Hormone therapy (HT)
Epidemiological aspects

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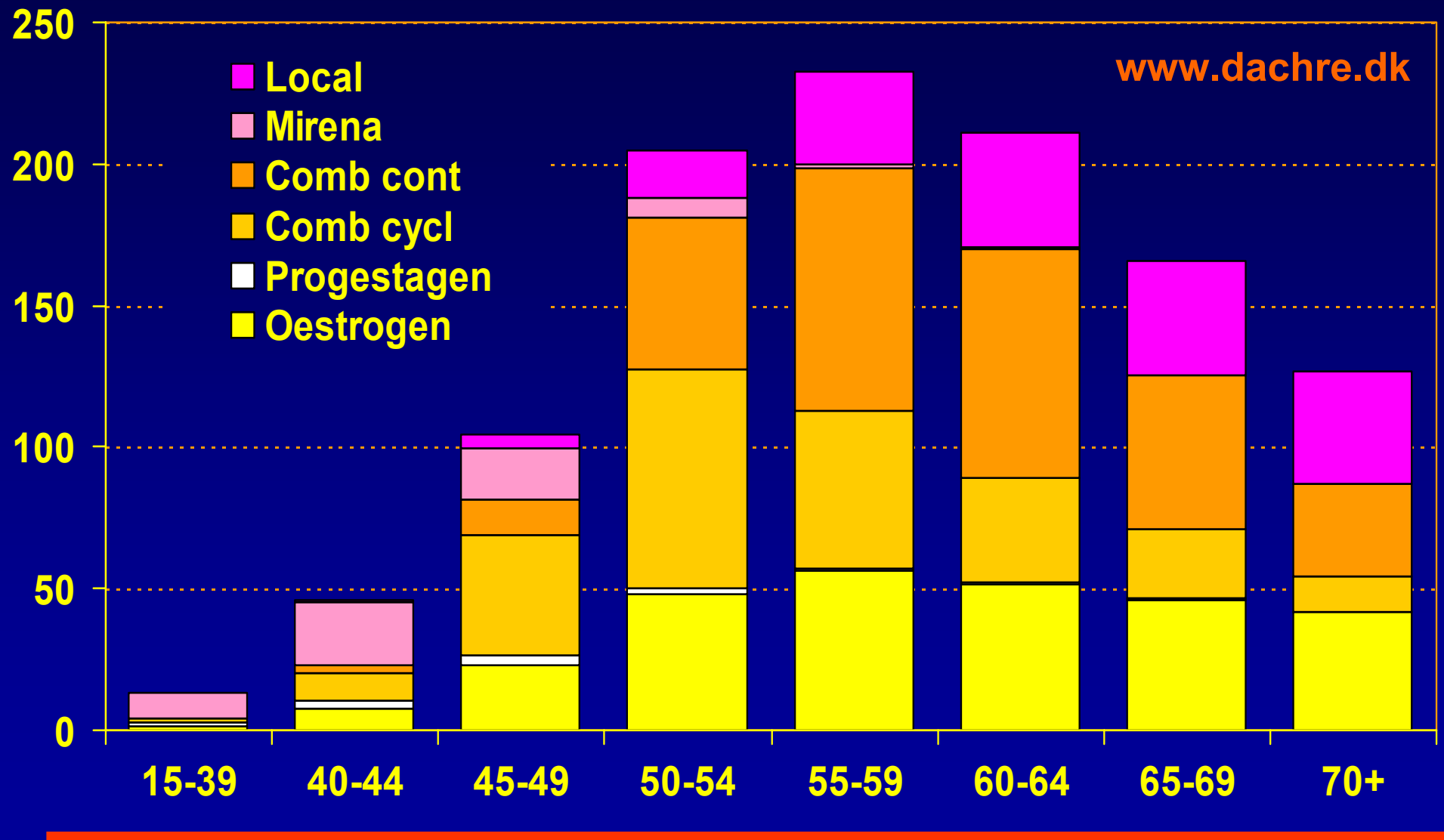
Hormone therapy; an update

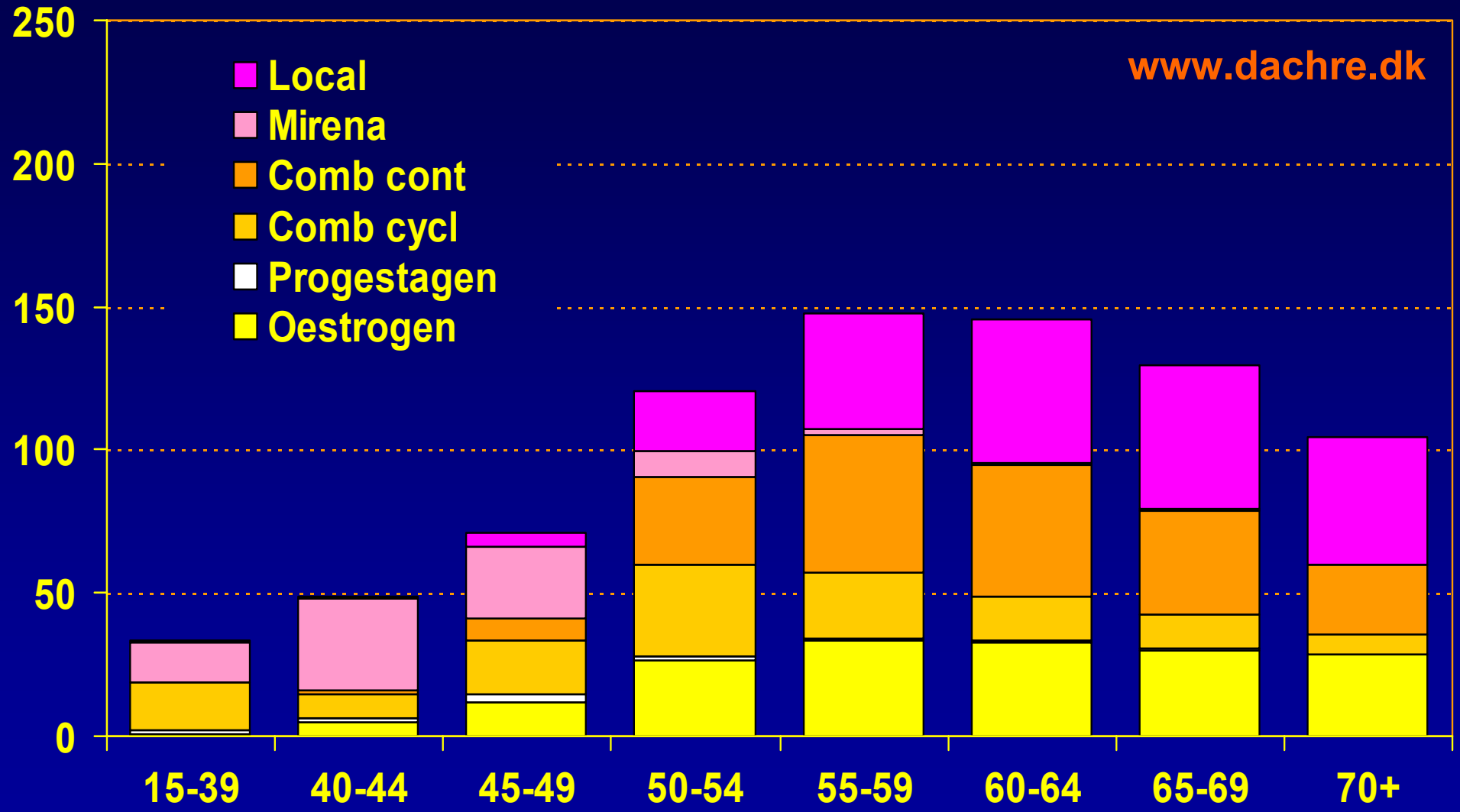
- **Hormone use**
- HT - breast cancer
- HT - endometrial cancer
- HT - ovarian cancer
- HT - colo-rectal cancer
- HT - heart and circulation
- HT - death
- Conclusion

