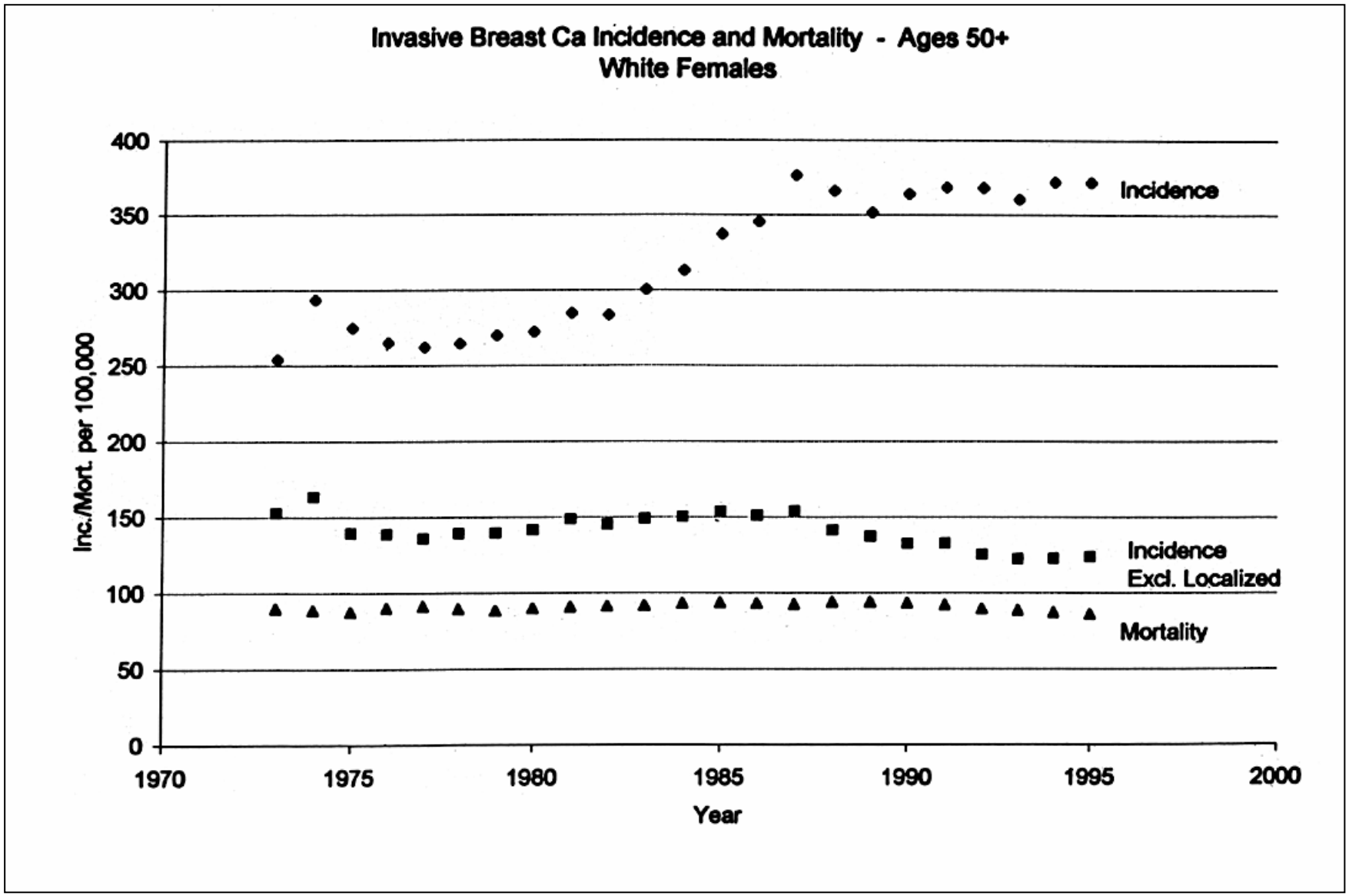
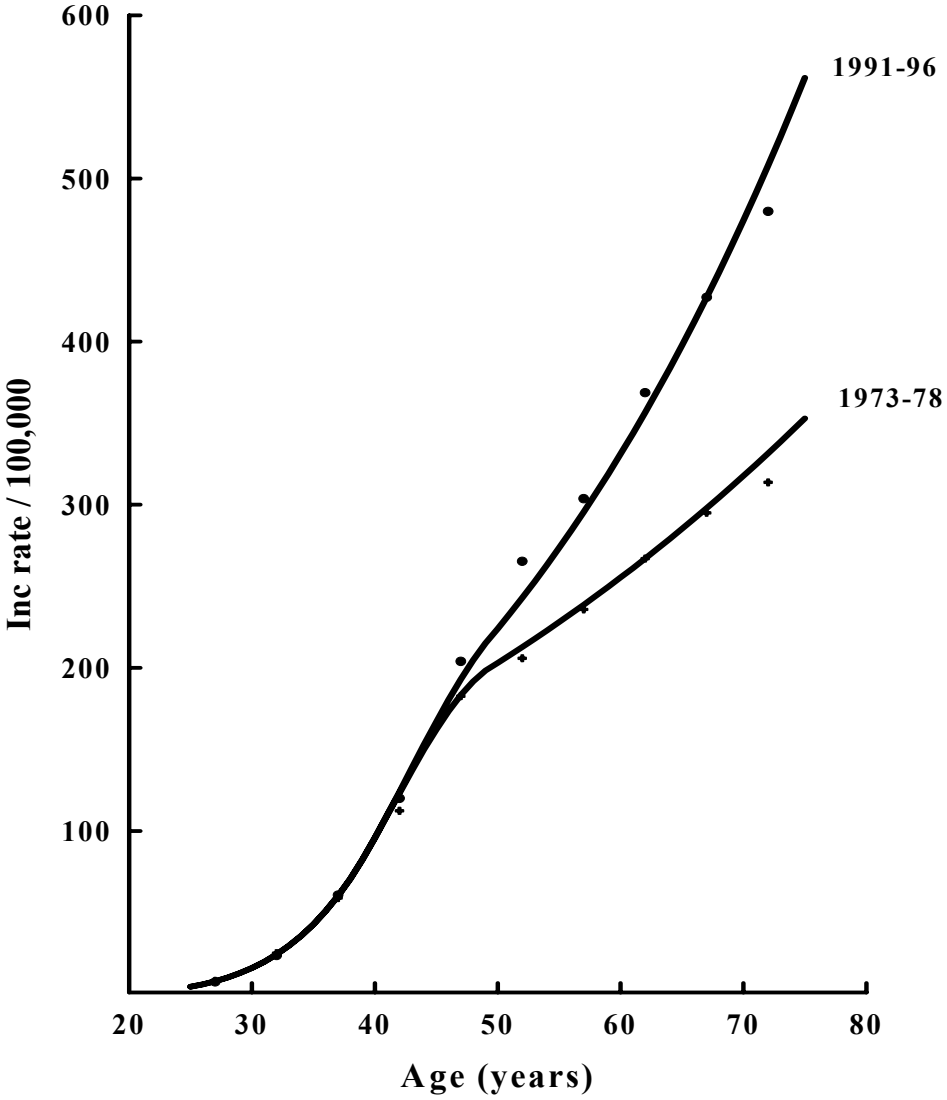
Total Ovulation Frequency of Modern Women Compared to Hunter-Gatherers

