

ESTROGEN, GENETICS and ENDOMETRIAL CANCER

THE EDGE STUDY

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November 9, 2006



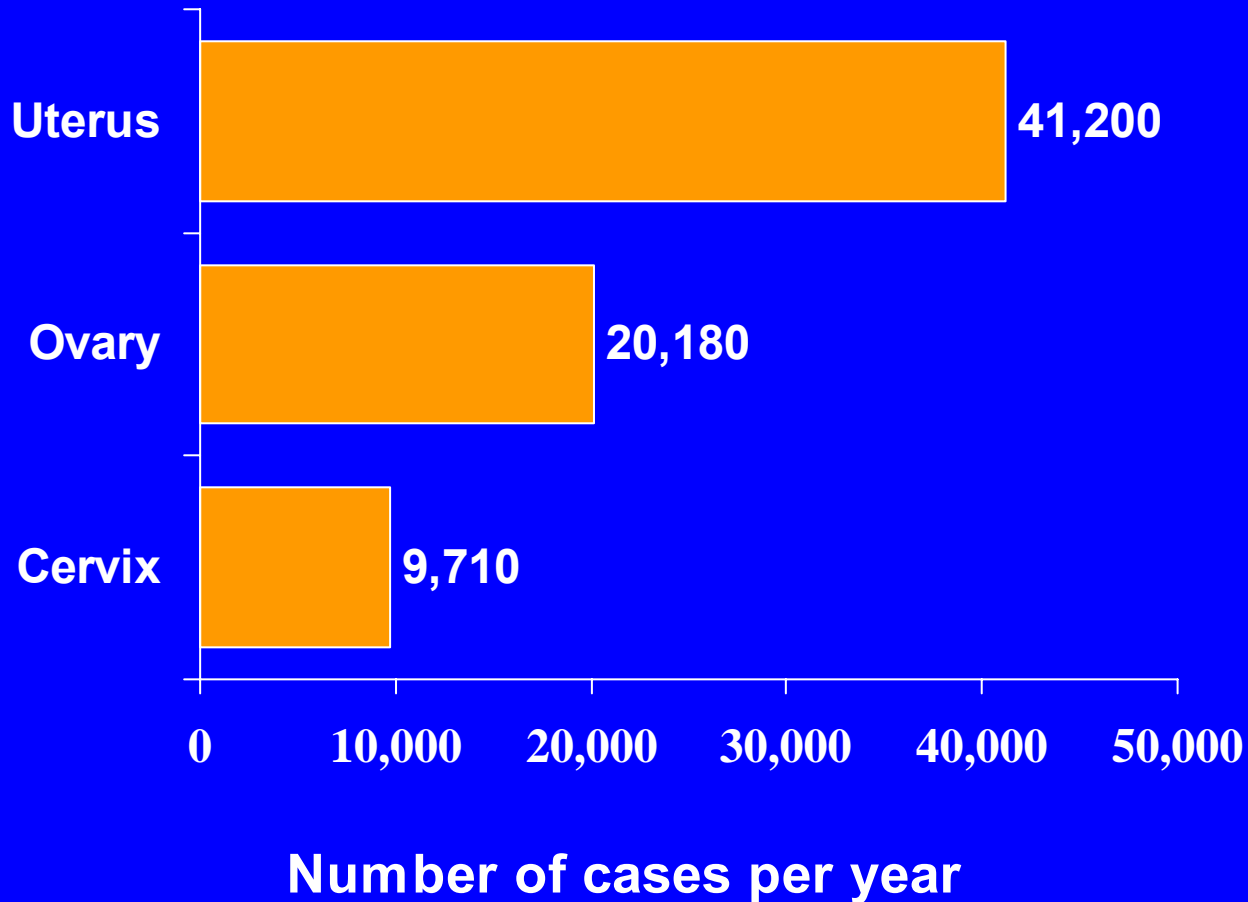
OUTLINE OF PRESENTATION

- **Epidemiology of endometrial cancer**
- **Purpose, methods, and findings of EDGE Study**
- **Findings on variants in estrogen biosynthesis genes**
 - **review of literature on association of genotypes and serum hormone levels**
 - **genotypes and risk of endometrial cancer from EDGE Study**

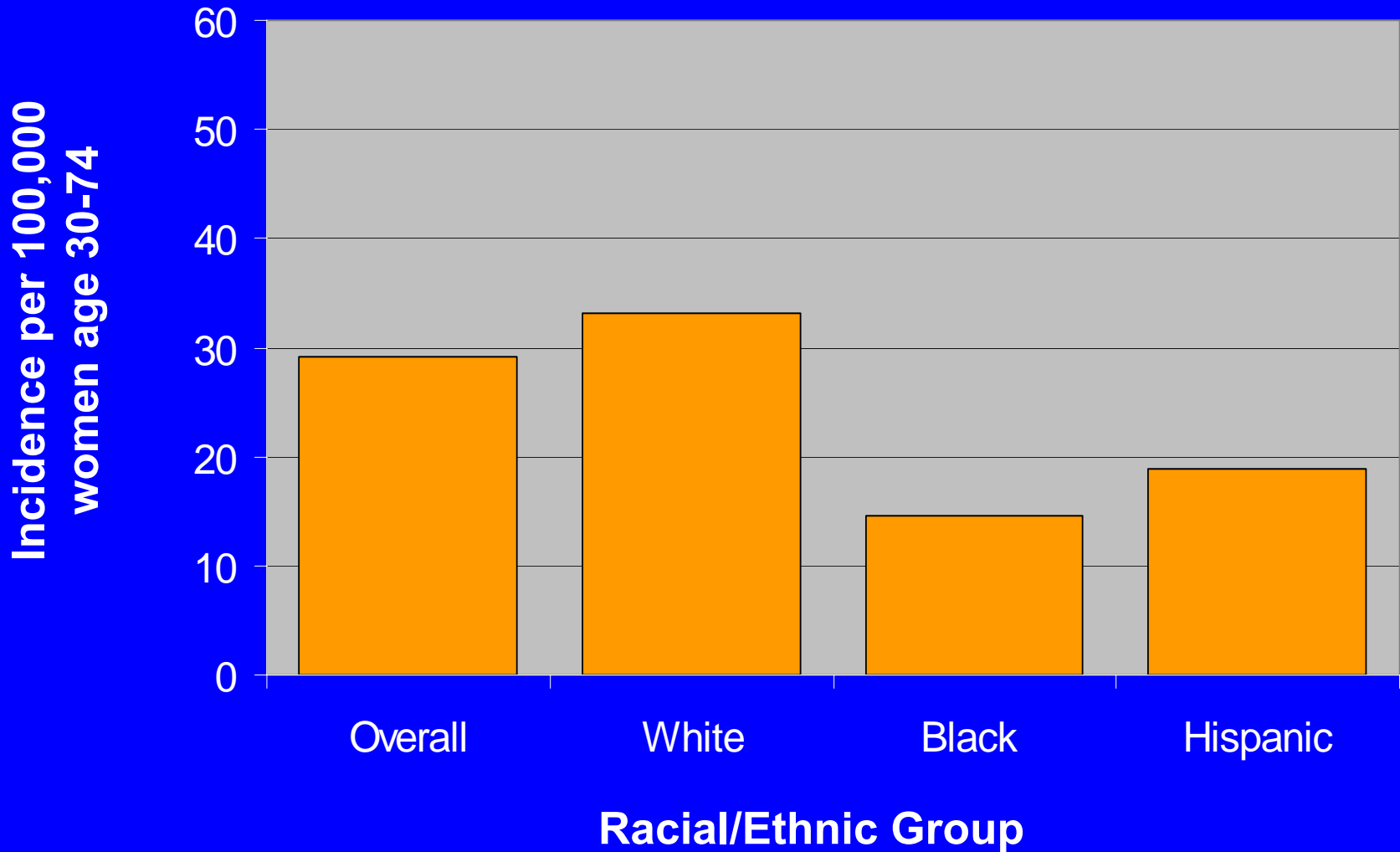
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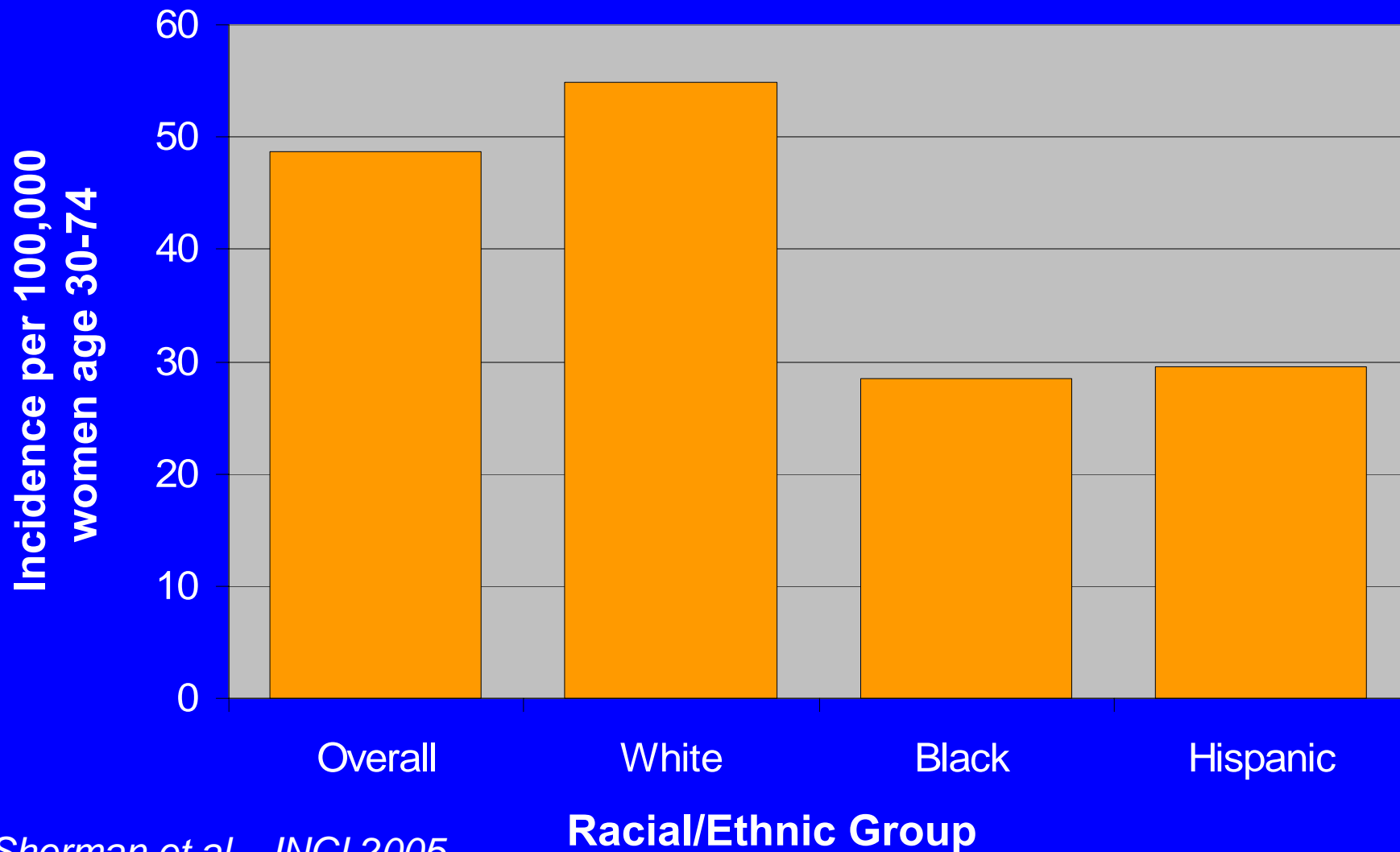
GYNECOLOGIC CANCERS IN THE U.S.



