CENTER FOR WOMEN'S HEALTH RESEARCH at UNC

Managing uterine fibroids: What do we really know?

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Funding Support & Disclaimer

- Based on research conducted by Duke University for the Agency for Healthcare Research and Quality (AHRQ).
- The presenter is solely responsible for its contents, including any clinical or treatment recommendations.
- No statement should be construed as an official position of AHRQ or the US Department of Health and Human Services.

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The AHRQ Evidence Report

- Topic proposed by ACOG in partnership with AHRQ
- Refined with Technical Expert Advisory Group
- Key Questions established
- Search strategy implemented
- Data abstracted and compiled

Focus of Key Questions

- Risks and benefits of surgical and medical interventions
  - Failure rates
  - Morbidity
  - Repercussions of deferring treatment
- Predictors of outcomes (number, location, size of fibroids, age, race, etc.)
  - Best candidates for specific treatments
- Cost of symptoms, treatments, complications

Sources of Evidence

Three resources contributed to the report:

- Systematic review of the literature
- Clinical care databases (DUMC, HCUP)
- Models using both sources of evidence

Will describe each source & then summarize.

Literature Review Methods

- Searched MEDLINE, HealthSTAR, CINAHL, CancerLit, EMBASE 1975-2000
- Required English, women with fibroids, health or economic outcomes
- Limited to randomized trials for medical interventions
- Included other designs for surgery

Systematic Review: Methods

- Dual review of all abstract
- Dual review of articles
- Abstraction of data into standardized forms with adjudication of discrepancies
- Articles graded on quality and validity

Results: Systematic Review

- Abstracts reviewed: 1084
- Articles identified: 637
- Number of relevant articles: 550
  - Original research on treatment 200
  - Review 144
  - Other (epidemiology, economics) 95
  - Basic science 102

Internal Validity

Description of:	Invasive Therapy (n=115)	Medical Therapy (n=50)
Allocation to treatment	8%	43%
If randomized, method	77%	19%
Criteria for participation	50%	61%
Length of follow-up specified	78%	84%
Loss to follow-up specified	60%	77%
Drop-out rates specified	22%	94%
Statistical method clarity	21%	14%

External Validity

Description of:	Invasive Therapy (n=115)	Medical Therapy (n=50)
Age distribution	86%	86%
Race/ethnicity	15%	10%
Pregnancy history	39%	22%
Prior surgical history	10%	18%
Fibroid/uterine size	58%	71%
Fibroid number	30%	10%
Fibroid location	29%	16%

External Validity

Description of:	Invasive Therapy (n=115)	Medical Therapy (n=50)
Timing of outcome assess.	54%	80%
Measures of outcome(s)	47%	57%
Reliability/validity of measures	29%	22%
Clinical care protocols	75%	78%
Clinical outcome definition	32%	20%

Q1: Risks and benefits of hysterectomy or myomectomy for symptomatic and asymptomatic fibroids?

Data for direct comparison of risks and benefits of myomectomy and hysterectomy are lacking

- Limited data on myomectomy and long-term symptoms
- Hysterectomy results in favorable outcomes in most patients up to 2 years after surgery (prospective cohorts)
- Differences in short-term complications between hysterectomy and myomectomy potentially attributable to differences in uterine size (multivariate analyses of retrospective case series)

Q2: Are outcomes different after myomectomy for a single clinically detectable fibroid compared to multiple fibroids?

- Complications of myomectomy increase with increasing number of fibroids (case series)
- Risk of recurrence lower when only one fibroid is detected and removed (case series)
  - May reflect differences in underlying biology

Q3: Who are appropriate candidates for the various treatment options?

- Hysterectomy is inappropriate for women wishing to retain fertility
- Otherwise, insufficient data to identify most appropriate candidates for each treatment
- No data to support prophylactic myomectomy or hysterectomy in asymptomatic women

Q4: How often do women need additional treatment after conservative therapy for fibroids?

- Data insufficient to estimate cumulative incidence of recurrent symptoms after conservative management
  - Reported "recurrence" up to 50% at 5 yrs after myomectomy (case series)
  - Up to 8% of patients later undergo hysterectomy (case series)
  - Multiple methodological issues

Q5: Does additional treatment result in increased morbidity compared to immediate definitive therapy?

- No data on whether morbidity associated with delay of therapy greater than immediate definitive therapy
  - Largely due to deficiencies in study design, lack of data on prior surgical history
- Even if morbidity is greater, data on how often additional therapy is needed to quantify risks

Q6: What are the risks and benefits of nonsurgical treatment?

- Other than GnRH agonists as adjunct to surgery, remarkable lack of RCT data on effectiveness of medical therapies for management of symptomatic fibroids
- Use of GnRH agonists prior to surgery reduces estimated blood loss, may facilitate certain surgical approaches
  - No data on long-term clinical significance of these effects

Q7: What are the costs of surgical and nonsurgical treatments?

