

# Welcome

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This is an online version of a lecture given by Dr Keith Merritt on gyn cancers. Its purpose is to help women become more aware of early symptoms, risk factors, screening strategies and the importance of knowing their family history of cancers. We hope that you will find this information helpful.

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If you do not have time for the entire presentation refer to the following table of contents. To navigate through the slides, right click on your mouse and then the slide of interest.

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- ❑ Vaginal cancer
- ❑ Vulvar cancer

# Glossary of Terms

- **Ovary-** the pelvic organ that contains and releases eggs for reproduction and secretes hormones such as estrogen, progesterone and testosterone. Each woman normally has two ovaries.
- **Fallopian Tube-** bilateral tubular structures with one end suspended over an ovary and the other end emptying into the uterine cavity. Its normal function is to capture an the egg released by the ovary, provide a space for fertilization of the egg by sperm and then transport that fertilized egg to the uterine cavity.
- **Uterus-** A woman's "womb". A pear shaped vessel with a muscular wall and a cavity lined with endometrium. The neck or constricted entry into this vessel is the cervix which protrudes into the vagina.

# Glossary of Terms

- **Cervix-** The constricted entry into or neck of the uterus. It protrudes into the top of the vagina and is the gateway for entry of sperm and exit pathway for menstrual flow. It is the part which must dilate during labor and birth. Its canal is lined with tall cells known as **glandular cells** which secrete a mucous-like fluid. Its outer vaginal part is coated with flat cells known as **squamous cells**. These two cell type meet on the outer face of the cervix. The line where these two cell types abut is known as the **transformation zone** and is the most common area for cervical dysplasia and cancer. This zone and the canal are the cervical parts that are swabbed during a pap smear.
- ~~**Vulva-** The mound-like tissue that is the woman's external genitals.~~







# Glossary of Terms

- **Endometrium-** The lining of the uterine cavity. During a normal 28 day menstrual cycle it thickens during the first 14 days in response to **estrogen** secreted by the ovary. This growth continues with the thickness increasing as long as estrogen exposure without progesterone continues. After midcycle ovulation, the ovary secretes **progesterone** in addition to continued estrogen secretion. This ‘tightens’ and organizes the endometrium in preparation for a fertilized egg to implant. If implantation does not occur, estrogen and progesterone secretion stop and the endometrium is shed creating the menstrual flow.
- **First degree relative-** parent or sibling
- **Second degree relative-** grandparents, aunts or uncles.

# Gyn Cancers



# Gyn Cancers

-  Ovarian
-  Uterine- endometrial  
- sarcoma
-  Fallopian Tube
-  Cervical
-  Vaginal
-  Vulvar





