

Defining Criteria for Lynch Syndrome in Women under 50 with Endometrial Cancer

Final Results of a Prospective, Multi-center Study

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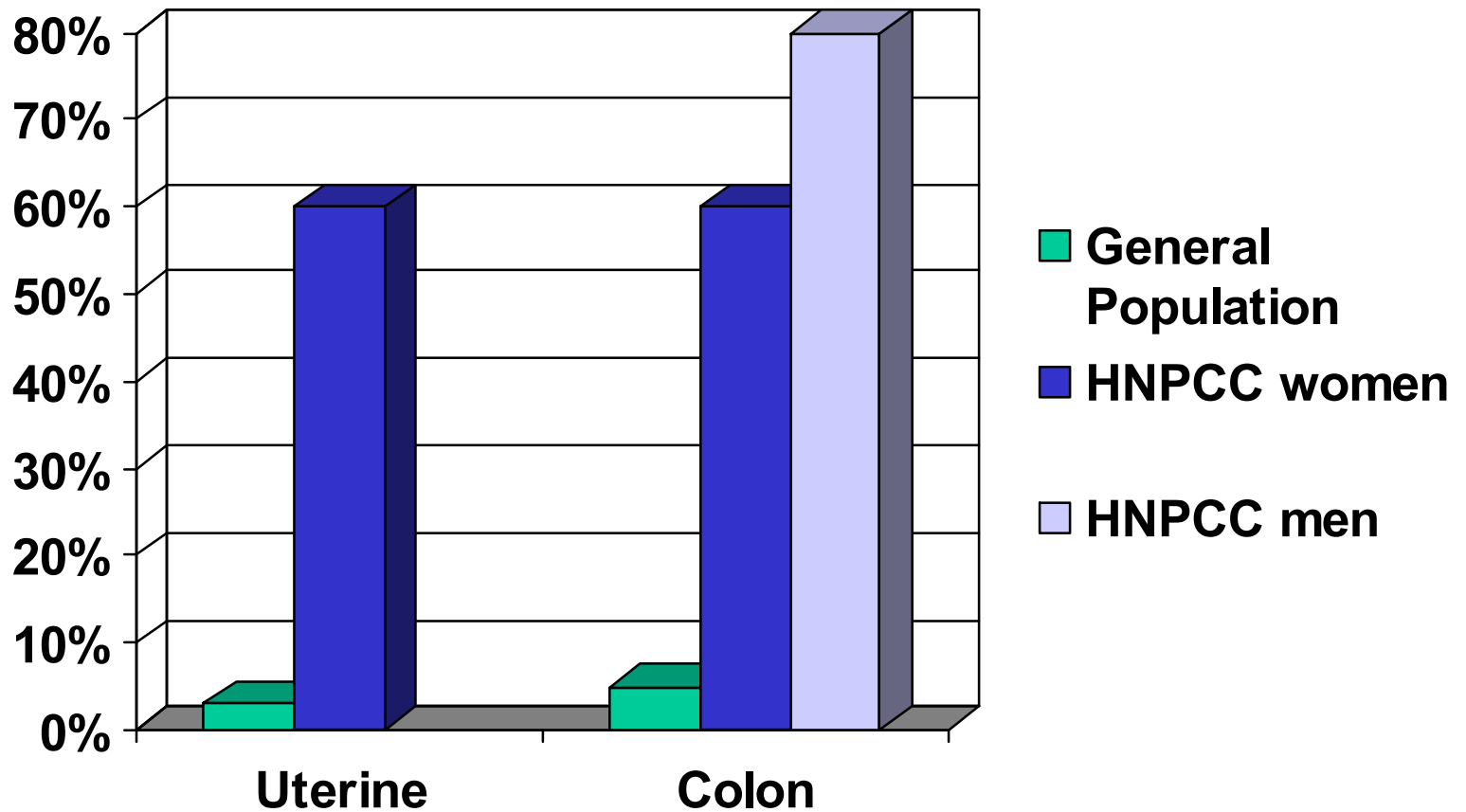


