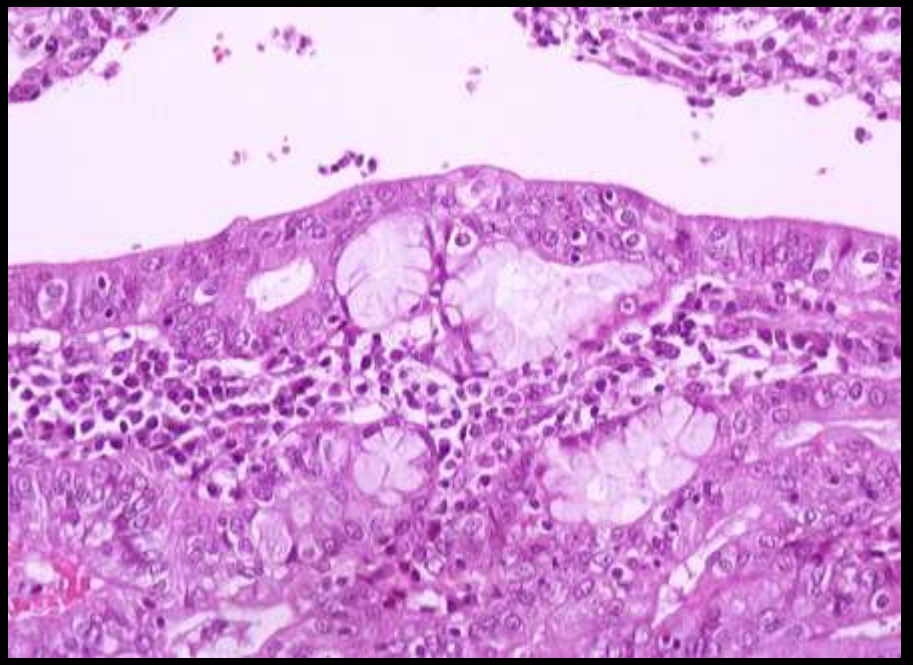


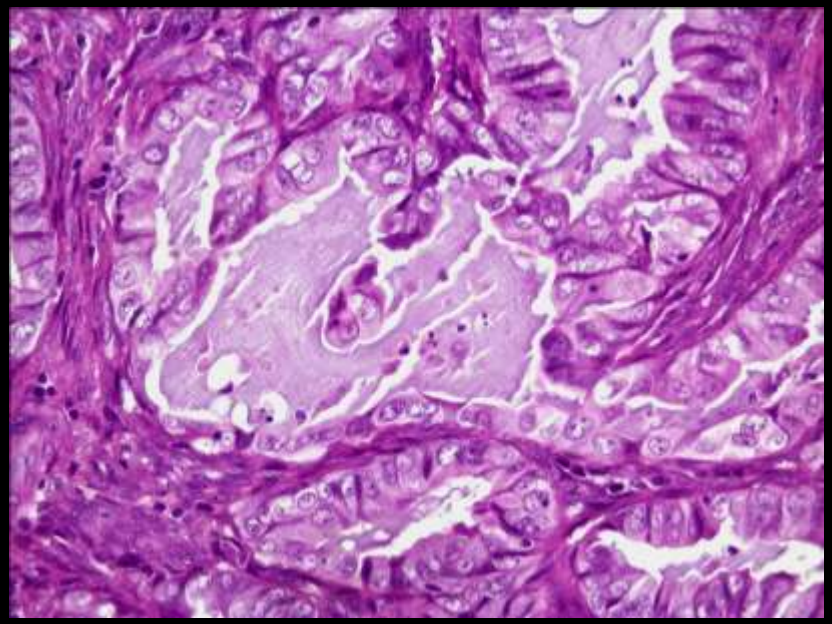




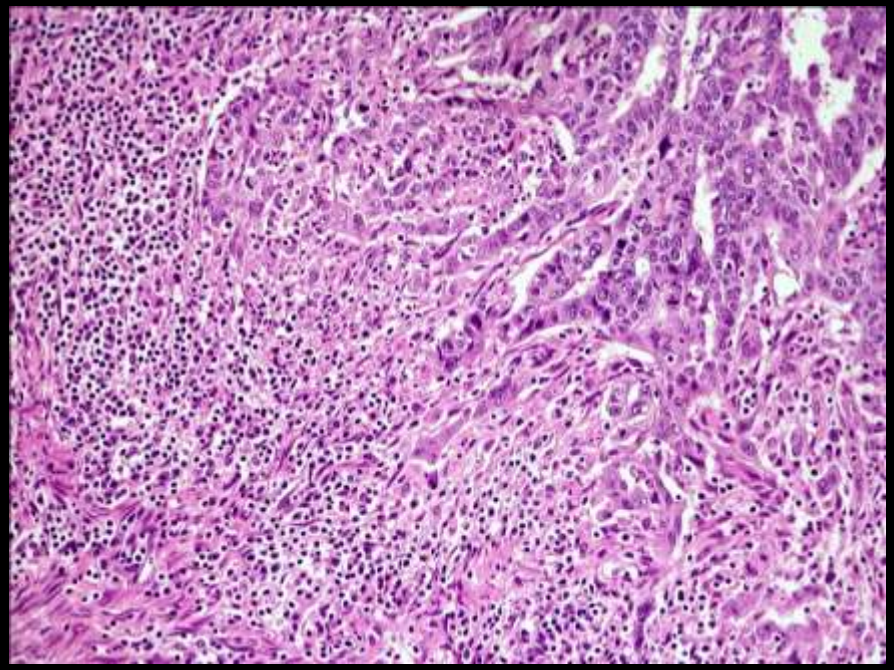
Lymphovascular invasion: 45.5%

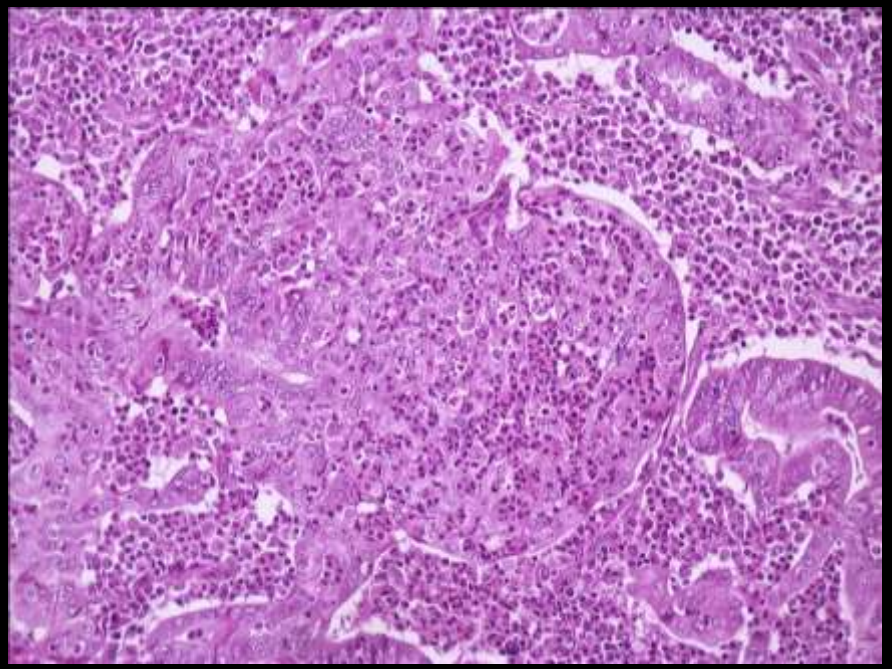


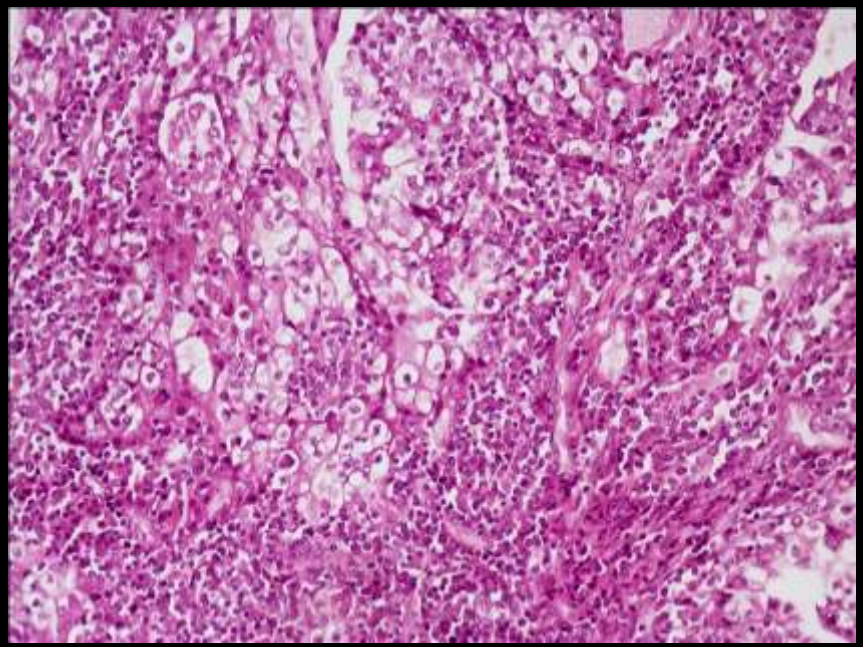




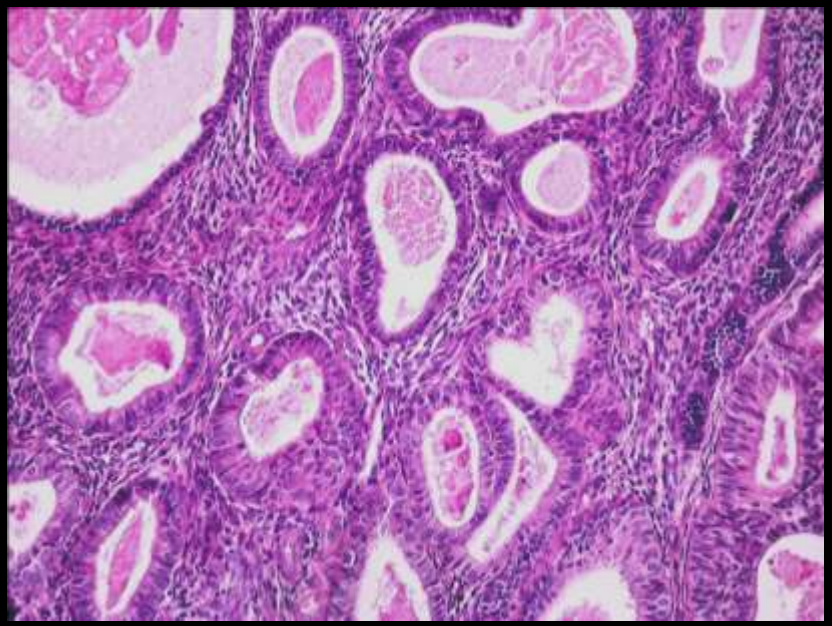
Mucinous differentiation:16%





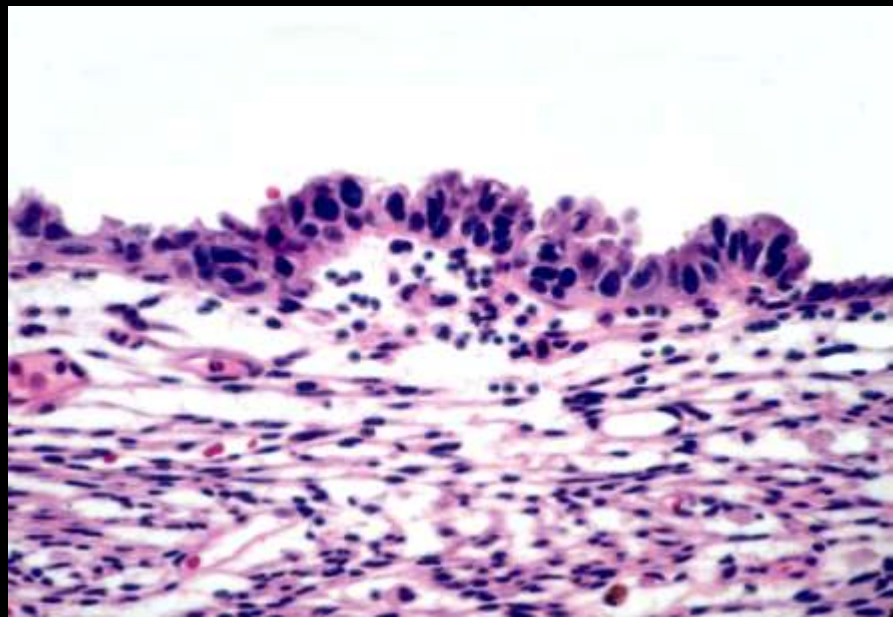


Inflammatory infiltrate: 50%



Endometrial glandular hyperplasia 52.2%

Endometrial Intraepithelial carcinoma (EIC): 6.8%

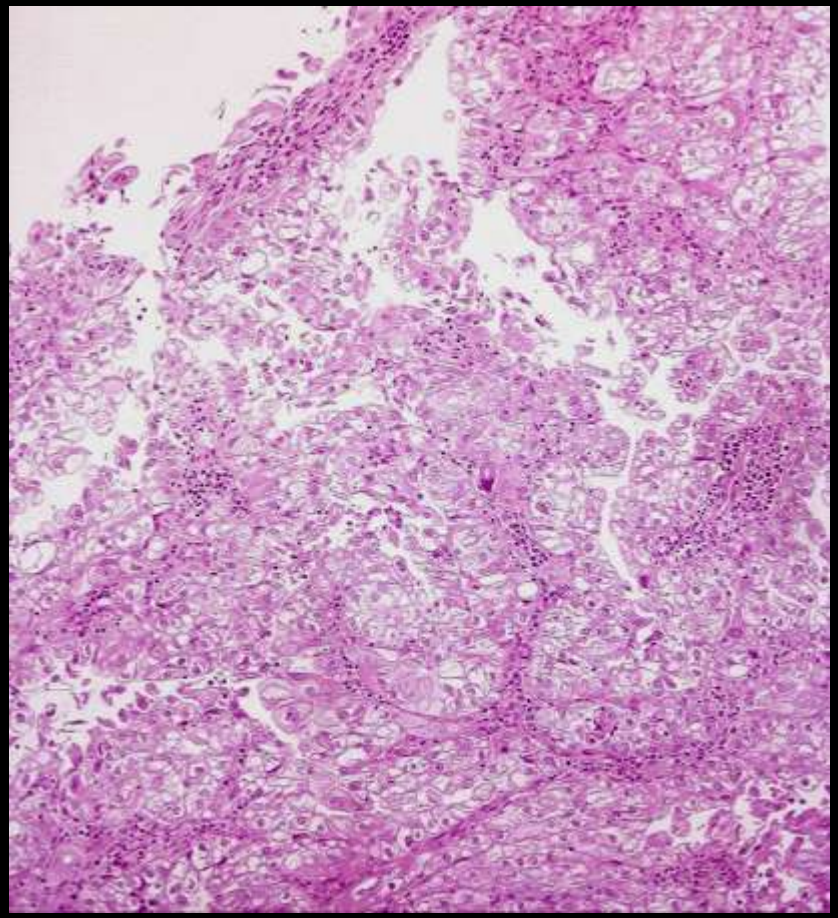


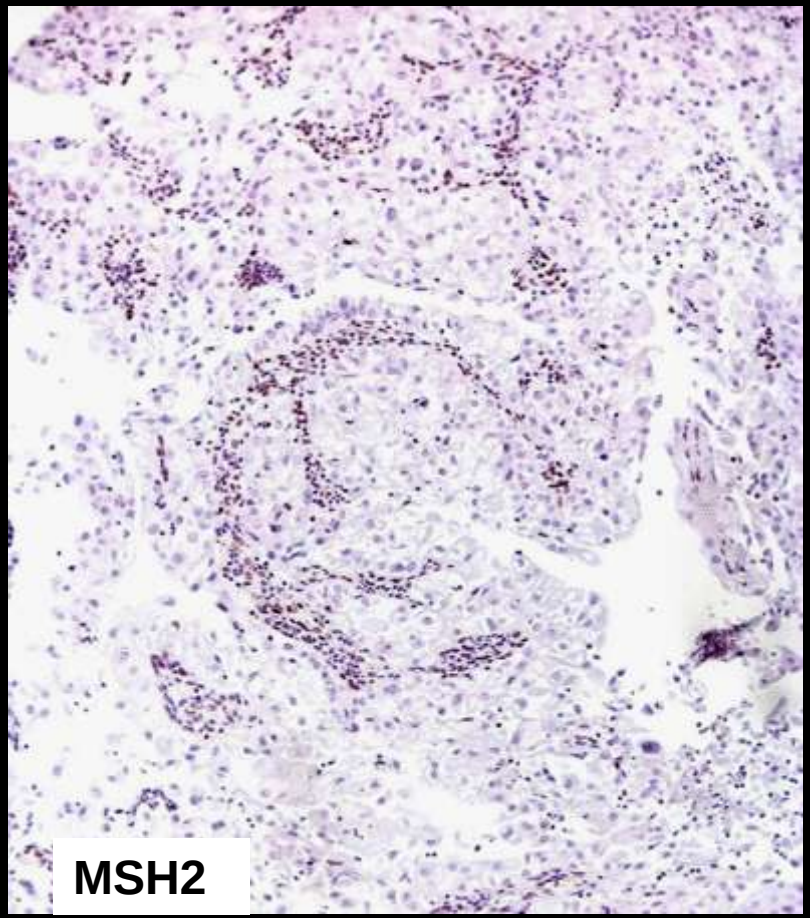
