

Estrogen, Progestins and Risk of Breast and Ovarian Cancer

Hormonal Chemoprevention in Young Women

Northern Indiana Oncology Society

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Increased Cell Division

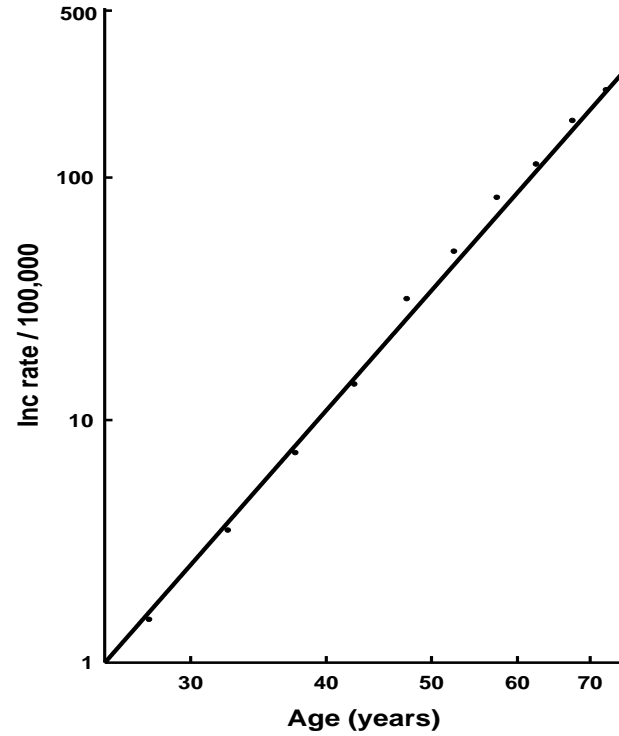
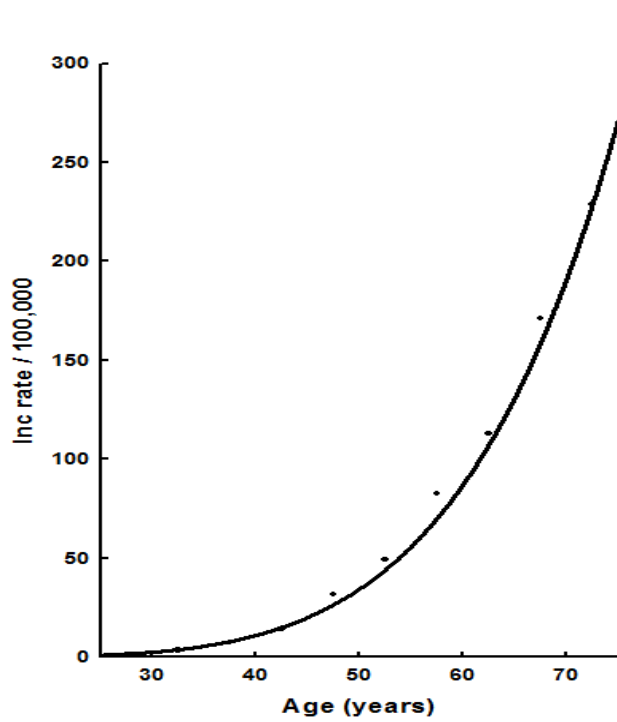
Early long-lasting - age at menarche

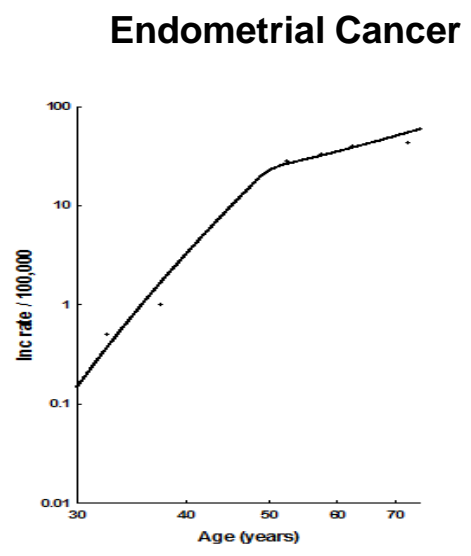
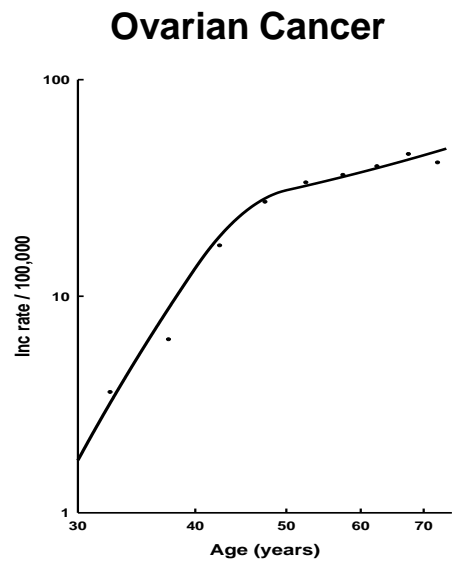
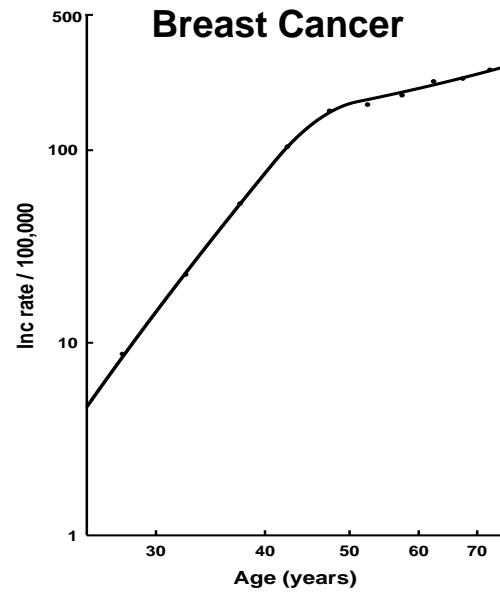
Late - age at menopause; SERMS

