

Exploring the Relationship Between Race and Pathways to Colorectal Neoplasia

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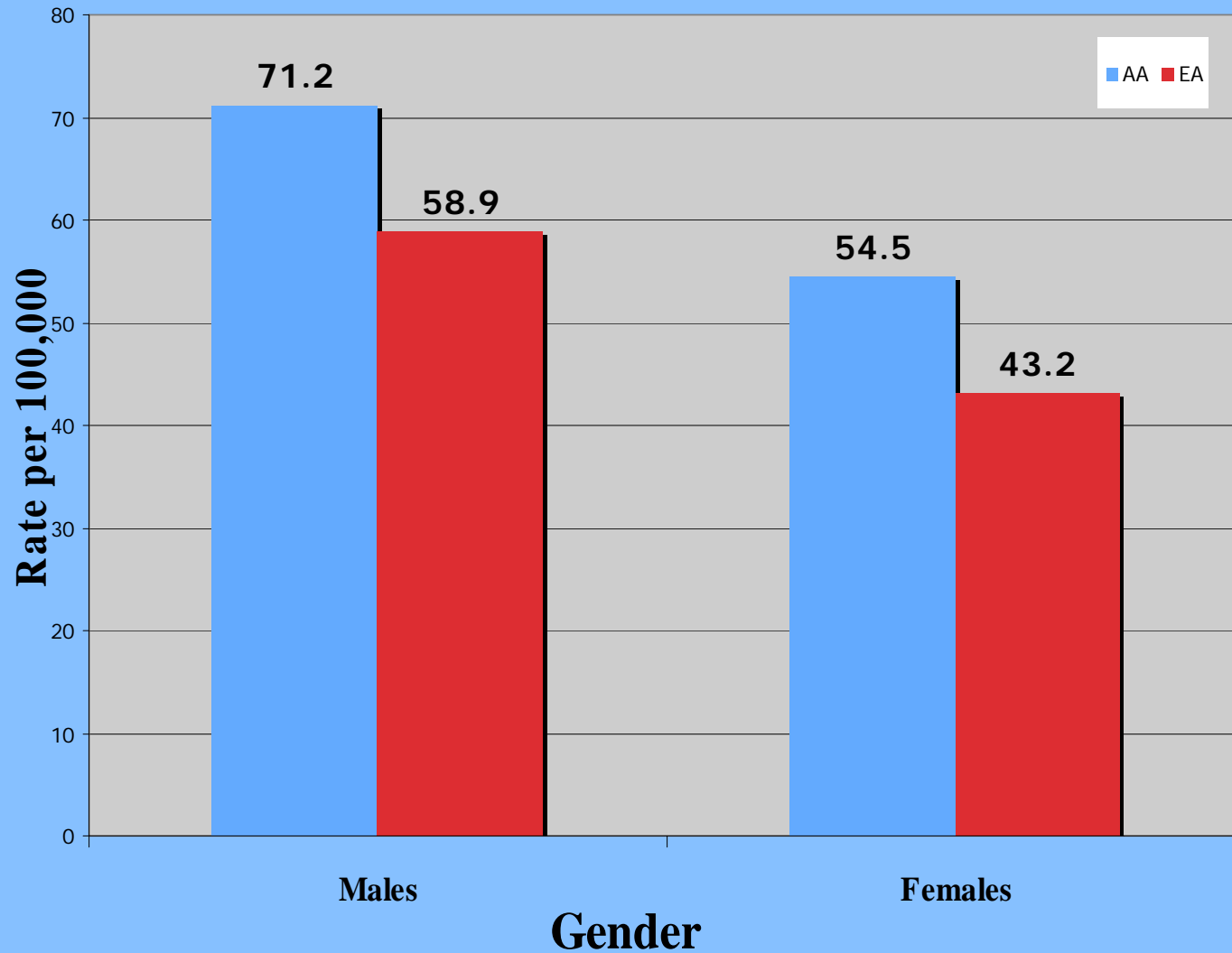
Presentation

1. Define the problem
2. Discuss process of carcinogenesis
3. Explore determinants of incidence and survival in AA and Caucasians
4. Highlight future research avenues