- No data on nonmedical or outpatient costs
  - Currently working on estimates
- Mean hospital costs slightly lower for myomectomy compared to hysterectomy

1997 Nationwide Inpatient Sample (AHRQ)

Procedure (women only)	Total Discharges	Mean Charge	Total Charges
C-section	808,991	$8,054	$6.5 billion
Surgeries for fibroids	231,718	$9,041	$2.1 billion
CABG (women)	114,403	$50,635	$5.8 billion
Cholecystectomy	54,165	$19,635	$1.1 billion
For ectopic pregnancy	40,134	$7,958	$319 million
Mastectomy	23,215	$8,764	$203 million

Q8: Do risks and benefits differ for women of different race, ethnicity, age, interest in future childbearing, etc.?

- Uterus-conserving treatments (GnRH agonists, myomectomy, uterine artery embolization) more effective for perimenopausal than premenopausal women (case series, subgroup analyses)
- Fibroids associated with increased risk of pregnancy complications: preterm labor, placental abruption, c-section, breech presentation (cohorts, case series, administrative data)
- Data on effectiveness of treatment of fibroids in management of infertility limited (case series)

Racial Differences

Clear differences in incidence of diagnosis

- Nurses Health Study (Marshall et al., 1997)

  Age-standardized rate/1000 women-years

  White: 12.5 Black: 37.9

  Hispanic: 14.5 Asian: 10.4

  Hysterectomy/1000 woman-years

  White: 2.0 Black: 4.5

  Hispanic: 1.3 Asian: 1.9

Racial Differences

- Black women reported to have larger and more numerous fibroids at time of treatment
- Black women more likely to have in-hospital complications of surgical therapy

Questions for Primary Data Analysis

- Are there racial differences in rates of myomectomy? Or hysterectomy?
- Are increased complication rates seen in black women attributable to differences in uterine anatomy?

