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LYNCH SYNDROME

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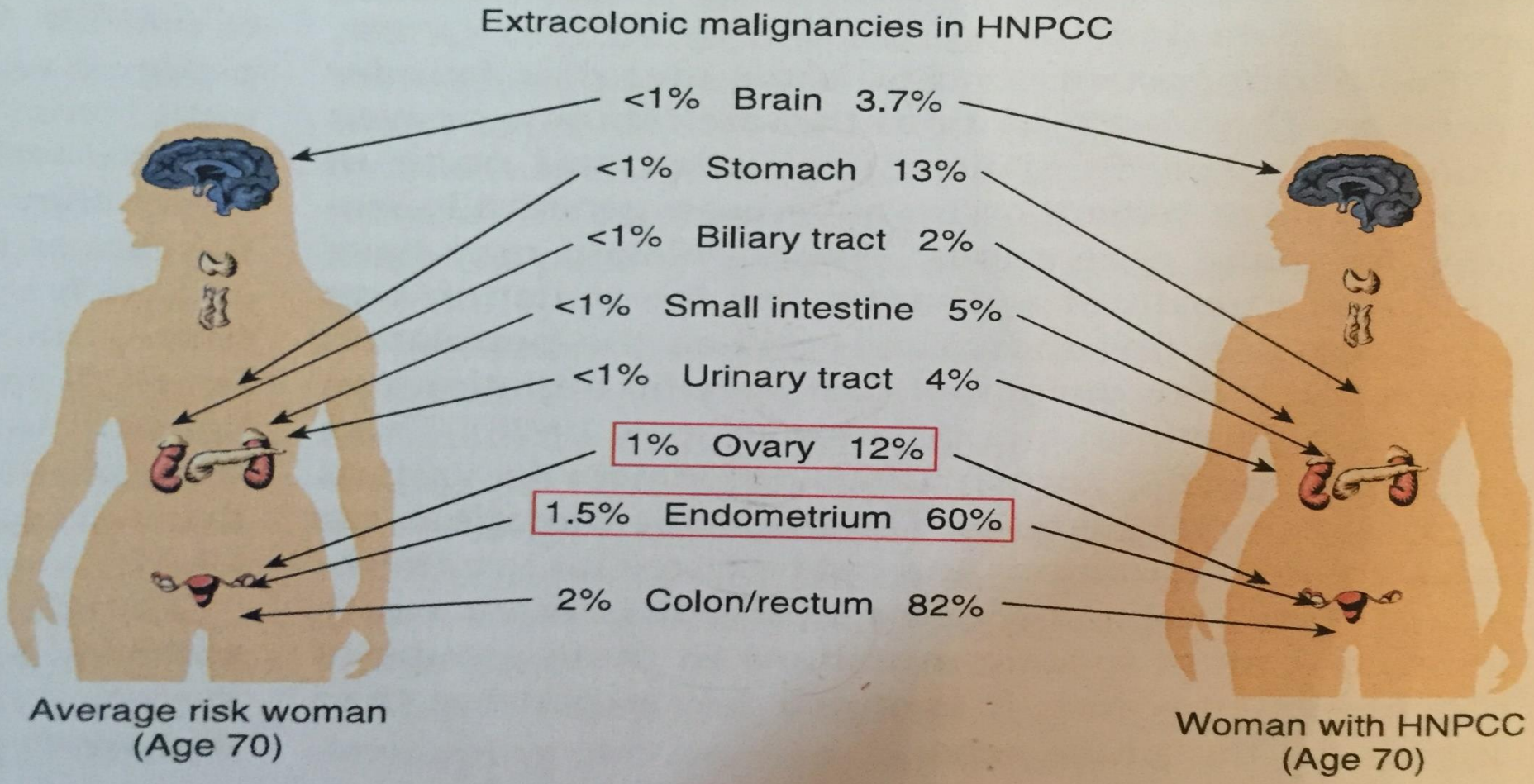
introduction