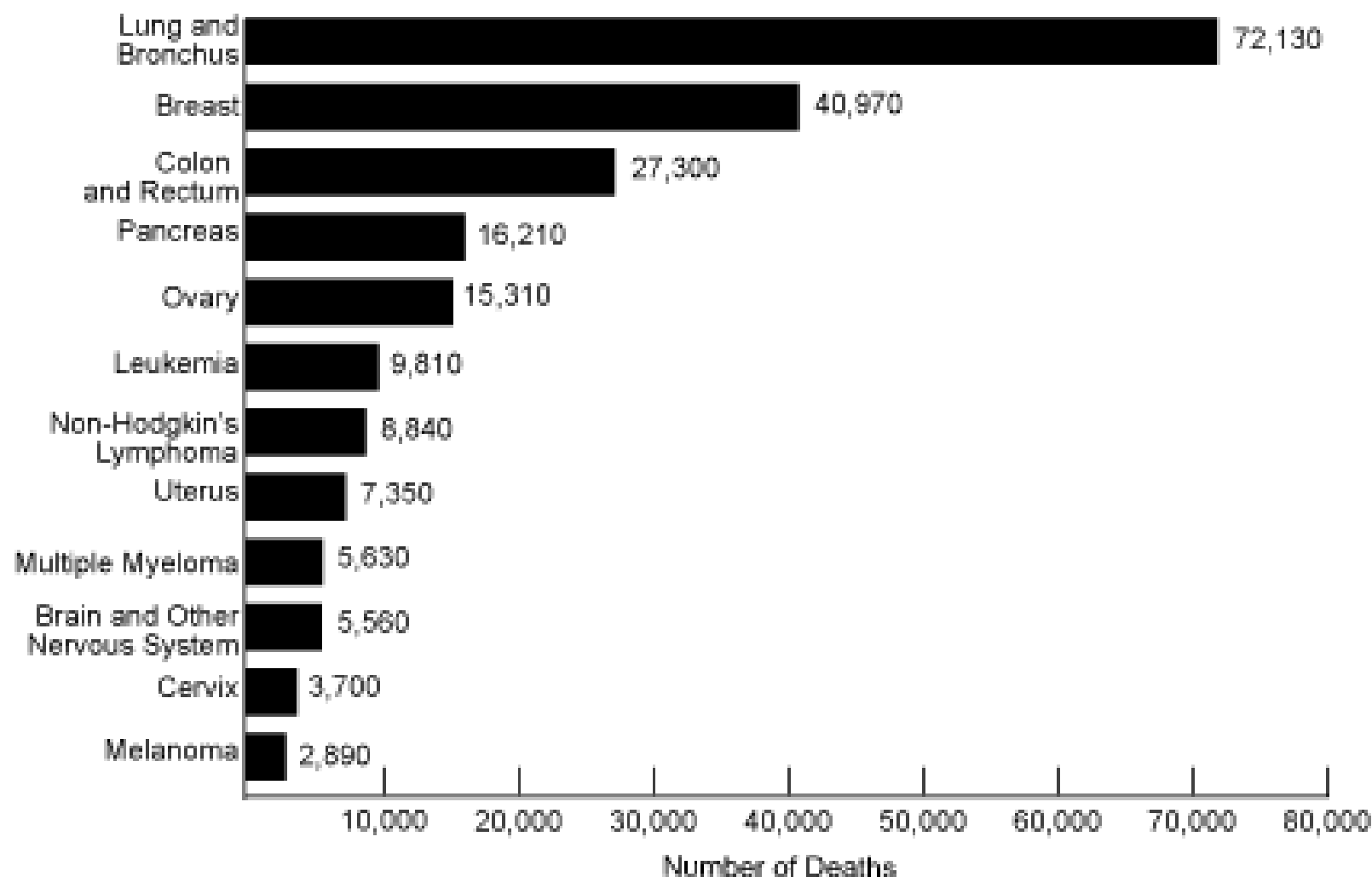
# First

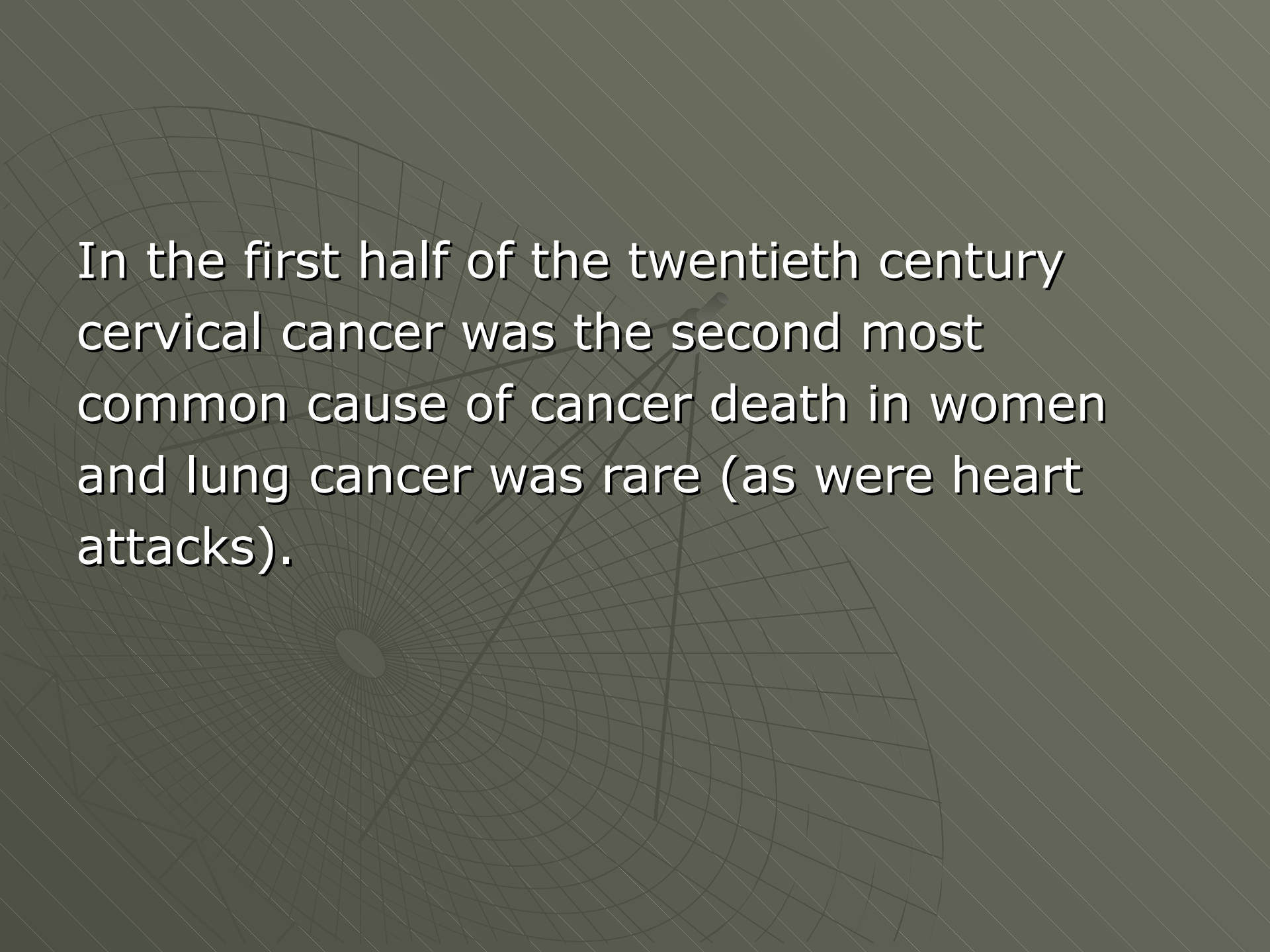
A little perspective



# Selected Causes of Cancer Deaths for Females, by Site, 2006 Estimates

Source: American Cancer Society





In the first half of the twentieth century cervical cancer was the second most common cause of cancer death in women and lung cancer was rare (as were heart attacks).

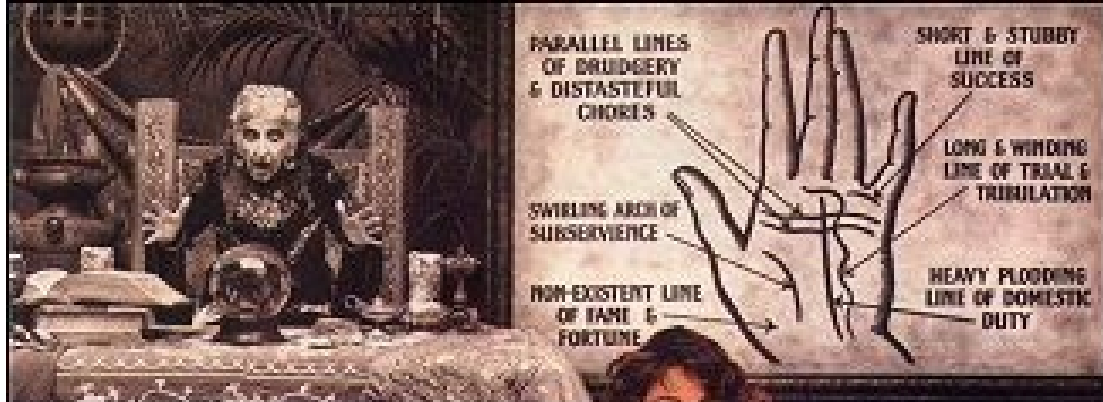
# Then two things changed

- ◆ Pap smears screening began in the 1940's
- ◆ Tobacco companies discovered that they could effectively market cigarettes to women as women began demanding equal treatment.

# CAMEL

PLEASURE  
TO  
BURN





*Virginia Slims remembers when a woman's future was*

*in the palm of her hand.*

You've come  
a long way, baby.