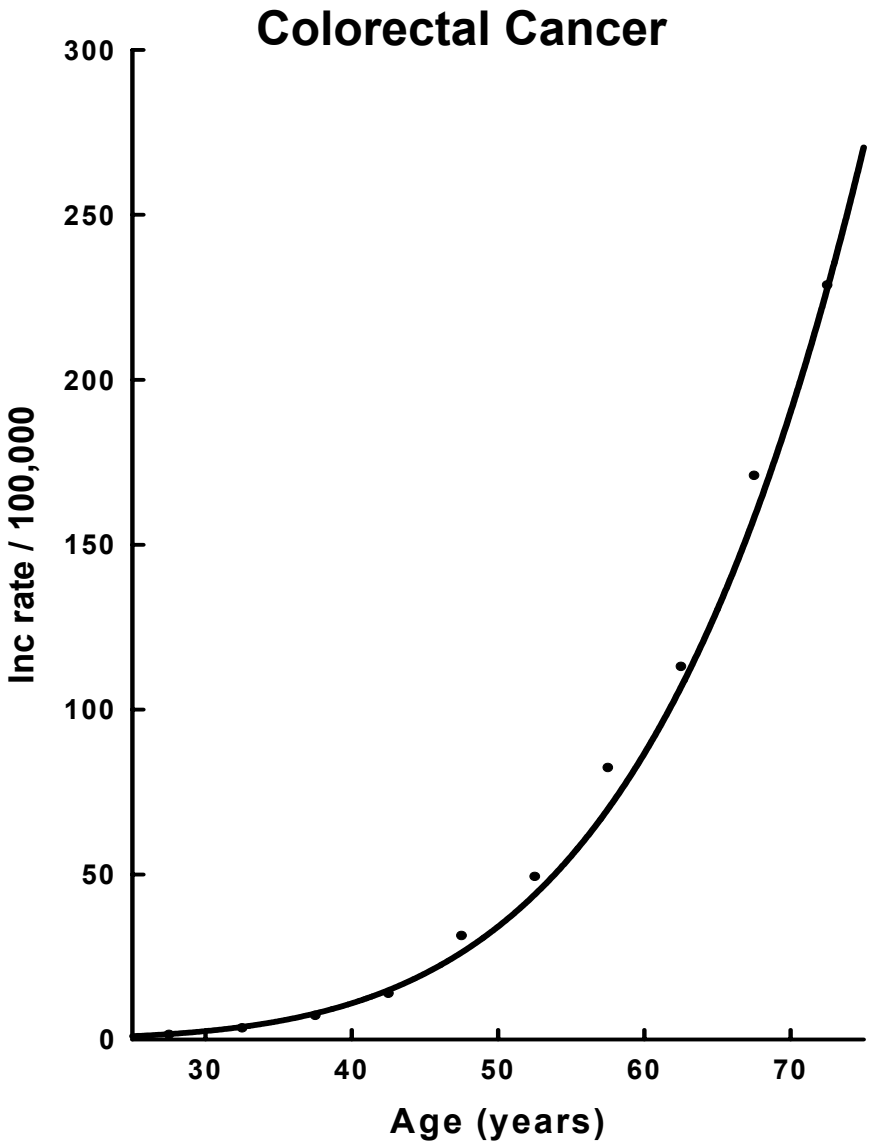
	Modern	Hunter-Gatherer
Menarche	12	16
First Birth	24	19
Lactation/birth	3 months	3 years
Parity	2	6
Menopause	50	47
Ovulations	450	160
Menarche-First birth	12 years	3 years

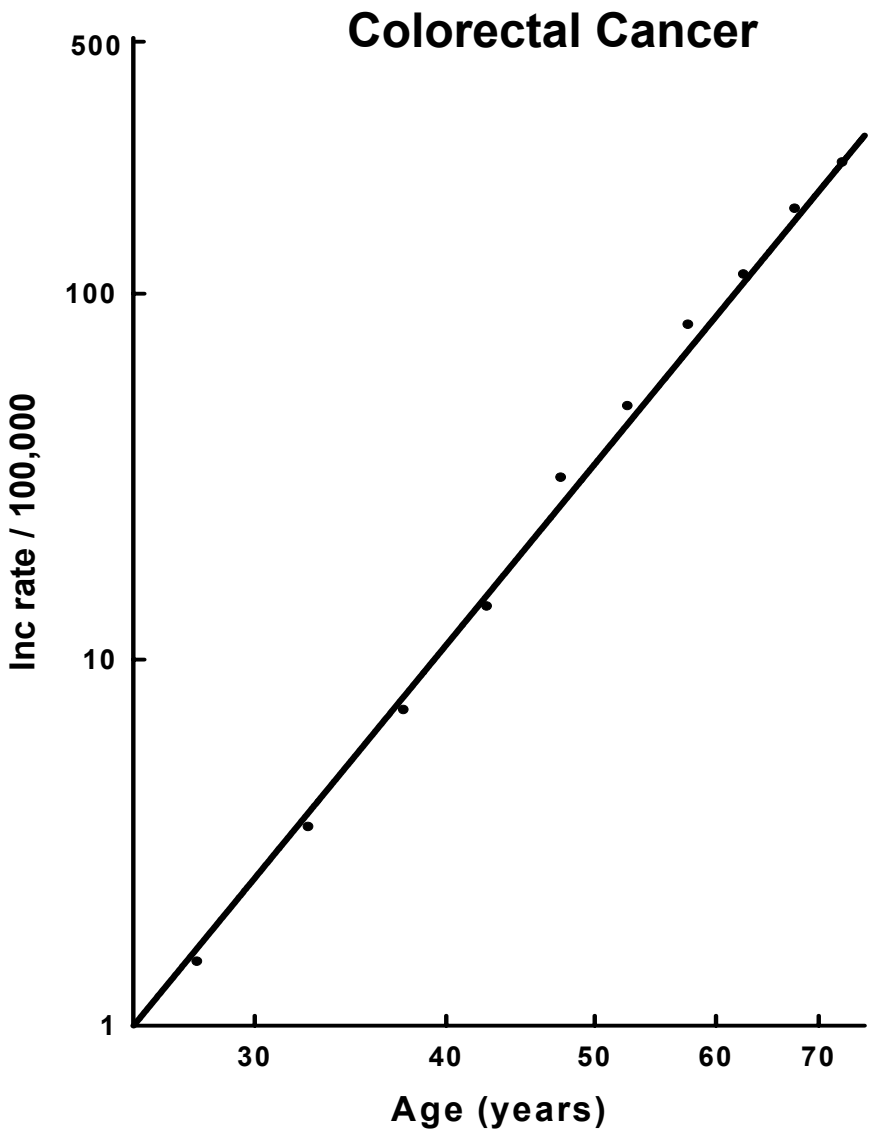
Breast cancer	120-fold increase
Ovarian cancer	20-fold increase
Endometrial cancer	40-fold increase