- AD
- germline mutation in MMR gene (MLH1,MSH2,MSH6,PMS1,PMS2) or loss of expression of *MSH2* due to deletion in the *EPCAM* gene

lynch related cancers

- CRC
- ovary
- stomach
- small bowel
- pancreatobiliary system
- genitourinary system
- brain (glioma)
- skin pathologies


Extracolonic malignancies in HNPCC
<1% Brain 3.7%
<1% Stomach 13%
<1% Biliary tract 2%
<1% Small intestine 5%
<1% Urinary tract 4%
1% Ovary 12%
1.5% Endometrium 60%
2% Colon/rectum 82%
Average risk woman
(Age 70)
Woman with HNPCC
(Age 70)

Who suspected for lynch syndrome?

- synchronous or metachronous CCR
- CCR prior to 50 y
- multiple Lynch-associated cancers
- cases of familial clustering of Lynch-associated cancers

Amsterdam II criteria for Lynch syndrome

There should be at least three relatives with any Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One should be a first-degree relative of the other two
At least two successive generations should be affected
At least one should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any
Tumors should be verified by pathological examination

Adapted from Vasen HF, Watson P, Mecklin JP, et al. Gastroenterology 1999; 116:1453.

Graphic 59832 Version 6.0

The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with the MSI-H¶-like histologyΔ diagnosed in a patient who is less than 60 years of age◊.
4. Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

Genetic testing in HNPCC

- ✓Tumor-based tests
  - MSI
  - IHC testing
- ✓**Germline genetic testing**

  (multigene panel)

Indications for germline testing

- **CRC or endometrial cancer prior to 50 years**
- **CRC or endometrial cancer diagnosed > 50 years with additional personal and family history suggestive of Lynch syndrome**
- **Identification of a pathogenic MMR variant on somatic tumor testing in any tumor type**
- **First-degree or second-degree relative of those with known MMR/*EPCAM* gene mutation**
- **Family cancer history meeting Amsterdam I or II criteria or revised Bethesda guidelines**

Indications for tumor testing

- **CRC at age 50 years or older**
- **Endometrial cancer at age 50 years or older**

MANAGEMENT

- annual physical examination

- beginning at age 25 to 30 with particular attention to the neurological exam given the increased risk of brain tumors

ENDOMETRIAL CANCER

- **2 to 5 percent of all endometrial carcinomas**
- **In patients with Lynch syndrome, lifetime risk of endometrial cancer 16 to 71 % for those with *MLH1, MSH2,* or *MSH6* and 13 to 24 % for those with *PMS2*, compared with 2 to 3 percent in the general population**