# VIRGINIA SLIMS

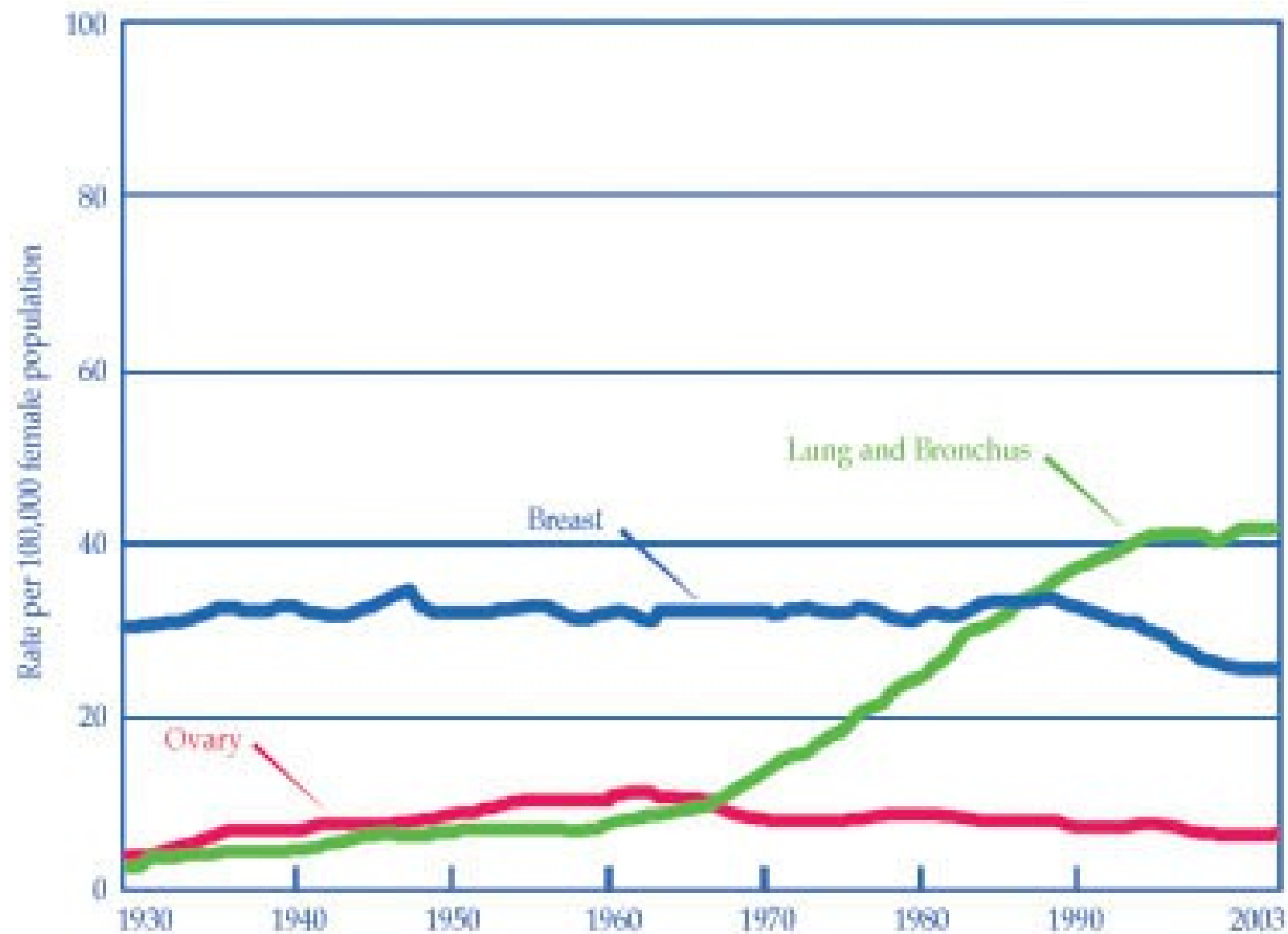
© Philip Morris Inc. 1997



*Also available in ZIP\**

**SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.**

Lights: 8 mg "tar," 0.8 mg nicotine  
100's: 14 mg "tar," 0.9 mg nicotine av. per  
cigarette, FTC Report Feb 95. 100's: 14 mg "tar,"  
1.0 mg nicotine av. per cigarette by FTC method.



# Ovarian Cancer



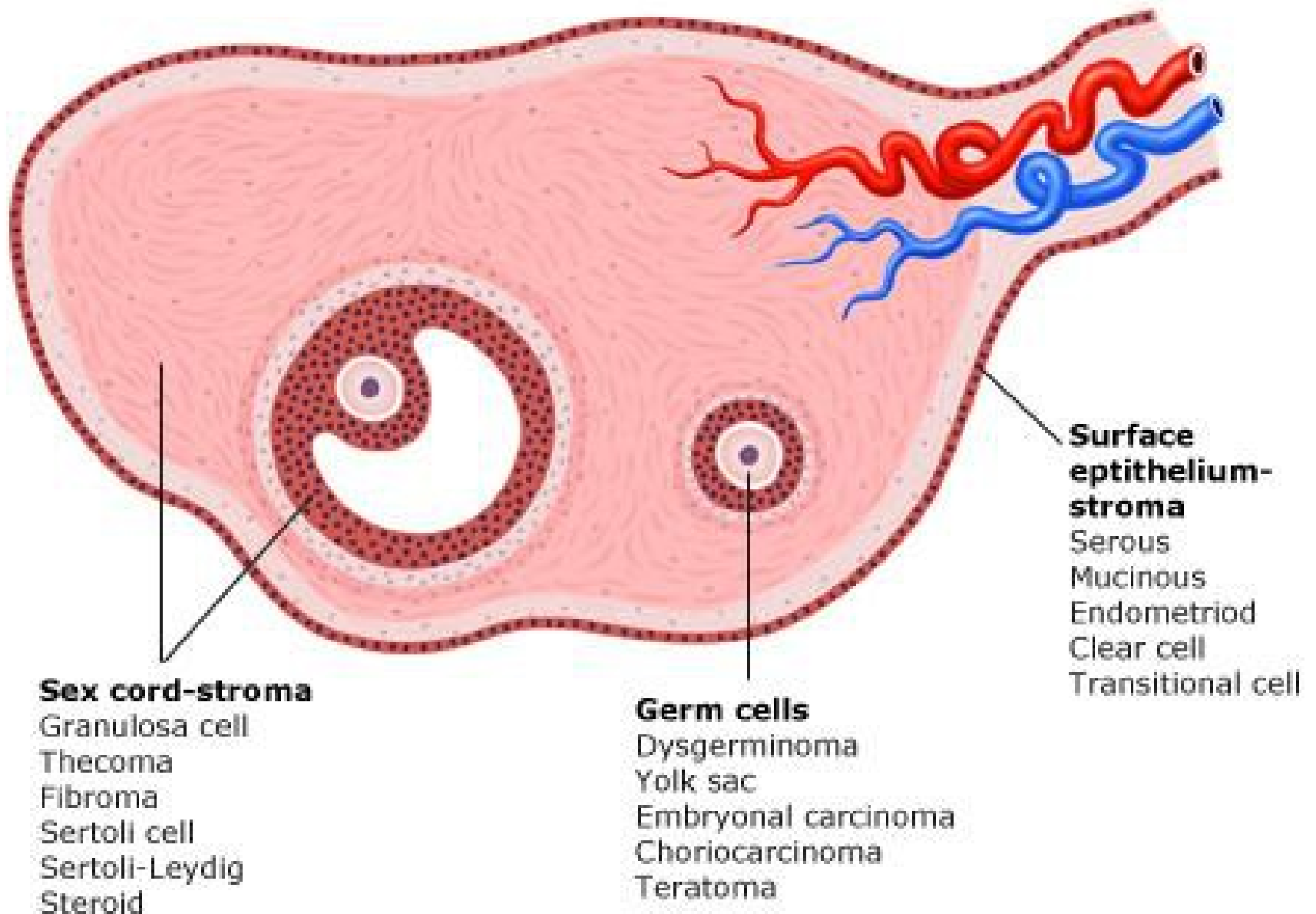


# Ovarian Cancer

- 2<sup>nd</sup> most common gyn cancer
  - 21,000 new cases per year
- Most deadly gyn cancer
  - 15,000 deaths per year
- No effective method of screening
- 70% are advanced at time of diagnosis

# 5 Year Survival

- 80-90% when confined to ovary
- 3-80% when spread outside of ovary
  - varies with degree of spread & type



Any cell type within the ovary may develop a cancer meaning the ovary may develop a very wide variety of cancers.

# The Ovary has three basic parts

## **Surface epithelium**

- A thin membrane covering not only the ovary but also every other structure and organ in the abdomen and pelvis.
- This membrane must rupture and be repaired during each cycle when an egg is released. The cells in this structure are the most common source of ovarian cancers.