HT sale DK 2002. DDD/1,000 per day



Danish Sex Hormone Register Study (DaHORS).

HT sale DK 2004. DDD/1,000 per day



Danish Sex Hormone Register Study (DaHORS).

Hormone therapy; an update

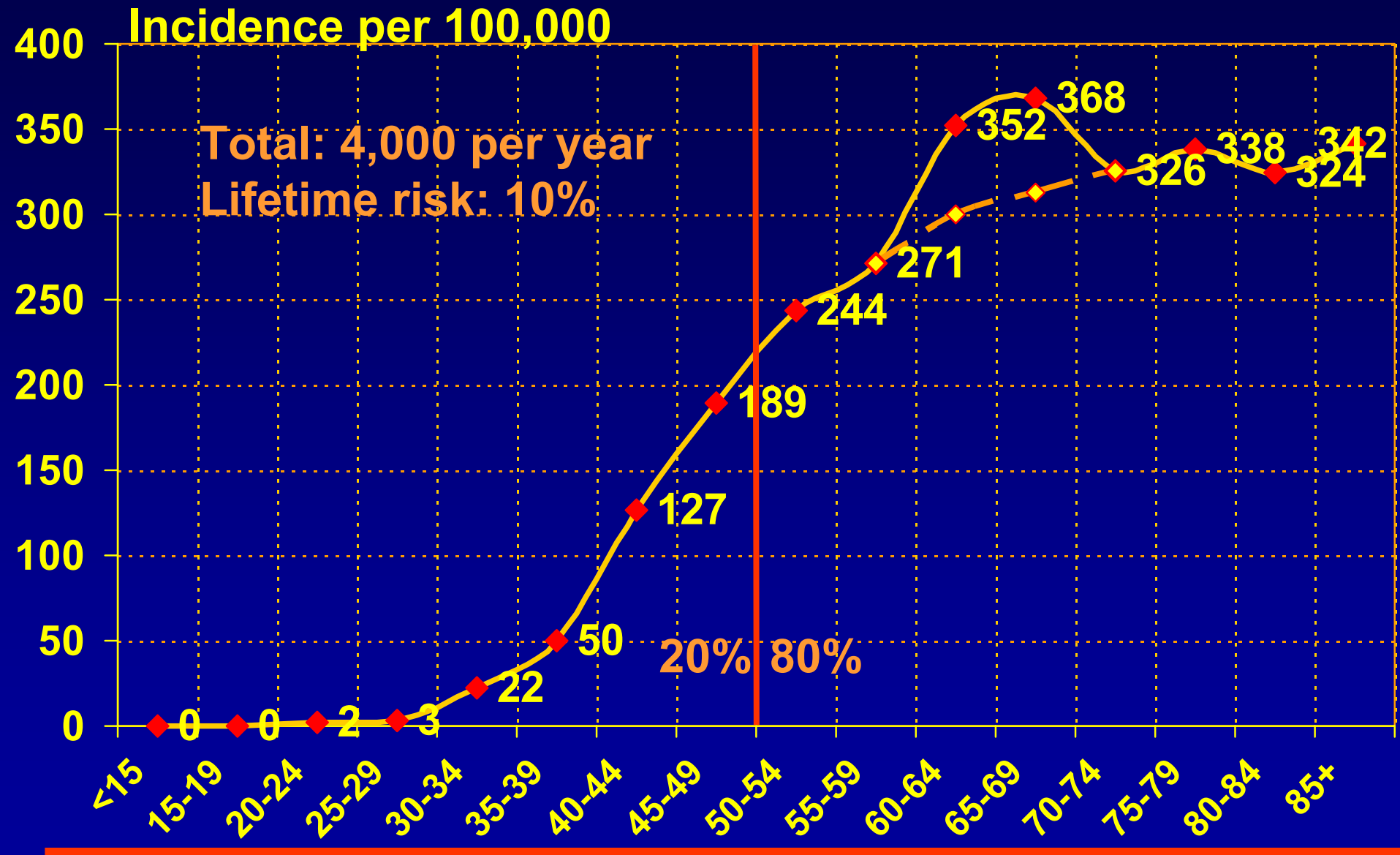
- Hormone use
- **HT - breast cancer**
- HT - endometrial cancer
- HT - ovarian cancer
- HT - colo-rectal cancer
- HT - heart and circulation
- HT - death
- Conclusion