Differentiation

Pregnancy effects on breast cancer risk

Colorectal Cancer





Endometrial Cancer

Late age at menopause ↑

Obesity ↑

Parity ↓

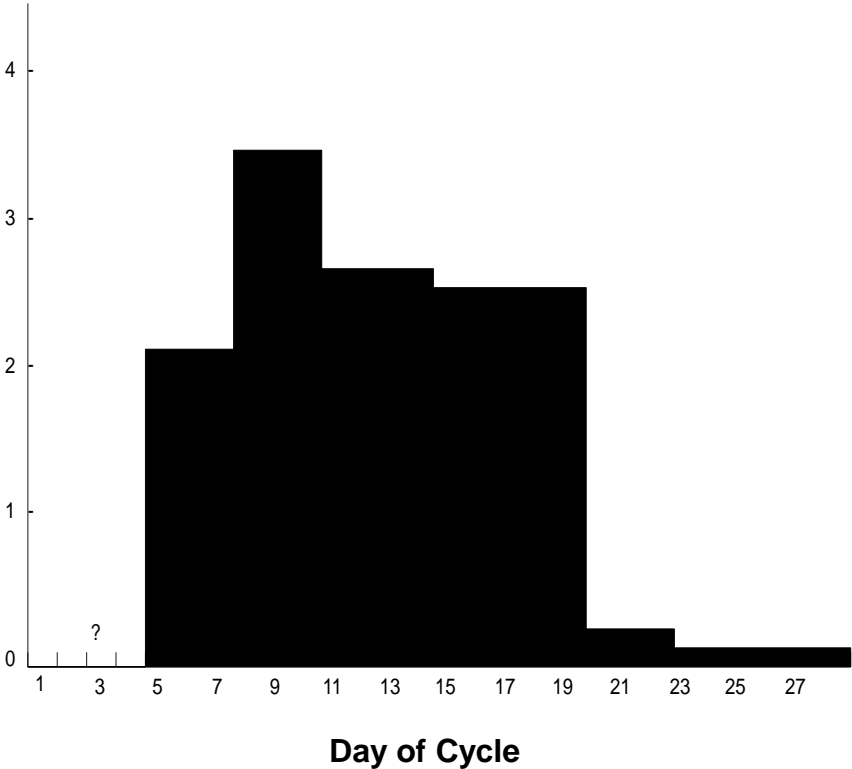
Menopausal estrogen therapy (ET) ↑

Menopausal estrogen-progestin therapy (EPT) ↑ ↓

Oral contraceptives (OCs) ↓

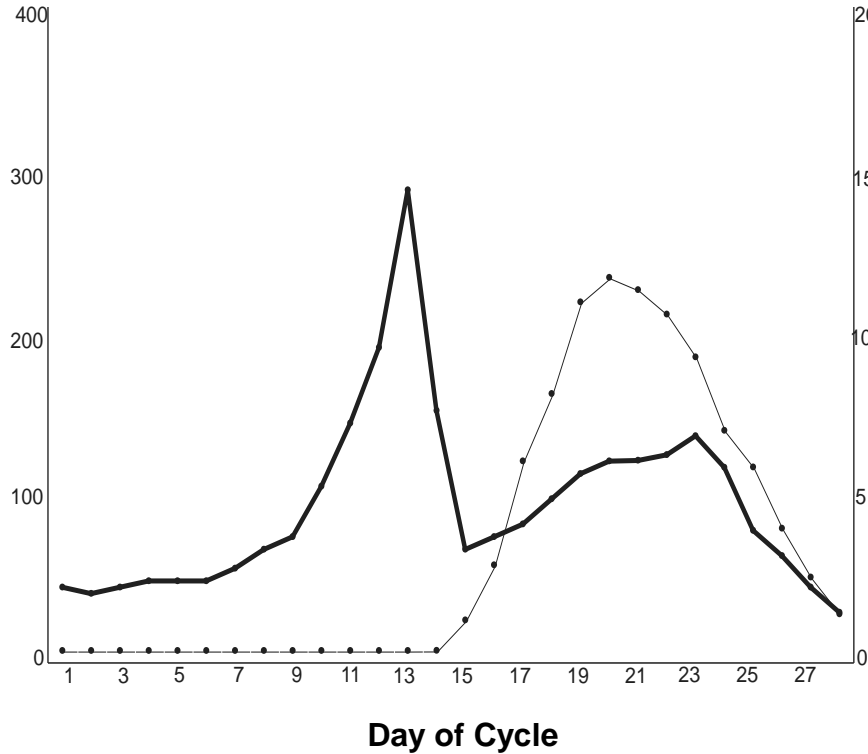
Endometrial Cell Proliferation

Labeling Index



Ferenczy A et al. (AJOG 1979;133:859)

Estradiol (pg/ml)