## **Germ Cells**

- The eggs. Structures formed from a fertilized egg include the membranes that surround a pregnancy
- The most common tumors formed by this structure are dermoid cysts.

## **Sex-cord Stroma**

- A matrix of cells that contain the egg follicles and that provide support for the developing eggs.
- The source of hormone secretion by the ovaries meaning that associated tumors may secrete hormones such as estrogen.

# Age at Diagnosis

- Mean age at diagnosis: mid 50's to 60's
  - borderline tumors: mid- 40's
  - 7 years earlier for hereditary
- Incidence increases until 80 years old
  - then declines



# Risk That an Ovarian Mass is Cancer

- Premenopausal: 6-11%
- Postmenopausal: 29-35%

# Ovarian Cancer Symptoms

- May occur at early stage
  - on average 6 months before diagnosis
- Large majority do not have cancer
- Consider if symptom is new onset or persistent & occurs daily

# Ovarian Cancer Symptoms

- Bloating
- Increased abdominal girth
- Urinary urgency or frequency
- Difficulty eating
- Feeling full early
- Pelvic or abdominal pain
- Leg pain, weakness or numbness

# Debate Over Origin of Ovarian Cancer

Begins at a single point and spreads

VS

Begins at multiple points  
(screening pointless)

# Family History

- Strongest known risk factor
- In women who develop ovarian cancer
  - 10-15% have a family history  
(that is- 85-90% do not)

# Risk Factors

- Genetic
- Lifestyle

# BRCA 1 & 2 Mutations

The most commonly identified ovarian genetic cancer syndromes

Also increases the risk of other cancers

Autosomal dominant inheritance  
(all children will be affected)

CANCER	BRCA1 Risk (Lifetime)	BRCA2 Risk (Lifetime)	General Population
Breast Ca	47-66%	40-57%	12.5%
Contralateral Breast Ca	65%	50%	0.5-1%
Ovarian Ca	35-46%	13-23%	1.8%
Colon Ca	None to very slight inc	None to very slight inc	5%
Prostate Ca	Increased (unknown)	35-40%	15%
Male Breast Cancer	0.2-2.8%	3.2-12%	0.1%
Pancreatic C	<10%	<10%	1.3%



# Lynch II Syndrome

- Hereditary nonpolyposis colorectal cancer  
-HNPCC
- 1% of ovarian cancers
- Lifetime risk
  - 9-12% for ovarian cancer
  - 22-60% for endometrial cancer

# Modifiable Risk Factors for ovarian cancer

- Nulligravity (no pregnancies) is the greatest known risk factor
- Risk reduced with
  - oral contraceptive use, progesterone use
  - large # of children
  - breast feeding
  - tubal ligation

# Modifiable Risk Factors for ovarian cancer

Mounting evidence that the most aggressive form of ovarian cancer originates in the fallopian tubes

- Consider removal of fallopian tubes instead of tubal ligation
- Remove tubes if having hysterectomy

# Risk of Ovarian Cancer

- Increases with # of reproductive years
- Decreased with oral contraceptive use
  - 25% decrease in risk for any use
  - 50% reduction for 5 years use
  - protection persists for up to 30 years

# Other Risk Factors

- Endometriosis- younger, better survival
- Talc- weak, may be due to asbestos
- Cigarettes- increase in mucinous only
- Diet- effect not clear
- Exercise- slight protection with high levels
- Obesity- slight increase in risk

	Relative risk ovarian ca	Lifetime probability %
Family ovary ca syndrome	unknown	30-50%
2-3 relatives w ovarian ca (1 <sup>st</sup> or 2 <sup>nd</sup> degree relative)	4.6	5% (15% if 1 <sup>st</sup> degree relative)
1 relative- 1 <sup>st</sup> or 2 <sup>nd</sup> degree	3.1	3.7% (5% if 1 <sup>st</sup> degree relative)
<b>No risk factors</b>	<b>1.0</b>	<b>1.8%</b>
Past oral contraceptive use	0.65	0.8%
Past pregnancy	0.5	0.6%
Infertility	2.8	
No deliveries	1.6	
Past breast feeding	0.8	
Tubal ligation	0.6	

# Incidence of ovarian cancer varies with race and with location

- Western countries 3-7X Japan
- Japanese Americans approach US rate
- Caucasians 1.5X African-Americans

# Screening for Ovarian Cancer

- To date, no screening strategy effective in reducing ovarian cancer deaths
- Trials now in progress
- No effective blood test yet
- Current recommendation- screen high risk



# High Risk Patients

- Age 25-35: every six months
  - transvaginal ultrasound
  - Ca-125
- Oral contraceptives may not help
- Surgical removal of ovaries after age 35

# Endometrial Cancer



# Endometrial Cancer

- Most common gyn cancer in the US
- 6% of all cancers in women
- 2.5% lifetime risk
- Usually diagnosed early due to bleeding

# 5 year survivals

- Localized- 95%  
(70% of cases)
- Regional- 67%
- Metastatic- 23%

# Endometrial Cancer

- More common in whites
- However mortality higher in blacks & Hispanics  
(7% vs 4%)

# Has two forms

Type I- 80% of cases

Type II

# Type I

- Due to excessive estrogen stimulation
- Often associated with hyperplasia



# Type1 Risk Factors

- Obesity
- No pregnancies
- Diabetes
- Hypertension
- Prolonged unopposed estrogen exposure



# Type II

- Not associated with estrogen
  - no preceding hyperplasia
- Tend to be higher grade tumors
  - worse outcomes
- No real known risk factors
- Those affected tend to be
  - older
  - have had multiple children

# Sources of Excessive Estrogen

- Unopposed estrogen replacement
- Tamoxifen
- Obesity
- Polycystic ovary syndrome  
-chronic inability to ovulate
- Estrogen secreting tumors

# Unopposed Estrogen Replacement

- One year of unopposed estrogen
  - hyperplasia found in 20-50%
- Absolute risks of endometrial cancer
  - in general population- 1/1000
  - on unopposed estrogen- 1/100

# Obesity

- Increases estrogen exposure  
-fat converts testosterone to estrogen
- Risk increases with increasing weight
- Greater weight increases risk of death from endometrial cancer

# 25% occur in premenopausal women

- 5-10% of these are less than 40 yo
- Reported in women less than 30 yo
- Probability of disease if less than 39 yo: 0.05%



# Characteristics of Younger Women with Endometrial Cancer

- 89% are type I (high estrogen exposure)
- 59% are obese
- 44% have had no pregnancies
- 23% are hypertensive and/or diabetic
- 19% had concurrent ovarian cancer

# Normal Weight Premenopausal Women with Endometrial Cancer

Are more likely to

- Be subfertile
- Have had no pregnancies
- Have irregular periods
- Have a concurrent ovarian cancer
- Have Lynch Syndrome (9%)

# Other Risk Factors

- Slightly higher risk in 1<sup>st</sup> degree relatives
- **Lynch Syndrome**
  - consider if family history of colon cancer
  - breast and ovarian cancers precede colon cancer in 50% (by 11 & 5 years)
- Prior breast cancer- similar risk factors



# No Clear Associations

- Diet
- Alcohol
- Early menarche or late menopause
- Level of physical activity

# Protective Factors

## Birth Control Pills

- 50-80% reduction in risk
- 12 month use decreases risk by 40%
- Protective effect lasts at least 15 years