HT and cancer

Axes of significance:

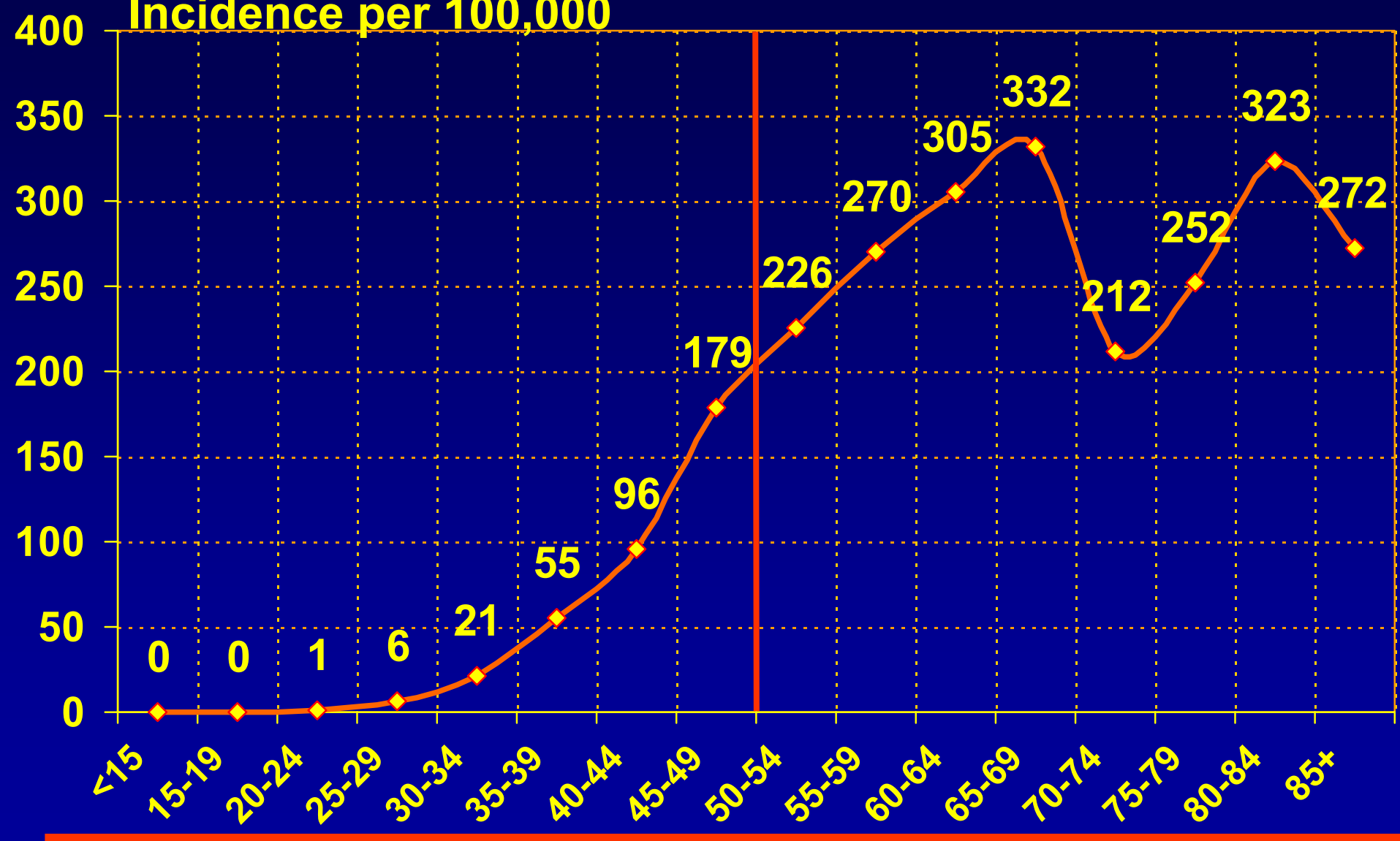
- Duration of therapy
- Regimen (ET, EPT, tibolone)
- Long cycle, cyclic, cont. combined
- Route: Oral, dermal, vaginal, IUD
- Estrogen dose
- Progestagen type
- Progestagen dose