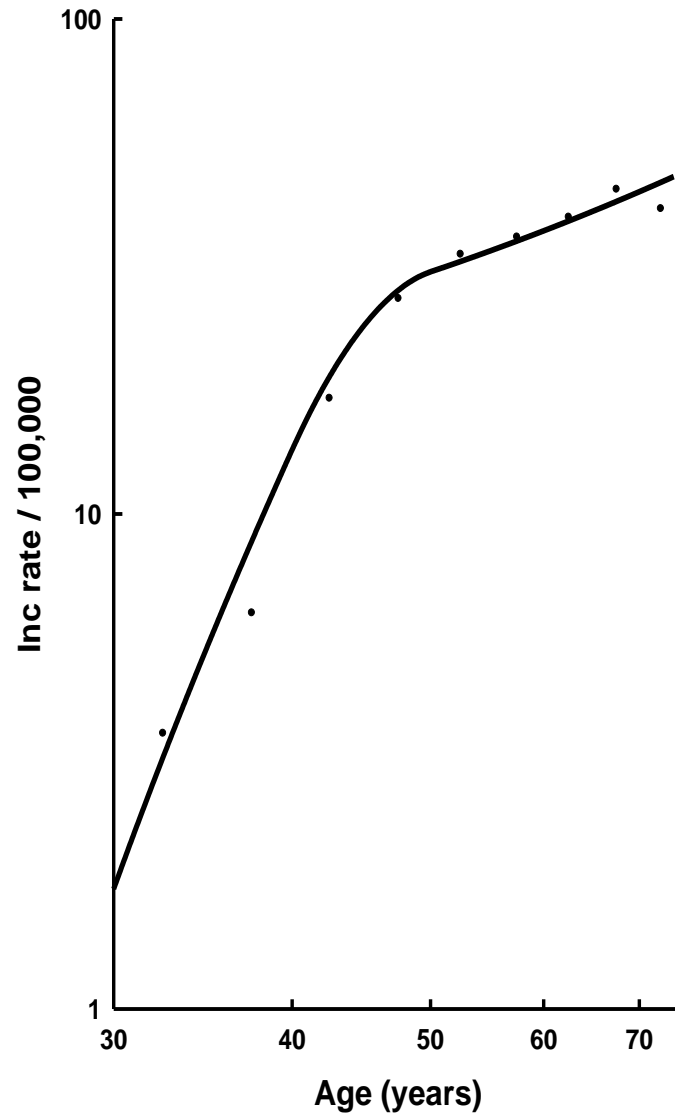


Goebelsmann U et al. (In Repro Endo Infertil Contracep 1979; pp 67)

Oral Contraceptive (OC) Use Prevents Endometrial Cancer

OC use (years)	Reduction in Risk
5	45%
10	71%
15	85%

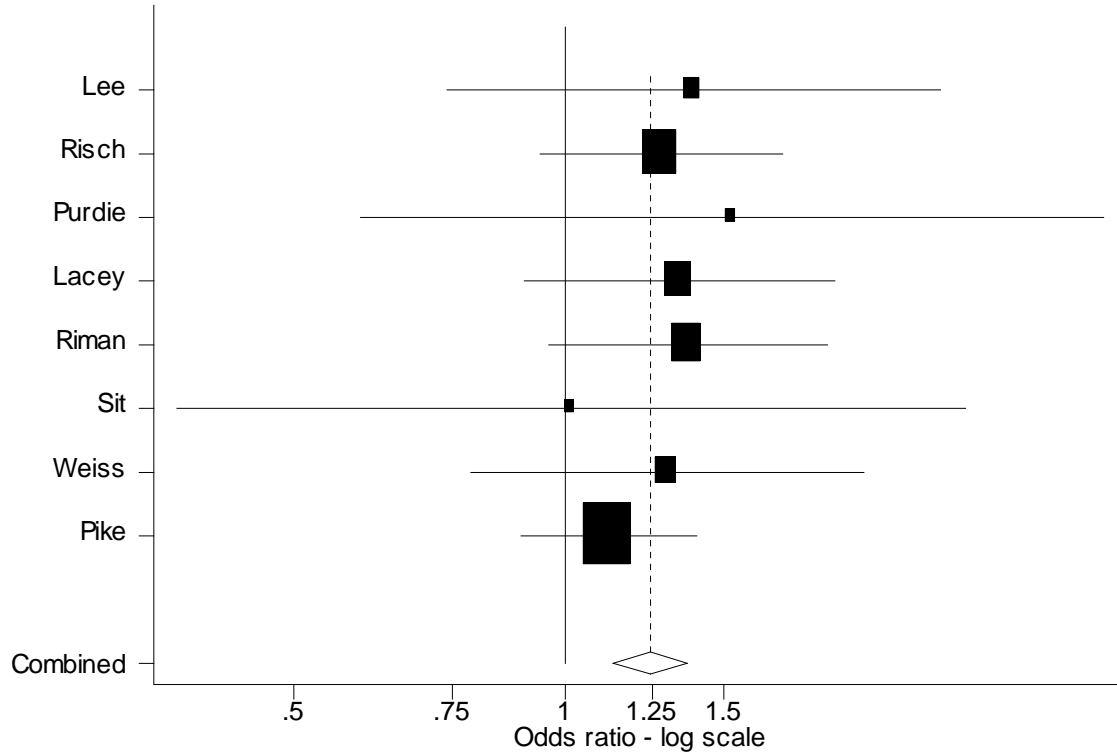
Ovarian Cancer



Oral Contraceptive (OC) Use Prevents Ovarian Cancer

OC use (years)	Reduction in Risk
5	32%
10	54%
15	69%

Relative Risk of Invasive Ovarian Cancer with 5 years ET Use



Pearce C *et al.* (Cancer 2009;115:531)

Ovarian Cancer

Late age at menopause ↑

Obesity ↑ (cf endometrial cancer)

Parity ↓

Menopausal estrogen therapy (ET) ↑ (cf endometrial cancer)

Menopausal estrogen-progestin therapy (EPT) ↑ ↓

Oral contraceptives (OCs) ↓ - Progestin dose?