HISTOLOGY AND GENE MUTATION IN LYNCH SYNDROME-RELATED ENDOMETRIAL CANCERS

HISTOLOGIC TYPE	MLH1	MSH2	MLH1 MSH2	TOTAL(%)
ENDO-METRIOID	5 (38.4%)	7 (53.8%)	1 (7.6%)	13
NON-ENDOME-TRIOID	2 (20%)	8° (80%)	0	10
TOTAL	7	15	1	23

°: INCLUDING 6 CASES WITH COMBINED NEEC AND ECC HISTOLOGY

Carcangiu ML, Radice P, Casalini P et al.
Int J Surg Pathol. 2010




MSH2

STAGE DISTRIBUTION OF LYNCH SYNDROME-RELATED ENDOMETRIAL CANCERS AND CONTROLS

STAGE	LYNCH SYNDROME-RELATED EC	CONTROL EC
IA	0	10(21.7%)
IB	13(56.5%)	24(52.1%)
IC	4(17.3%)	3(6.5%)
IIB	3(13.0%)	5(10.8%)
IIIA	1(4.3%)	3(6.5%)
IIIC	2(8.7%)	1(2.1%)
TOTAL	23	46

EC:endometrial cancer

Carcangiu ML, Radice P, Casalini P et al.
Int J Surg Pathol. 2010

SURVIVAL OF PATIENTS WITH LYNCH SYNDROME-RELATED ENDOMETRIAL CANCER ACCORDING TO FIGO STAGE

STAGE	A&W	DOD	DOC	TOT
I	13(76.4%)	2(11.7%)	2(11.7%)	17
II	2(66.6%)	1(33.3%)	0	3
III	0	2(66.6%)	1(33.3%)*	3
TOTAL	15(65.2%)	5(21.7%)	3 (13.0%)	23

* Patient ç recurrent endometrial carcinoma

SURVIVAL OF PATIENTS WITH LYNCH SYNDROME-RELATED ENDOMETRIAL CANCER ACCORDING TO HISTOLOGY

	ENDO-METRIOID	NON - ENDOMETRIOID	TOTAL (%)
A&W	10(76.9 %)	5(50.0 %)	15 (65.2%)
DOD	1 (7.6 %)	4 (40.0 %)	5(21.7%)
DOC	2+° (15.3 %)	1*(10.0 %)	3(13.0%)
TOTAL	13	10	23