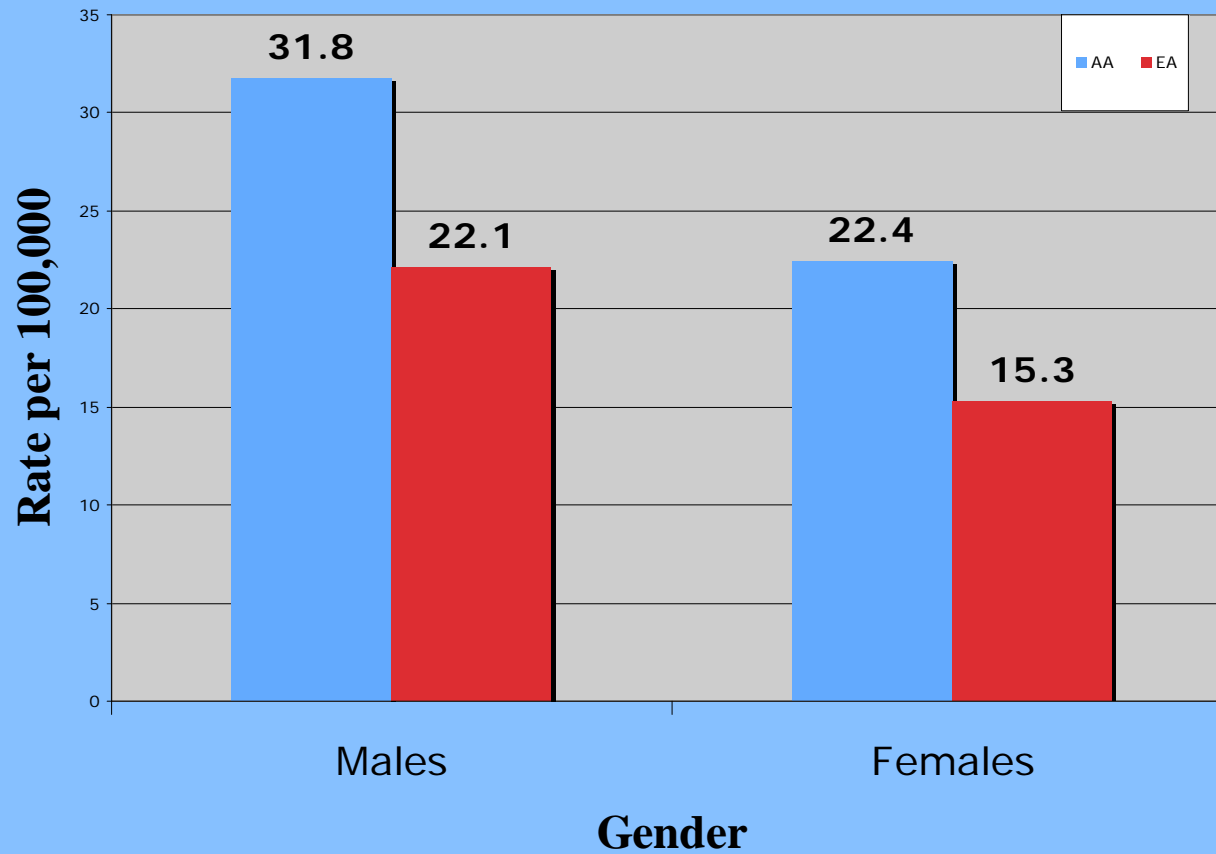
Section 1: Define the Problem

- CRC 3rd in incidence and mortality
 - AA 20% ↑ incidence CRC
 - AA 45% ↑ mortality rate
- The 5-year survival rate is
 - 55% in AA
 - 65% in Caucasians