Surgery Rates: Methods

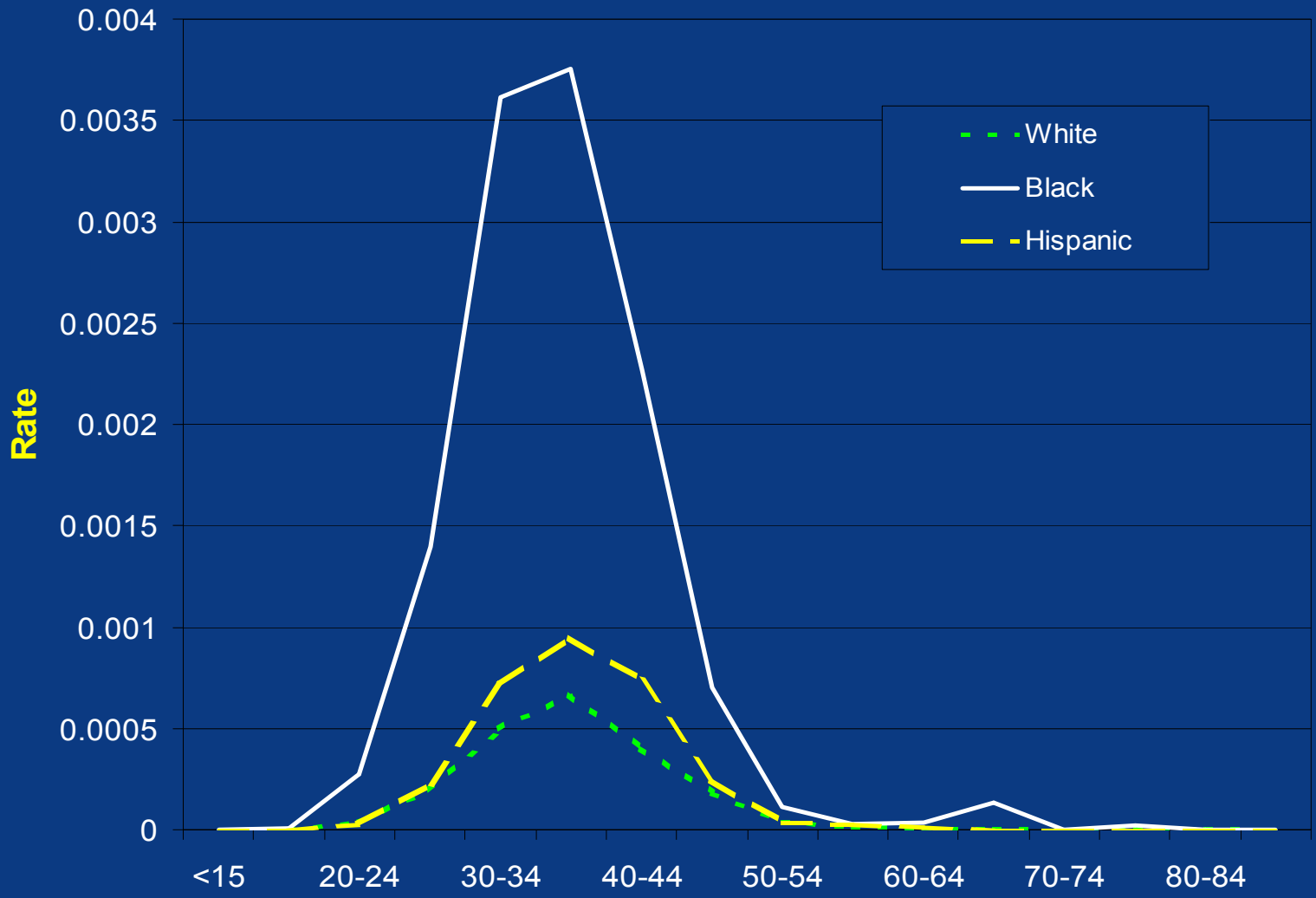
1997 Nationwide Inpatient Sample

- Stratified sample of 20% of US hospitals (22 states)
- Data on demographics, hospital characteristics, diagnoses and procedures
- Hysterectomy
  - All ICD-9 procedure codes of 68.3, 68.4, 68.5 with diagnosis codes 218.0, 218.1, 218.2, 218.9
- Myomectomy
  - ICD-9 procedure code of 68.29 with diagnosis codes of 218.0, 218.1, 218.2, 218.9
  - Validated at DUMC: only 3 non-myomectomies

Surgery Rates: Methods

- Identified cases stratified by age (5-year groups), race (black/white only)
- National estimates derived using weights
- Age-specific incidence calculated by dividing cases by age, race-specific population from US census data
- Cumulative incidence estimated using Markov modeling

Myomectomy Rate



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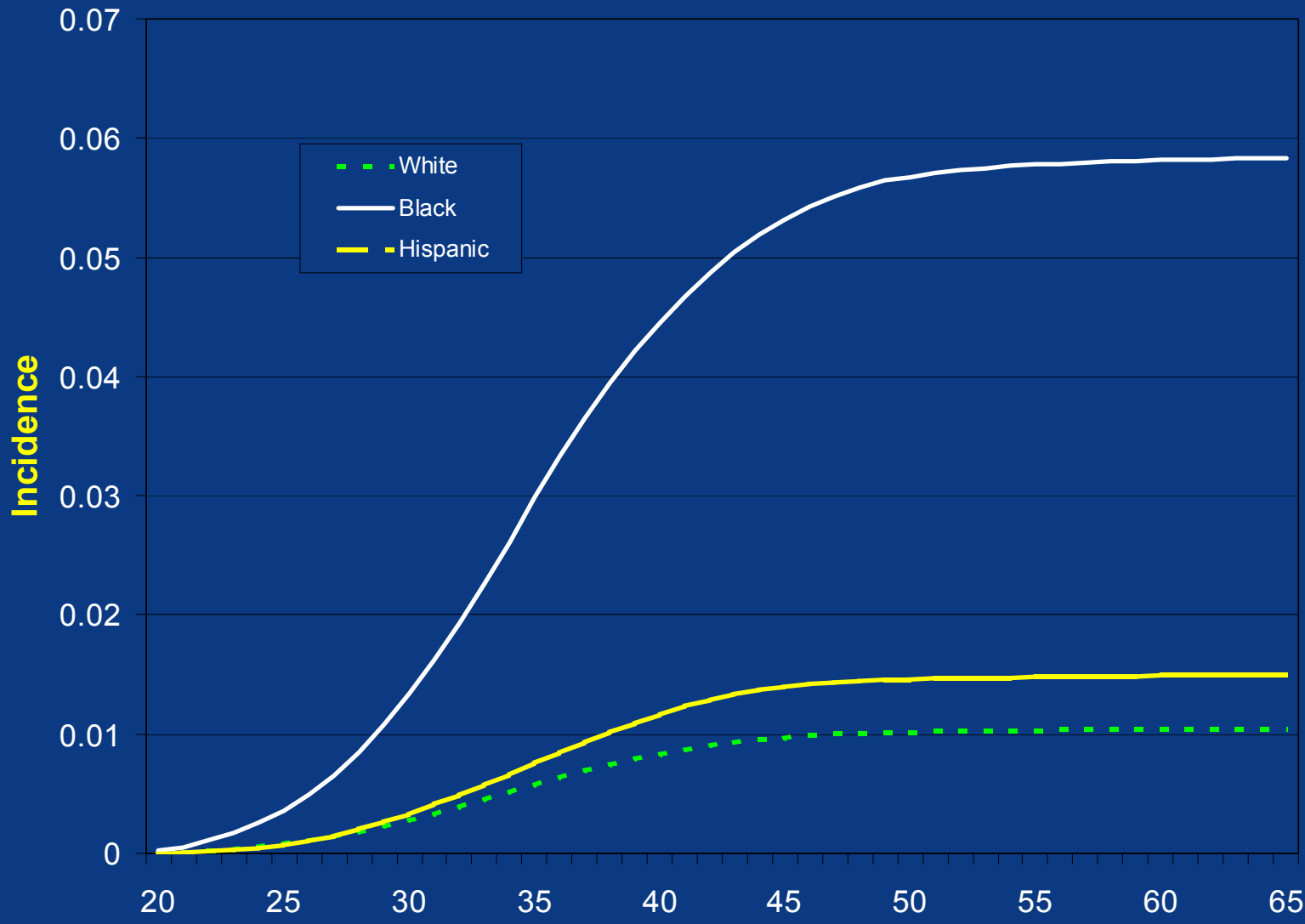
Cumulative Incidence of Myomectomy