Breast cancer incidence rate by age



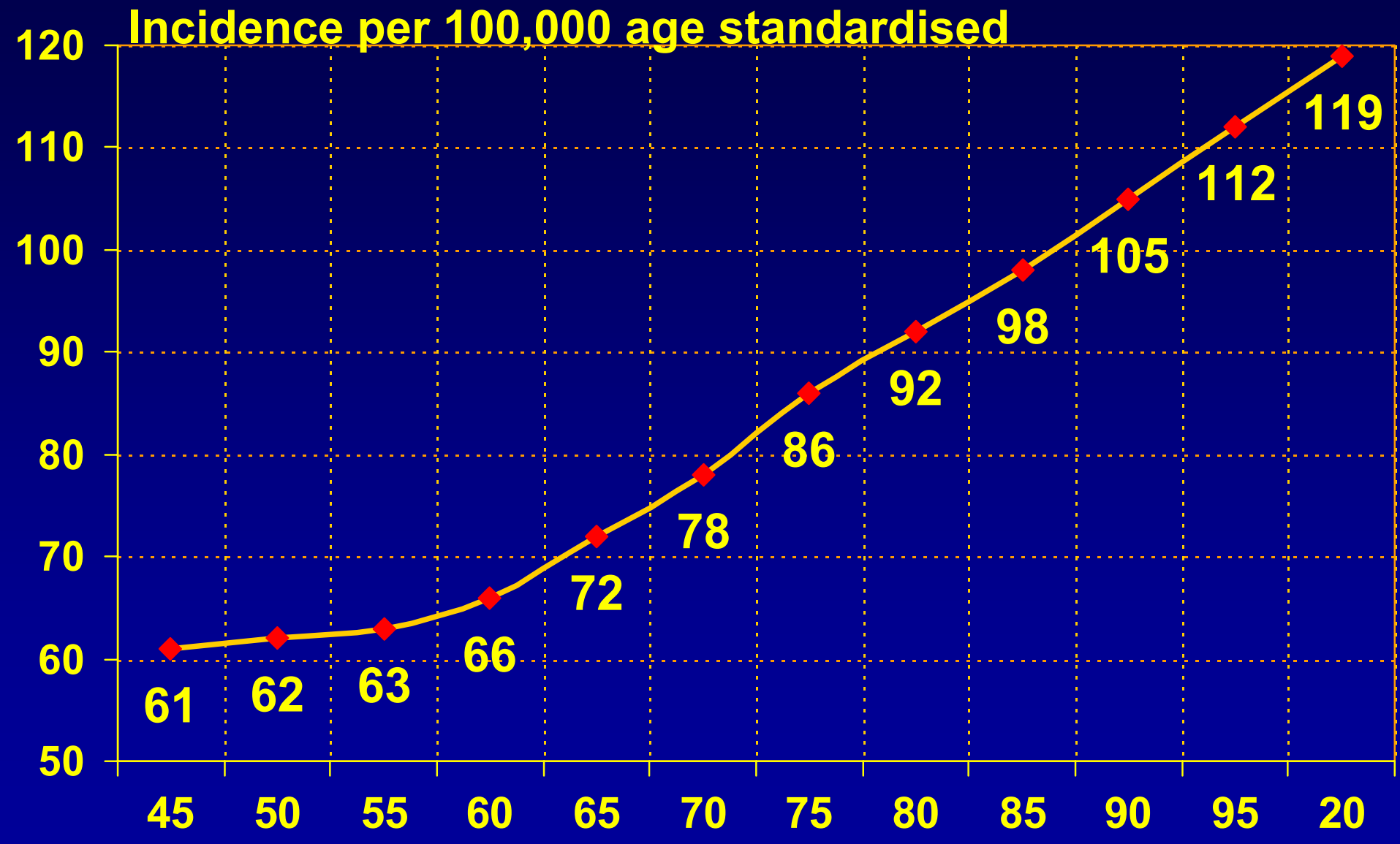
Health statistics, National Board of Health, DK 2003

BC incidence rate in Norway 2005



Cancer Registry, Norway

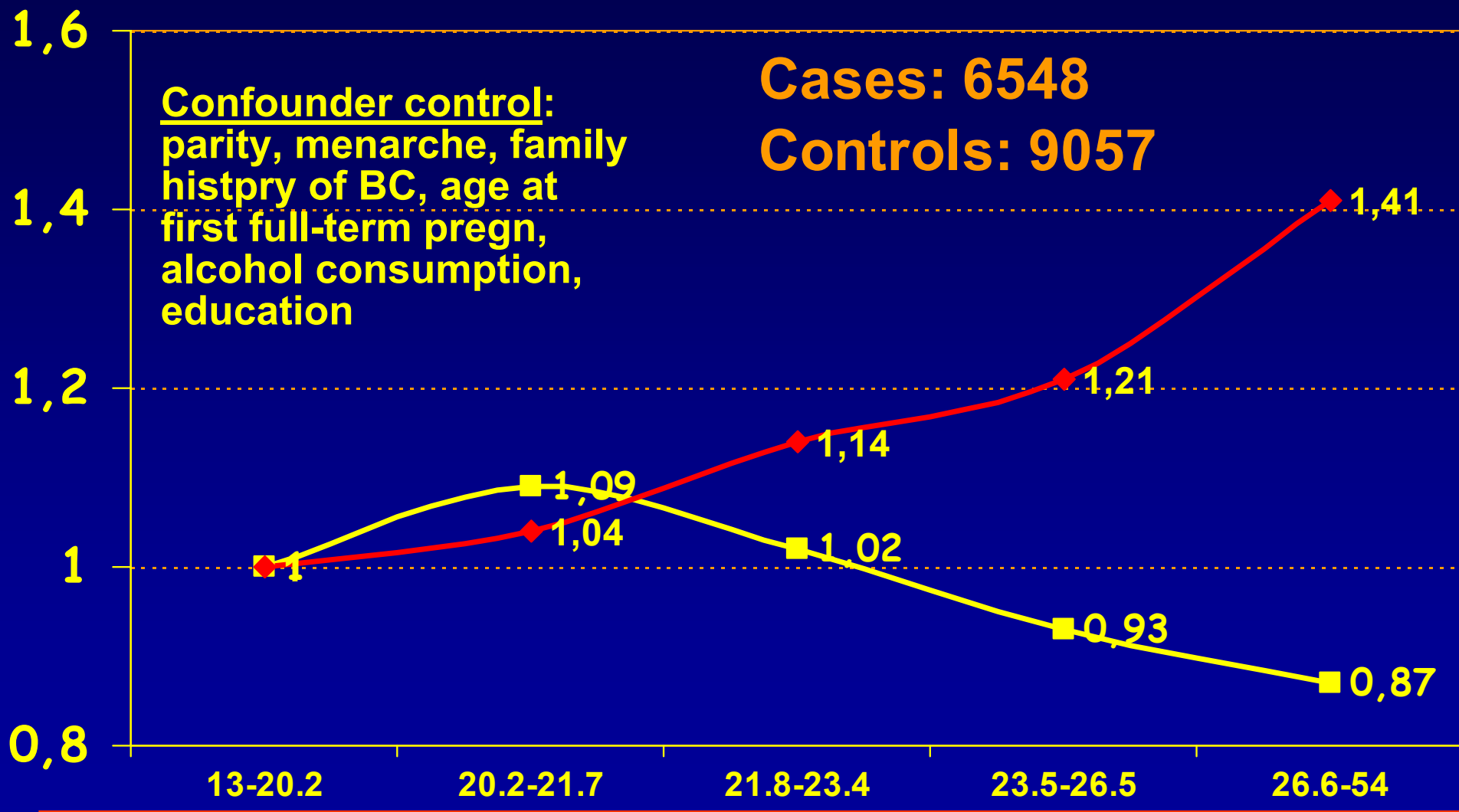
BC incidence rate in DK 1945-2000



Oksbjerg S. Ugeskr Læger 1997; 159: 7134-40.