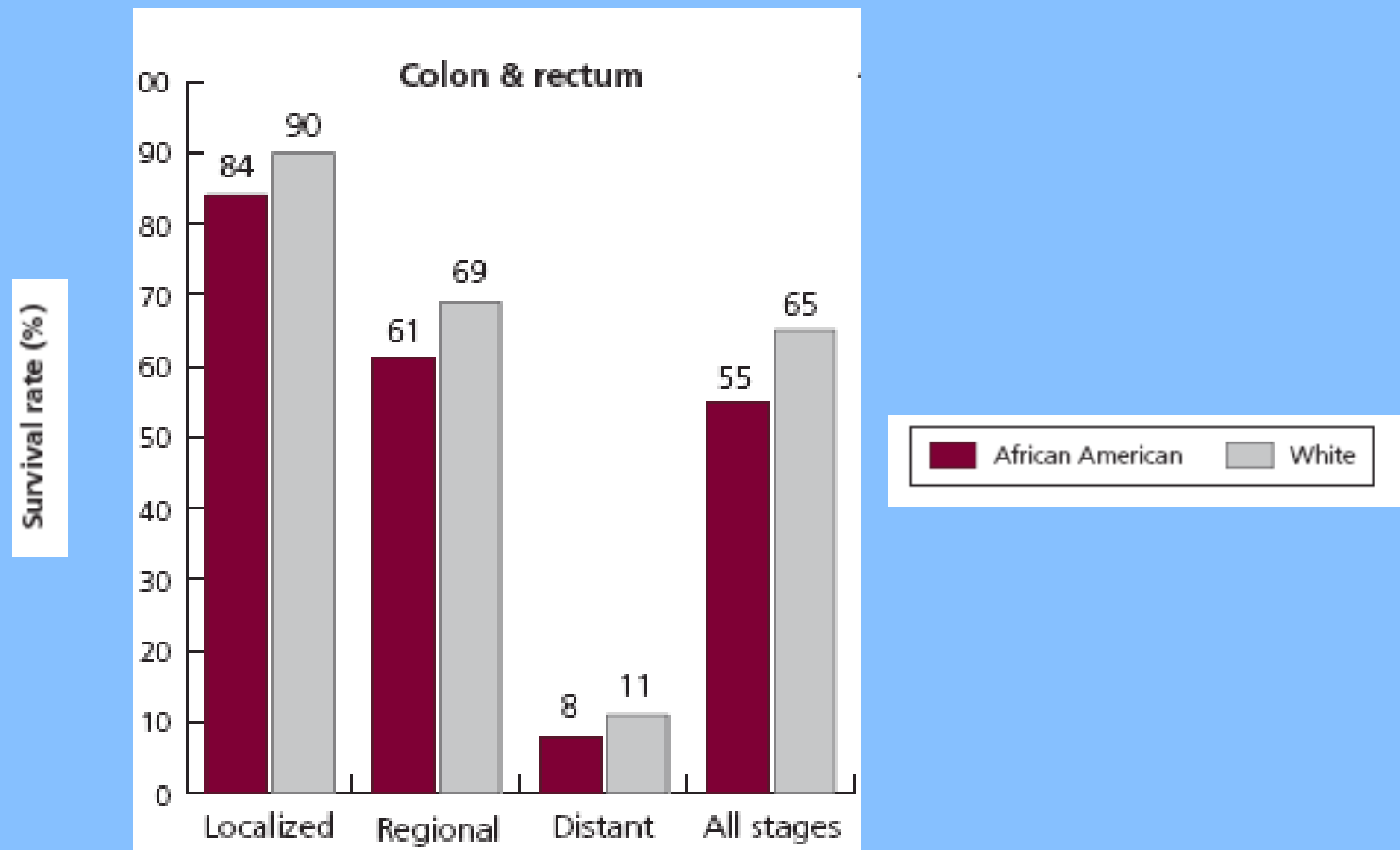
Incidence Rates for CRC 2001-05



Mortality Rates for CRC 2001-05

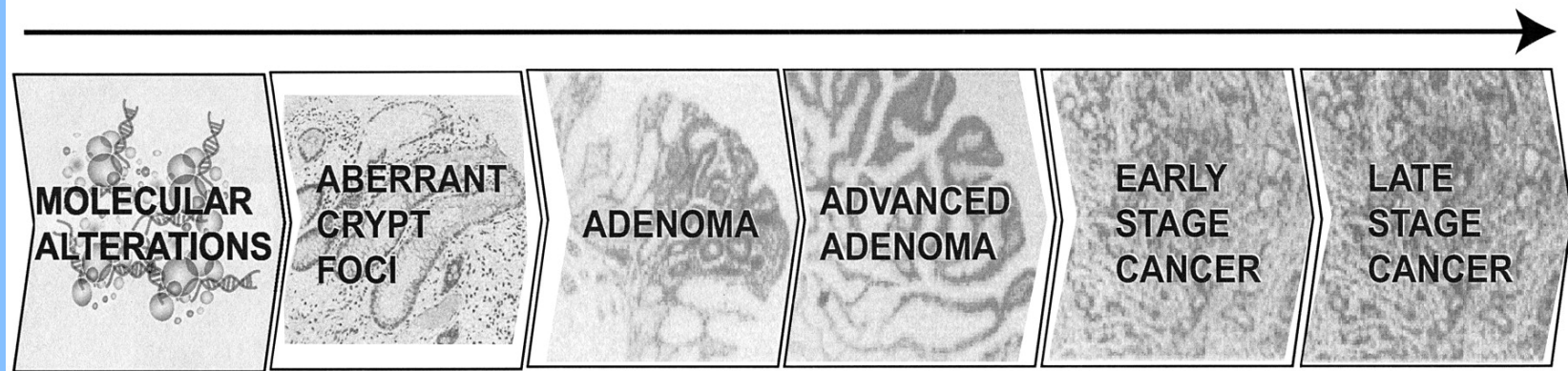


Survival Difference Persists at Each Stage



Section 2: How Colorectal Cancer Develops

Colorectal carcinogenesis



Pathways of Carcinogenesis: The Adenoma

- Polyps classified into two groups:
 - Neoplastic (e.g. adenoma)
 - Presence of dysplasia (cytological, architectural)
 - Malignant potential
 - Non-Neoplastic (e.g. hyperplastic)
 - No classic dysplasia
 - No malignant potential

Pathways of Carcinogenesis:

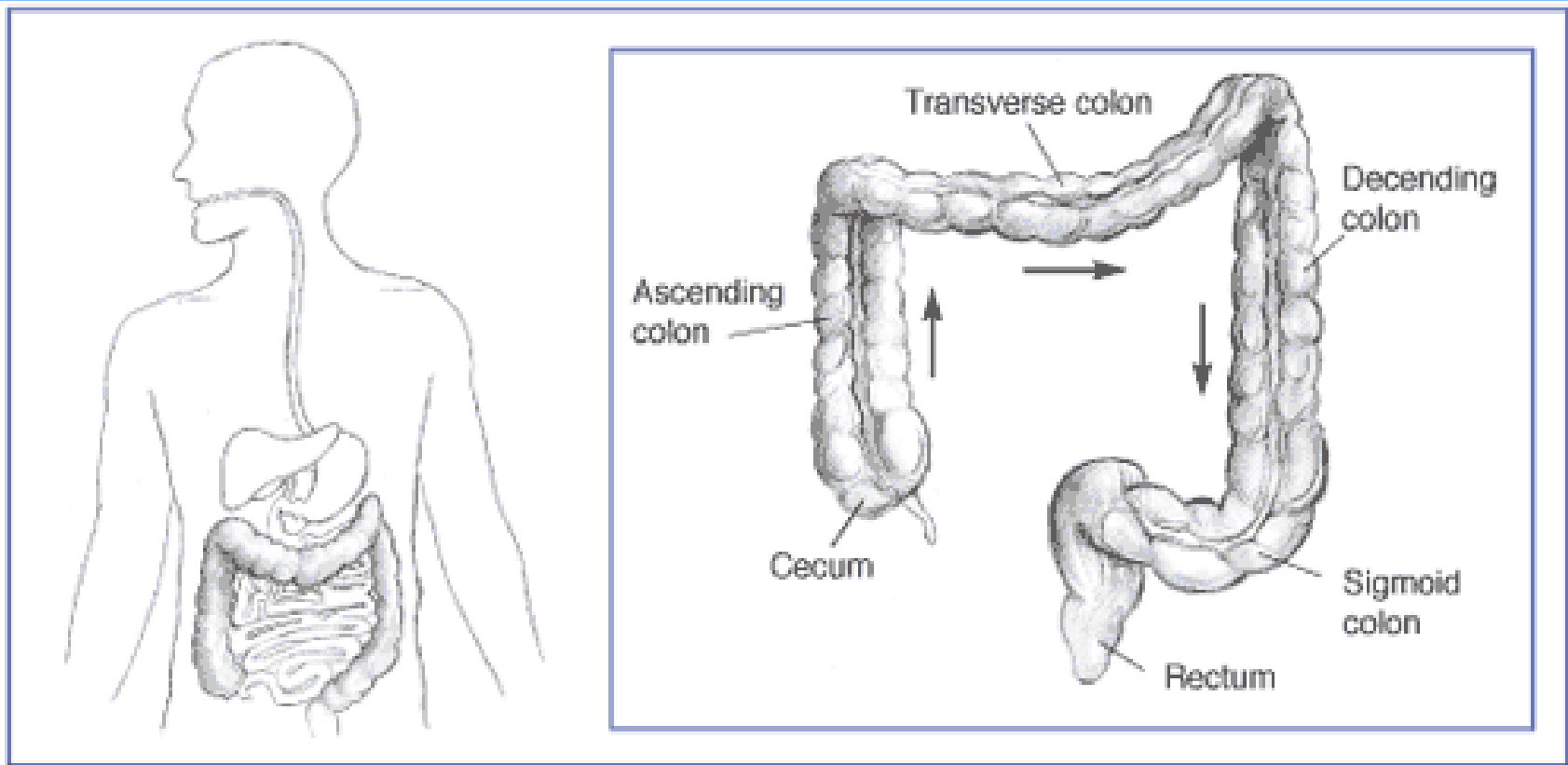
Polyp Types

- **Traditional adenomas**
 - Tubular adenoma
 - Tubulovillous adenoma
 - Villous adenoma
- **Serrated polyps**
 - Hyperplastic Polyp
 - Traditional serrated adenoma
 - Sessile serrated adenoma
 - Mixed adenoma (HP/SA, HP/SSA)

Two Known Hereditary Pathways

- **Chromosomal Instability (CIN)**
 - Familial adenomatous polyposis (FAP)
 - APC mutation
 - About 1% of all CRC
- **Microsatellite Instability (MSI-H)**
 - Hereditary nonpolyposis colorectal cancer (HNPCC)
 - Mutation or epigenetic silencing in MMR gene
 - About 3% of all CRC