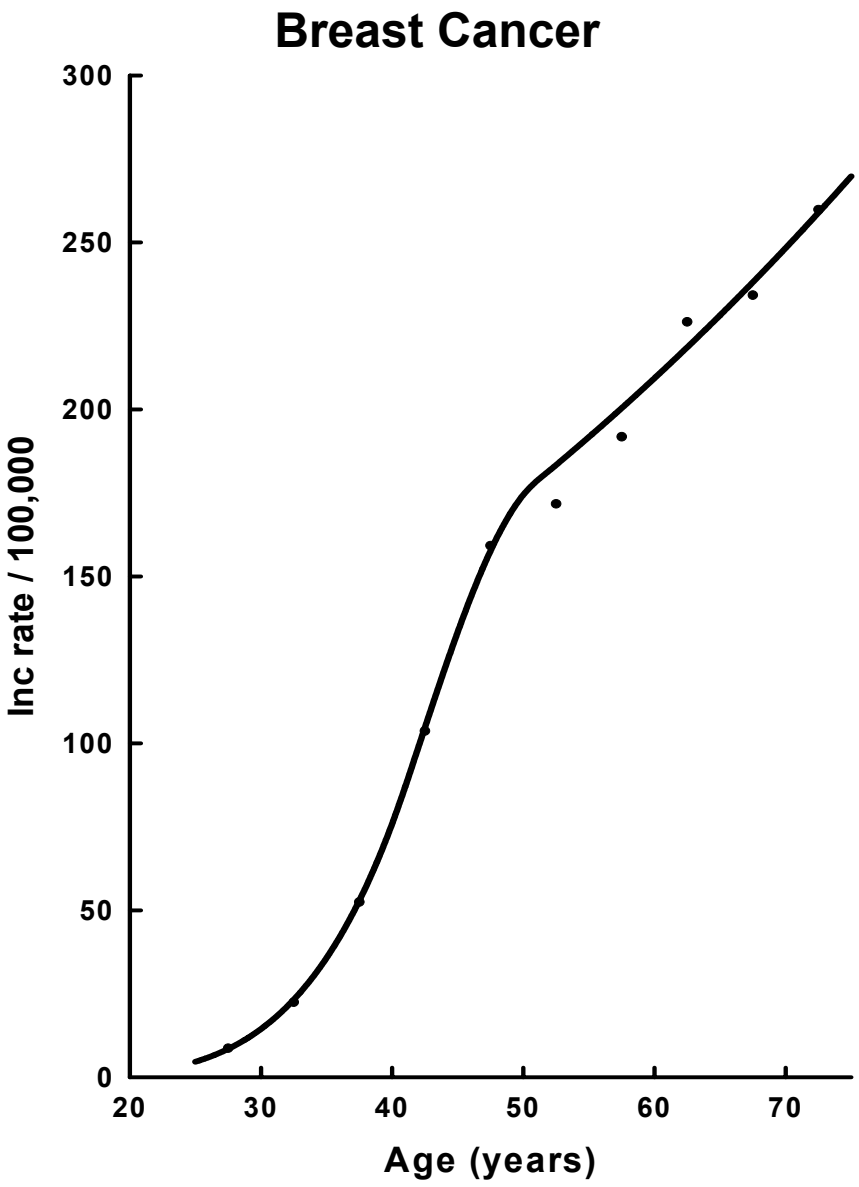

Invasive Breast Ca Incidence and Mortality - Ages 50+
White Females
Inc./Mort. per 100,000
400
350
300
250
200
150
100
50
0
1970
1975
1980
1985
1990
1995
2000
Year
Incidence
Incidence
Excl. Localized
Mortality