INCIDENCE OF ENDOMETRIAL CANCER



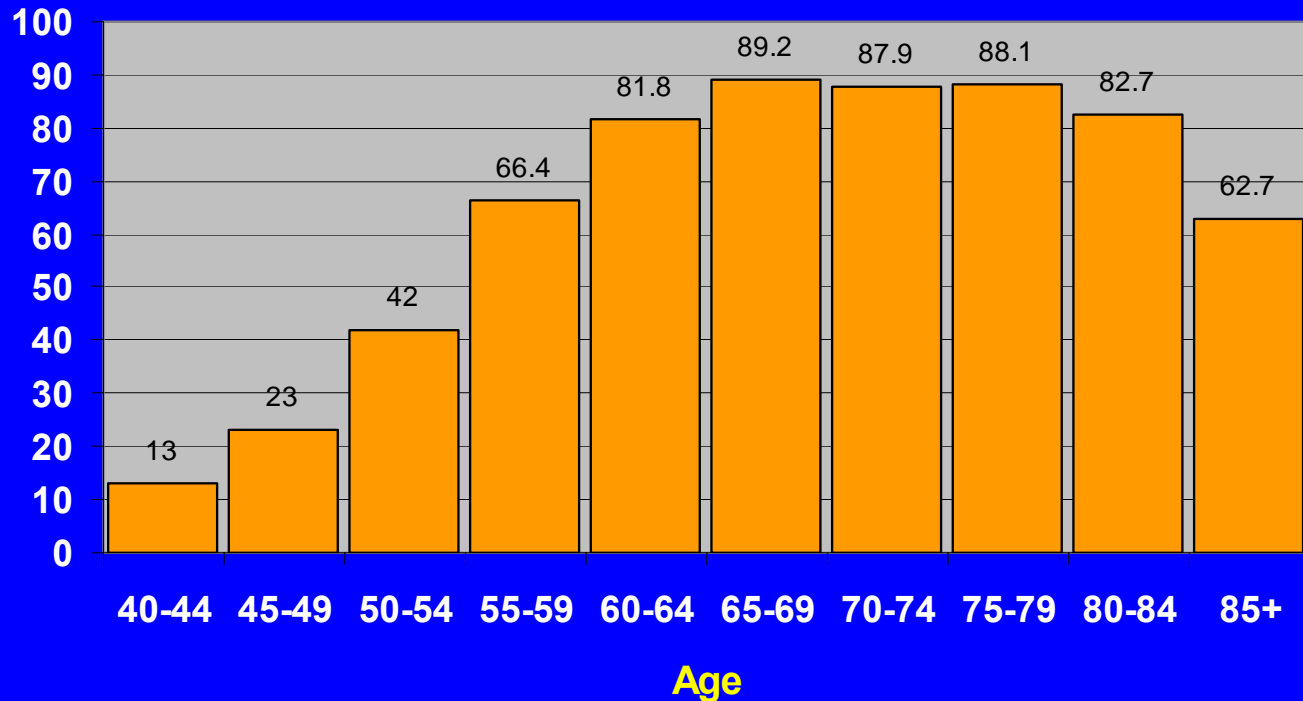
INCIDENCE OF ENDOMETRIAL CANCER ADJUSTED FOR HYSTERECTOMY



Sherman et al., JNCI 2005

A DISEASE OF POST-MENOPAUSAL WOMEN

Incidence
per 100,000
women*

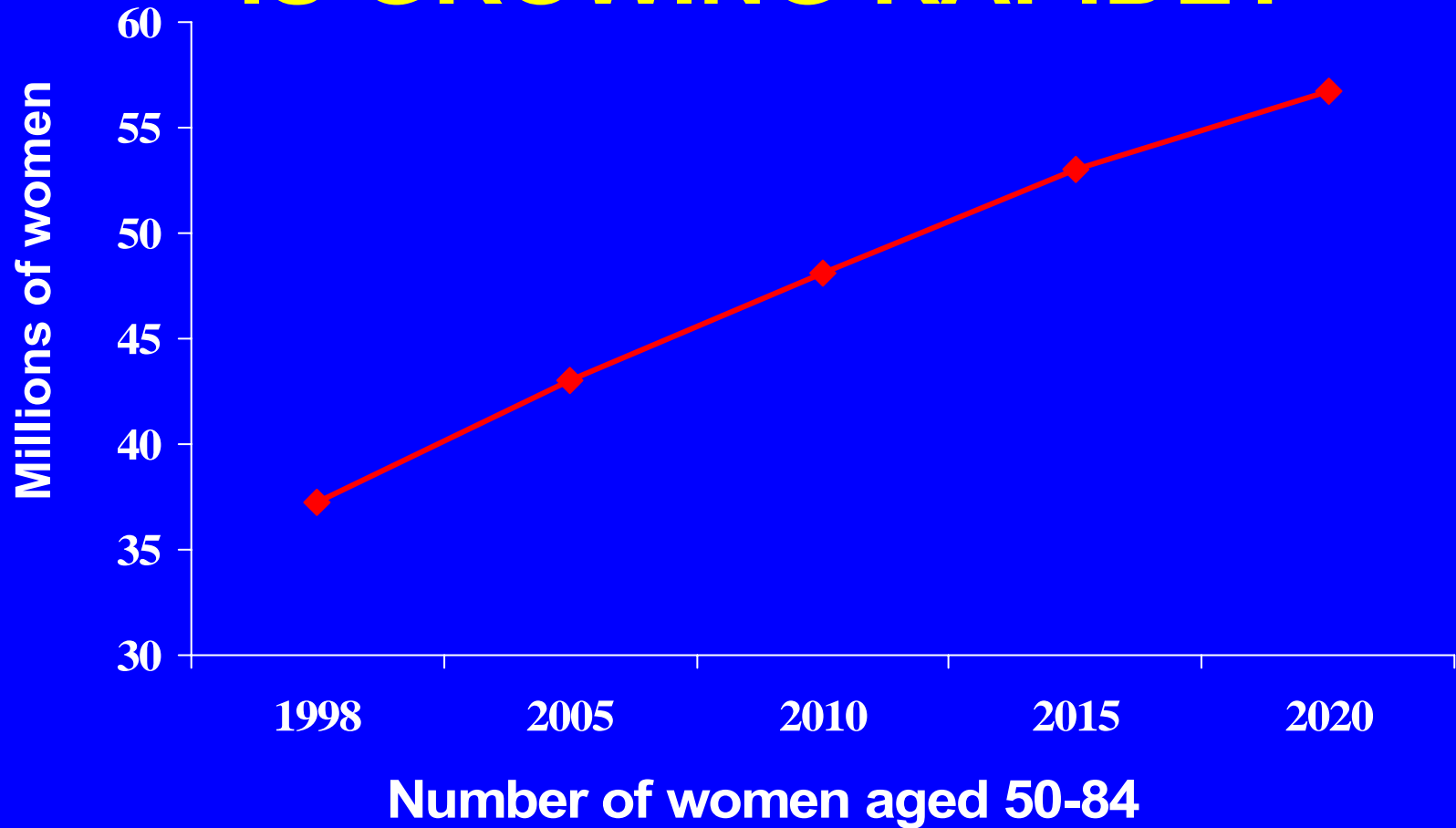


***Corpus & Uterus, NOS Cancer (Invasive)**

SEER Cancer Statistics Review 1975-2003

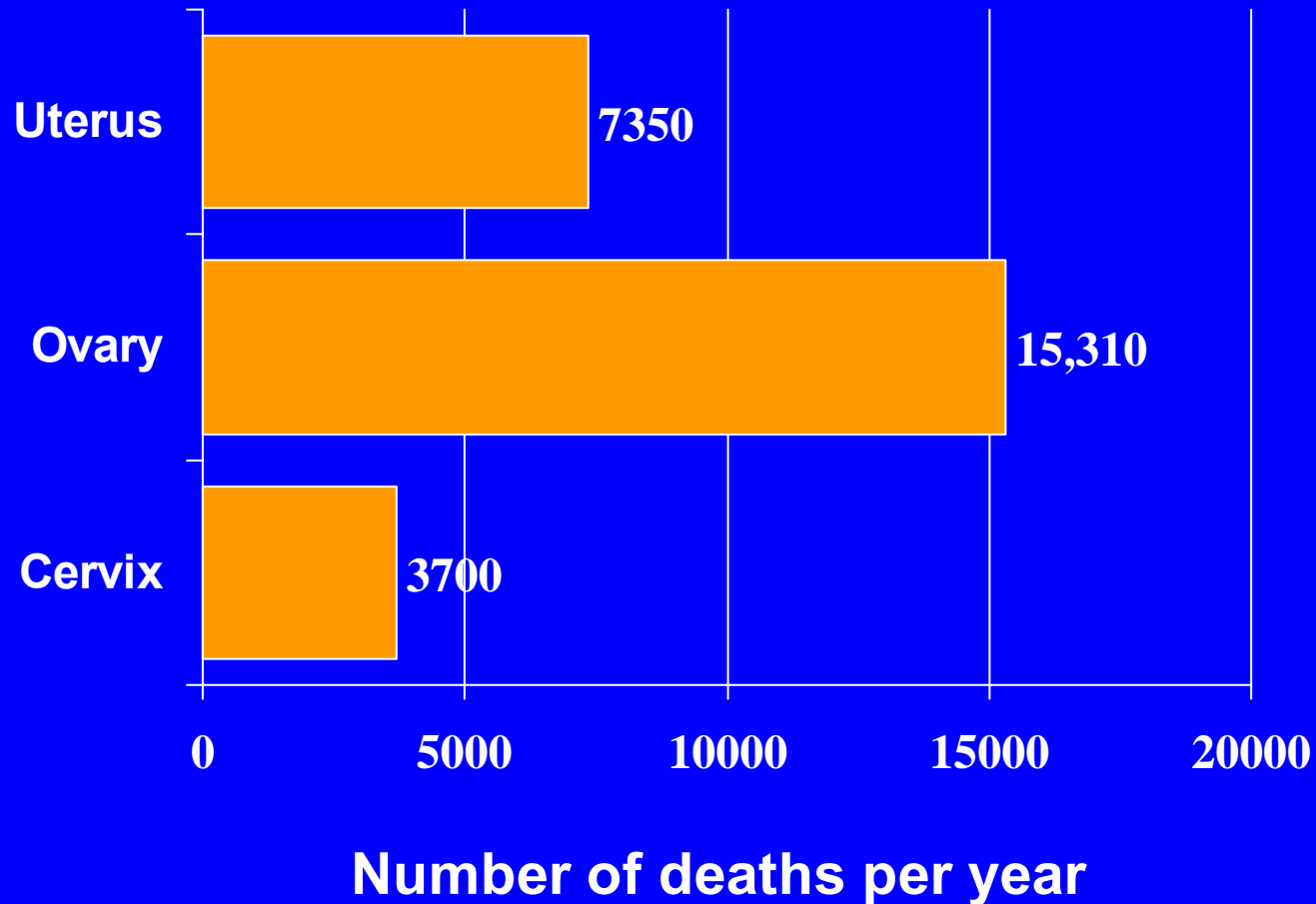
SEER 17 areas. Rates are per 100,000 and are adjusted to the 2000 US Std Population

NUMBER OF OLDER WOMEN IS GROWING RAPIDLY



U.S. Bureau of the Census, Current Population Reports, Series P25-1130, "Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995-2050". Middle Series Projections.

MORTALITY FROM ENDOMETRIAL CANCER



HORMONES AS RISK FACTORS

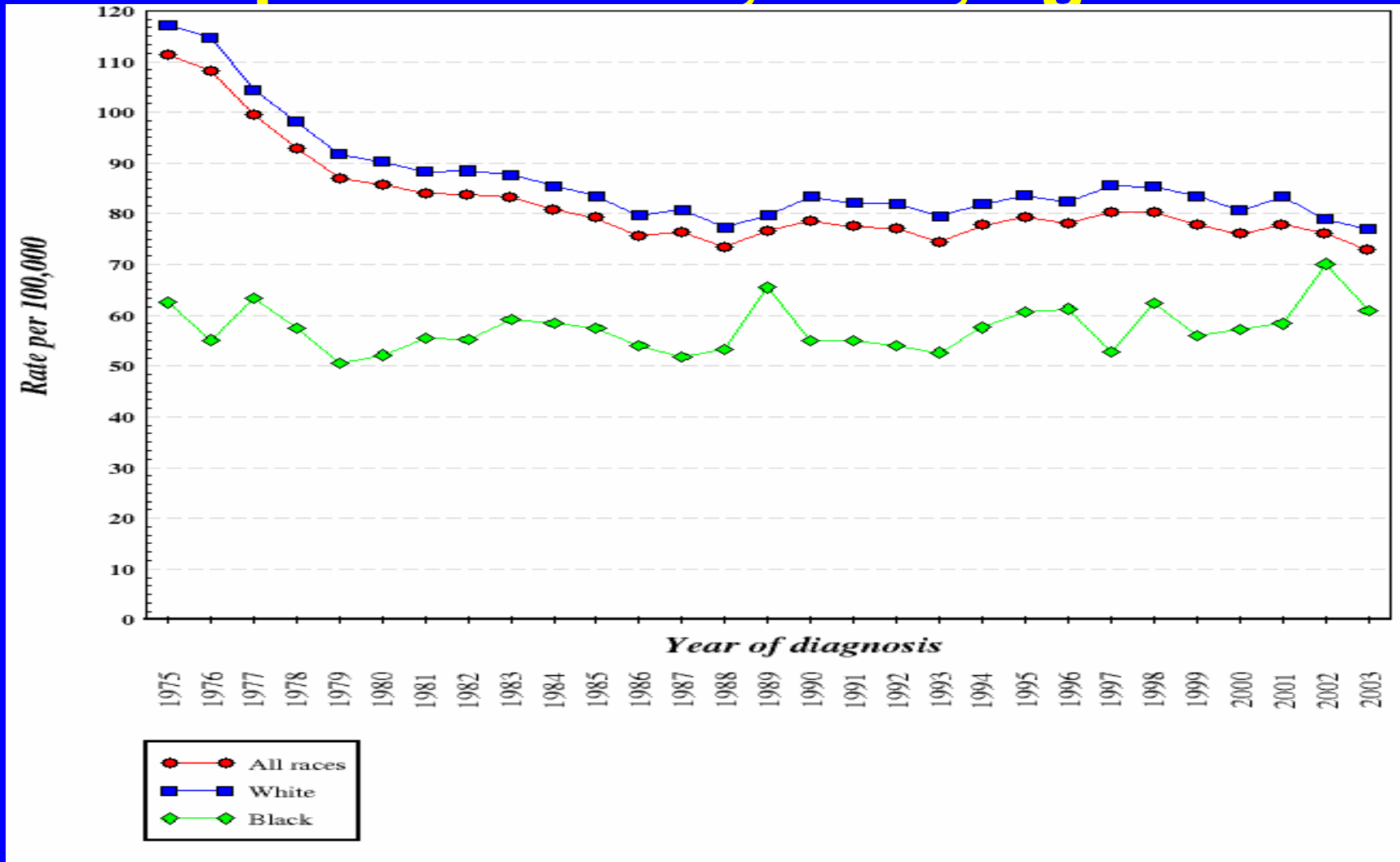
- **Unifying risk factor: Long-term exposure to estrogens unopposed by progesterone**
 - **Estrogen has a proliferative effect on endometrial tissue**
 - **Progesterone counteracts effects of estrogen**
 - **Also some evidence that estrogen may be directly carcinogenic**