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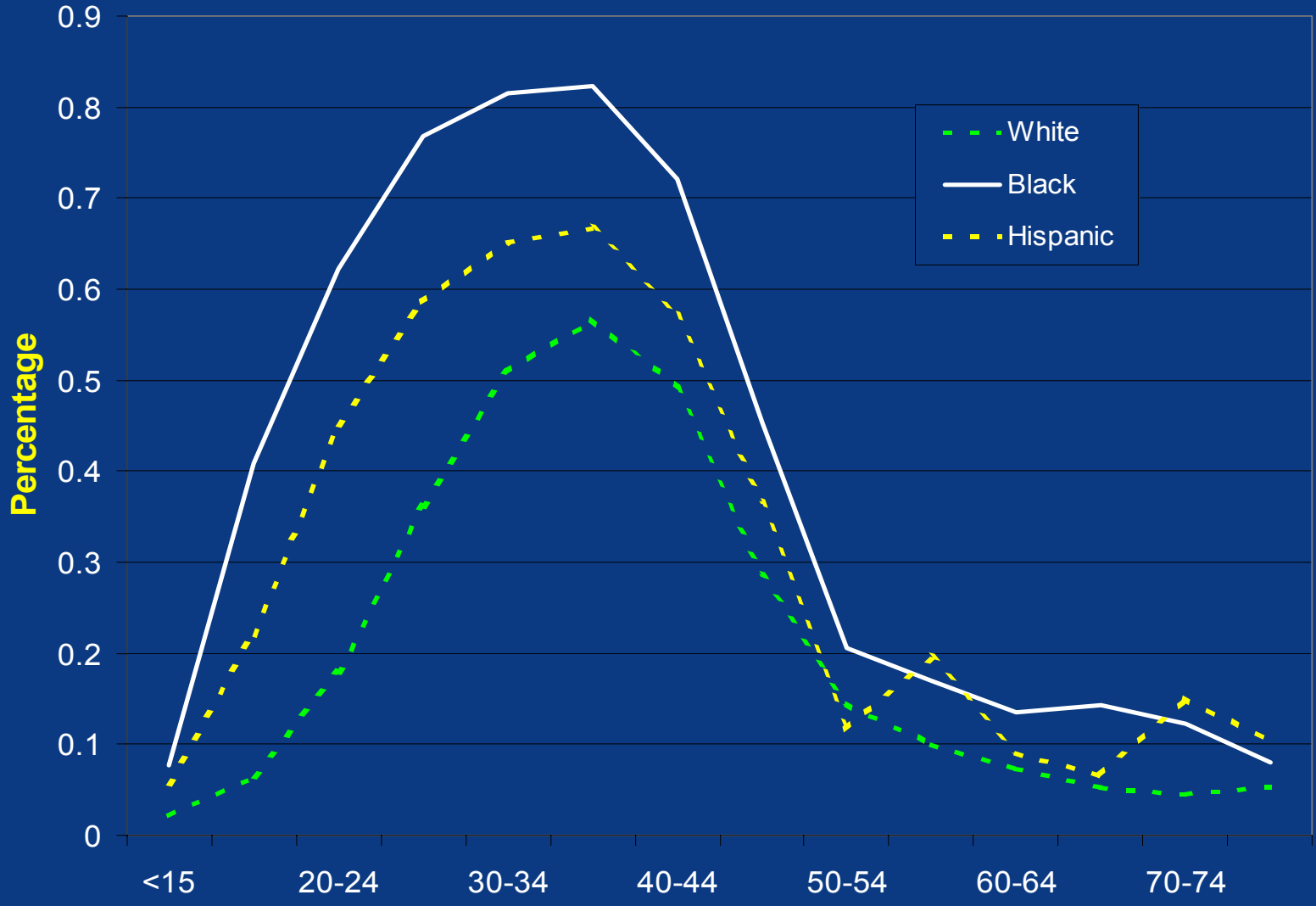
Hysterectomies for Fibroids