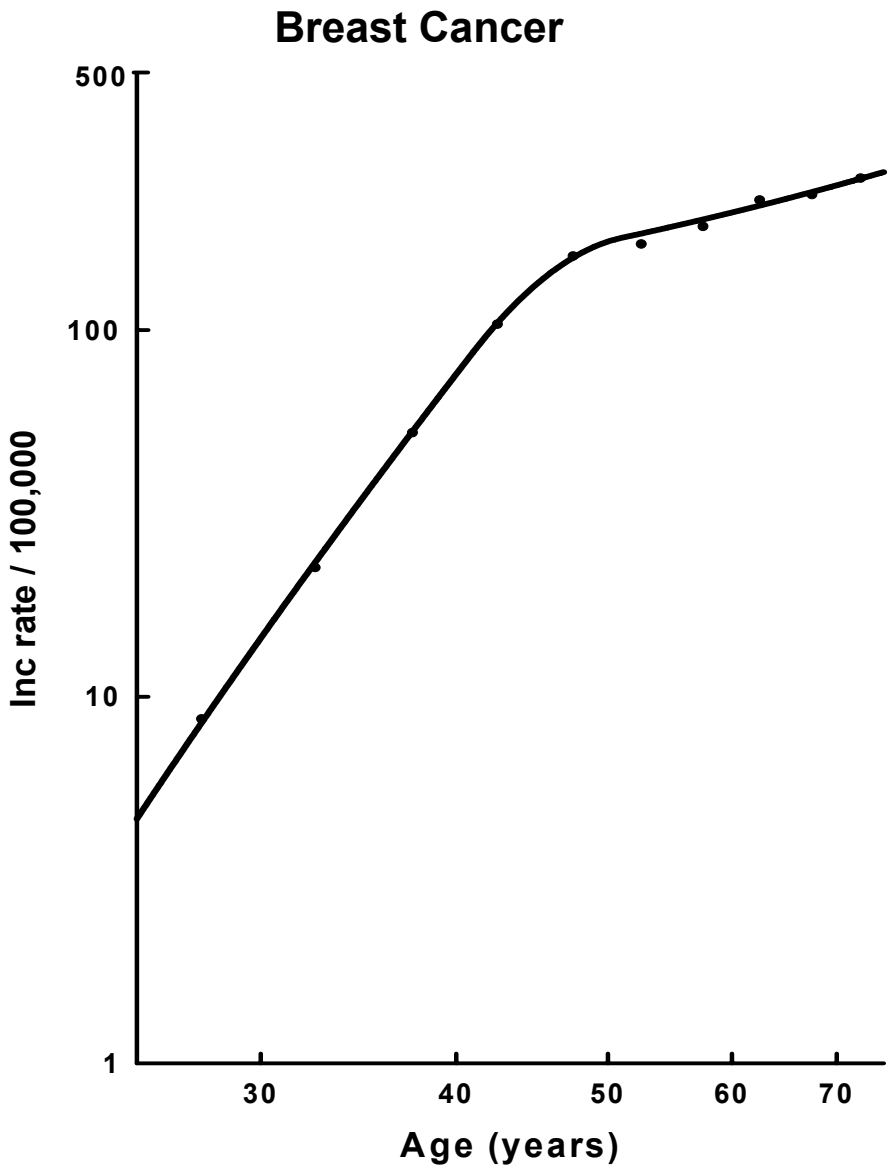
TR034


600
500
400
300
200
100
Inc rate / 100,000
1991-96
1973-78
20
30
40
50
60
70
80
Age (years)


Colorectal Cancer
Inc rate / 100,000
300
250
200
150
100
50
0
30
40
50
60
70
Age (years)


Colorectal Cancer
500
100
10
1
Inc rate / 100,000
30
40
50
60
70
Age (years)


Breast Cancer
300
250
200
150
100
50
0
Inc rate / 100,000
20
30
40
50
60
70
Age (years)


Breast Cancer
500
100
10
1
Inc rate / 100,000
30
40
50
60
70
Age (years)

Key Epidemiologic Evidence on Breast Cancer Risk

(i) Risk increases much slower in the postmenopausal period than at reproductive ages; oophorectomy is very protective.

(ii) Obesity increases risk at postmenopausal ages but decreases risk at premenopausal ages.

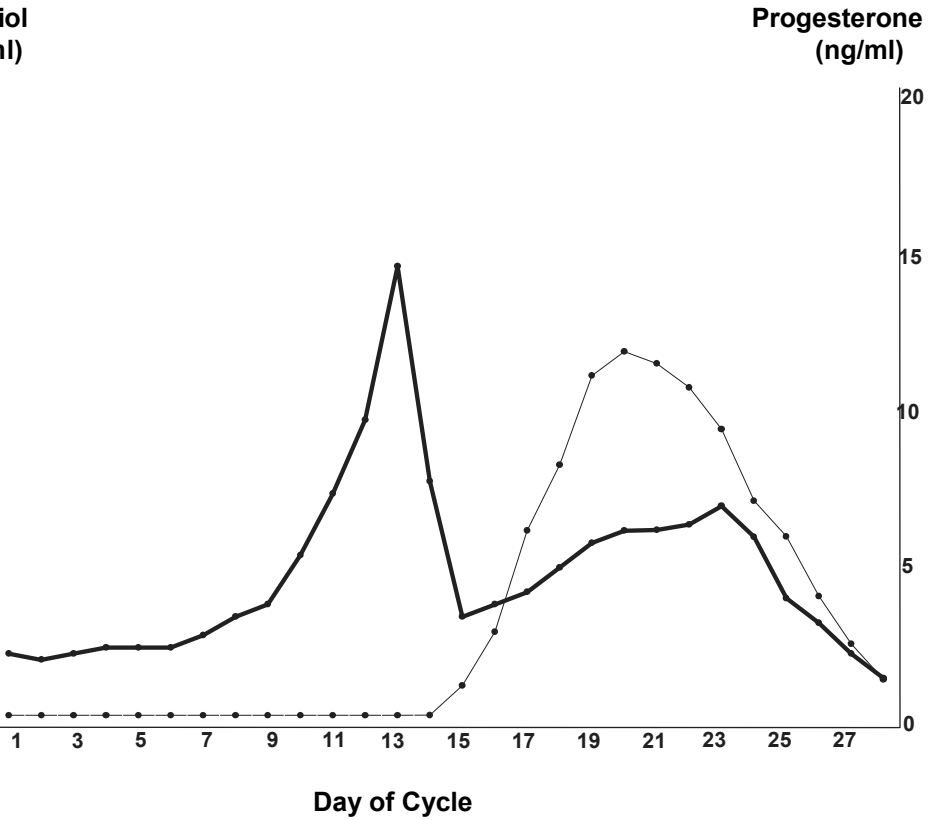
(iii) Early first birth and increasing parity reduce risk.

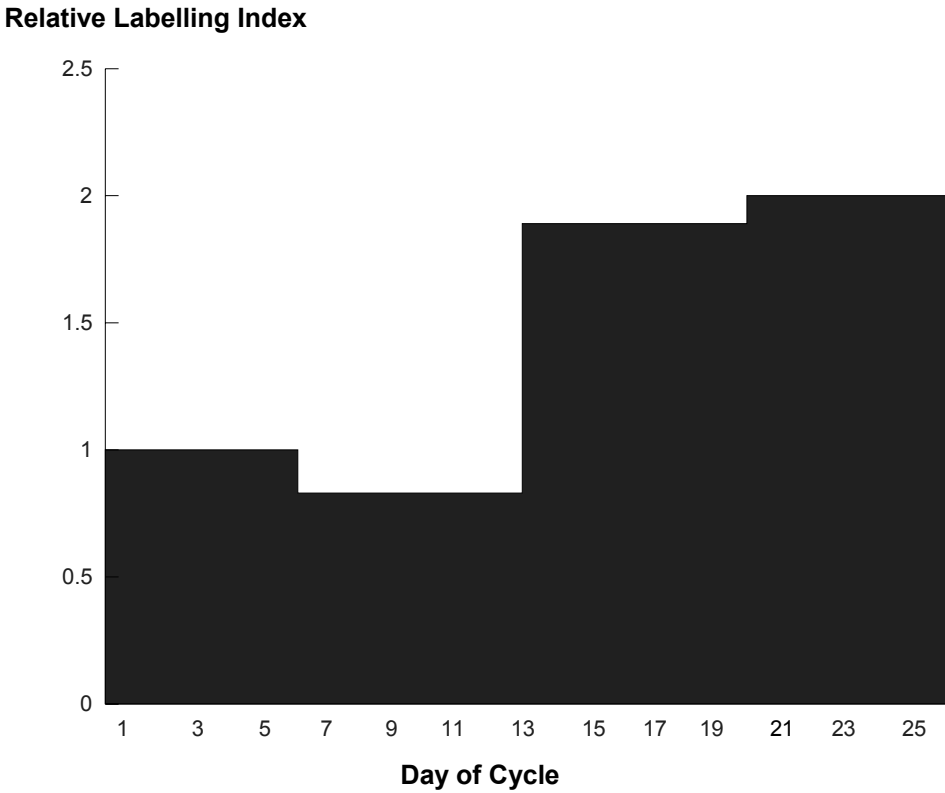
(iv) OCs have very little effect.