Li/07

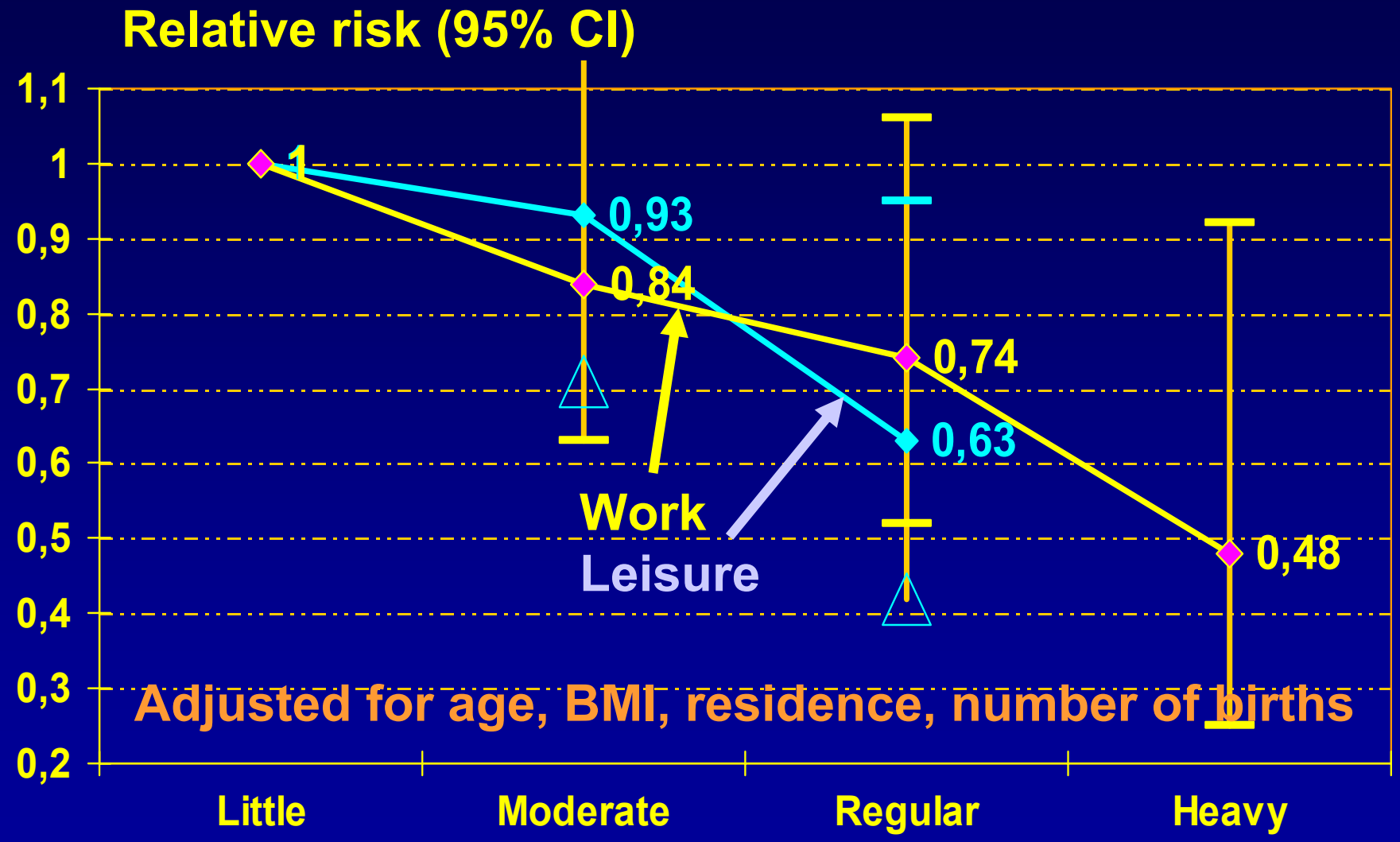
Body mass index and risk of breast cancer



Trentham-Dietz. Am J Epidemiol 1997; 145: 1011-9.