ENDOMETRIAL CANCER

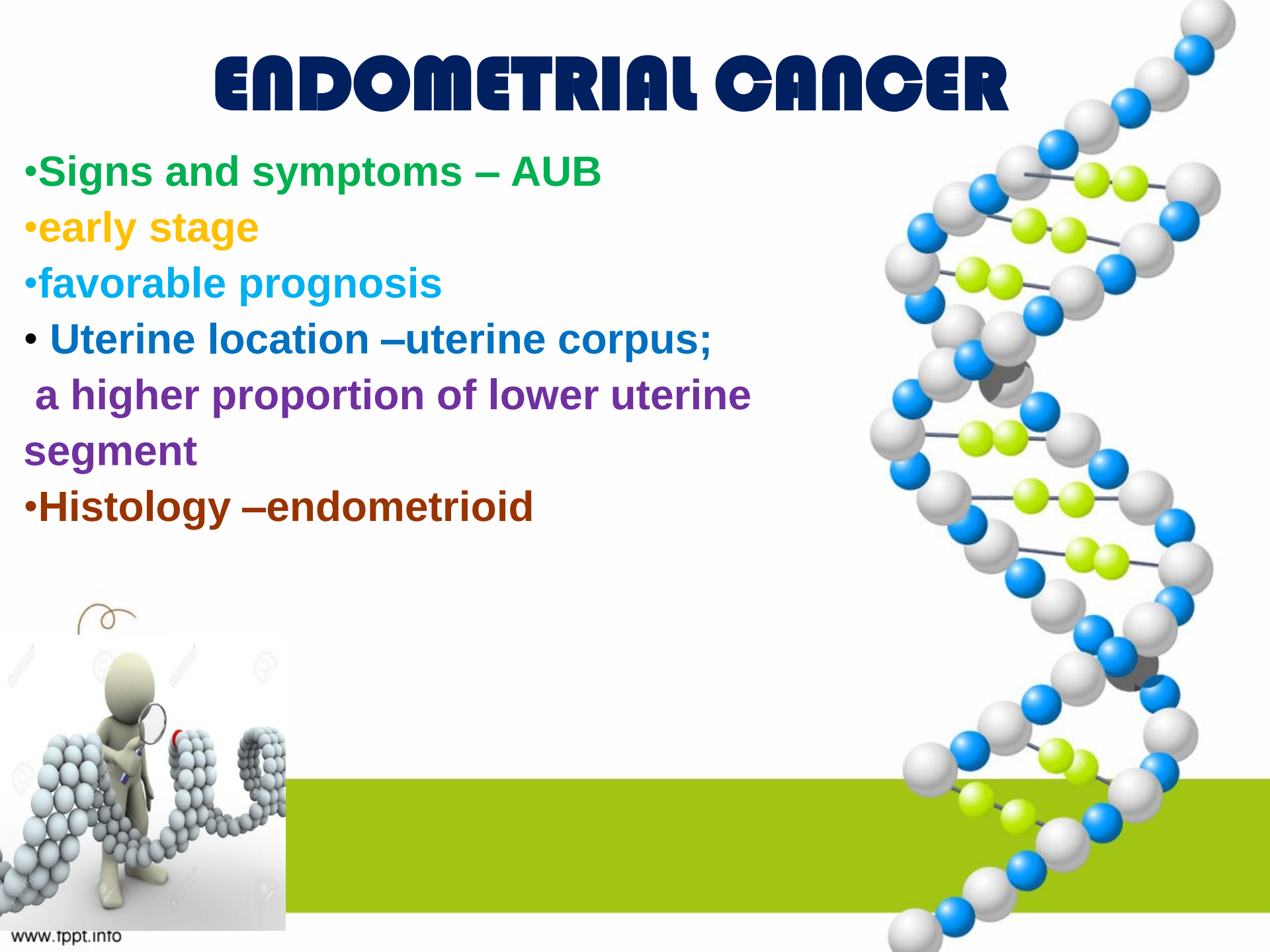
- mean age range 47 to 55 years for *MLH1, MSH2,* or *MSH6*

- 49 to 56 years for those with *PMS2*

- compared with a mean age of 60 years in those without Lynch syndrome

ENDOMETRIAL CANCER

- Signs and symptoms – AUB
- early stage
- favorable prognosis
- Uterine location –uterine corpus; a higher proportion of lower uterine segment
- Histology –endometrioid



ENDOMETRIAL CANCER

surveillance

- **informed and counseled about AUB**
- **annual pelvic examination and endometrial biopsy Q 1-2 y , starting at 30 to 35 years or 3 to 5 years earlier than the earliest age of DX of these cancers in the family**
- **Surveillance is continued until risk reducing**

OVARIAN CANCER

- lifetime risk of ovarian cancer ranges from 11 to 20 % in *MLH1*, 15 to 24 % in *MSH2*, and 0 to 1 % in *MSH6*, compared with 1.3 % in the general population
- Mean age range 43 to 48 versus age 60

OVARIAN CANCER

- early stage (stage I or II: 85 versus 30 percent).
- well or moderately diff (70 versus 50%)
- Epithelial carcinoma is the most common histology
- excess of the endometrioid subtype and a lower frequency of nonepithelial histology