(v) ET increases risk (~10% per 5 years of use) but EPT increases risk much more (~40% per 5 years of use).

(vi) Large differences in rates in different countries; migrants slowly assume rates of host countries.

Breast Cell Proliferation



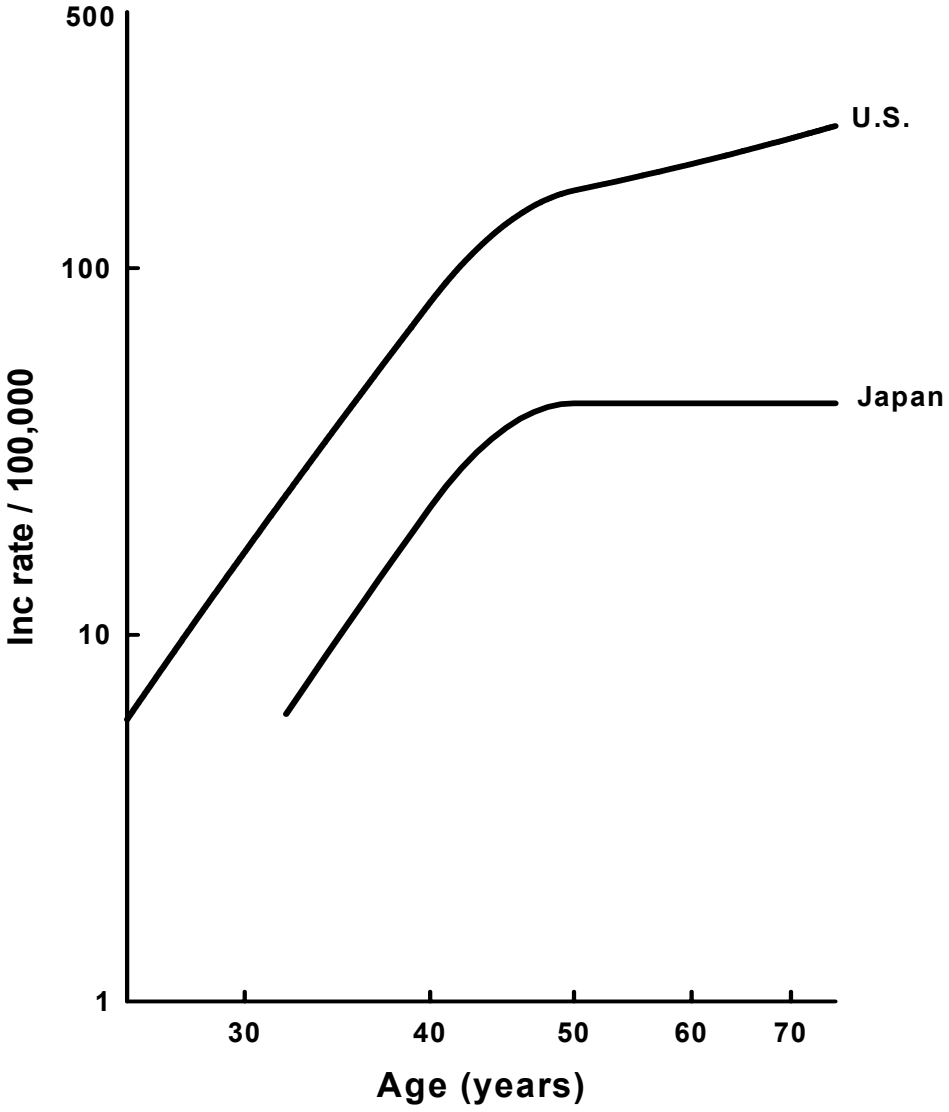


B051

Increase in Breast Cancer Risk with Use of ET and EPT

Study	HRT Type	Increase in risk per 5 years of use
Magnusson *et al.*[a]	ET	16%
	EPT	40%
Schairer *et al.*[b]	ET	1%
	EPT	40%
Ross *et al.*[c]	ET	6%
	EPT	24%
WHI[d]	EPT	26% to 49%

[a]Int J Cancer 1999; 81:339-344.
[b]JAMA 2000; 283:485-535.
[c]J Natl Cancer Inst 2000; 92:328-332.
[d]JAMA 2002; 288:321-333.


500
100
10
1
Inc rate / 100,000
U.S.
Japan
30
40
50
60
70
Age (years)

Characteristics of 'Traditional' Japanese Women at Low Risk of Breast Cancer

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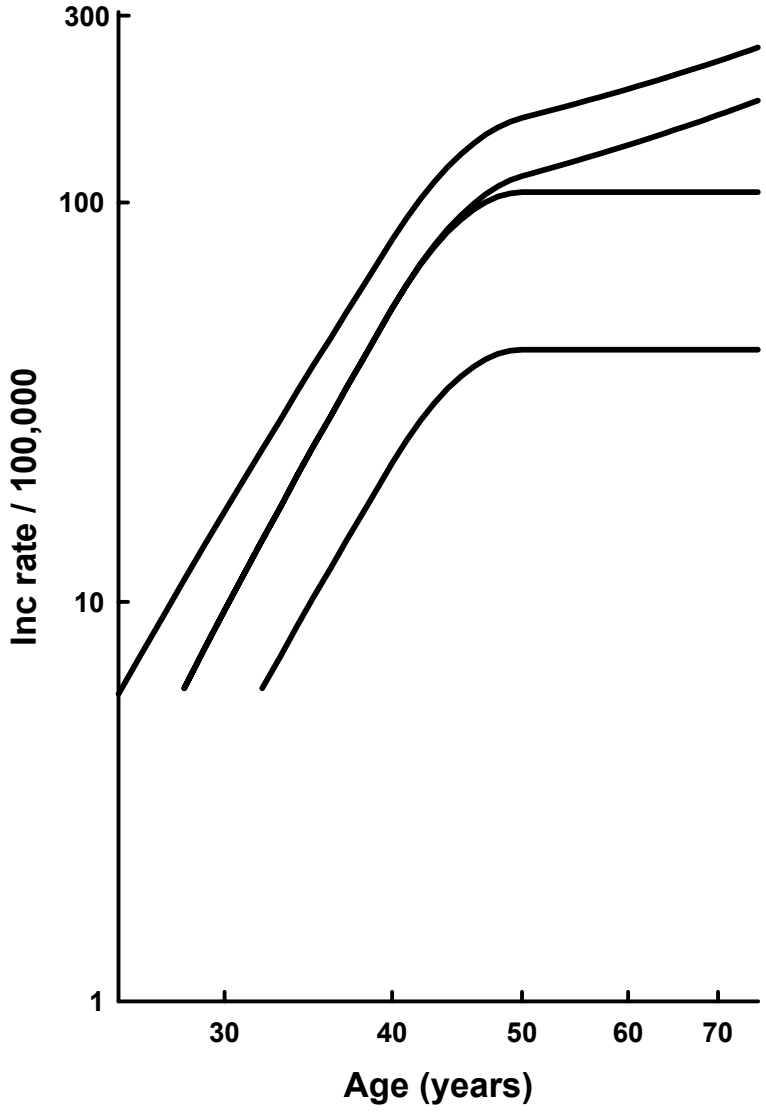
Late menarche: average age 16-17 yrs

Weight: average ~45 kg

Diet: 8% calories from fat
High soy consumption



(1) U. S.