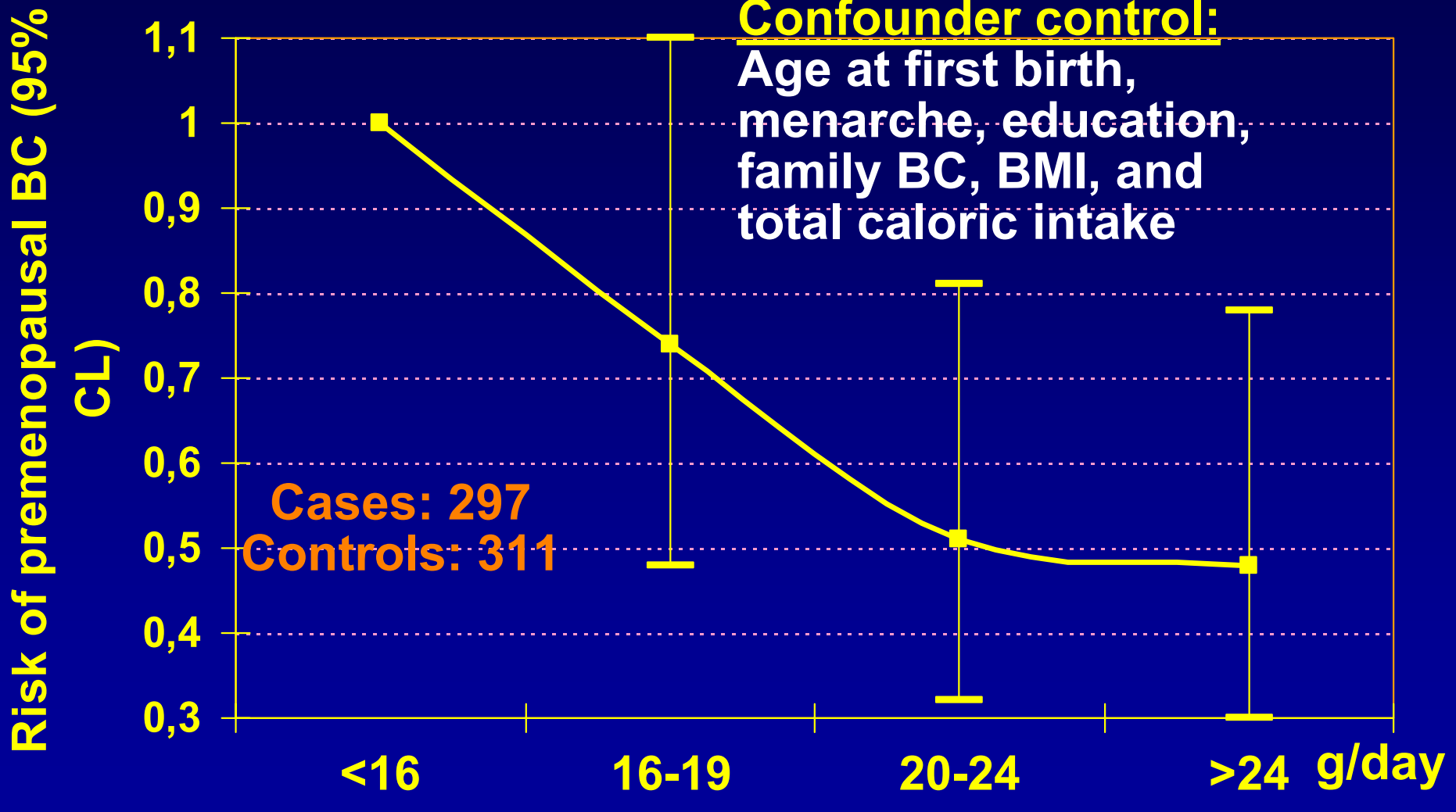
Physical activity and breast cancer

Cohort study of 25,624 women. Follow up: 13.7 years



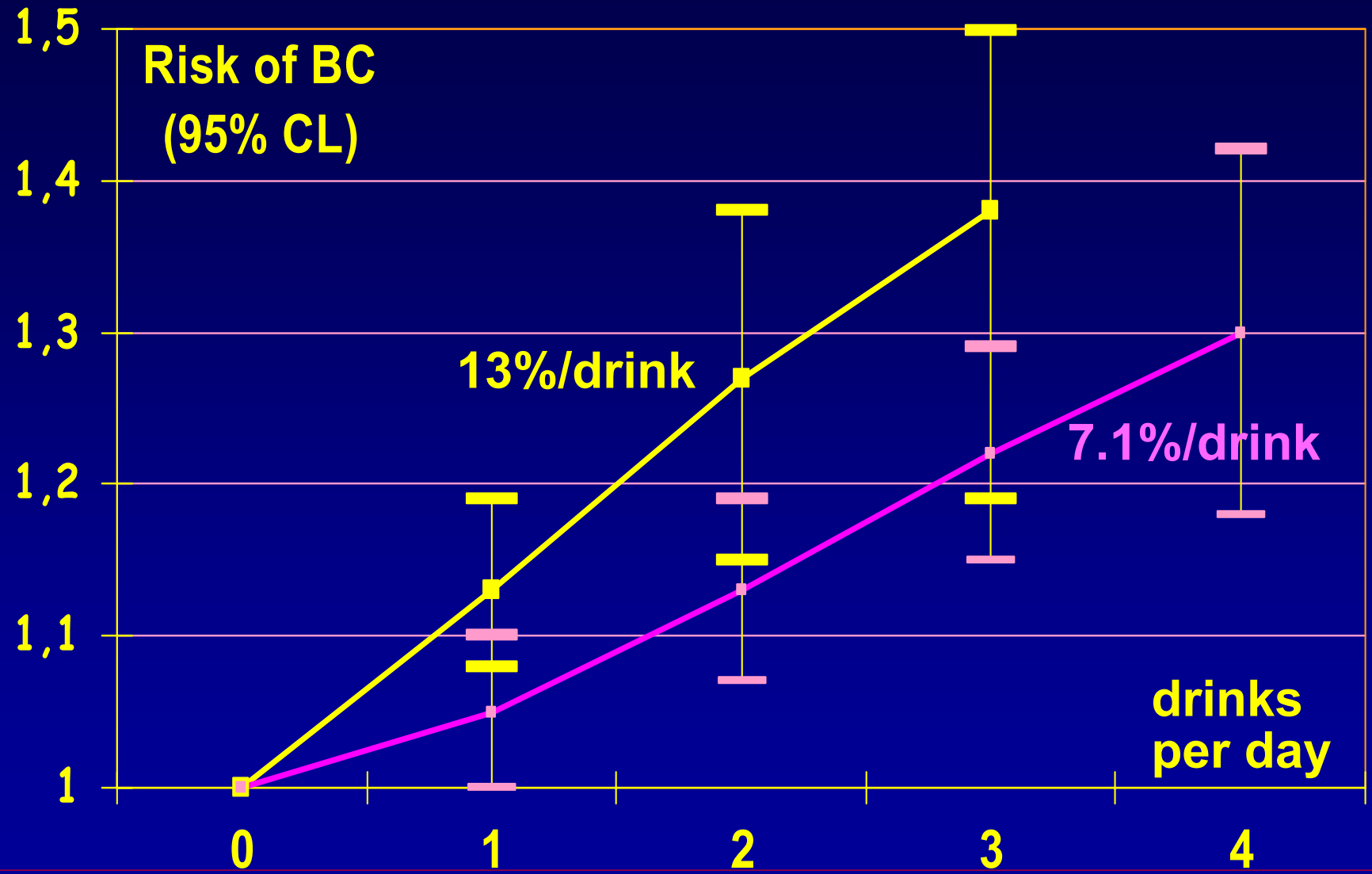
Thune I, N Engl J Med 1997; 336: 1269-75