SOURCES OF ESTROGENS

- **Unopposed estrogen replacement therapy**
- **Excess weight**

INCIDENCE 1975-2003

Corpus & Uterus, NOS, age ≥ 50



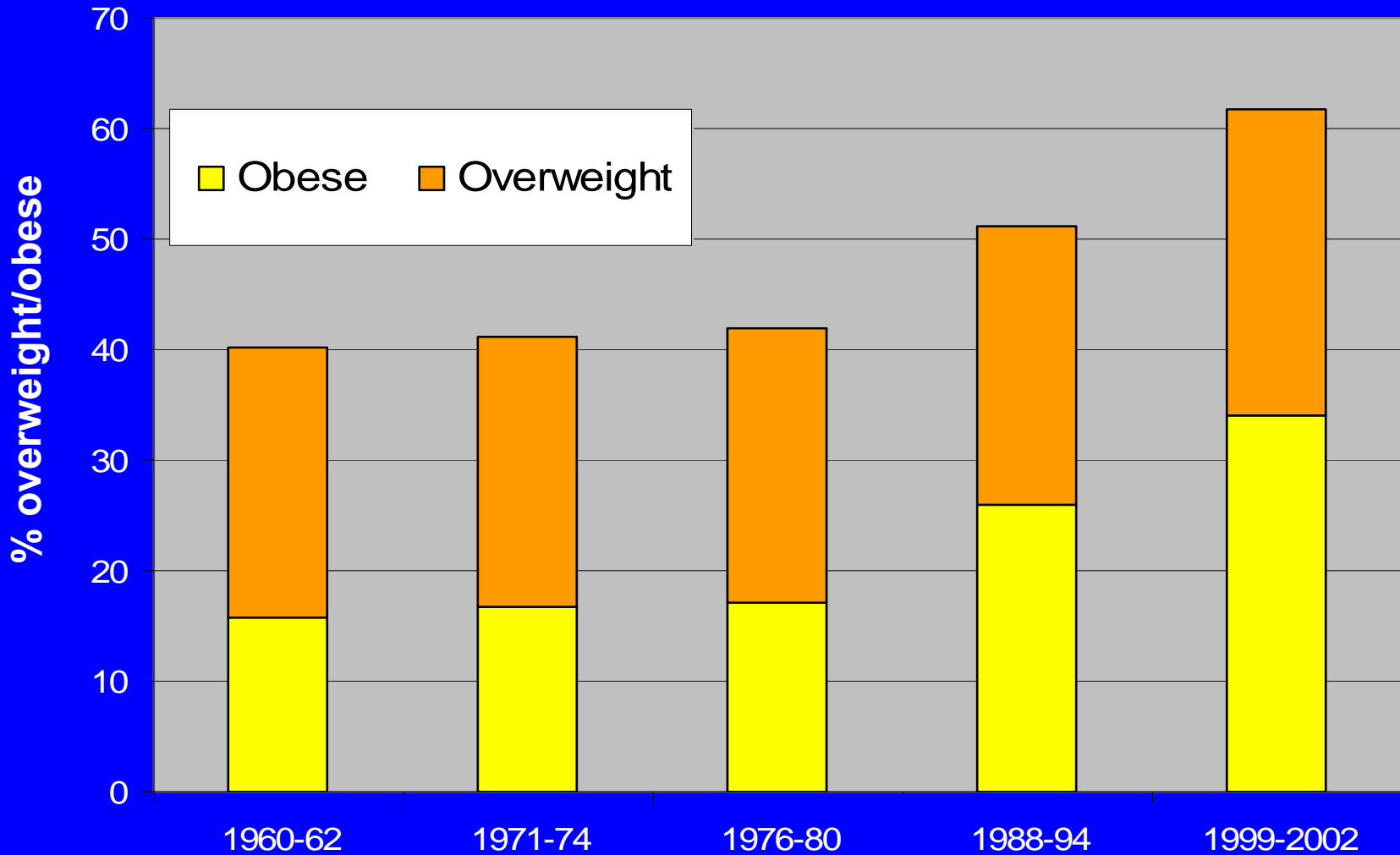
*Age-adjusted to 2000 U.S Standard population

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Public-Use, Nov 2005 Sub (1973-2003)

EXCESS WEIGHT

- **Pre-menopausal women:**
 - excess weight leads to irregular cycles and lack of progesterone
- **Post-menopausal women:**
 - main source of estrogen is conversion of androstenedione to estrone in adipose tissue
- **Heavier women also have lower levels of sex-hormone binding globulin**

WOMEN ARE GETTING HEAVIER



OTHER “LIFESTYLE” RISK FACTORS

- No / few children
- Early menarche / late menopause
- No oral contraceptive use
- Not smoking
- Diet?
- Physical activity?
- Diabetes?

GENETIC SUSCEPTIBILITY

- **Endometrial cancer is rare even in women with risk factors**
- **Do differences in genetic make-up help explain why some women get disease and others do not?**

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EDGE STUDY

SPECIFIC AIM

- **To investigate the role of weight, diet, and genetic susceptibility in risk of endometrial cancer**

STUDY PARTICIPANTS

- 487 Cases: endometrial cancer up to one year before contact (2001-2005)
- 467 Controls: no hysterectomy; matched to cases by age group
- Aged 21 and over
- Resident of selected counties in northern NJ
- Speak English or Spanish
- Able to sign informed consent

LOCATING CASES

- **Rapid case ascertainment: NJDHSS representative reviewed pathology records at hospitals**
- **Physician contacted and approval given**
- **Patient contacted to obtain informed consent and for interview**

LOCATING CONTROLS

Three sources of controls:

- 1. Random digit dialing for women <65**
- 2. Medicare lists for women aged ≥ 65**
- 3. Neighborhood sampling for women aged ≥ 60**

MEASUREMENTS

- **Main questionnaire**
 - Known and potential risk factors
- **Diet questionnaire**
 - Block food frequency
 - Supplement for phytoestrogens
- **Mouthwash sample for DNA (87%)**
- **Hip/waist measurement**
- **Genotyping of 10 variants in 7 genes**
- **Centralized pathology review at MSKCC**

LITERATURE REVIEW

- **Studies investigating relation between genotypes of genes in estrogen biosynthesis pathway and serum hormone levels**
 - **Seven genes**
 - **Serum levels of progesterone, androgens, estrogens**
- **In normal women**
- **Summarized these as a HuGE Review**

RISK FACTORS

	Cases (430)	Controls (402)	Odds ratio* (95% CI)
Mean age (SD)	61.9 (9.6)	64.8 (11.0)	
Body Mass Index			
Normal (<25)	26%	47%	1
Overweight (25-<30)	27	31	1.2 (1.2-2.3)
Obese (30-<34)	16	16	1.8 (1.2-2.8)
Very obese(≥35)	30	6	7.8 (4.8-12.6)
Mean BMI (SD)	31.1 (8.8)	26.0 (5.4)	

*adjusted for age

RISK FACTORS

	Cases (345)	Controls (301)	Odds ratio* (95% CI)
Parity			
0-1	35%	23%	1
2	34	36	0.62 (0.43-0.87)
>= 3	30	41	0.52 (0.36-0.74)
Age at last birth			
Nulliparous	20%	12%	1
<35	68	66	0.64 (0.43-0.95)
>=35	12	22	0.38 (0.23-0.63)