 - HNPCC: Mutation of the MLH1
 - Sporadic: Epigenetic silencing of MLH1

Pathways of Carcinogenesis: Importance of Location



Features of Proximal and Distal Tumors

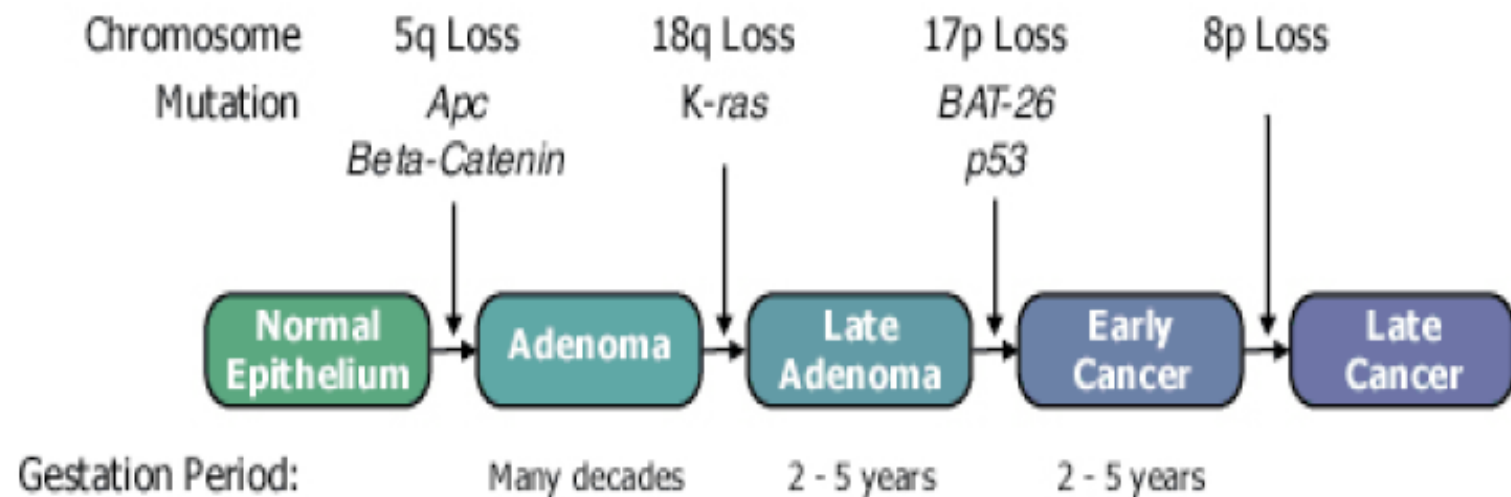
Features	Proximal	Distal
Familial cancer	HPNCC	FAP
Age	Older	Younger
Gender	> Females	> Males
Mucinous	Frequent	Infrequent
Loss Of Heterozygosity (LOH)	Infrequent	Frequent
MSI-high	25%	2-3%
TP53 mutation	20-30%	50-60%
CIMP+	25-40%	3-10%
K-Ras	Less Frequent	More Frequent
B-RAF	More Frequent	Less Frequent

Adapted from Iacopetta (2002) Int J. Cancer; 101, 403-408.