(2) 2 year delay in menarche

(3) No increase after menopause

(4) Japan

How much lower does breast cell proliferation rate have to be to explain a 2.6-fold reduction in breast cancer risk?

$$r^{4.5} = 1/2.6$$

$$r = 0.81$$

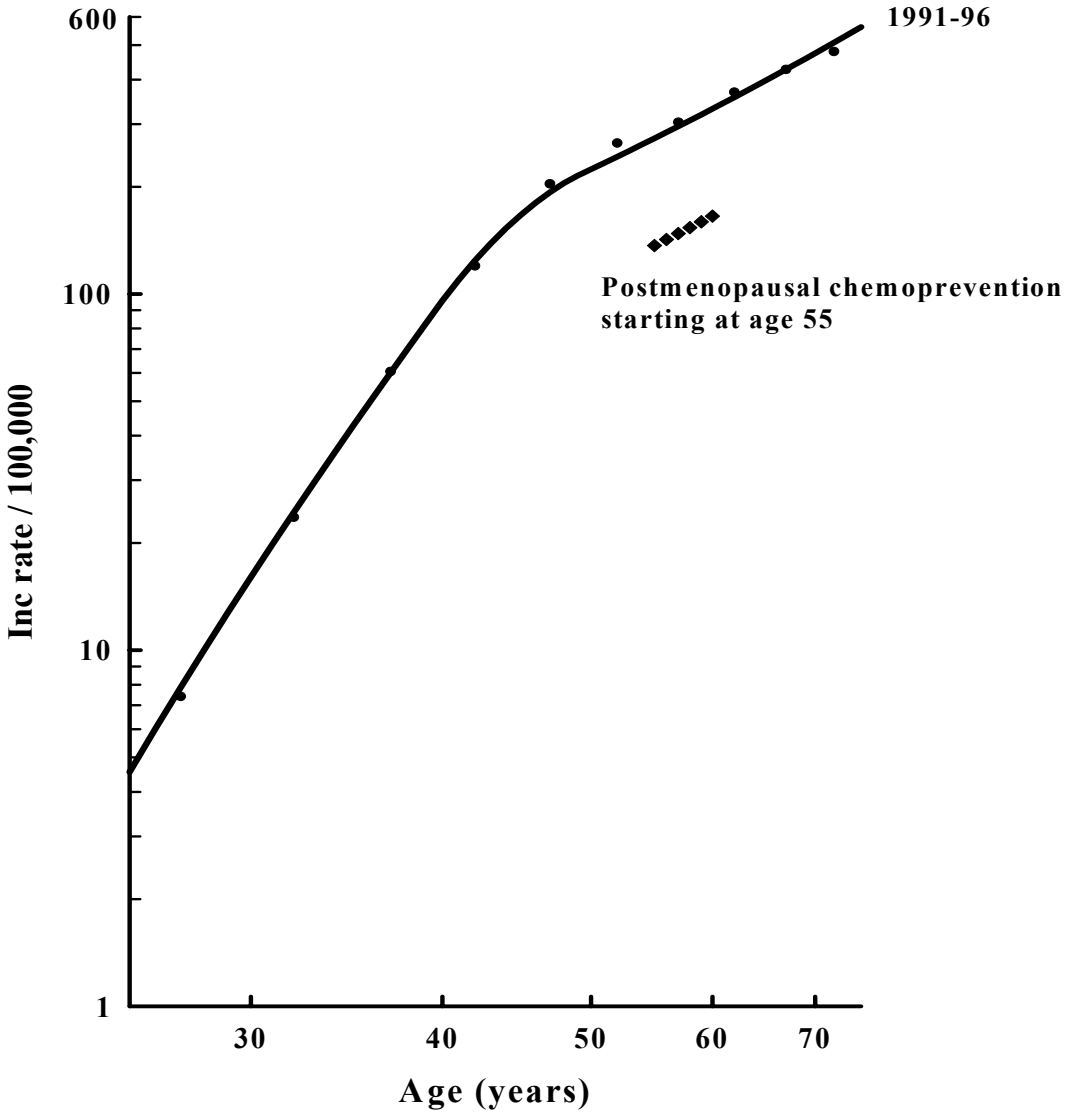
Premenopausal Serum Estradiol (E_2) and Progesterone (P_4) Levels in Asia and in the U.S. and U.K.

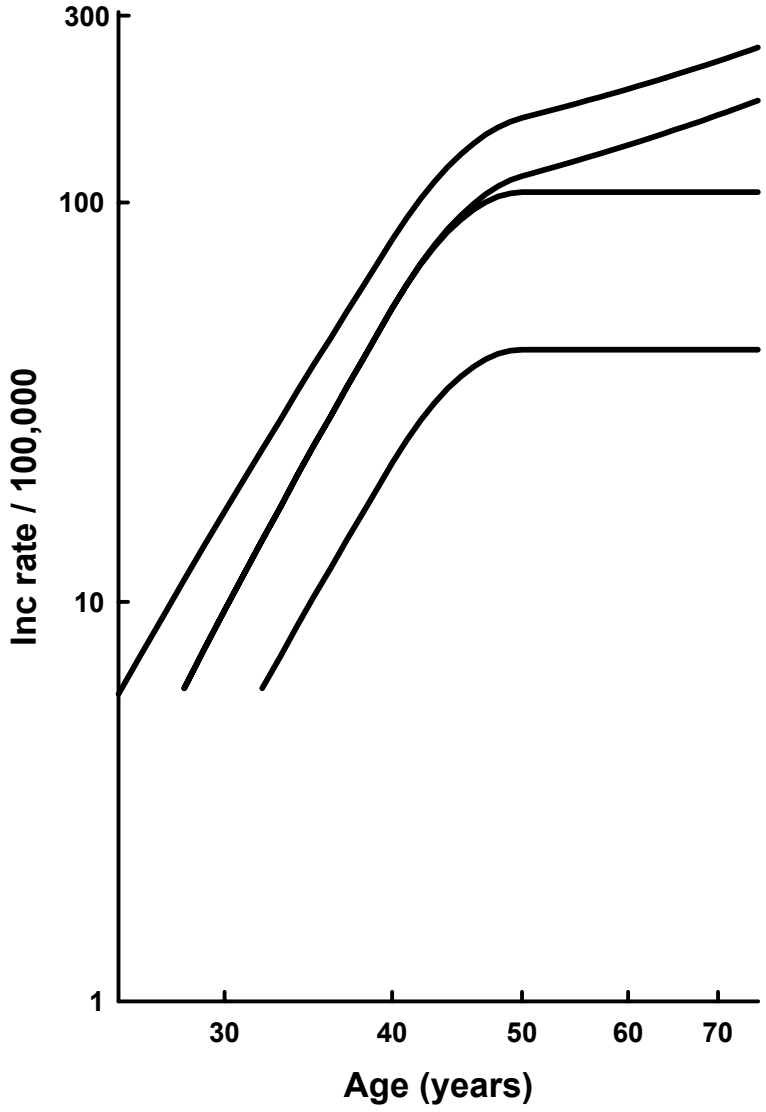
Study		# Asians/ # Whites	Cycle Phase	Reduction in Asian Subjects
Goldin *et al.* (1986)	Southeast Asians in Hawaii ≤2 yrs	12/10	Mid-follicular	E_2: 44%
Key *et al*. (1990)	Chinese in rural China	300/30	Random	E_2: 26%
Bernstein *et al.* (1991)	Chinese in Shanghai	39/42	Day 22	E_2: 17% P_4: 9%