Fruit and vegetables: influence on pre-menopausal BC



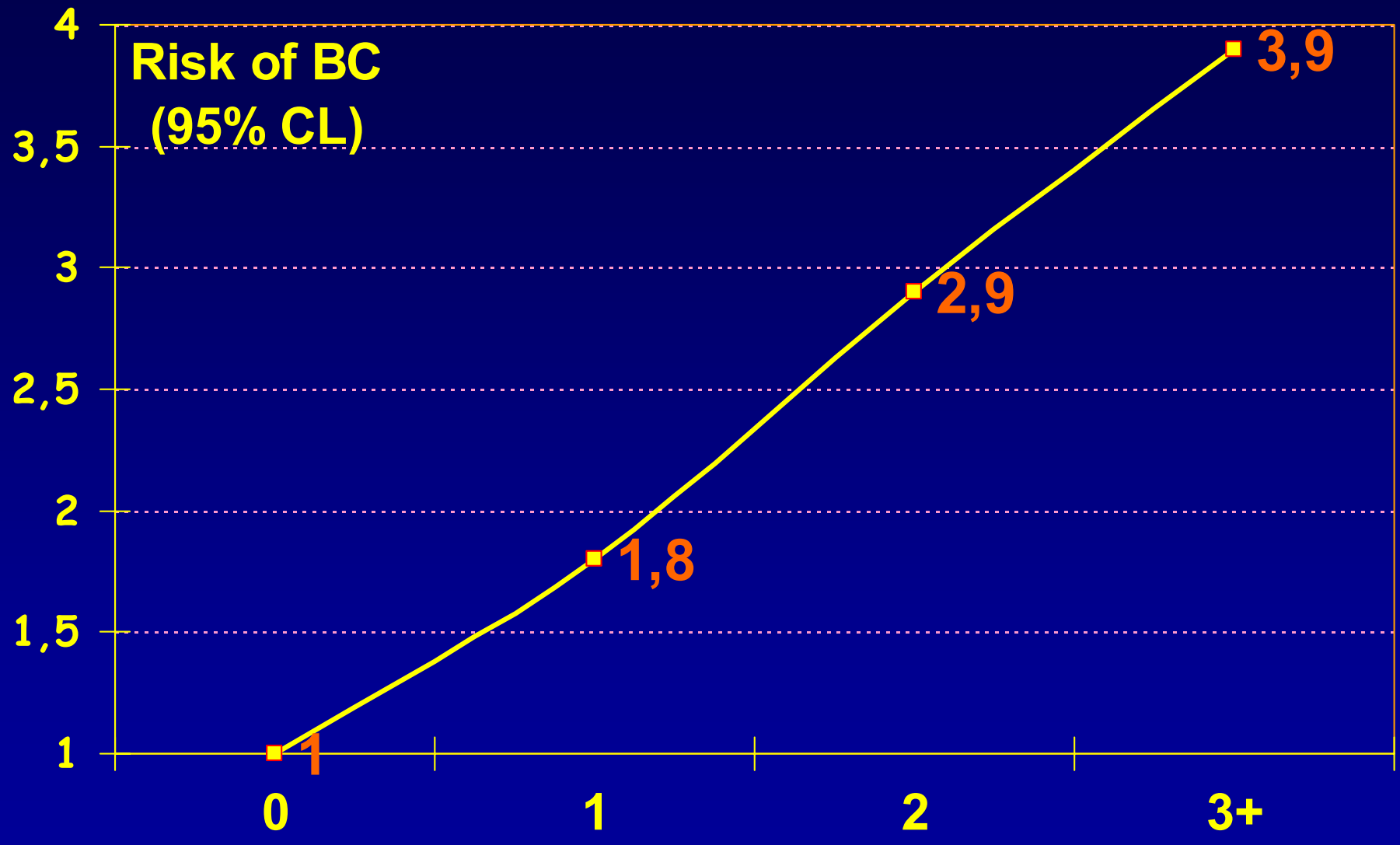
Freundenheim. J Natl Canc Inst 1996; 88: 340-8.