*adjusted for age

RISK FACTORS

	Cases (430)	Controls (402)	Odds ratio* (95% CI)
Age at menarche			
≥13	57%	49%	1
<13	43	51	1.3 (1.0-1.7)
Age at menopause			
<50	26%	33%	1
≥50	47	42	1.5 (1.0-1.7)
Post , age unknown	11	13	1.1 (0.7-1.8)
Premenopausal	16	12	1.2 (0.68-2.1)

*adjusted for age

RISK FACTORS

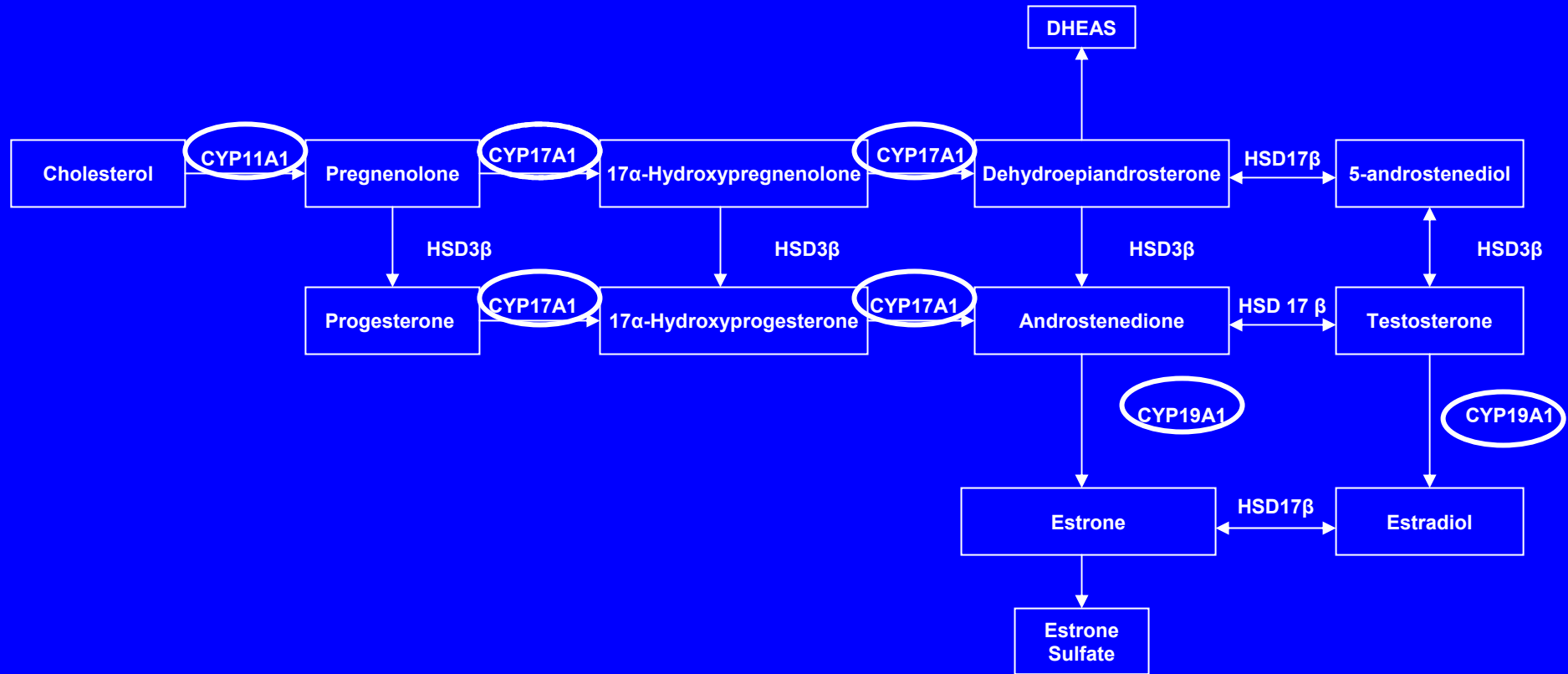
	Cases (430)	Controls (402)	Odds ratio* (95% CI)
OC use			
Never used	54%	50%	1
Ever used	46	50	0.65 (0.48-0.87)
Smoking			
Never smoked	55%	52%	1
Past smoker	39	39	0.95 (0.71-1.3)
Current smoker	6	9	0.52 (0.30-0.89)

*adjusted for age

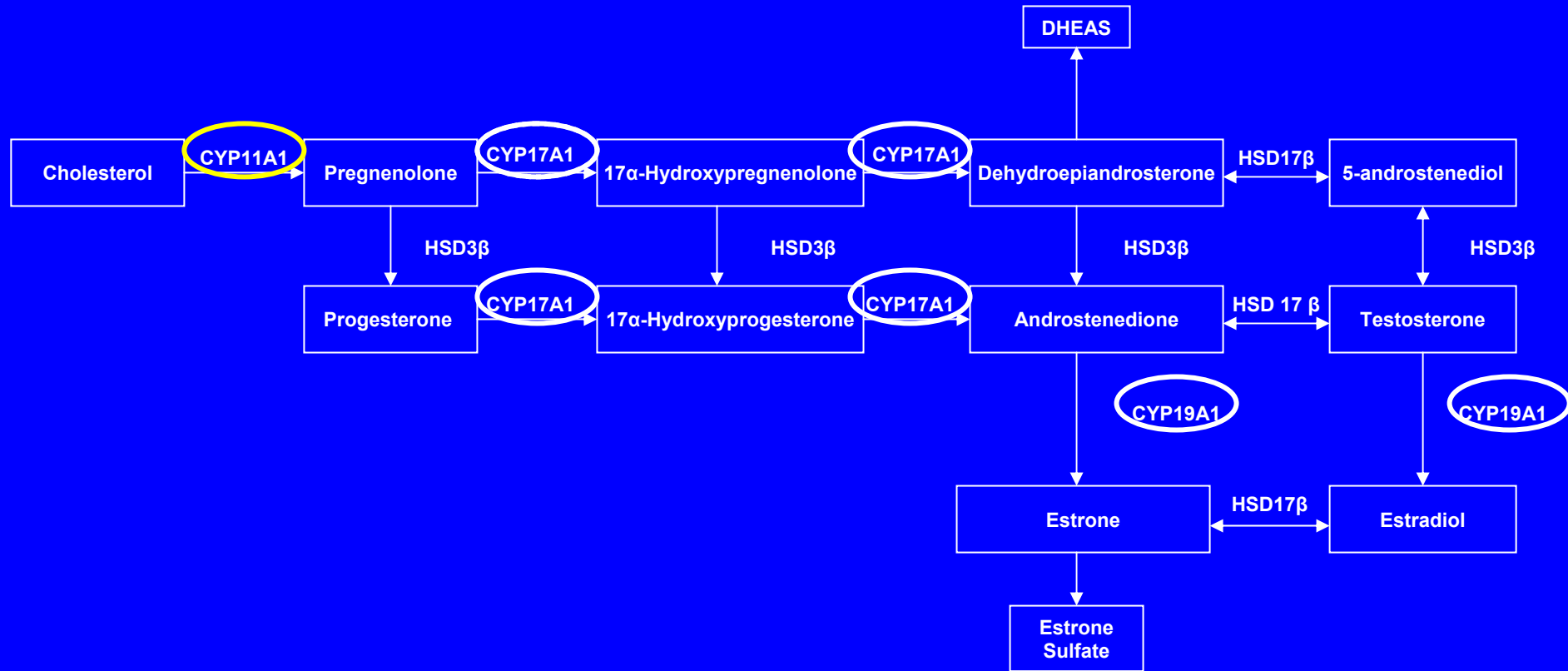
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ESTROGEN BIOSYNTHESIS



ESTROGEN BIOSYNTHESIS



CYP11A1 GENOTYPE AND HORMONE LEVELS

- **Pentanucleotide repeat in promoter region**
 - **-528 [TTTTA]_n**
 - **4 to 10 repeats, 4 most common**
 - **commonly studied in relation to polycystic ovarian syndrome**
 - **no relation between genotype and serum levels of progesterone, androgens or estrogens in normal women**
 - **6 studies, 18 comparisons**

CYP11A1 REPEAT AND RISK OF ENDOMETRIAL CANCER

	Cases (430)	Controls (402)	Odds ratio* (95% CI)
4 / 4	29%	28%	1
4 / longer	51	50	0.89 (0.65-1.24)
Both longer	24	22	1.05 (0.72-1.54)