Risk of Breast Cancer and Postmenopausal Serum Estradiol Concentration[a]

Serum E2 Concentration (pmol/L)	Odds Ratio (with 95% CI)
<30.7	1.0
30.7-41.0	2.5 (1.0-6.4)
>41.0	5.0 (2.0-12.5)

[a]Thomas *et al*. (Br J Cancer 1997; 76: 401-405).


600
100
10
1
Inc rate / 100,000
30
40
50
60
70
Age (years)
1991-96
Postmenopausal chemoprevention
starting at age 55



(1) U. S.

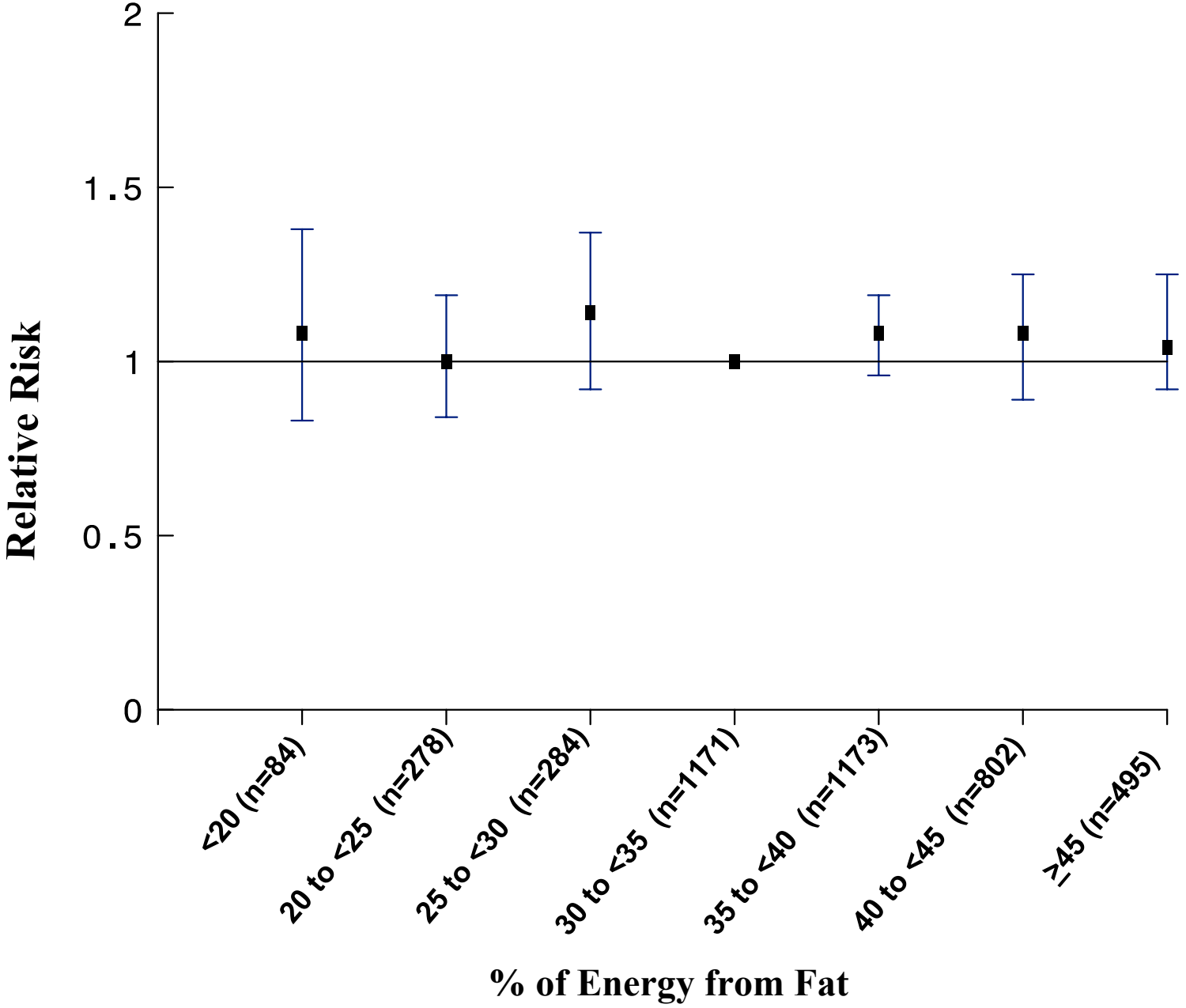
(2) 2 year delay in menarche

(3) No increase after menopause

(4) Japan

Effect of Reduction in Cell Proliferation Rate on Breast Cancer Risk

Age	Years of Change	Reduction in Cell Proliferation Rate	Reduction in Breast Cancer Risk
40	5		
		5%	3%
		10%	7%
		20%	13%
	10		
		5%	7%
		10%	13%
		20%	25%
	Lifetime		
		5%	21%
		10%	38%
		20%	63%