*Dead of colonic cancer (patient ç recurrent endometrial carcinoma)
+Dead of pancreatic cancer
°Dead of colonic cancer

NEOPLASMS AT OTHER SITES ASSOCIATED WITH LYNCH SYNDROME-RELATED ENDOMETRIAL CANCERS ACCORDING TO GENE MUTATION

	ALL CASES	MLH1	MSH2	MLH1/ MSH2
COLORECTUM	12	2	9	1
SKIN	1	1		
STOMACH	1		1	
BREAST	2		2	
PANCREAS	1			1
OVARY	2+		2	
URINARY TRACT	3	1	2	
TOTAL	22	4	16	2

+ (8.6%) BOTH CLEAR CELL CARCINOMAS

CONCLUSIONS

1) THE FREQUENCY OF NON ENDOMETRIOID CARCINOMA (PARTICULARLY CLEAR CELL CARCINOMA, PURE OR ADMIXED WITH ENDOMETRIOID CARCINOMA) IS HIGHER AMONG UTERINE TUMORS IN HNPCC WOMEN THAN AMONG WOMEN WITH SPORADIC UTERINE TUMORS, DESPITE THE TENDENCY OF HNPCC-RELATED TUMORS TO OCCUR IN YOUNGER PATIENTS, AN AGE GROUP IN WHICH NON ENDOMETRIOID CARCINOMAS ARE DISTINCTLY RARE;

2) PURE ENDOMETRIOID CARCINOMAS OCCURRING IN HNPCC WOMEN TEND TO BE OF HIGHER FIGO GRADE THAN THEIR SPORADIC COUNTERPARTS;

3) BOTH ENDOMETRIOID AND NON ENDOMETRIOID CARCINOMAS IN HNPCC WOMEN SHOW FIGO STAGE DISTRIBUTIONS SIMILAR TO THOSE SEEN IN THE CORRESPONDING SPORADIC CASES

4) AS A GROUP, HNPCC-RELATED UTERINE CARCINOMA IS MORE LIKELY TO EXHIBIT MICROSCOPICALLY AGGRESSIVE FEATURES THAN ITS SPORADIC COUNTERPART (GREATER NUMBER OF CASES WITH A NON ENDOMETRIOID COMPONENT AND HIGHER FIGO GRADES AMONG THE PURE ENDOMETRIOID CARCINOMAS), BUT FROM THIS STUDY IT DOES NOT EMERGE AS A DISTINCT PATHOLOGIC SUBTYPE OF UTERINE CARCINOMA.

More differences between HNPCC-related and sporadic carcinomas from the endometrium as compared to the colon.

van den Bos M, van den Hoven M, Jongejan E, et al.

Am J Surg Pathol. 2004;28:706-11

6 CASES

	HNPCC-RELATED CARCINOMA	CONTROLS
Poorly differentiated	83%	27%
Crohn-like lymphoid reaction	100%	13%
Lymphangioinvasi-ve growth	67%	0
High number of tumor-infiltrating lymphocytes	100%	36%

Pathologic features of endometrial carcinoma associated with HNPCC

Broaddus RR et al.

Cancer. 2006;106:87-94.

	HNPCC	SPORADIC CA < 50 YS
N. OF CASES	50	42
MEAN AGE	46.8%	39.9%
ENDOMETRIOID TYPE	86.0%	97.6%
GRADE I	44.2%	39.0%
GRADE II	39.5%	51.2%
GRADE III	16.3%	9.8%
STAGE I	78.0%	66.7%
STAGE II	10.0%	7.1%
STAGE III/IV	12.0%	26.2%
MYOMETRIAL INV >50%	26.0%	23.8%
LYMPH/VASC INVASION	24.0%	40.5%

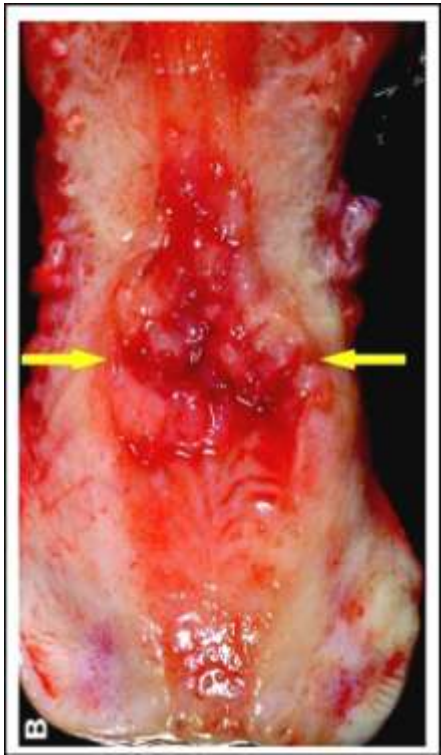
Carcinoma of the Lower Uterine Segment: A Newly Described Association With Lynch Syndrome

Westin, S. N. et al.

Journal of Clinical Oncology, 26, 2008:5965-5971

- **35 (3.5%) of 1,009 women with endometrial cancer had endometrial carcinoma of the LUS.**
- **LUS patients were younger, had higher stage tumors, and had more invasive tumors**

10 (29%) of the 35 women with LUS tumors were confirmed to have Lynch syndrome or were strongly suspected to have Lynch syndrome on the basis of tissue-based molecular assays



Carcinoma of the Lower Uterine Segment: A Newly Described Association With Lynch Syndrome

Westin, S. N. et al.

Journal of Clinical Oncology, 26, 2008:5965-5971

	LUS WITH LS	LUS WITHOUT LS
ENDOMETRIOID	6 (60.0%)	21(84.0%)
NONENDOMETRIOID	4 (40.0%)	4 (16.0%)

Selection of endometrial carcinomas for DNA mismatch repair protein immunohistochemistry using patient age and tumor morphology enhances detection of mismatch repair abnormalities.

Garg K, Leitao MM Jr, Kauff ND, Hansen J, Kosarin K, Shia J, Soslow RA.