Germinal inclusion cysts (GICs)

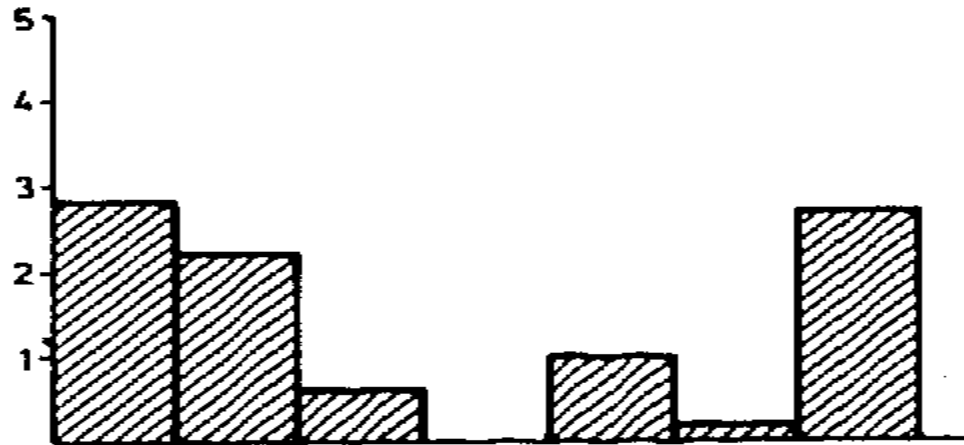
Endometriosis

Fallopian tube fimbriae

Mullerian origin cysts (MOCs)

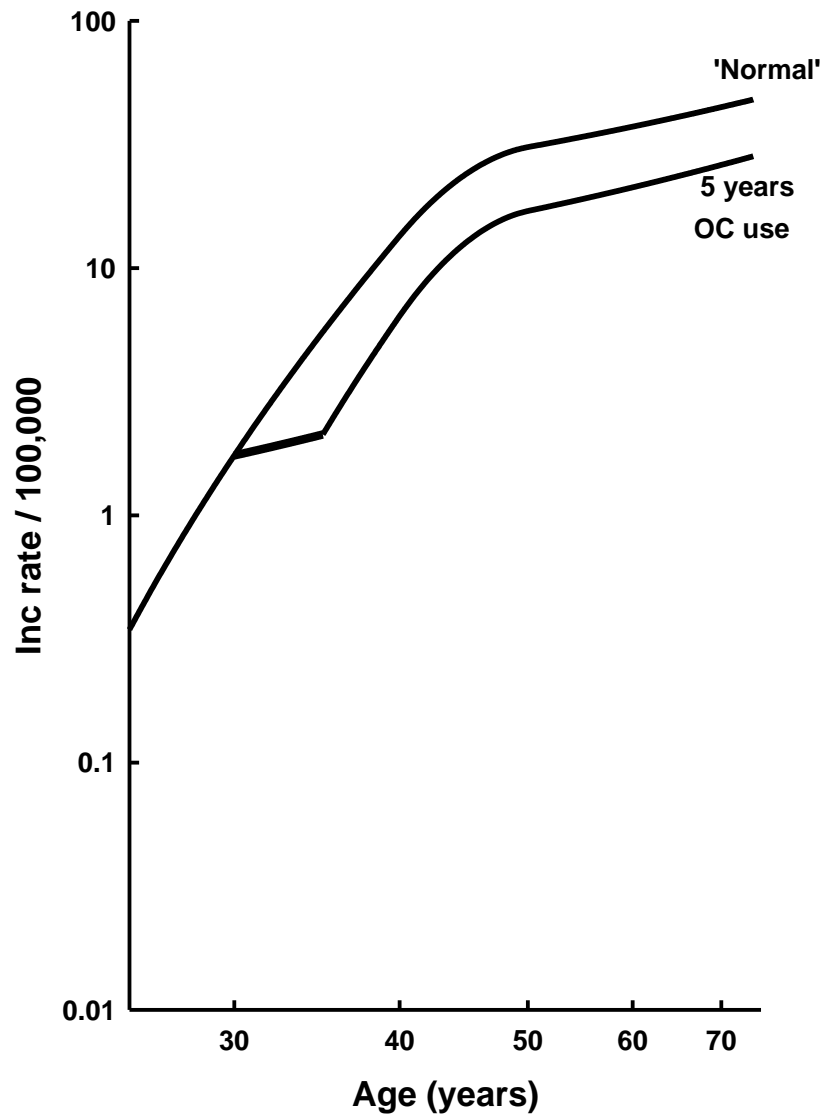
FIMBRIA

MENSTRUAL CYCLE				CONTINUOUS PROG. THE TAPY		PROG. STOPPED
EP	LP	ES	LS	> 3 < 3 months	> yes.	○
2.8 (4.2)	2.2 (5.7)	0.6 (1.8)	0 (0.8)	1.0 (1.5)	0.2 (1.1)	2.7 (2.9)
n=8	n=38	n=30	n=22	n=17	n=14	n=12