## Hormone Replacement Therapy

Smoking- seen only with postmenopausal

# Clinical Presentation

- Bleeding in 90%
- If postmenopausal- just one drop of blood
  - 5-20% will have endometrial cancer
  - risk increases with age
  - risk not related to amount of bleeding

# Abnormal Premenopausal Bleeding

Should also have a biopsy- especially if

- Obese
- Diabetic
- Hypertensive
- No pregnancies
- Chronic lack of ovulation
- Prior tamoxifen use

# Abnormal Premenopausal Bleeding

Risk of endometrial cancer increases with either family or personal history of

- Breast cancer
- Ovarian cancer
- Colon cancer
- Endometrial cancer
- Endometrial hyperplasia



# Diagnosis

- Office biopsy
- Ultrasound
- Sonohystogram
- Hysteroscopy

# Screening

Only recommended in women with possible Lynch Syndrome

- Women known to carry the mutation
- Family member with the mutation
- Autosomal dominant inheritance of colon cancer without identified gene

# Who to Test for Lynch Syndrome

Endometrial cancer before age 50 plus at least one 1<sup>st</sup> degree relative with a related cancer

- Breast

- Ovarian

- Colon



# Uterine Sarcoma



# Uterine Sarcoma

- May arise from either the lining of the uterine cavity or the wall of the uterus
- Much more aggressive with much worse survival than endometrial cancer
- Several types
- Rare- 3.6/100,000 women

# Uterine Sarcoma

- 2X more common in African Americans
- Average age at diagnosis- 60 years
- Risk may be increased with
  - prior pelvic radiation therapy
  - prior tamoxifen use (weak association)

# Clinical Presentation

- Bleeding- especially if foul smelling
- Pelvic pressure, urinary frequency
- Constipation
- Enlarged uterus (may be normal size)

# Cannot distinguish between fibroid and sarcoma by

- Exam
- Ultrasound
- History

# Suspect

In postmenopausal

- If presumed fibroids bothersome enough to consider hysterectomy
  - 1 to 2% will have a sarcoma

In premenopausal

- Bleeding disproportionate to size of uterus
- Significant pain

# Diagnosis

- Requires either removal or biopsy of mass
- Office biopsy is not adequate
- U/S, MRI, CT scan are not adequate

# Fallopian Tube Cancer





# Fallopian Tube Cancer

- Very rare
- Annual incidence 4.1/1,000,000 women
- More often due to metastatic spread from
  - breast, ovary, uterine, colon cancers
- Shares same risk factors as ovarian
  - BRCA mutation

# Clinical Presentation

- Often in 50's and 60's
- Blood tinged discharge in 50-60%
- Pelvic pain in 30-50%
- Pelvic mass in 12-60%

# Common Presentation

- Discharge and bleeding with negative endometrial biopsy
- 10% have abnormal cells on pap with negative cervical & endometrial biopsies

# Diagnosis

- Requires removal of the fallopian tube
- Ca-125 is usually elevated
- Mass often seen on imaging

# Cervical Cancer



# Cervical Cancer

- Sexually transmitted disease
- Human papilloma virus (HPV)
- Over 100 strains of HPV
  - 40 known to infect genital surfaces

# HPV Infection

- Affects majority of sexually active humans
  - majority are low risk HPV (cleared easily)
- High risk strains more likely to persist & progress to dysplasia then to cancer
- 5-20 years between infection and cancer

# HPV Infection

- There are fifteen high risk strains
- 70% of cases caused by strains 16 & 18
- Thought to interfere with p53 gene  
-cancer protection



# Two types of Cervical Cancer

- Squamous cell cancer
  - most common
- Adenocarcinoma
  - incidence increasing

# Symptoms

- Often asymptomatic when early
- Abnormal bleeding
- Bleeding after intercourse
- Discharge- persistent, abnormal

# When advanced

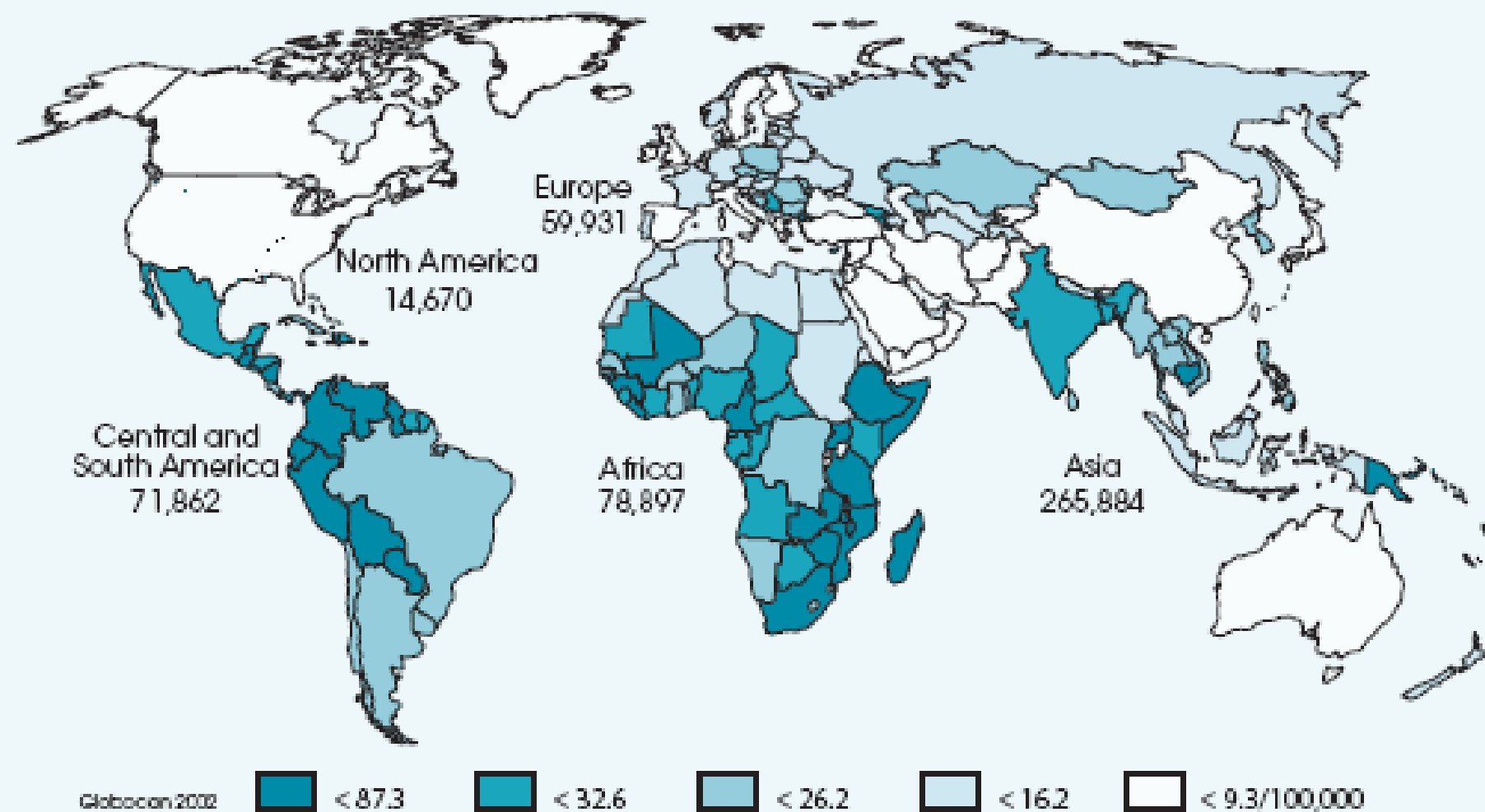
- Pelvic or back pain
  - may radiate along outer sides of legs
- Bowel or urinary symptoms
  - pressure & frequency
  - blood in urine or stool