Exploration of CRC Pathways

	Chromosomal Instability (CIN)
Molecular features	
MSI status	MSS
CIMP status	Negative
Chromosomal instability	Present
KRAS	+++
BRAF	---
MLH1 status	Normal
MGMT	---
Location	Distal predominance
Precursor lesion	Traditional adenoma

Chromosomal Instability (CIN) Pathway

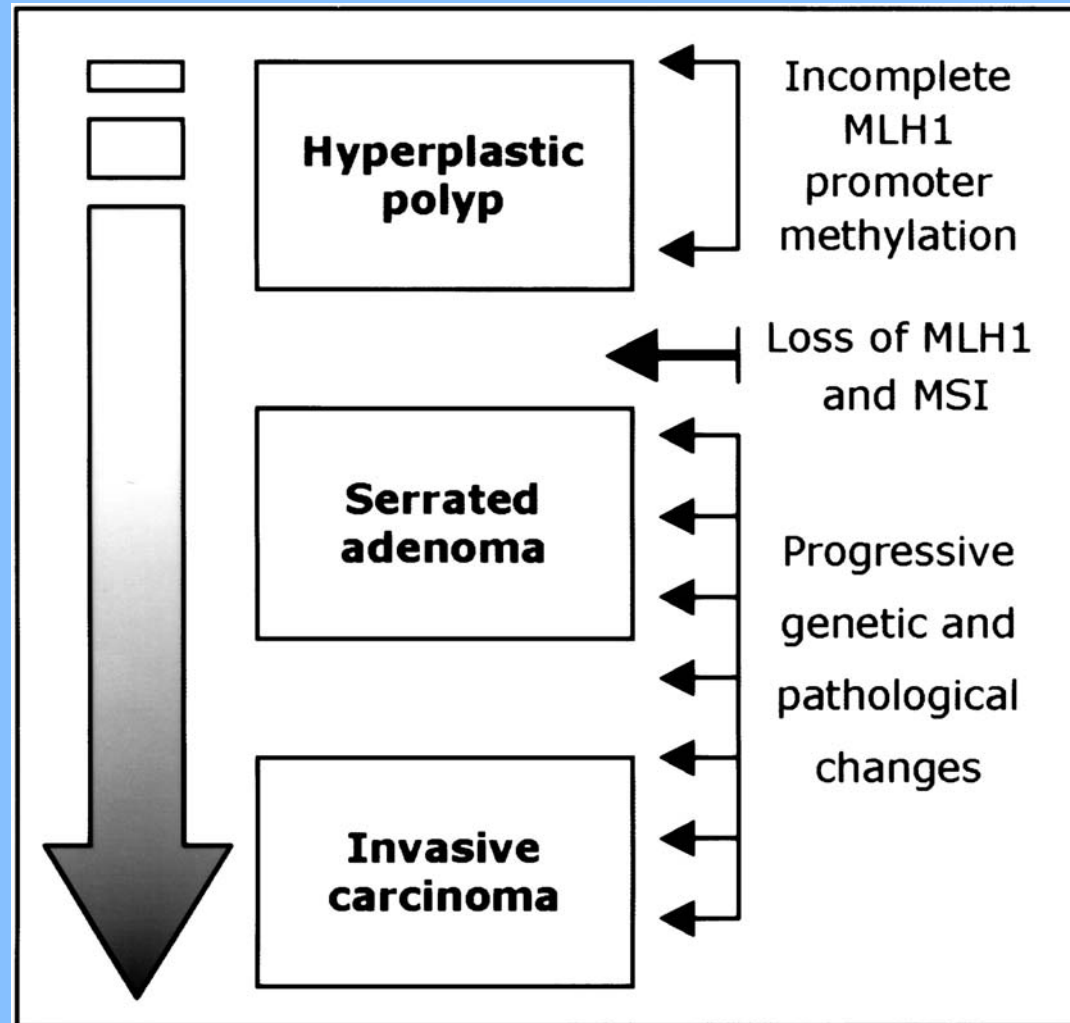


*Classical "Vogelgram" developed by Fearon and Vogelstein, demonstrating the multi-step progression of the germ-line *Apc* mutation to familial adenopolyposis (FAP) and on to full-blown hereditary colorectal cancer*