OVARIAN CANCER

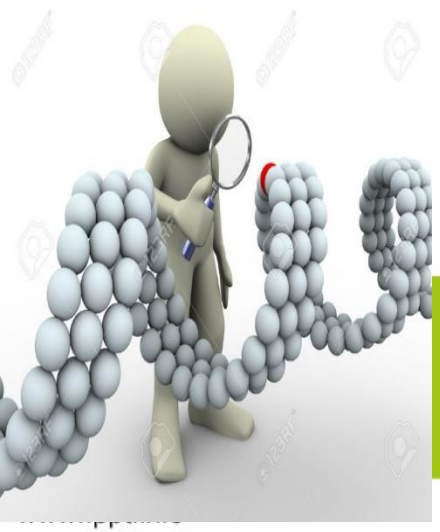
- **signs/symptoms**

pelvic or abdominal pain, bloating, early satiety, constipation, urinary urgency or frequency

OVARIAN CANCER

surveillance

- counseled about nonspecific symptoms
- high rate of false-positive tests
- start at 30 to 35 years or 5 to 10 years prior to earliest age of first DX of cancer in the family
- annual pelvic examination and TVS, CA125every 6 to 12 months



CCR

- annual colonoscopy
- beginning at age 20 to 25 years, or two to five years prior to the earliest age of CRC diagnosis in the family (whichever comes first).

GASTRIC CANCER

•upper Endoscopy with biopsies and RX for *H. pylori* infection if detected

• starting at 30 to 35 y Q 2-3 years in individuals with RF for gastric cancer

(gastric atrophy, extensive or incomplete intestinal metaplasia, FH of gastric cancer)

SMALL INTESTINAL CANCER

- **Routine screening is not recommended**

- **NCCN guidelines : wireless capsule endoscopy be performed Q 2-3y**
  - **in unexplained abdominal pain or**
  - **iron deficiency anemia**

URINARY TRACT CANCER

- annual urinalysis beginning at age 30 to 35 years

- annual or biannual renal US for *MSH2* mutation carriers, especially males, after age 35

SKIN CANCER

- annual skin examinations

- counsel patients on protection from ultraviolet exposure (avoid excessive sun exposure, use of a high-strength sunscreen, and sun protective measures

STRATEGIES FOR CANCER RISK REDUCTION

- TH-BSO at completion of childbearing
- Patients should be informed that BSO does not eliminate the risk for peritoneal cancer, but this risk is much lower than for ovarian cancer
- NCCN guidelines : no specific age is recommended, and individualize decisions based on desire for childbearing, comorbidities, family history, and gene mutation
- Patients undergo surgery for colorectal cancer should be offered concurrent prophylactic TH-BSO (individualized, based on childbearing plans and prognosis

STRATEGIES FOR CANCER RISK REDUCTION

- **Risk-reducing hysterectomy with delayed or no BSO**

  estrogen-progestin contraceptive until menopause and then undergo BSO

  If BSO is not performed, we would continue ovarian cancer surveillance because the risk of ovarian cancer continues after menopause despite cessation of ovulation.

Preoperative assessment

before prophylactic (TH-BSO) should include the following to exclude occult cancer [5,51]:

- **Endometrial biopsy**
- **Transvaginal ultrasound examination of uterus and adnexa**
- **Baseline cancer antigen 125 level**
- **Appropriate nongynecologic cancer screening**

Intraoperative procedures

- route of hysterectomy is based on patient characteristics and the surgeon's preference
- uterus, ovaries, and bowel carefully assessed for evidence of tumor
- The pathologist should be advised of the high risk of endometrial and ovarian cancer and the specimens carefully examined intraoperatively
- The surgeon should be prepared to perform a complete staging operation in the case of occult carcinoma

GYNECOLOGIC FOLLOW-UP AFTER RISK-REDUCING SURGERY

two options:

- **For patients who have undergone risk-reducing TH-BSO, screen primary peritoneal cancer by performing annual pelvic examination and checking a CA 125 every 6 to 12 months**
- **Not screening**

Chemoprevention

- **Aspirin**
- **hormonal contraception : Estrogen-progestin contraceptives reduce the risk of both endometrial and ovarian cancer; progestin-based contraceptives reduce the risk of endometrial cancer**
- **risk-reducing hysterectomy with BSO after completion of childbearing is better than continuation of hormonal therapy**

با تشکر از توجه شما