Results are expressed as median
() : mean values

Ovarian Cancer



Endometrial Cancer

Oral contraceptives (OCs) ↓ - dose

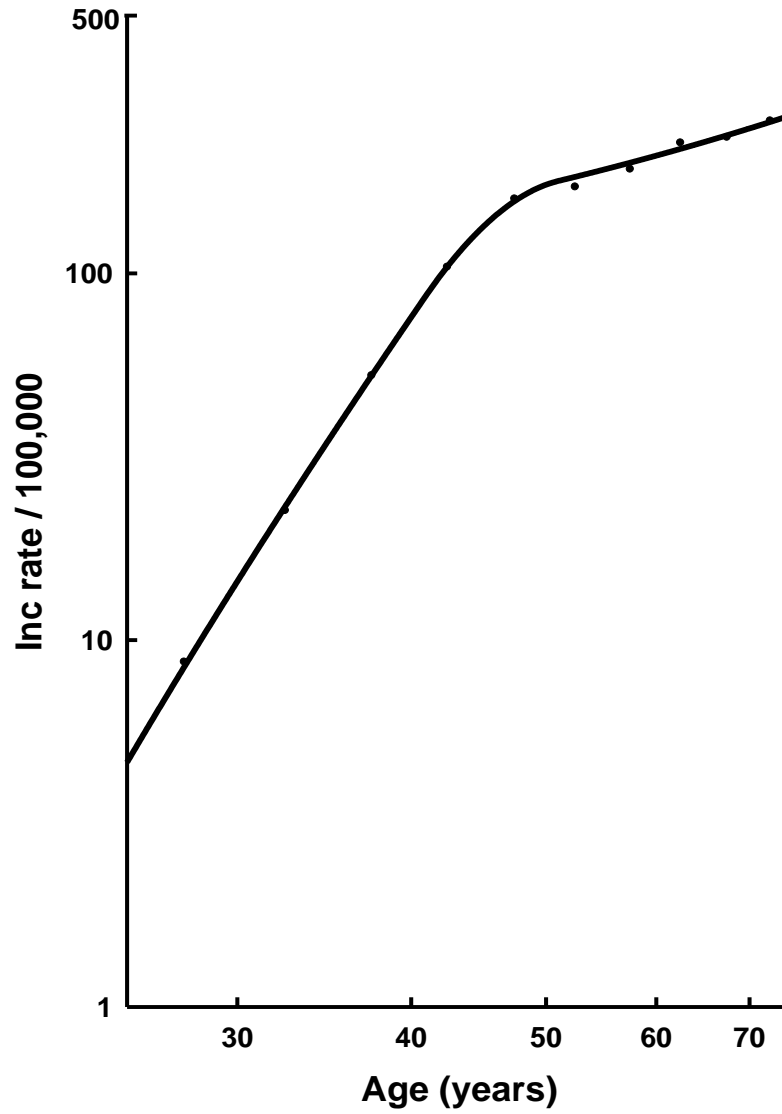
21/28 vs 24/28 vs 28/28

Ovarian Cancer

Oral contraceptives (OCs) ↓ - dose

21/28 vs 24/28 vs 28/28

Breast Cancer



Breast Cancer

Late age at menopause ↑

Early age at menarche ↑

Early age at first live birth ↓

Parity ↓

Obesity ↓ premenopause; ↑ postmenopause

Menopausal estrogen therapy (ET) ?

Menopausal estrogen-progestin therapy (EPT) ↑

Oral contraceptives (OCs) ↑?