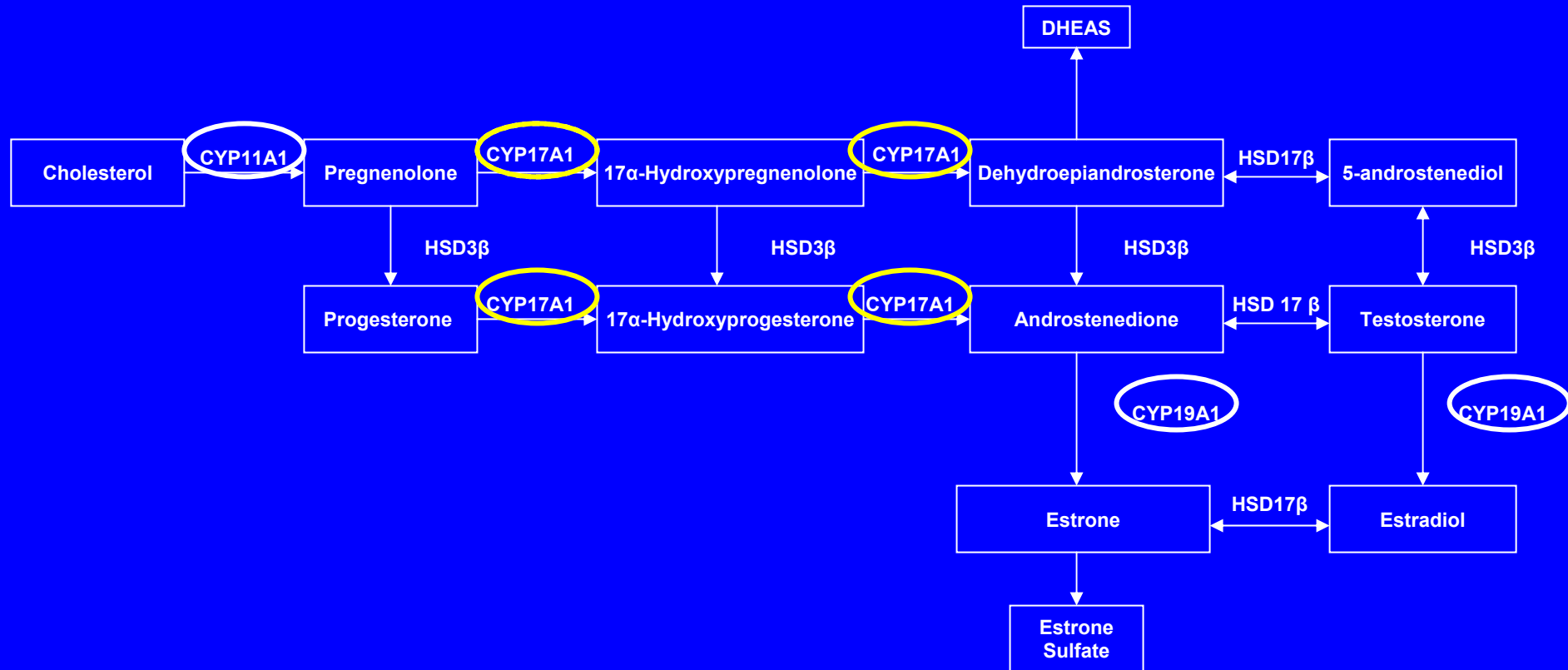
*adjusted for age, BMI, menopausal status, ERT use

CONCLUSIONS

CYP11A1

- **No association between this genotype and either serum hormone levels or risk of endometrial cancer**