# Risk Factors

- Early age of 1<sup>st</sup> intercourse
- Multiple partners
- High risk partner
- STD's
- Smoking
- Large number of children
- Immunosuppression
- Low socioeconomic class
- Prolonged use of oral contraceptives
- Uncircumcised partner

- Still causes large number of cancer deaths in countries without adequate screening
  - 1.5% risk of death before 65 yo
- More common in minorities

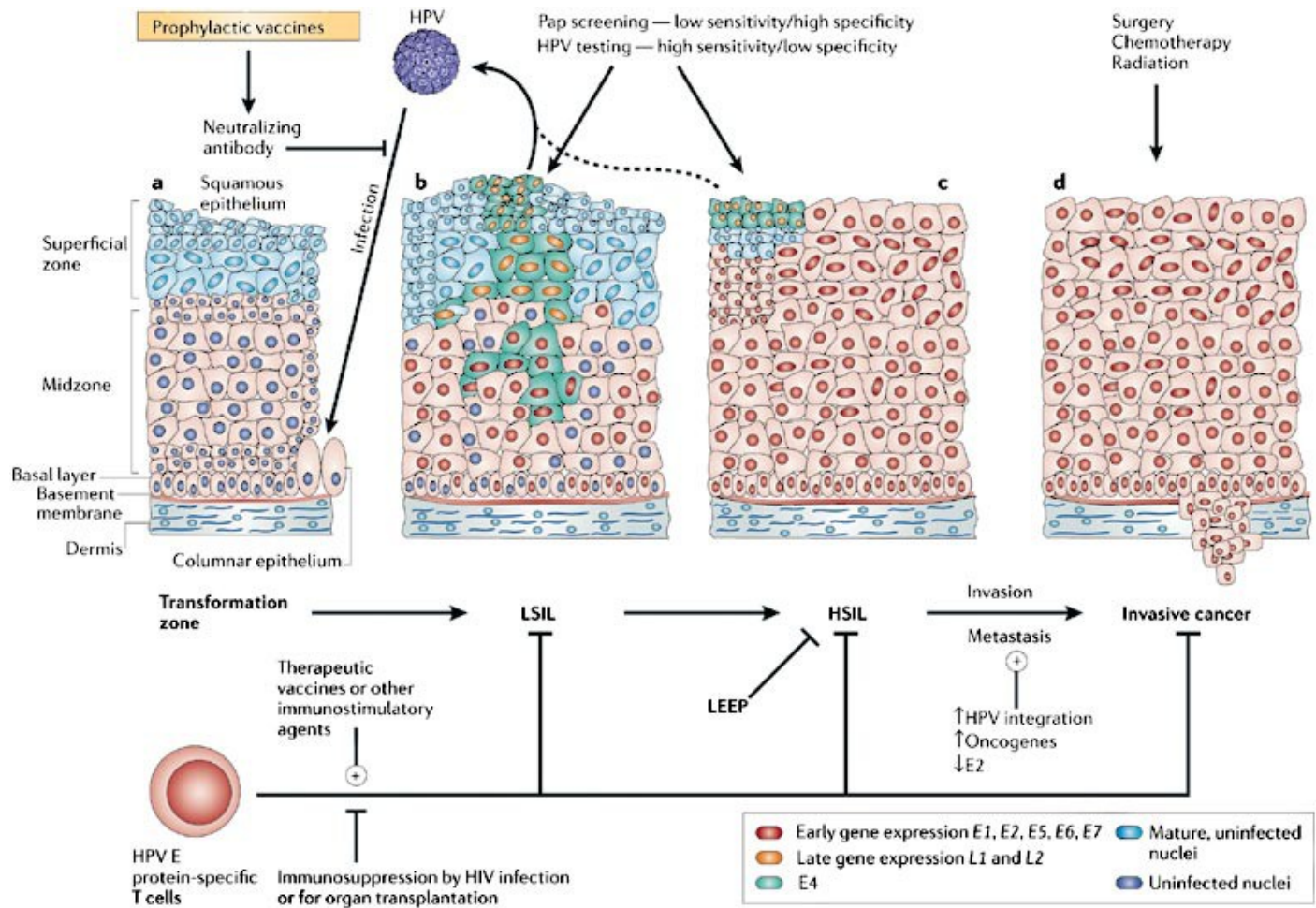
# Figure 1. Estimated number of cases and incidence of cervical cancer



Source: Ferlay et al.<sup>2</sup>

# Cervical Cancer Prevention

- Don't ever have sex (good luck with that)
- Gardasil
- Condoms
- Pap smears
- HPV testing