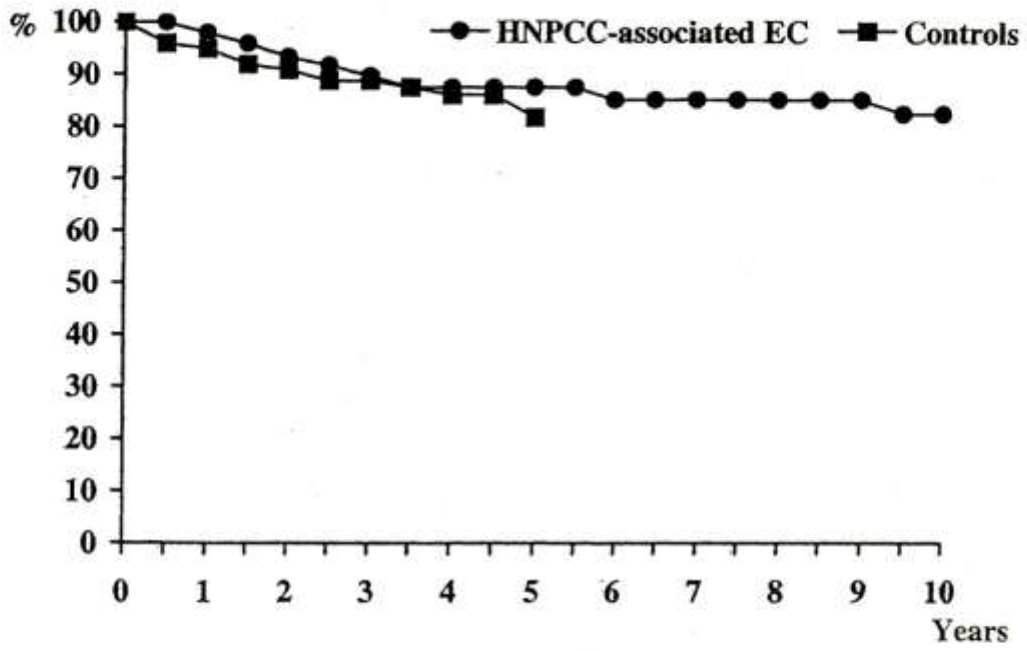
Am J Surg Pathol. 2009;33:925-33.

- **THE IHC ABNORMAL GROUP SHOWED MORE FREQUENT:**
- **tumor infiltrating lymphocytes**
- **dedifferentiated EC**
- **more tumors centered in the lower uterine segment**
- **more frequent synchronous clear cell carcinomas of the ovary**

Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer.

Boks DE et al.

Int J Cancer. 2002;102:198-2000.



Log-rank: p=0.59

FIGURE 1 – Cumulative survival of patients with HNPCC-associated endometrial carcinoma and age- and stage-matched controls with endometrial carcinoma.

Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer.

Boks DE et al.

Int J Cancer. 2002;102:198-2000.

TABLE I – CHARACTERISTICS OF PATIENTS WITH HNPCC-ASSOCIATED ENDOMETRIAL CARCINOMA VERSUS AGE- AND STAGE-MATCHED CONTROL PATIENTS WITH ENDOMETRIAL CARCINOMA[1]

Characteristic	Study group $n = 50$ (%)	Control group $n = 100$ (%)
Age, mean (range)[2]	49.9 (31–69)	53.7 (30–72)
Stage		
IA	11 (22)	22 (22)
IB	21 (42)	42 (42)
IC	7 (14)	14 (14)
IIIA	9 (18)	18 (18)
IIIC	2 (4)	4 (4)
Histological type		
Endometrioid/adenocarcinoma	46 (92)	88 (88)
Papillary/serous carcinoma	1 (2)	7 (7)
Clear-cell carcinoma	0 (0)	0 (0)
Other	2 (4)	5 (5)
Unknown	1 (2)	0 (0)

[1]Stage IA, IB, IC, IIIA AND IIIC.–[2]*t*-test: $p = 0.004$.

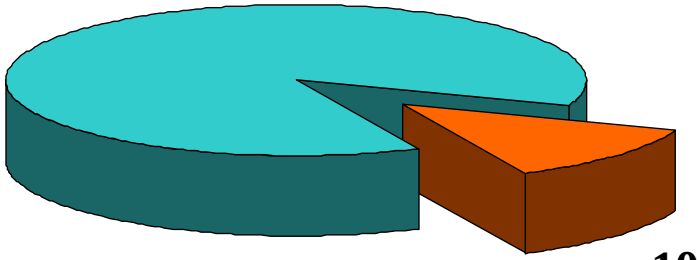
OVARIAN CARCINOMA

CAUSES OF HEREDITARY SUSCEPTIBILITY TO OVARIAN CANCER

OVARIAN CANCER

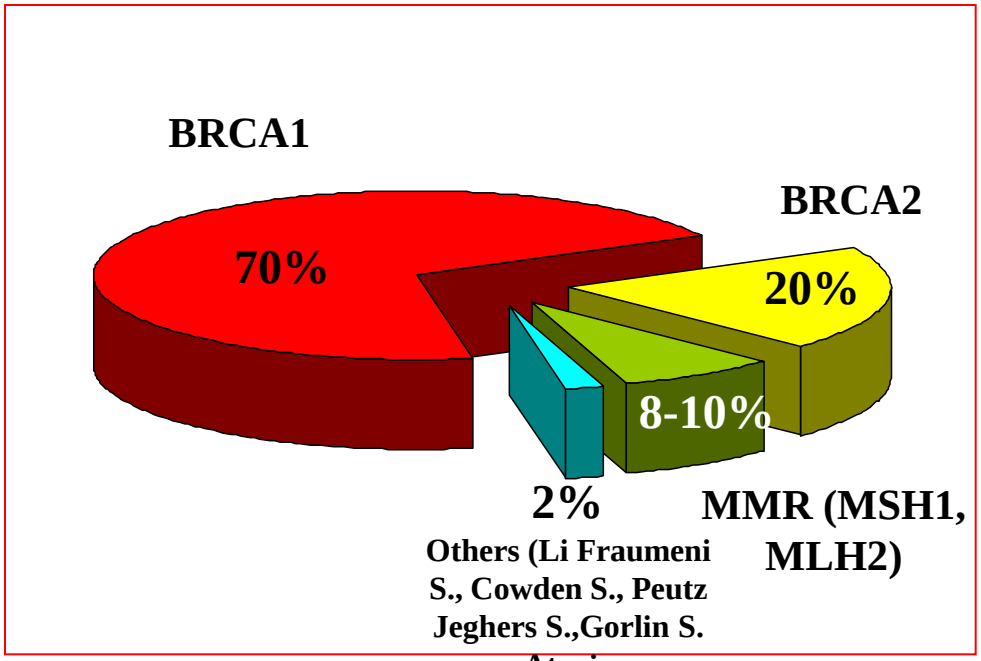
Sporadic

90%



10%

Hereditary



LIFETIME RISK OF CANCER REPORTED IN FAMILIES WITH AN IDENTIFIED MISMATCH REPAIR MUTATION

- Colorectal cancer (men): 28–75%
- Colorectal cancer (women): 24–52%
- Endometrial cancer: 27–71% [2.3%]
- Ovarian cancer: 3.6 –13% [1.8%]
- Gastric cancer: 2–13%
- Urinary tract cancer: 1–12%
- Brain tumour: 1–4%
- Bile duct/gallbladder cancer: 2%
- Small-bowel cancer: 4–7%

Vasen, H F A et al. J Med Genet 2007;44:353-362

Mean age at diagnosis:

HNPCC-ovarian cancer: 41-49 yrs

Sporadic ovarian cancer: 60-65 yrs

ELSEVIER

Gynecologic Oncology 101 (2006) 238 – 243

www.elsevier.com/locate/ygyno

The contribution of the hereditary nonpolyposis colorectal cancer syndrome to the development of ovarian cancer

Susanne Malander [a,*], Eva Rambech [a], Ulf Kristoffersson [b], Britta Halvarsson [c], Mona Ridderheim [a], Åke Borg [a], Mef Nilbert [a]

[a] Department of Oncology, Institute of Clinical Sciences, Lund University Hospital, SE-221 85 Lund, Sweden
[b] Department of Clinical Genetics, Institute of Laboratory Sciences, Lund University Hospital, 22185 Lund, Sweden
[c] Department of Pathology, Institute of Clinical Sciences, Lund University Hospital, 22185 Lund, Sweden

- **A consecutive series of 128 tumors <u>unselected for age</u> at diagnosis**

- **Loss of MMR protein expression was identified in 3 ovarian cancers (2%), all MSI-H.**

Germline mutation was identified in 2 cases: *MLH1* (mucinous-endometrioid) and *MSH6* (clear cell)

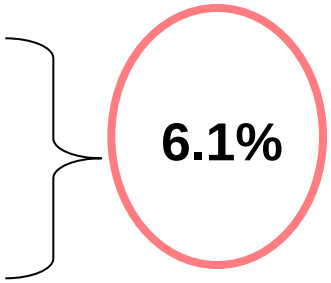
Ovarian cancer at young age: the contribution of mismatch-repair defects in a population-based series of epithelial ovarian cancer before age 40.

Domanska K, Malander S, Måsbäck A, Nilbert M.

Int J Gynecol Cancer. 2007;17:789-93.

- **98 invasive epithelial ovarian cancers that developed before 40 years from the Swedish Cancer Registry.**

  - **Loss of expression of :**
  - **MLH1/PMS2 in two cases**
  - **MSH2/MSH6 in one case**
  - **MSH6 only in three tumors**



  - **A microsatellite instability-high phenotype was verified in five of the six tumors.**

Microsatellite instability and mismatch repair protein defects in ovarian epithelial neoplasms in patients 50 years of age and younger.

Jensen KC, Mariappan MR, Putcha GV et al.

Am J Surg Pathol. 2008;32:1029-37

- 52 ovarian surface epithelial carcinomas in patients < =50 ys
- Defects in MMR in 5 of 52 (10%)
- MMR inactivation in 17% of ovarian clear cell carcinomas including 4 with synchronous endometrial carcinomas

Gynecologic Oncology 82, 223–228 (2001)
doi:10.1006/gyno.2001.6279, available online at http://www.idealibrary.com on IDEAL®

The Clinical Features of Ovarian Cancer in Hereditary Nonpolyposis Colorectal Cancer

Patrice Watson, Ph.D.,* Ralf Buttow, M.D.,† Henry T. Lynch, M.D.,* Jukka-Pekka Mecklin, M.D.,‡ Heikki J. Järvinen, M.D.,‡ Hans F. A. Vasen, M.D., Ph.D.,§ Lisa Madlensky, M.Sc.,¶ Paulo Fidalgo, M.D.,‖ Inge Bernstein, M.D., Ph.D.,** and the International Collaborative Group on HNPCC

*Department of Preventive Medicine, Creighton University School of Medicine, Omaha, Nebraska, 68178; †Helsinki University Central Hospital, Helsinki, Finland; ‡Department of Surgery, Jyväskylä Central Hospital, Jyväskylä, Finland; §Foundation for the Detection of Hereditary Tumors, c/o Leiden University Hospital, Leiden, The Netherlands; ¶Familial GI Cancer Registry, Mount Sinai Hospital, Toronto, Ontario, Canada; ‖Gastroenterology Department, Portuguese Institute of Oncology, Lisboa, Portugal; and **The Danish HNPCC Register, Department of Surgical Gastroenterology, Hvidovre Hospital, Hvidovre, Denmark

79 ovarian cancer patients who were members of HNPCC families

- Mean age at diagnosis of ovarian cancer : 42.7 ys.
- Nonepithelial tumors: 6.4% of the cancers
- Borderline tumors : 4.1% of the epithelial cancers.
- HISTOLOGIC TYPES OF INVASIVE CARCINOMA: serous (30%), mucinous (7%), endometrioid (13%), clear cell (7%), other (4%)
- Most malignant epithelial cancers were well or moderately differentiated
- 85% were FIGO stage I or II at diagnosis
- Synchronous endometrial cancer was reported in 21.5% of the cases

Watson P

Ovarian cancer linked to Lynch syndrome typically presents as early-onset, non-serous epithelial tumors.

Ketabi Z, Bartuma K, Bernstein I, Malander S, Grönberg H, Björck E, Holck S, Nilbert M.

Gynecol Oncol. 2011 Mar 7. [Epub ahead of print]

HNPCC-register, Department of Gastroenterology, Hvidovre University Hospital, Faculty of Health Sciences, Copenhagen University, Denmark.

- 63 epithelial ovarian cancers
- mean age 48 (range 30-79 years of age)
- 47% FIGO stage I
- MSH2:49%, MSH6:33%, MLH1:17%. Immunohistochemical loss of the corresponding MMR protein was demonstrated in 33/36 (92%) tumors analyzed.
- The ovarian cancer was the sentinel tumor in 12 patients
- Synchronous endometrial carcinoma: 4 patients

- Histologic type:
- endometrioid :35%; clear cell :17%; serous: 28%; mucinous:5%; undifferentiated:15%

Ovarian tumors in lynch syndrome:genotype-fenotype correlation.

Ryan P et al. Poster 1124, USCAP 2011

- **15 ovarian cancers identified retrospectively from the cancer registries in Toronto,Vancouver and Montreal**
- **Mean age: 42.8 yrs (range 31-53yrs, 1>50 years old)**
- **MSH2 mutations:12**
- **MLH1 mutations:3**
- **Ovarian cancer was the sentinel tumor in 12 patients**
- **Colonic cancer was the sentinel tumor in 3 patients**
- **Stage I: 7 cases (4 with synchronous endometrial carcinoma)**

- **Histologic type:**
- **Mixed: 6, Endometrioid: 3, Clear cell: 2, Serous: 2, Mucinous:1, Squamous cell:1**

OVARIAN CA IN MMR MUTATION CARRIERS

- ~ 2% OF ALL OVARIAN CANCERS
- ~ 10% OF ALL HEREDITARY OVARIAN CANCERS
- MORE FREQUENT IN WOMEN WITH MUTATIONS IN MSH2 AND MSH6 GENES
- EARLY AGE ONSET
- MOSTLY EPITHELIAL
- MODERATELY OR WELL DIFFERENTIATED
- FREQUENTLY CLEAR CELL, MUCINOUS AND ENDOMETRIOID TYPE
- MOSTLY LOW STAGE
- ARE MORE LIKELY TO HAVE A SYNCHRONOUS ENDOMETRIAL CANCER
- SURVIVAL RATE SIMILAR TO THAT OF SPORADIC OVARIAN CANCER ?