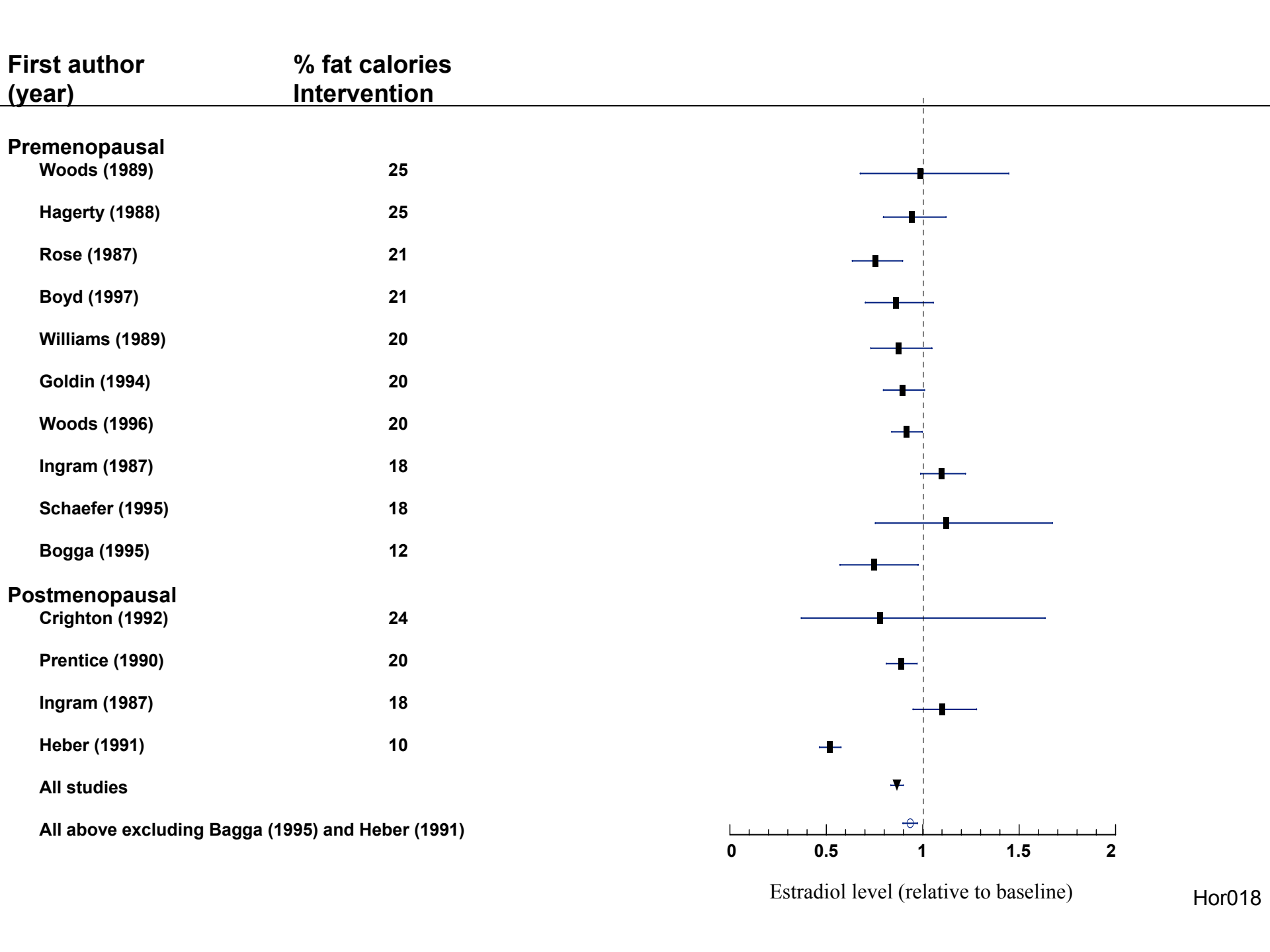

Relative Risk
2
1.5
1
0.5
0
<20 (n=84)
20 to <25 (n=278)
25 to <30 (n=284)
30 to <35 (n=1171)
35 to <40 (n=1173)
40 to <45 (n=802)
≥45 (n=495)
% of Energy from Fat

B112-1

Measurement Issues in FFQ Diet Studies

Correlations of FFQ with ‘unbiased food records’
are worse than they appear as their errors are correlated.

FFQ methods can only find large effects
which as we have seen are not likely
unless the diet has been maintained for many years.


First author (year)
% fat calories Intervention
Premenopausal
Woods (1989) 25
Hagerty (1988) 25
Rose (1987) 21
Boyd (1997) 21
Williams (1989) 20
Goldin (1994) 20
Woods (1996) 20
Ingram (1987) 18
Schaefer (1995) 18
Bogga (1995) 12
Postmenopausal
Crighton (1992) 24
Prentice (1990) 20
Ingram (1987) 18
Heber (1991) 10
All studies
All above excluding Bagga (1995) and Heber (1991)
0
0.5
1
1.5
2
Estradiol level (relative to baseline)
Hor018

Issues in Intervention Studies

How long must intervention be maintained to see an effect?

Is effect a result of weight loss?

Hawaii/USC Studies of Dietary Modifiers of Serum Hormones

Kolonel et al	FFQ Micronutrients
Wu	Phytoestrogens (Soy) Low fat diet Green tea
Monroe	Dietary fiber in Mexican Americans

Multi-Ethnic Cohort Study

215000 men & women 45-74 recruited 1993-1996 from DMV files
African-Americans, Hawaiians, Japanese-Americans, Latinas & 'Whites'

University of Hawaii
L.N. Kolonel (P.I.)
J.H. Hankin
A.M.Y. Nomura
L. LaMarchant
L. Wilkins
M.E. Earle

USC
B.E. Henderson
M.C. Pike
D.O. Stram
K.R. Monroe

Multi-Ethnic Cohort Study: Incident breast cancer[a]

	W	AA	NH	JA	L-US	L-NUS
No. of women	14,079	9,527	3,636	16,576	5,930	5,616
No. of breast cancer cases	306	175	95	366	103	71
RRs (age adjusted)	1.0	0.78	1.33	0.99	0.77	0.60
Parity 4+	24%	36%	55%	19%	47%	55%
Weight (kg)	68	78	73	57	71	68
EPRT (current)	31%	10%	18%	31%	18%	10%
Alcohol (1+ drinks/day)	22%	10%	9%	3%	6%	4%
RRs (age & risk factor adjusted)	1.00	0.98	1.65	1.11	0.95	0.84

[a]Women with natural menopause or bilateral oophorectomy

Fat and Fiber in Latina Women in the MEC

	Quintile 1 (low)[a]	Quintile 3 (mid)	Quintile 5 (high)
% calories from fat	35%	32%	26%
Dietary fiber density (g/6720 kJ/day)	15.0	23.5	35.7

[a]As defined by dietary fiber density.

Fiber and Serum Estrogen in Postmenopausal Mexican American Women

(1) To investigate the correlation between a serum biomarker of dietary intake (the lignan enterolactone) and fiber intake measured by a food frequency questionnaire (FFQ).

(2) To determine the effect of dietary fiber intake, as measured by serum enterolactone and as measured by the FFQ, on blood levels of endogenous estrogens.