Endometrial Cancer

- **Most common gynecologic cancer in U.S.**
- **40,880 cases in 2005; 7,310 deaths**
- **Mean age 61 years**

- **10% diagnosed under age 50**
- **Young women (under age 50) typically obese, nulliparous (*Soliman et al, Obstet Gynecol 2005*)**

Lifetime risk of cancer in general population and Lynch Syndrome



Identification of women with Lynch Syndrome

Traditionally, GI physicians, GI medical oncologists and GI surgeons have identified individuals with colon cancer as potentially having Lynch Syndrome. Gyn oncologists have not played a significant role.

What are “red flags” that can be used by gyn oncologists to identify women with endometrial cancer as having Lynch Syndrome?

Age as a Red Flag for Lynch Syndrome

- Young age of onset is a hallmark of hereditary cancers
- Revised Bethesda criteria includes **individuals with colon cancer under age 50** as one criteria for considering Lynch Syndrome

Purpose

What is the prevalence of Lynch syndrome mutations in women with endometrial cancer under age 50?

Methods

- **Prospective, multi-center study**
 - UT MD Anderson (Houston, TX)
 - UT Southwestern (Dallas, TX)
 - Roswell Park (Buffalo, NY)
- **Eligibility**
 - Women diagnosed with endometrial cancer under age 50
 - Willing to undergo genetic testing

Methods: Molecular studies

- **Mutational analysis by full sequencing of MLH1 and MSH2**
 - Myriad Genetics Laboratory
- **Mutational analysis by full sequencing of MSH6 and large deletion testing of MLH1 and MSH2**
 - Baylor Clinical Genetics Lab

Methods: Molecular studies

- Tumor blocks (and normal control) obtained
- Immunohistochemistry of MLH1, MSH2 and MSH6
- MSI
- Hypermethylation of MLH1 promoter performed on all tumors with loss of MLH1 by IHC

Demographics (n=100)

Median age 43 years (24 - 49)

Median BMI 34 kg/m² (18 - 77)

Family history

Amsterdam 7

1st degree w/ Lynch ca 15

No FH 77

Results

9/100 women, or 9% (CI 4.2-16.4%), were found to have a germline HNPCC mutation

- 7 had MSH2 mutations**
- 1 had MSH6 mutation**
- 1 had MLH1 mutation**

Characteristics of the mutation carriers

	n	Median age (years)	Median BMI (kg/m ²)
Mutation carriers	9	41	29*
Non-mutation carriers	91	42	32

*p < 0.05

Characteristics of the mutation carriers

- **7/9 had significant family histories, and fulfilled Amsterdam criteria**
- **8/9 had at least 1 relative w/Lynch associated cancer**
- **1/9 had a synchronous ovarian cancer**
- **2/9 had a synchronous or metachronous colon cancer**

Tumor characteristics in mutation carriers

- 4/9 had advanced stage disease
- 5/9 had Grade 2 or 3 cancers

Molecular features

- **All tumors from pts with germline mutations had loss of the corresponding protein by IHC**
- **All tumors from pts with germline mutations were MSI-H**




Molecular features of non-mutation carriers

- Of the **91 non-mutation carriers**, 18 (20%) had MSI-H tumors
 - 13/18 had hypermethylation of the MLH1 promoter
 - 3/18 had normal IHC of MLH1, MSH2, MSH6
 - 2/18 had loss of MSH2 but no germline mutation

Conclusions

- 9% rate of *identified* germline MLH1, MSH2 and MSH6 mutations in women with endometrial cancer under age 50
- Overall, 11% rate of Lynch syndrome in women with endometrial cancer under age 50

Increasing the probability of detecting germline mutations in women with endometrial cancer under age 50

- 1st degree relative w/ Lynch associated cancer
  39%
- MSI -H  33%
- IHC status (loss of MSH2)
  77%

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