Familial Cancer (2005) 4: 301–305
DOI 10.1007/s10689-005-6573-2

Survival of patients with ovarian cancer due to a mismatch repair defect

Th.E.M. Crijnen[1], M.L.G. Janssen-Heijnen[2], H. Gelderblom[3], J. Morreau[4], M.A. Nooij[3], G.G. Kenter[5] and H.F.A. Vasen[1,3]

- **26 patients with OC from the Dutch HNPCC Registry.**
- **Control group (52 cases) matched for age, stage and year of diagnosis derived from the population-based Eindhoven Cancer Registry.**

- **The mean age at diagnosis of OC-HNPCC was significantly lower than the age of sporadic OC (49.5 vs 60.9 years).**

- **In comparison to sporadic OC significantly more OC-HNPCC tumors were diagnosed at an early stage.**

- **The distribution of histologic types was not significanly different between the study and control group.**

- The **survival rate was not significantly different** between patients with OC-HNPCC and the age-and stage mached controls.
- The cumulative 5-year-survival rates were 64.2 and 58.1% respectively.

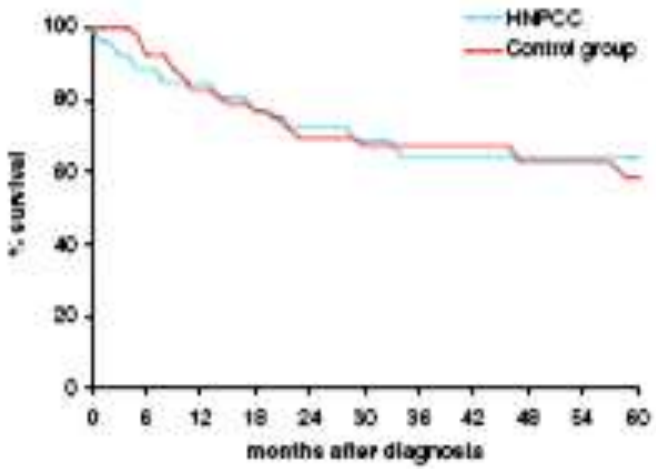


Figure 1. Cumulative survival of patients with HNPCC-associated ovarian cancer and age- and stage-matched controls with ovarian cancer. Stages I, II and III.

Histological type (%)		
Epithelial cases		
Serous cystadenocarcinoma	12 (46.2)	17 (32.7)
Mucinous cystadenocarcinoma	1 (3.8)	10 (19.2)
Endometrioid adenocarcinoma	4 (15.4)	6 (11.5)
Clear cell adenocarcinoma	1 (3.8)	3 (5.8)
Unspecified adenocarcinoma	1 (3.8)	13 (25)
Undifferentiated adenocarcinoma	1 (3.8)	1 (1.9)

Survival in women with MMR mutations and ovarian cancer: a multicentre study in Lynch syndrome kindreds

Eli Marie Grindedal,[1] Laura Renkonen-Sinisalo,[2] Hans Vasen,[3] Gareth Evans,[4] Paola Sala,[5] Ignacio Blanco,[6] Jacek Gronwald,[7] Jaran Apold,[8] Diana M Eccles,[9] Ángel Alonso Sánchez,[10] Julian Sampson,[11] Heikki J Järvinen,[2] Lucio Bertario,[5] Gillian C Crawford,[9] Astrid Tenden Stormorken,[1] Lovise Maehle,[1] Pal Moller[1]

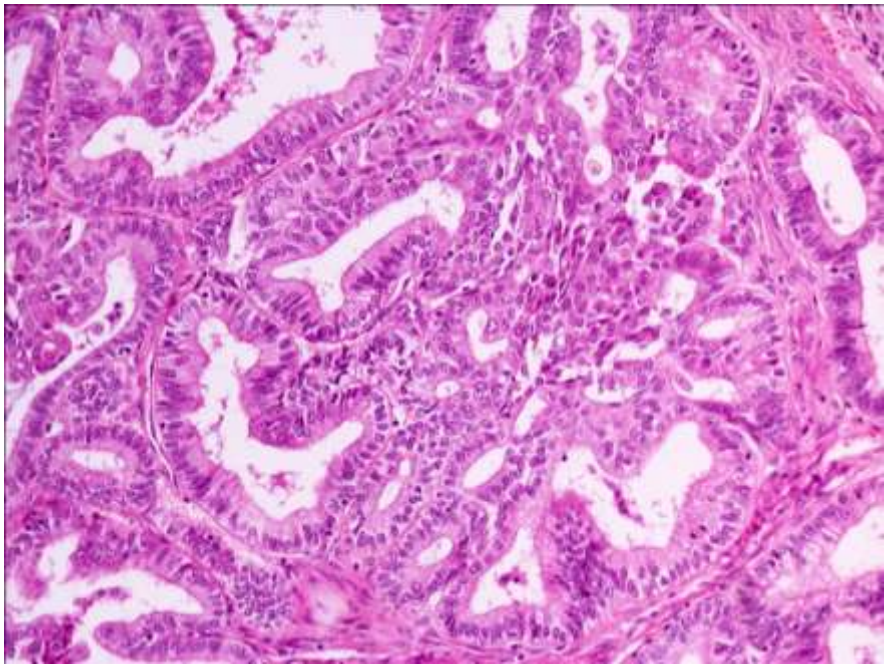
J Med Genet. 2010;47:99-102.

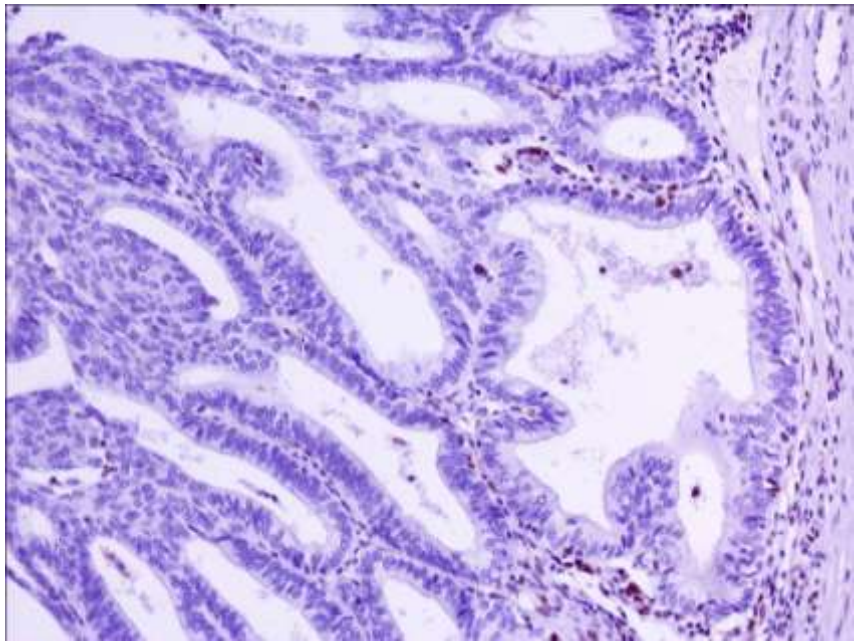
Survival in women with MMR mutations and ovarian cancer; A multicentre study in Lynch Syndrome kindreds.