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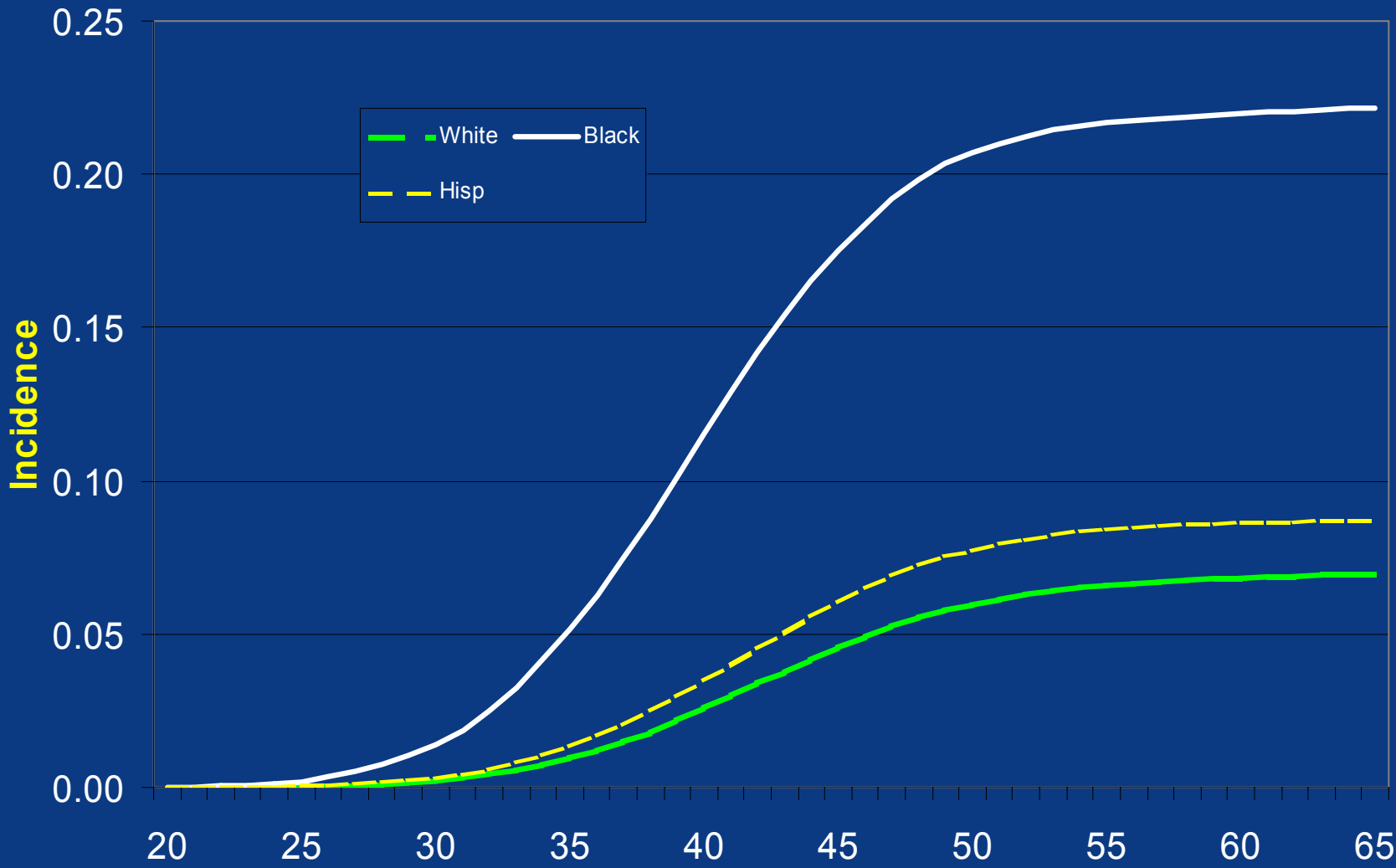
Cumulative Incidence of Hysterectomy