Classification of CRC

	Serrated Pathway (MSI)	
Molecular features		
MSI status	MSI-H	MSI-L
CIMP status	High	
Chromosomal instability	Absent	Absent
KRAS	---	---
BRAF	+++	+++
MLH1 status	methylated	partial
MGMT	+/-	+++
Location	Proximal Predominance	
Precursor lesion	Serrated adenoma	

Serrated Pathway



Hawkins, N. J. et al. J Natl Cancer Inst 2001;93:1307-1313

Classification of CRC

	Hybrid Path
Molecular features	
MSI status	MSI-L or MSS
CIMP status	Low
Chromosomal instability	Present
KRAS	+++
BRAF	---
MLH1 status	Normal
MGMT	+++
Location	both
Precursor lesion	Traditional or Serrated

Section 3: Determinants of Incidence and Survival By Race

- Socio-cultural
- Health behavioral
- Biologic Determinants

Sociocultural Determinants

- Lower SES is associated with higher incidence, lower survival
 - Higher percentage of AA have lower SES
- Insurance status associated with worse survival
 - Higher percentage of AA are under insured, uninsured
- Treatment related differences
 - Differential rate of uptake to standard therapy
 - Low volume hospitals and surgeons affect outcomes

Health Behavioral Determinants

- **Obesity**
 - 20-30% excess risk of colon cancer
- **Physical Activity**
 - 30-50% lower risk in physically active
- **Diet**
 - Red meat, processed meat increased risk
- **Screening**
 - lower rate of screening increase risk

% Obese higher in AA

Obesity	AA	EA
Men	37.2	33.1
Women	52.9	32.9
Both	45.9	33.0

Obese defined as BMI >30 kg/m²

% In Leisure Time Activity

Leisure Time Activity	AA	EA
Inactive	48.6	35.2
Some	26.3	31.1
Regular	25.0	33.7

% Screening Is Lower in AA

Screening	AA	EA
Endoscopy	36.9	45.8
Fecal occult	10.3	12.6
FOBT or Endo	40.1	49.5

Biologic Determinants

- Proximal tumors associated worse survival
 - AA have higher incidence of proximal
- Mucinous adenocarcinoma worse survival compared to adenocarcinoma
 - AA have higher incidence of mucinous
- High-grade tumors worse survival
 - AA tumors worse survival than Caucasians.

Do AA Have More MSI-H CRC?

- AA may have higher % of MSI-H tumors
- Preliminary Reports of 30- 45% (compared to ~15% in population) MSI-H tumor
 - Recent study suggests the MSI-H cancers may be different in AA and Caucasians
 - Different precursor lesions

A Conundrum

MSI-H

- 15% overall CRC, but 30-45% in AA
- Better survival
 - 35% higher survival rate among patients with MSI-H tumors compared to others

Other Serrated or Hybrid Pathway Tumors

- CIMP in CRC
 - poorer survival (HR 3.22, $p < 0.0001$) in patients with CIMP compared to non-CIMP.
- BRAF mutation in CRC
 - poorer survival (HR 3.19 ($p < 0.001$)) in patients with BRAF compared to WT
- Need detailed articulation of molecular phenotypes by race!

Review

- AA higher incidence, lower survival at all stages
- Pathways:
 - AA have a higher incidence of proximally located neoplasia
 - Possible connection to the serrated or hybrid pathways
- Socio-cultural, health behaviors, and biologic determinants differ by race

Future Directions

- **Reduce Incidence:** Development of Cohort of African Americans at high risk of CRC
 - Cohort of high-risk patients
 - Examine socio-cultural, health behavioral, and tumor related variables
- **Improve Survival:** Development of a cohort of African Americans with CRC
 - State or Clinical Trial Network study
 - Examine socio-cultural, health behavioral, and tumor related variables on response to treatment and survival in AA and Caucasians