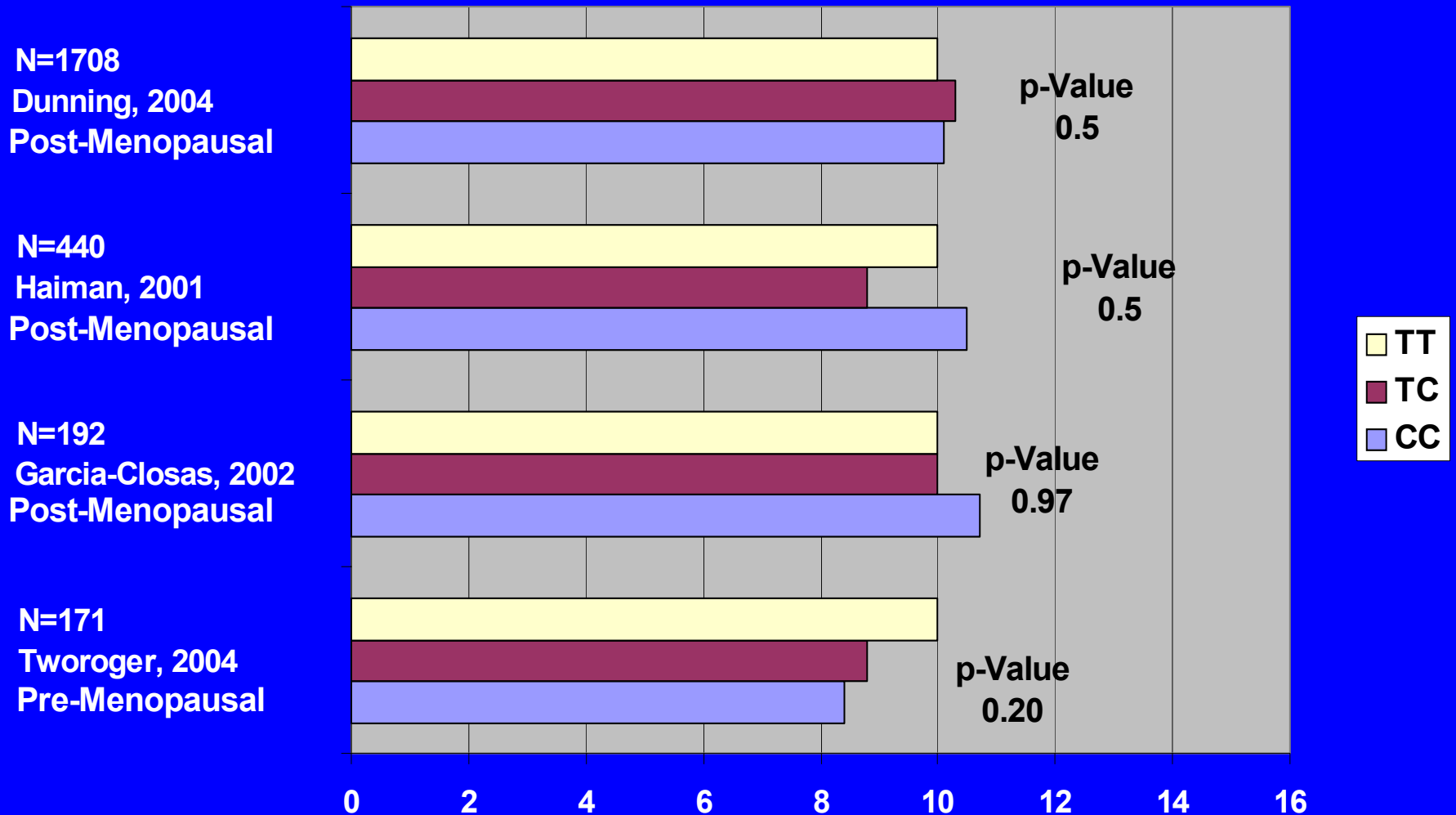
ESTROGEN BIOSYNTHESIS



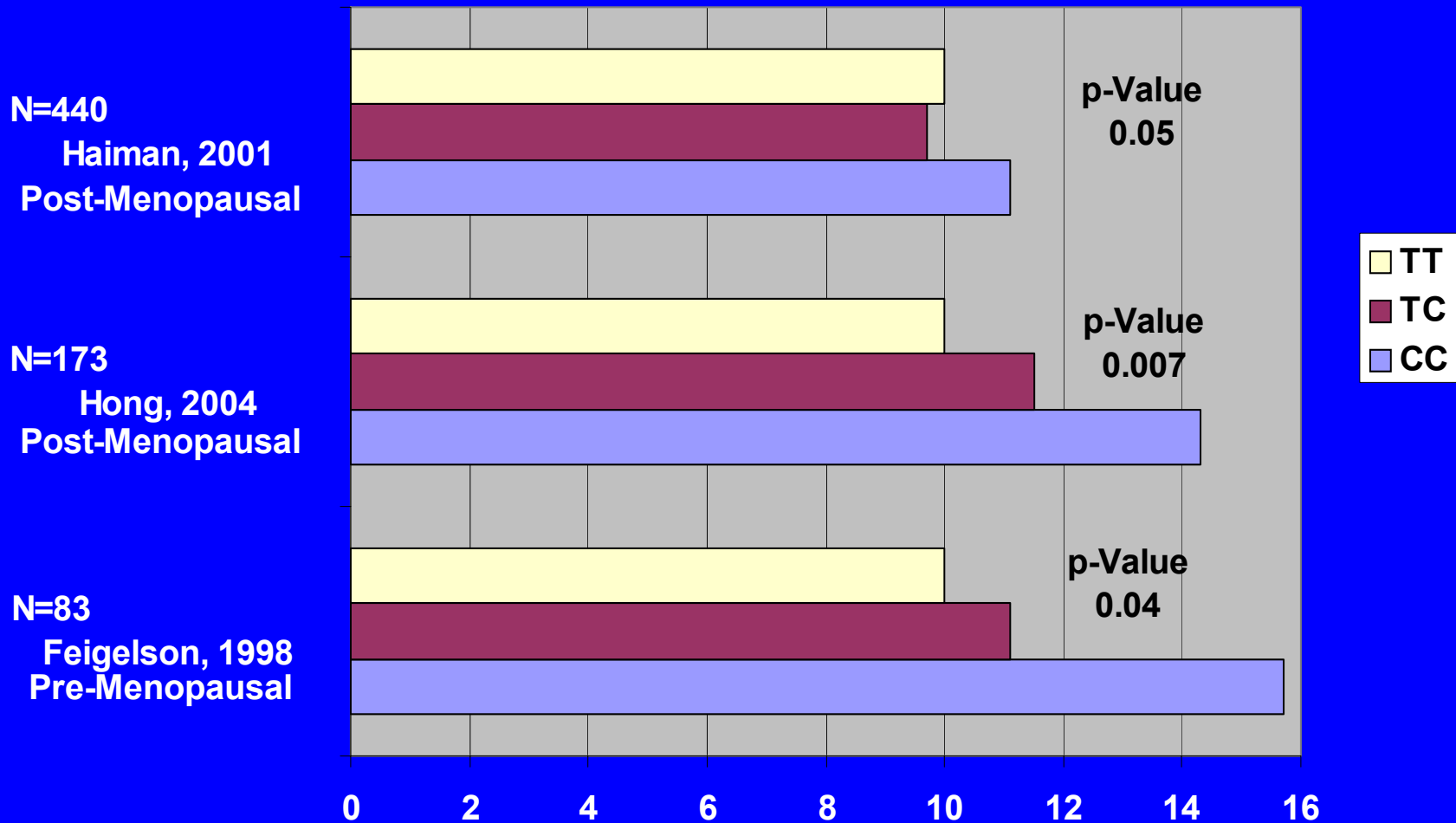
CYP17A1 GENOTYPE AND HORMONE LEVELS

- **CYP17A1 T-34C change in promoter region**
 - **No relationship with progesterone**
 - 4 studies, 7 comparisons
 - **No relationship with androgens**
 - 9 studies, 20 comparisons
 - **Most studies show no association of variant C allele with serum estrogen levels**
 - Out of 12 studies (22 comparisons), 3 showed the C allele related to higher levels of estrogens but rest did not