Early age at pregnancy

Rodent results – chemoprevention

Rodent vis-à-vis human

Oocyte donors

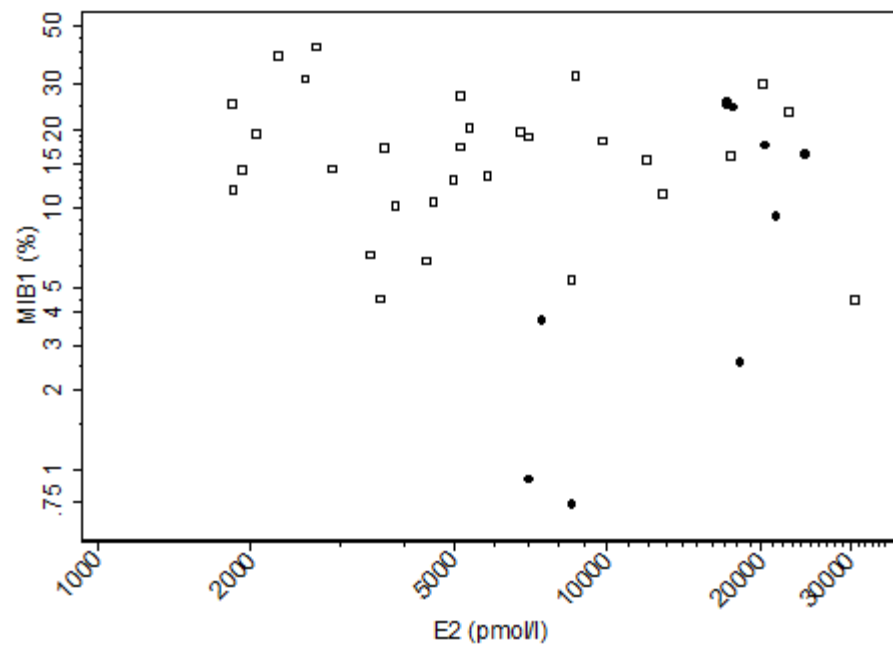
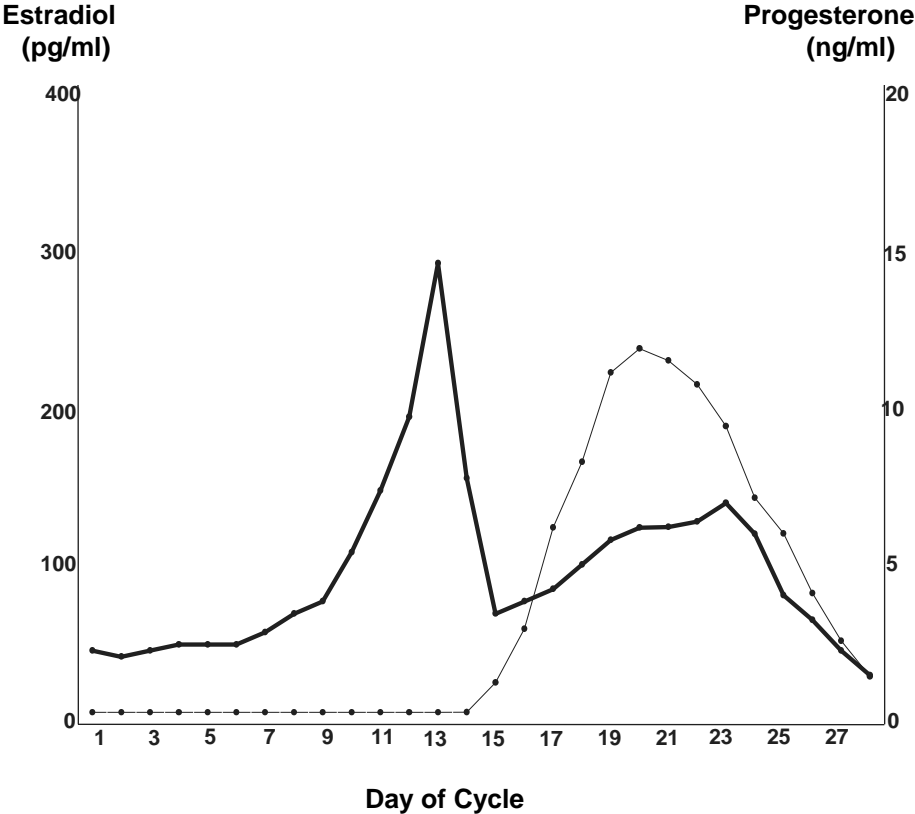
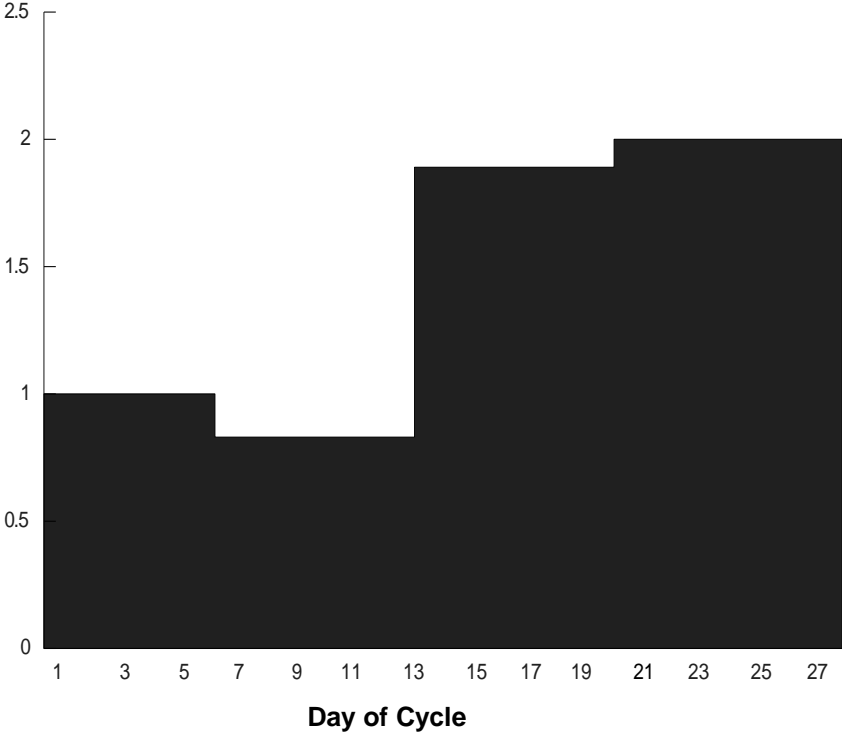


Figure 3. Individual woman TDLU epithelial cell MIB 1 values vs estradiol (E2) values - E2 values for oocyte donors on the day before biopsy (•); E2 values for “pregnant” women on the day of biopsy (◻).

Breast Cell Proliferation



Relative Labelling Index



Anderson T *et al.* (Human Pathol 1989;20:1139)

Menopausal Estrogen-Progestin Therapy

Estrogen

Early follicular phase: E2 ~180 pmol/L

Premarin at 0.625 mg/d: roughly equivalent to a 50 mcg E₂ patch
E2 ~140-200 pmol/L