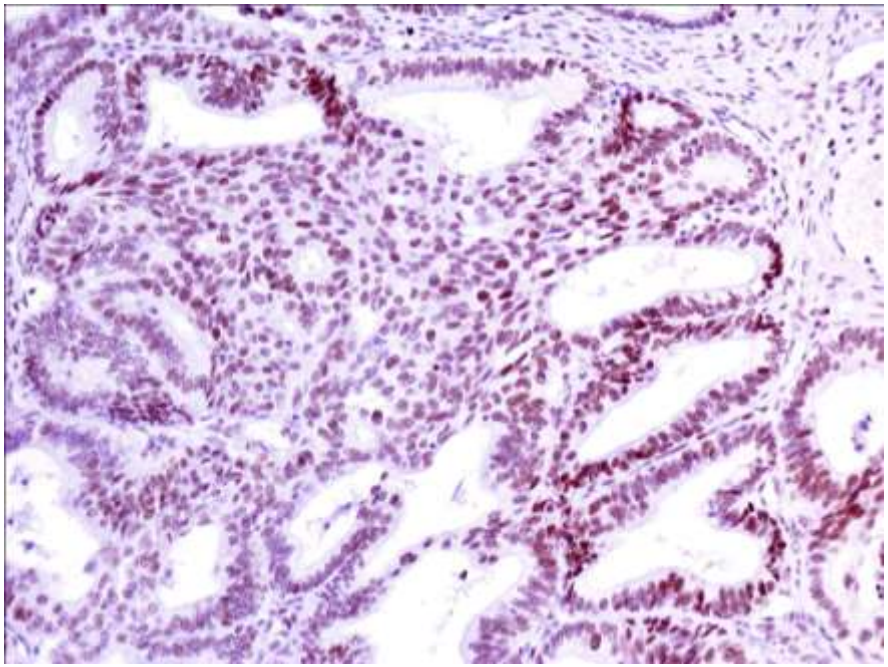
Grindedal EM, Renkonen-Sinisalo L Dr, Vasen H,et al.

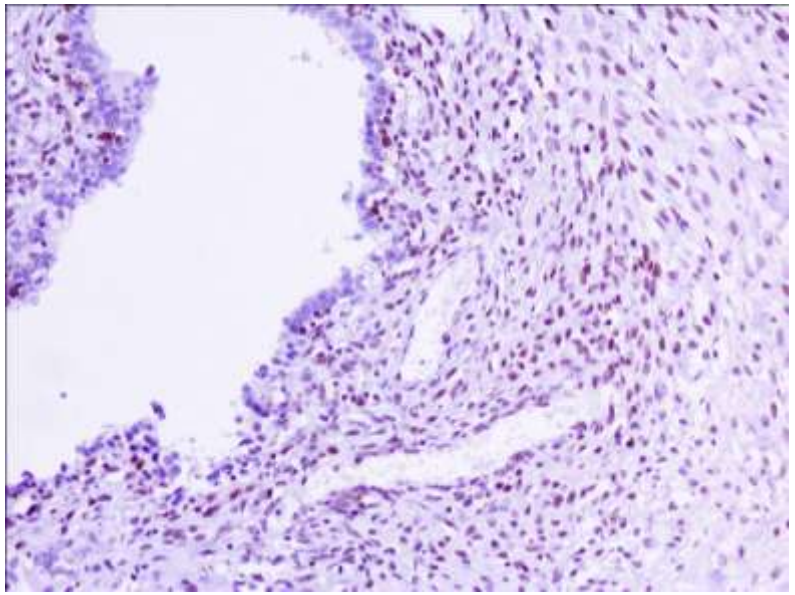
J Med Genet. 2009 Jul 26

- **144 women**
- **81.5% FIGO stage I or II**
- **10-year specific survival independent of staging: 80.6% vs.<40% survival reported both in population based series and in BRCA-mutation carriers**
- **Disease specific 30 years survival: 71.5%**
- **Lifetime risk of ovarian cancer of about 10% and a risk of dying of ovarian cancer of 20% gave a lifetime risk of dying of ovarian cancer of about 2% in female MMR-mutation carriers**









Papillary serous carcinoma in situ in ovarian endometriosis in an MSH2 mutation carrier.

Vaknin Z, Gotlieb WH, Arseneau J, Ferenczy A.

Int J Gynaecol Obstet. 2009;107:68-9.

High risk for neoplastic transformation of endometriosis in a carrier of Lynch syndrome.

Nyiraneza C, Marbaix E, Smets M, Galant C, Sempoux C, Dahan K.

Fam Cancer. 2010;9:383-7

Report of a case of a healthy woman carrying a germline mutation in MLH1 gene with endometrial intra-epithelial neoplasia and ovarian endometriotic lesions exhibiting a loss of MLH1 protein expression

Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome

Schmeler KM, Lynch HT, Chen LM,et al.

N Engl J Med. 2006;354:261-9

Retrospective study of 315 pts

Hysterectomy done in 61

Salpingo-oophorectomy done in 47

- **In operated pts no endometrial, ovarian or peritoneal cancer**
- **In unoperated pts 69 (33%) cases of endometrial cancer and 12 (5%) cases of ovarian cancer**
- **Prevented fraction 100%**

Primary peritoneal cancer after bilateral salpingo-oophorectomy in two patients with Lynch syndrome.

Schmeler KM, Daniels MS, Soliman PT, Broaddus RR, Deavers MT, Vu TM, Chang GJ, Lu KH.

Obstet Gynecol. **2010 ;115(2 Pt 2):432-4**

- 44-year-old woman who underwent hysterectomy with BSO for benign disease. She presented 12 years later with a pelvic mass and was diagnosed with a high-grade serous primary peritoneal cancer. Genetic testing showed a mutation in the MSH2 DNA mismatch repair gene.
- 58-year-old woman who had a hysterectomy and BSO for endometrial cancer. She developed a high-grade serous primary peritoneal cancer 8 years later and was found to have a mutation in the PMS2 DNA mismatch repair gene.