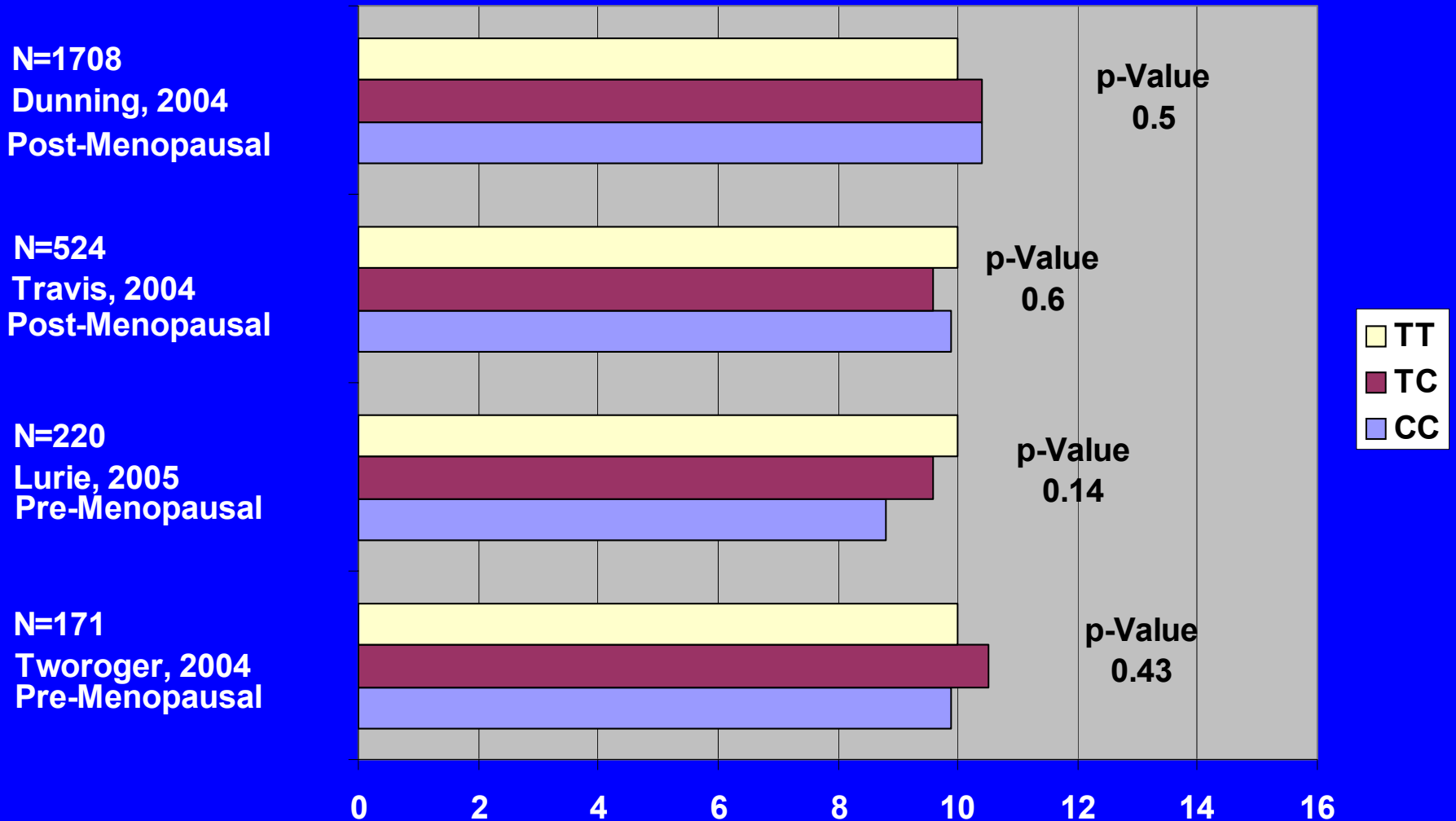
EXAMPLES: STUDIES OF CYP17A1 T-34C GENOTYPE AND SERUM ANDROGENS



POSITIVE STUDIES OF CYP17A1 T-34C GENOTYPE AND SERUM ESTROGENS



EXAMPLES: LATER STUDIES OF CYP17A1 T-34C GENOTYPE AND SERUM ESTROGENS



CYP17A1 T-34C GENOTYPE AND RISK OF ENDOMETRIAL CANCER

	Cases (429)	Controls (400)	Odds ratio* (95% CI)
TT	36%	31%	1
TC	50	52	0.75 (0.54-1.04)
CC	14	18	0.63 (0.40-0.99)

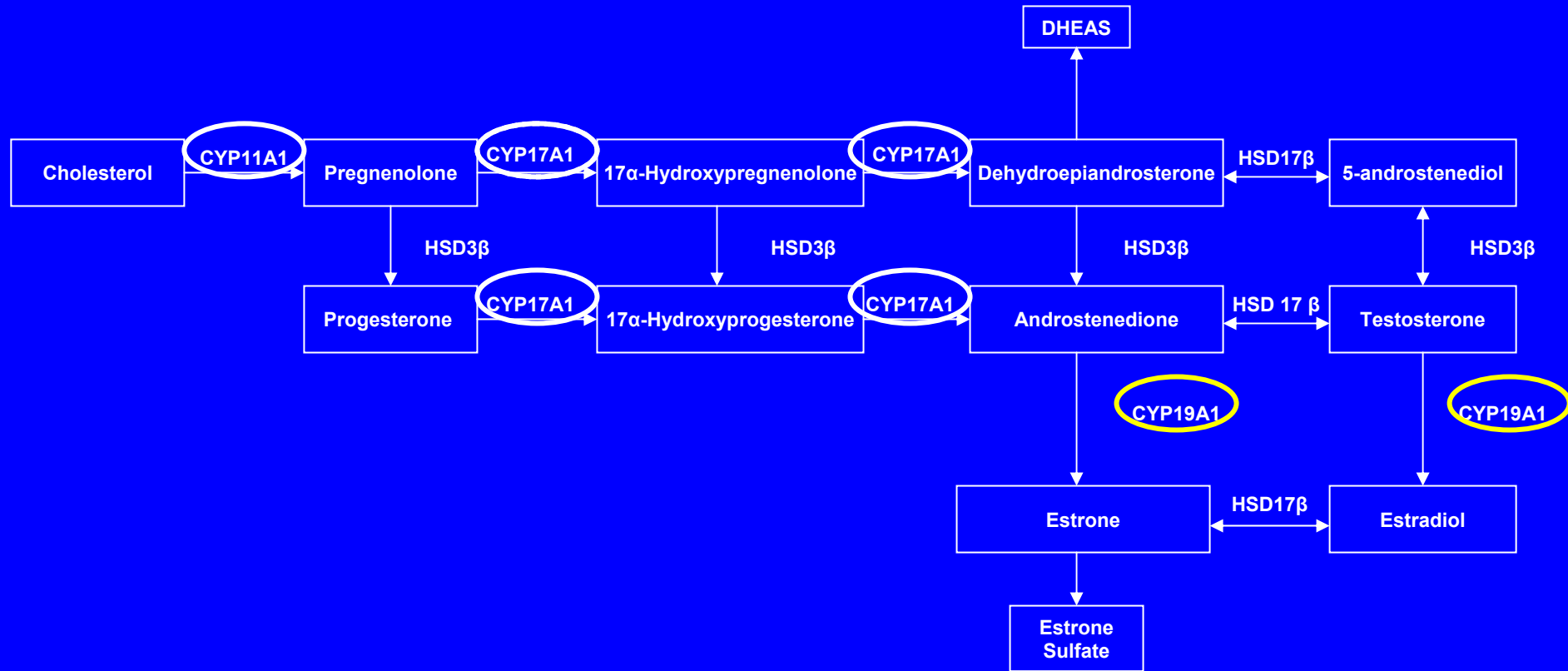
*adjusted for age, BMI, menopausal status, ERT use