Progestin

Average over menstrual cycle: P4 ~12.9 nmol/L

MPA at 2.5 mg/d: P4 ~11.4 nmol/L

**Increased Risk of Breast Cancer
Per 5 years of Use of Estrogen-Progestin Therapy:
Studies in the US**

**Sequential:
% Increase**

**Continuous-
Combined:
% Increase**

32%

**CEE: 0.625 mg/d
MPA: 10 mg,
10 d per 28 d cycle:
Total MPA dose
= 100 mg**

21%

**CEE: 0.625 mg/d
MPA: 2.5 mg,
28 d per 28 d cycle:
Total MPA dose
= 70 mg**

**Increased Risk of Breast Cancer
Per 5 years of Use of Estrogen-Progestin Therapy:
Studies in Scandinavia**

Sequential: Increase	Continuous- Combined: Increase
40%	88%
E₂V: 2 mg/d NET: 1 mg, 10 d per 28 d cycle Total NET dose = 10 mg	E₂V: 2 mg/d NET: 1 mg, 28 d per 28 d cycle Total NET dose = 28 mg

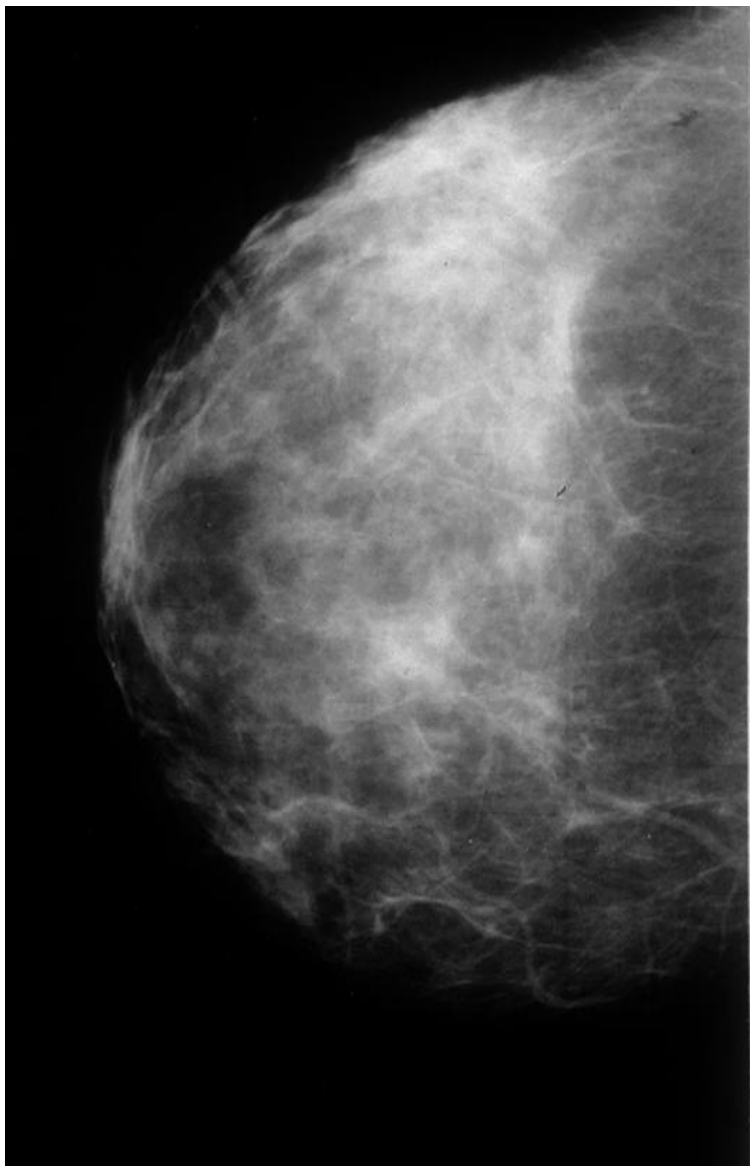
Menopausal Estrogen Therapy and Risk of Breast Cancer

GnRH Analog Contraceptive Approach to Breast Cancer Chemoprevention

Use a GnRH analog to block ovarian function.

Use minimal estrogen dose (~10 mcg of EE₂).