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 Nature Reviews | Cancer

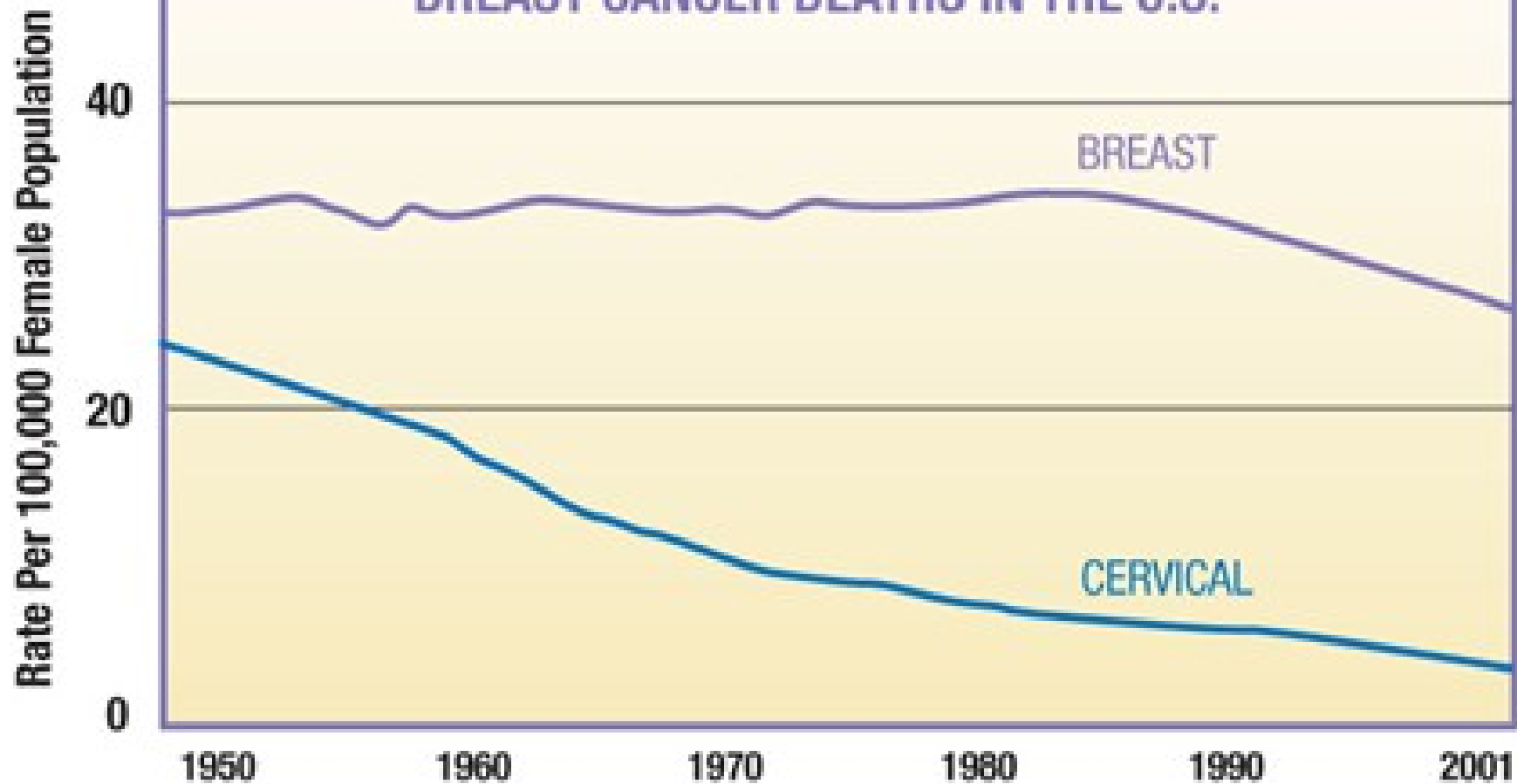
Roden and Wu *Nature Reviews Cancer* 6, 753–763 (October 2006) | doi:10.1038/nrc1973



# Pap Smears

- One of the few truly successful screening tests in medicine
- Reduced cervical cancer from 2<sup>nd</sup> to 13<sup>th</sup> most common cause of female cancer death
- Dr George Papanicolaou  
(Γεώργιος Παπανικολάου)

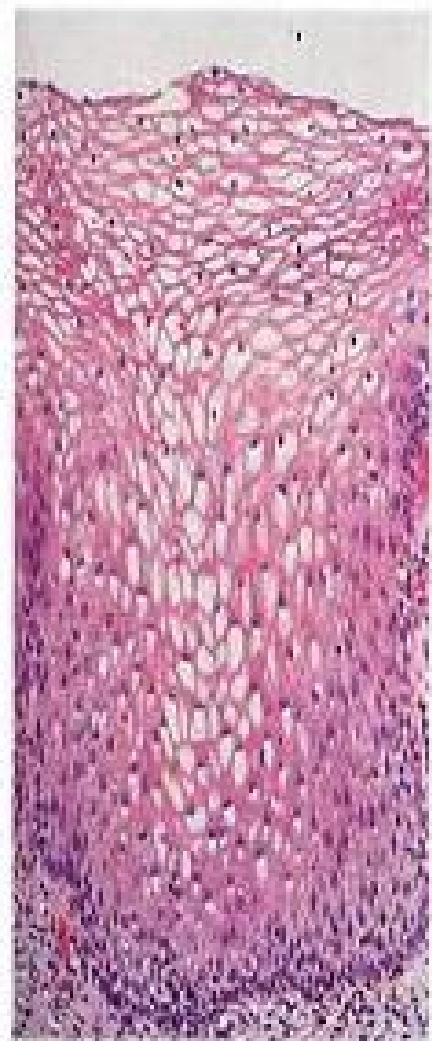
## BREAST CANCER DEATHS IN THE U.S.



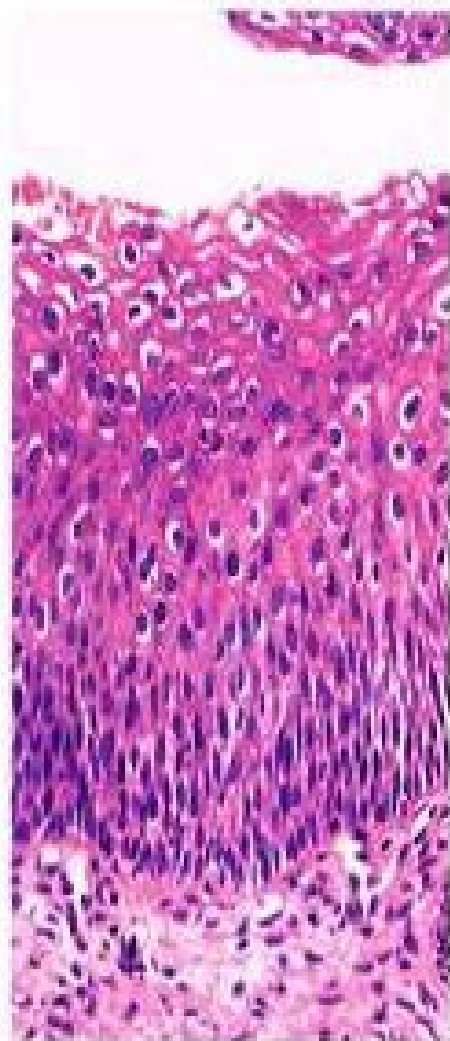
Source: American Cancer Society, Surveillance Research 2005

# Pap Smears

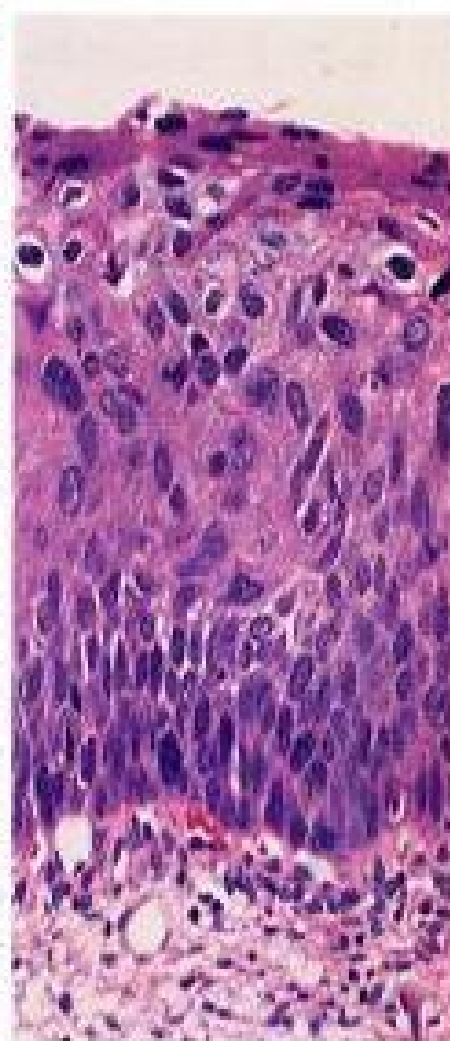
- Purpose is not to diagnose cancer
  - not reliable if cancer is suspected
- Purpose is to find dysplasia
  - precancerous changes
  - untreated, 2-70% progress to cancer