CONCLUSIONS

CYP17A1

- **CYP17A1 T/C variant does not seem to be related to hormone levels**
- **But does appear to be related to risk**
 - C allele may be protective
- **Consistent with several small studies**

ESTROGEN BIOSYNTHESIS



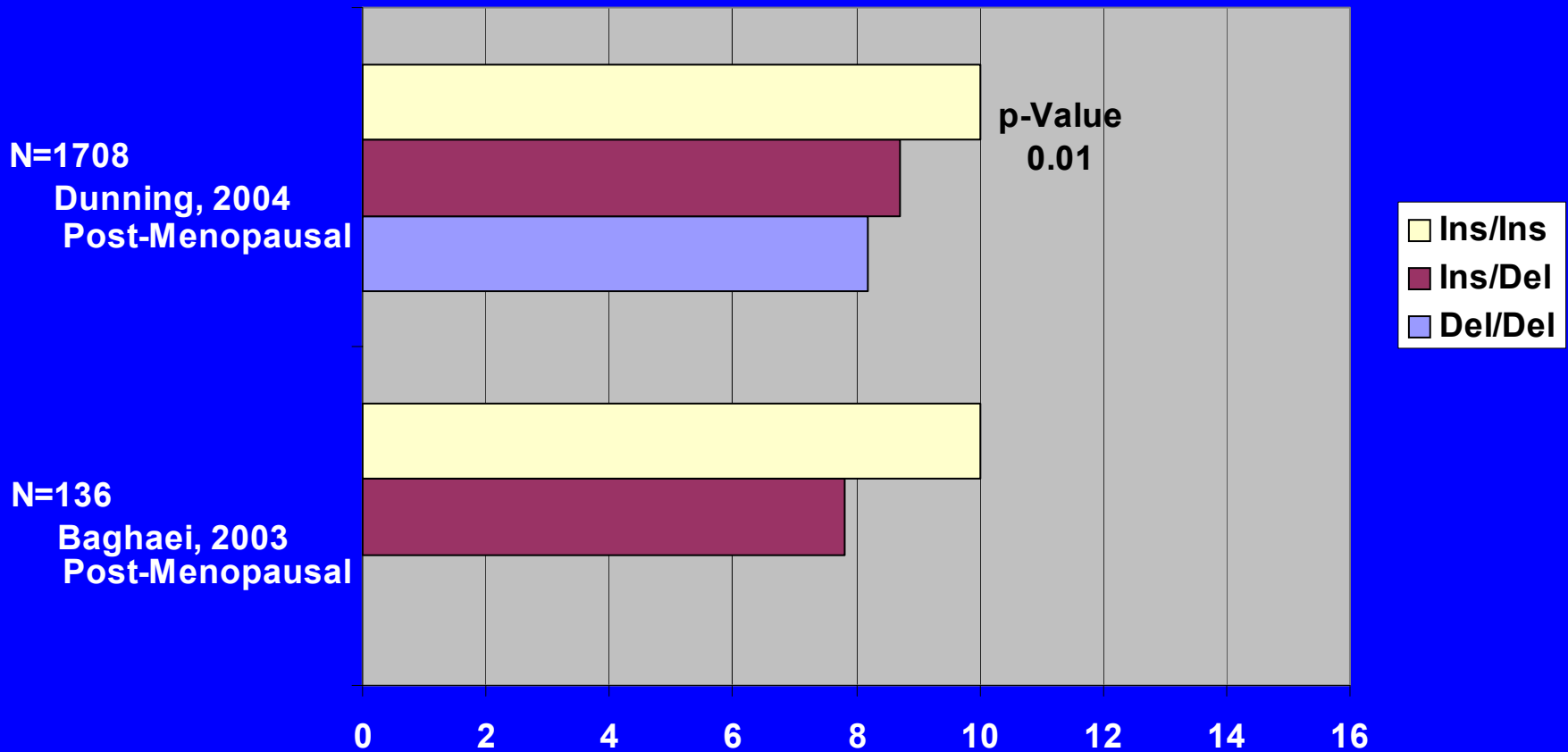
CYP19A1 GENOTYPES

- **aromatase converts androstenedione to estrone in adipose tissue, as well as converting testosterone to estradiol in ovarian granulosa cells.**
- **large area of this gene is in linkage disequilibrium; includes several variants:**
 - **tetranucleotide repeat [TTTA]_n (7 to 13)**
 - **3 base-pair deletion found only with 7 repeats**
 - **C/T change in exon 10 (5' UTR)**

CYP19A1 GENOTYPES AND HORMONE LEVELS

- **No consistent association of estrogens or androgens with these polymorphisms**
 - 12 studies, 69 comparisons
- **Fairly consistent findings that variants are associated with increased ratios of estrogens to androgens**
 - 6 studies, 11 comparisons

EXAMPLES: STUDIES OF CYP19A1 INS/DEL AND RATIO OF ESTRONE TO ANDROSTENEDIONE



CYP19A1 3 BASE PAIR INS/DEL AND RISK OF ENDOMETRIAL CANCER

	Cases (429)	Controls (401)	Odds ratio* (95% CI)
Ins/Ins	44%	44%	1
Ins/Del	48	43	1.15 (0.84-1.57)
Del/Del	8	13	0.48 (0.28-0.81)

*adjusted for age, BMI, menopausal status, ERT use

CYP19A1 TTTA_n GENOTYPE AND RISK OF ENDOMETRIAL CANCER

	Cases (428)	Controls (301)	Odds ratio* (95% CI)
7 / 7	27%	29%	1
7 / longer	50	47	1.0 (0.70-1.45)
Both longer	24	25	0.81 (0.54-1.22)

*adjusted for age, BMI, menopausal status, ERT use

CONCLUSIONS

CYP19A1

- **CYP19A1 variants in linked sites appear to be associated with conversion of androgens to estrogens**
- **These variants also appear to be associated with risk**
- **Consistent with other smaller studies**

SUMMARY

- **Relatively large study**
- **Collected extensive data on risk factors**
- **Confirmed importance of weight, other factors**
- **One of first studies to look at genetic risk factors for endometrial cancer**
- **Focused on genes in estrogen biosynthesis pathway**
- **Variants in CYP17A1 and CYP19A1 likely to affect risk**

NEXT STEPS

- **Diet data**
- **Genes in hormone metabolism pathway**
- **Investigate whether effects of genetic variants are stronger in certain subgroups of women**
- **Pool data from this and other ongoing studies for adequate power for gene-gene and subgroup analysis**
 - **E2C2 Consortium**

COLLABORATORS

- **NJDHSS**

- Tara Blando, Betsy Kohler, Kevin Masterson, Lisa Roche, Helen Weiss, Homer Wilcox

- **CINJ**

- Elisa Bandera, Dina Considine

- **MSKCC**

- Sharon Bayuga, Shameka Faulkner, Irene Orlow, Katie Pulick, Louise Salant, Camelia Sima, Robert Soslow, Michelle Sriprasert, Diana Tomassi, Ann Zauber
- Field staff: Silvia Brendel, June Kittredge, Mathilde Saxon, Elizabeth Ward, Doreen Wass, Kay Yoon