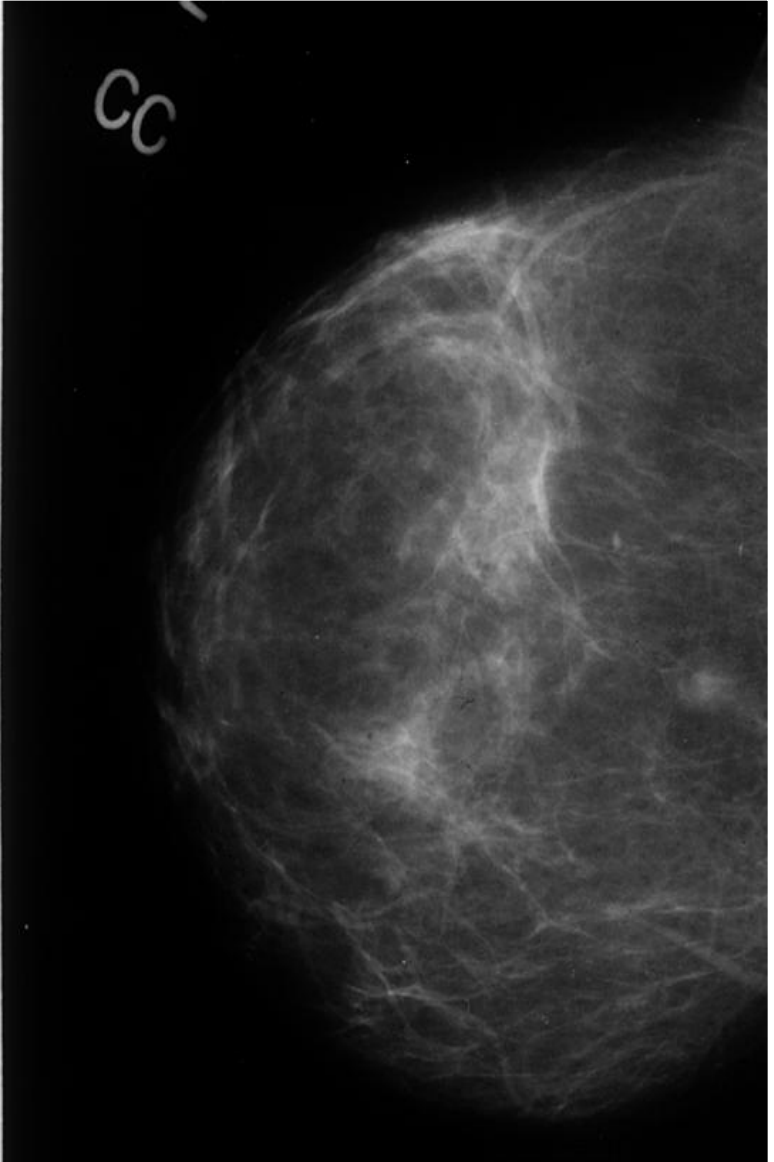
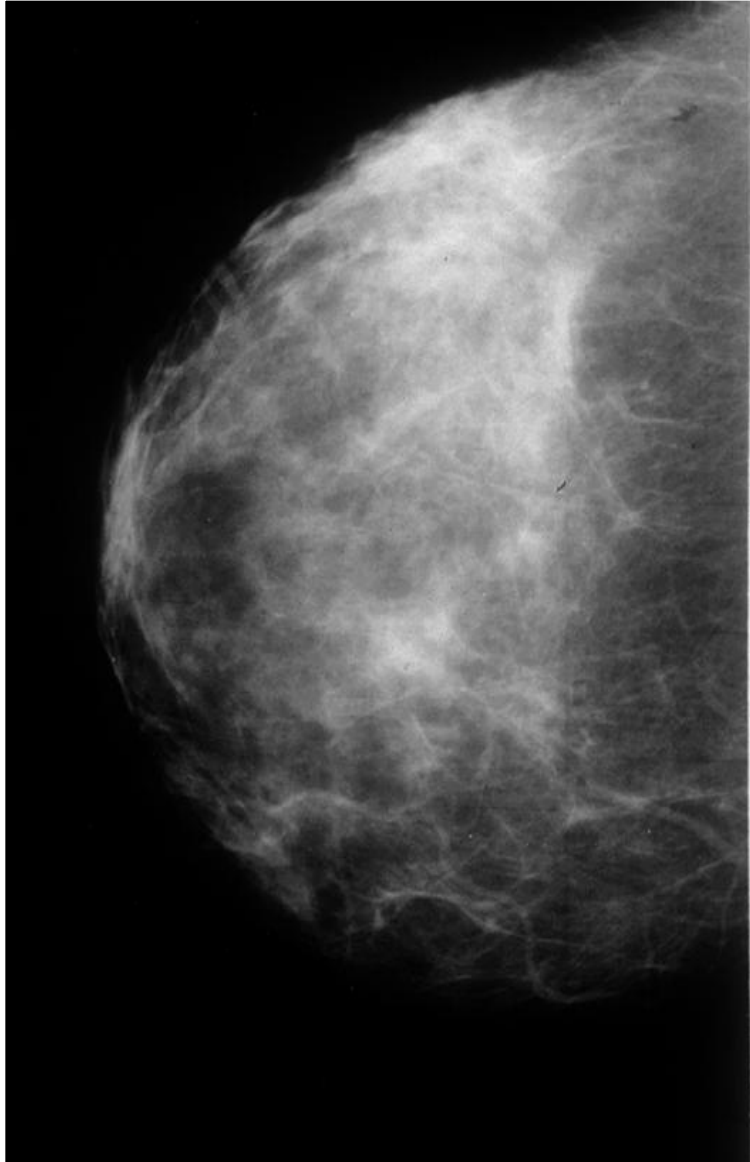
Use progestin at current standard OC dose of 1 mg/d of norethindrone for less time - 12 days every 3 months.



Mammographic Density and Breast Cancer

Density (%)	Risk
None	Baseline
<10	↑ 20%
10-	↑ 120%
25-	↑ 140%
50-	↑ 240%
75+	↑ 430%

Boyd N *et al.* J Natl Cancer Inst 1995; 87:670.



Problems with GnRH Analog with Ultra Low-Dose Estrogen-Progestin Approach

Mode of delivery

**Loss of protection against
endometrial and ovarian cancer**

**Based on the Scandinavian
Menopausal Estrogen-Progestin Results**

OC: 35 mcg EE2, 1 mg NET

Increase in breast ca risk - 7% per 5 years of use

OC: 35 mcg EE2, 0.4 mg NET

Decrease in breast ca risk - 34% per 5 years of use

Comparison of OCs with 35 mcg EE and Different Doses of NET

NET	Ki67	ER α	PRA	PRB
1.0 mg	7.8%	9.0%	7.6%	12.0%
0.4 mg	14.1%	17.6%	16.3%	22.4%
P-value	0.14	0.058	0.040	0.044

**How is this affected by different progestins?
What would be the effect of reducing the estrogen dose?**

Change to constant low dose delivery system?

Use GnRH agonist for ovarian suppression to separate the contraceptive efficacy from the required steroid dose.

Can a intra-uterine delivery system for progestin achieve the protective effect in the endometrium and 'ovary'?

How do we know what we have achieved?

Mammographic density/Breast biopsy/MRI

Endometrial biopsy

'Ovarian' biopsy