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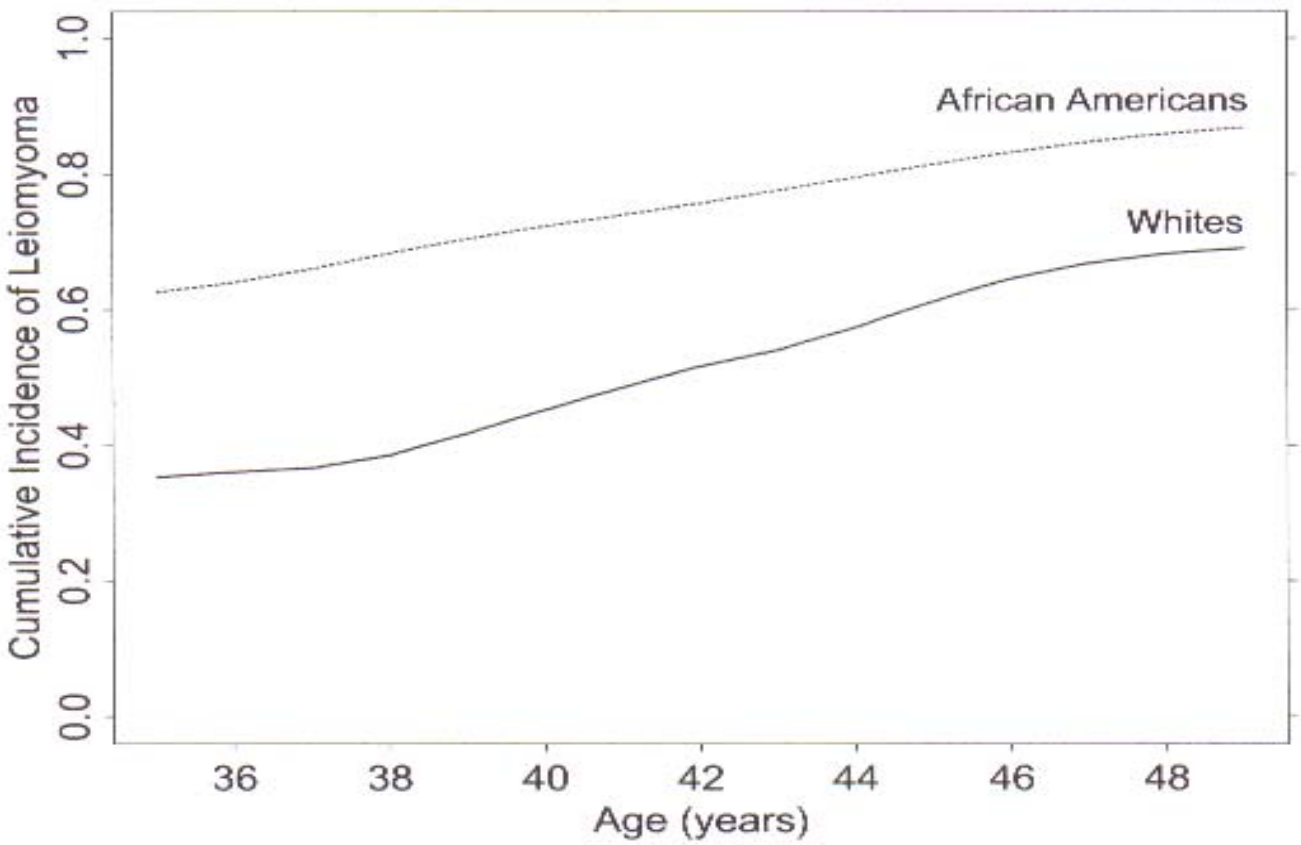
Population-based Incidence



Baird et al. 2003

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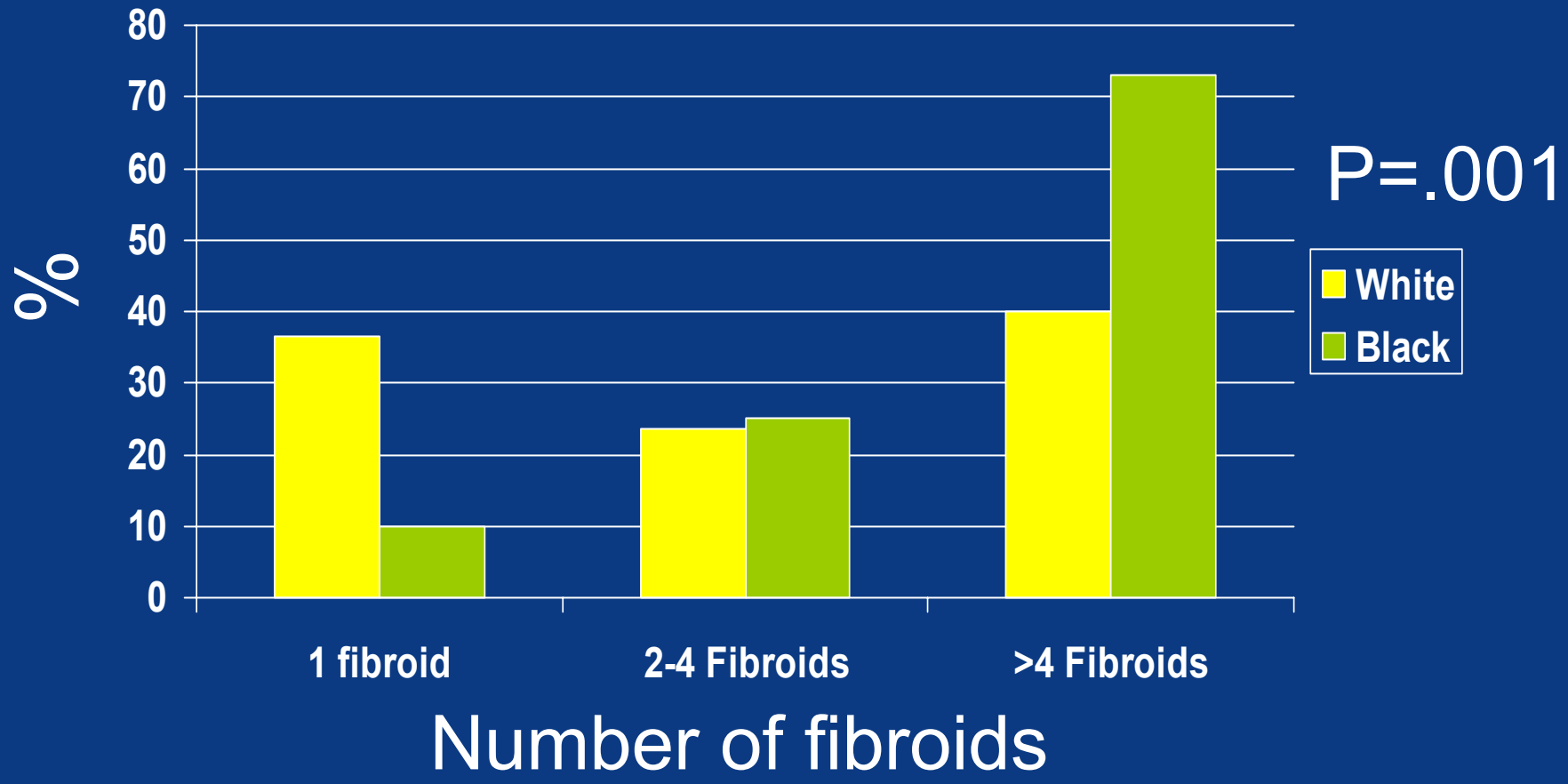
Hospital-based data