Normal



CIN I



CIN II



CIN III

# When to Begin Pap Smears

- Adolescents: 3 years after 1<sup>st</sup> intercourse
- When 20 years old

(HPV screening not recommended if  $< 30$ )

# HPV Testing

- May offer when 30 years old
  - combine with pap smear
  - if both are negative, repeat both in 3 yrs  
(does not apply if HIV +)
- Follow-up to low level abnormality on pap smear (ASCUS)
- Still needs annual exam

# When to Stop Pap Smears

- After hysterectomy if no prior dysplasia
- After 65-70 yo if
  - no prior dysplasia
  - no immunosuppression (HIV)
  - no new sexual partners
- **All women still need annual exam**

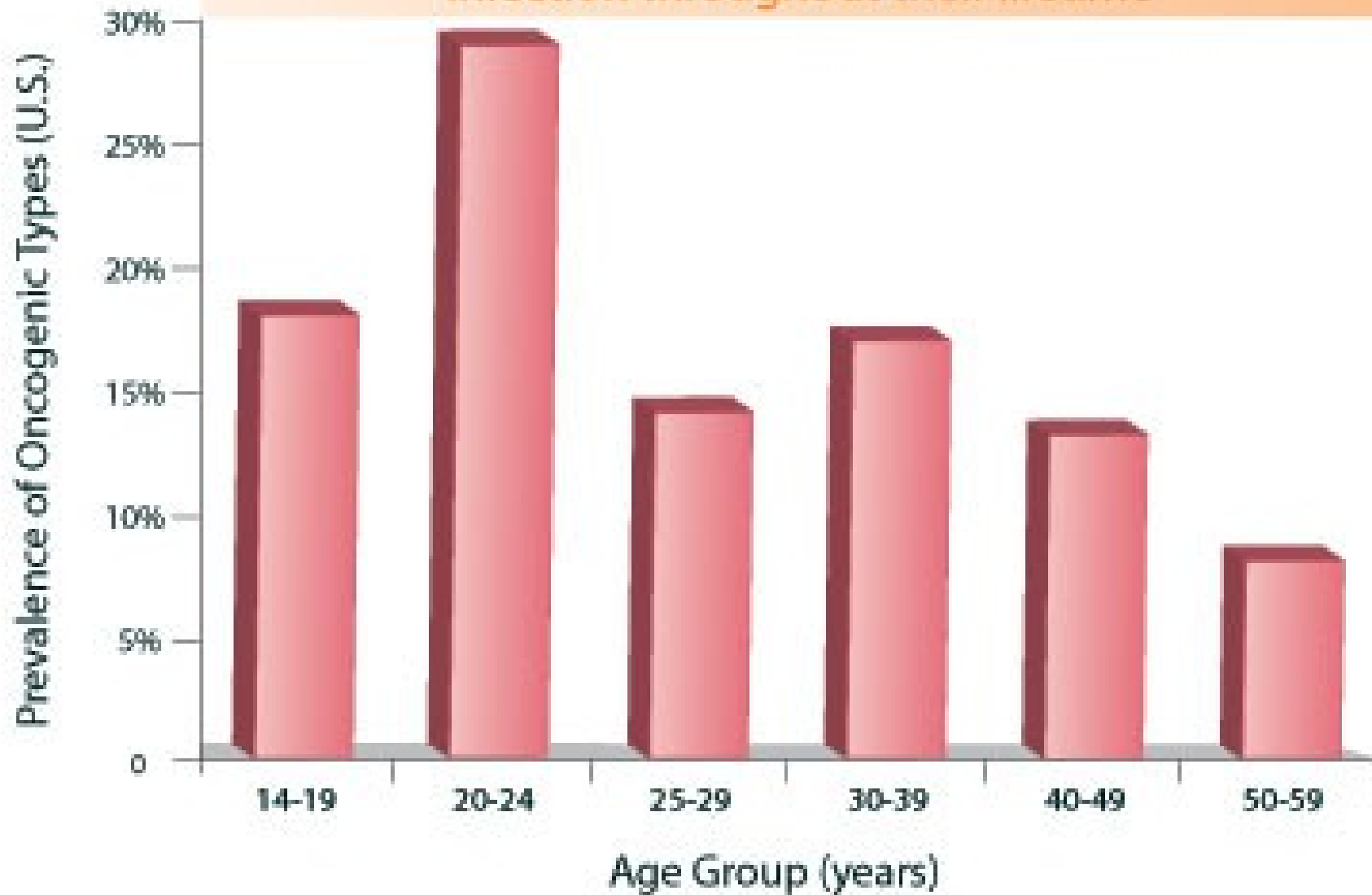
# Cervical cancer incidence varies with age

- Average age at diagnosis- 47 years
- Incidence at < 20 years: 0/100,000/yr

20-24	1.7
40-49	16.5
- 10% are > 75 years old



Patients remain at risk for oncogenic infection throughout their lifetime



# Vaginal Cancer



# Vaginal Cancer

- Squamous cell- 85% of cases
- Adenocarcinoma- all of cases in < 20 yo's
- Sarcoma- vaginal mass in childhood
- Melanoma- seen only in Caucasians

# Squamous Cell Vaginal Cancer

- Caused by HPV
- Much less common than cervical cancer
- Mean age at diagnosis- 60 years  
-however can occur in 20's
- Ulcer, mass, erosion

# Vaginal Melanoma

- ▶ Mean age at diagnosis- 58 years
- ▶ Black, brown, blue or skin color
- ▶ Biopsy every new
  - pigmented area
  - lump

# Vulvar Cancer



# Vulvar Cancer

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- Majority are postmenopausal
  - mean age has declined from 69 to 55 years
- HPV causes 60% of cases
  - strains 16 & 33
- Chronic inflammation causes 40%
- Preceded by dysplasia
  - treatment prevents cancer

# Risk Factors

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- Cigarette smoking
- Vulvar dystrophy (lichen sclerosis)
- Immunodeficiency (HIV)
- HPV infection
- Northern European heritage
- History of cervical dysplasia or cancer



# Symptoms

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- Mass, plaque, ulcer
- Itching
- Bleeding, discharge- usually advanced
- Lump in groin- usually advanced

Synchronous malignancy is present in 22%  
-most commonly cervical

# In Summary



# Lifestyle is important

- Protected sex- insist on condom use
- Know your partners sexual history
- Healthy diet is extremely important
  - vegetables, fruit
  - limit sugar, processed & refined foods
  - pasture raised meat
- Keep your weight under control
- Don't smoke

# Remember

- Get your pap smears
- Have an annual exam
- Know your family history
- **If you are trying to decide if you should call your doctor, call!!!!!!**

# Report any

- Changes in bowel movements
- Urinary symptoms
- Increase in waist size
- Weakness or numbness in legs
- New onset pelvic or back pain
- Abnormal bleeding or discharge
- Lumps or scaling
- Persistent localized itching



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