- Review of DUMC charts for hysterectomy & myomectomy 1992-1998
- Charts abstracted for
  - Demographics, past surgery, OB history
  - Uterine size, size & # of fibroids if documented
  - Complications
- Myomectomy 239 (data available for 200)
- Hysterctomy 753 (data available for 646)

Myomectomy: Race and number of fibroids



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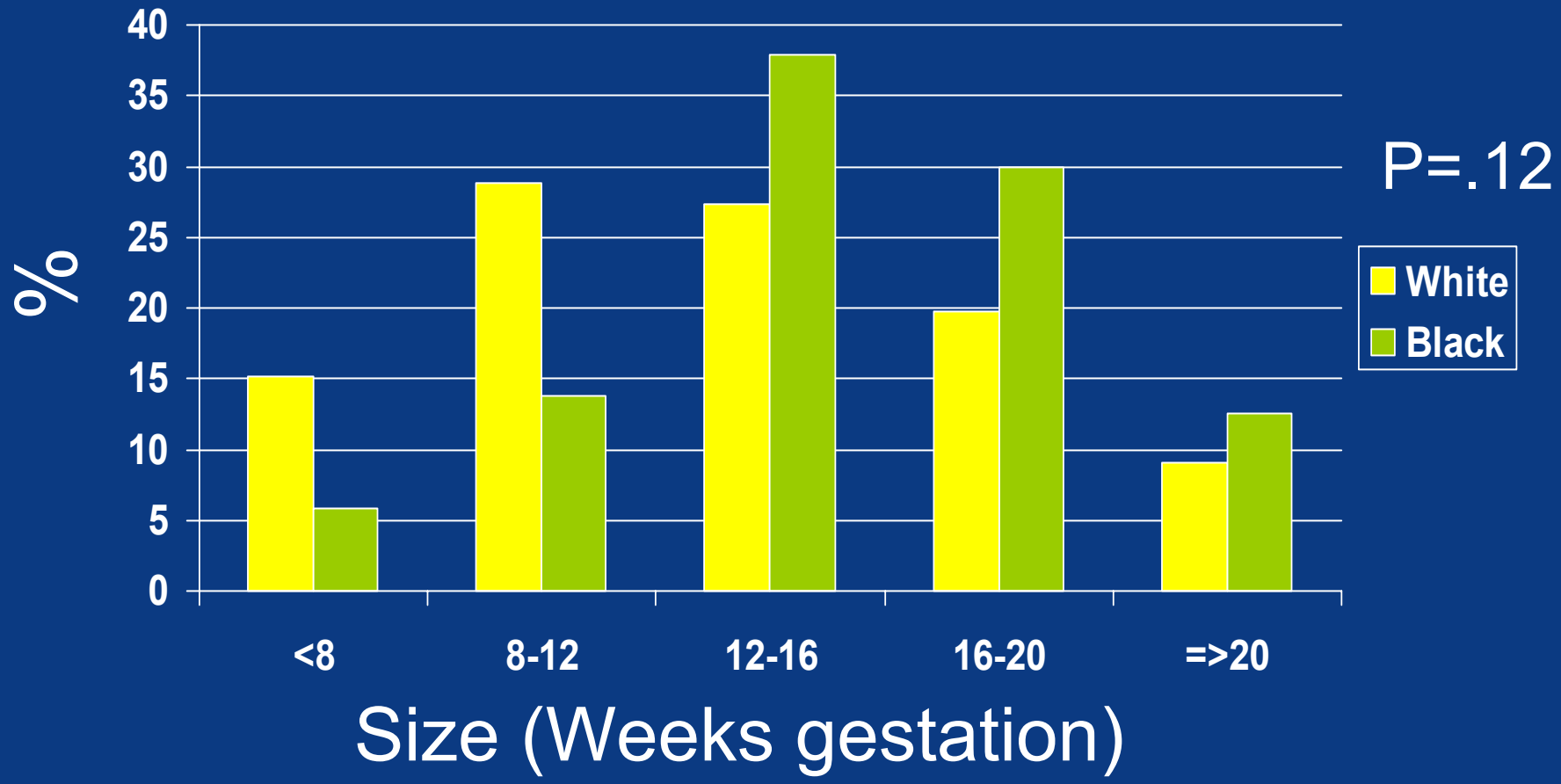
Myomectomy: Race and Uterine size



Myomectomy: Complications by Race

Complication	Black	White	Total
Yes	41	17	58
No	70	72	142
Total	111	89	200
	RR= 1.93	p< .006	

(Unadjusted Risk Ratio)

Myomectomy: Adjusted Odds Ratios for Complications

Variable	OR	(CI 95%)
Uterine size	1.86	(1.3-2.67)
Number of fibroids	1.83	(1.1-3.14)
Comorbidities	2.77	(1.1-7.69)
Race	1.36	(0.6-3.15)

Hysterectomy Complications: Multivariate Analysis

Covariate	Odds Ratio	95% CI
BMI >25	1.76	1.03, 2.87
Uterine size in weeks (<8, 8-11, 12-15, >16)	1.16	0.97, 138
Preoperative Hct <32	3.79	2.12, 6.75
Other procedures	2.27	1.27, 4.05
Oophorectomy	1.90	1.17, 3.07
Adhesions	2.36	1.36, 4.08

Hysterectomy Complications: Multivariate Analysis

	OR	95% CI
Unadjusted		
African-American (vs. white)	1.94	1.26, 2.99
Adjusted for BMI, uterine size, Hct, other procedures:		
African-American	1.48	0.88, 2.49

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Duke Case Series Review: Conclusions

- Excess risk of complications in black women largely attributable to differences in
  - Severity of disease
    - Size of uterus, # of fibroids, anemia
  - Other surgical risk factors
    - Obesity, presence of adhesions
- Other causes may contribute to excess risk

Racial differences: Summary

- Excess risk of complications in black women largely attributable to differences in severity of disease and other surgical risk factors.
- Black women have more and larger fibroids, at younger ages; and compared to white women, a greater degree of anemia
- Black women more likely to have surgery, at younger ages, compared to white women
- ? Causes for discrepancy: genetic, cultural (symptom thresholds), quality of care, access

Results 2000: Literature Review

Common limitations

- Study design
- Failure to characterize symptoms
  - Bleeding vs... pain vs... other
  - Limited use of validated measures pre- and post-treatment
- Failure to characterize anatomy
  - Uterine size, fibroid size, number, location
- Failure to characterize population
  - Race, parity, obstetric/surgical history
- Lack of long-term follow-up

Results 2005: Literature Review

- 17 new RCT/prospective outcome studies
- Common limitations improving
  - Study designs more sophisticated
  - Symptoms better described
    - New measures, including QOL scale
    - Validation of imaging tools underway
  - Characterization of anatomy improving
  - Population covariates better measured
    - Race, parity, obstetric/surgical history
  - Lack of long-term follow-up persistent

Results 2005: Literature Review

- Low-dose mifepristone improves symptoms
- Anti-progestins improve symptoms/anemia
- Long-term follow-up still needed
- Direct comparison of options still needed
- Natural history studies underway
- Basic science funding continues to expand
- Little new health services data

Managing Fibroids: Key Points

- Hysterectomy is effective and improves quality of life in most women
- We do not have good data to compare expected outcomes across treatments
- There are no studies that document medical therapy is effective for long-term treatment
- Short-term data on UAE looks reasonable, long-term results pending

Research Opportunities

- Incidence and prevalence studies
- Natural history studies
- Long-term follow-up of therapy
- Randomized trials of medical therapies
- Randomized trials of invasive therapies
- Development and validation of a staging system
- Exploration of factors influencing racial differences
- Estimates of nonmedical and outpatient costs associated with symptomatic fibroids