Alcohol intake and risk of breast cancer



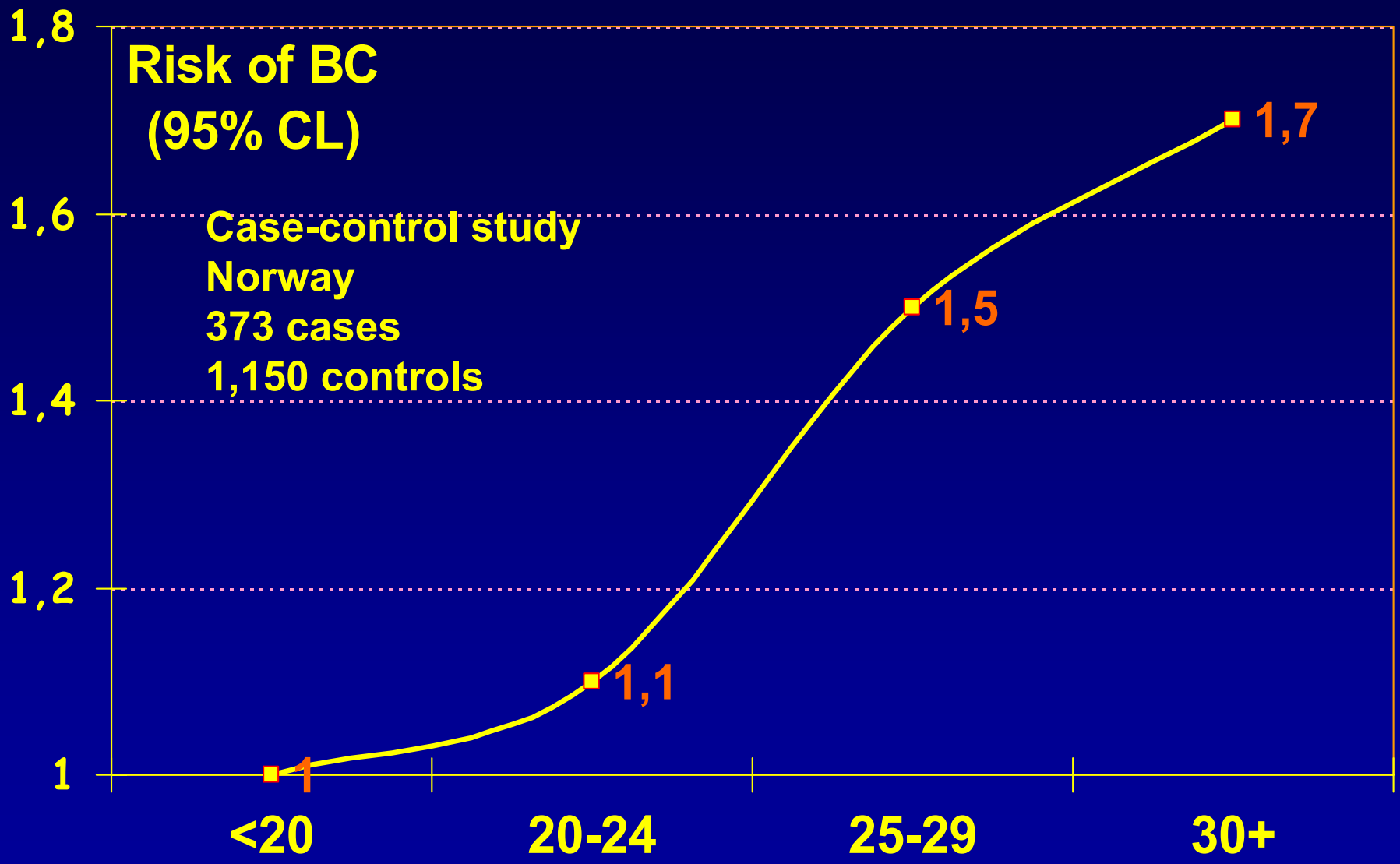
Longnecker. Canc Causes and Control 1994; 5: 73-82
Beral V et al. Lancet 2002; 87: 234-45

Family disposition and BC



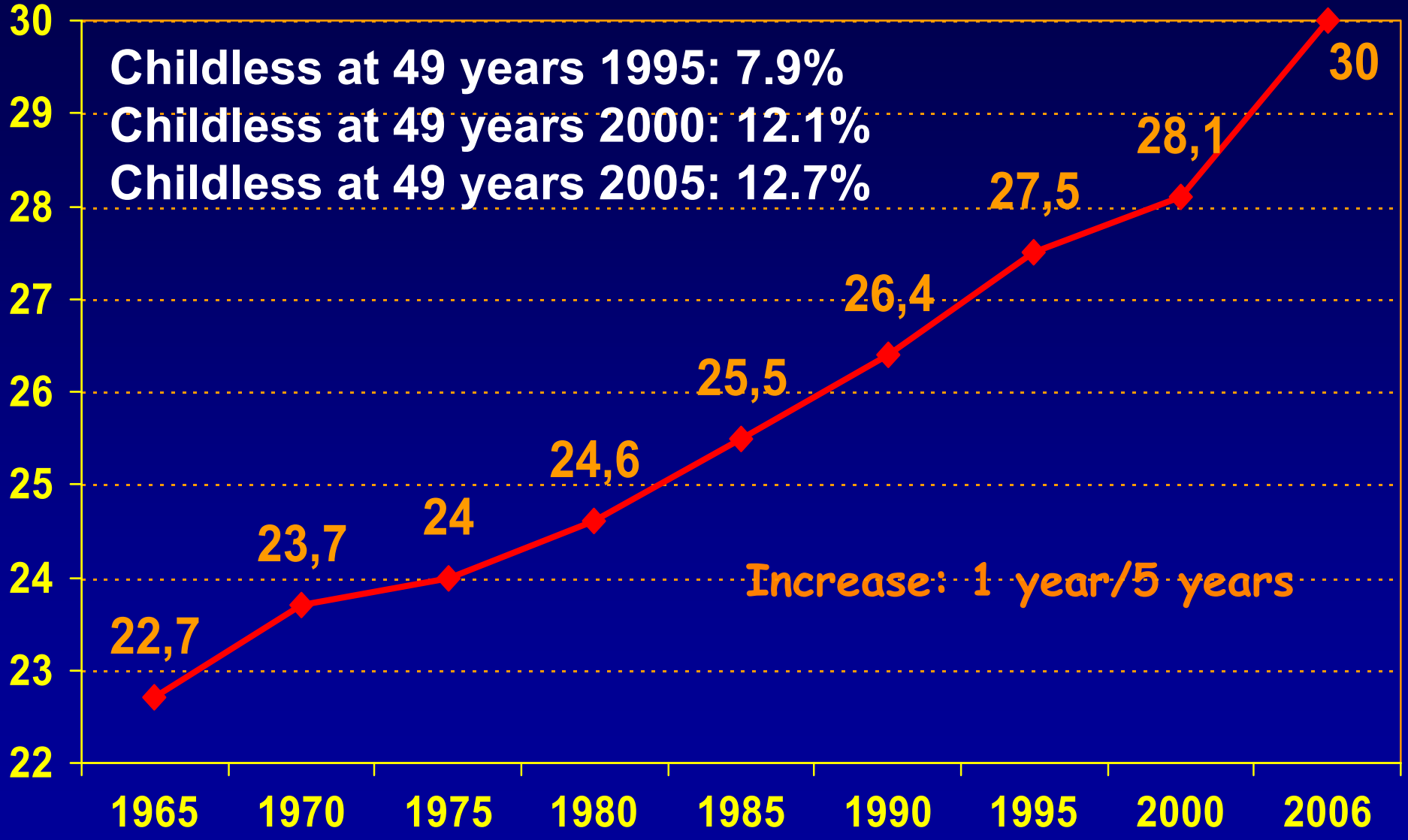
Collaborative group, Lancet 2001; 358: 1389-99

Age at first birth and risk of BC



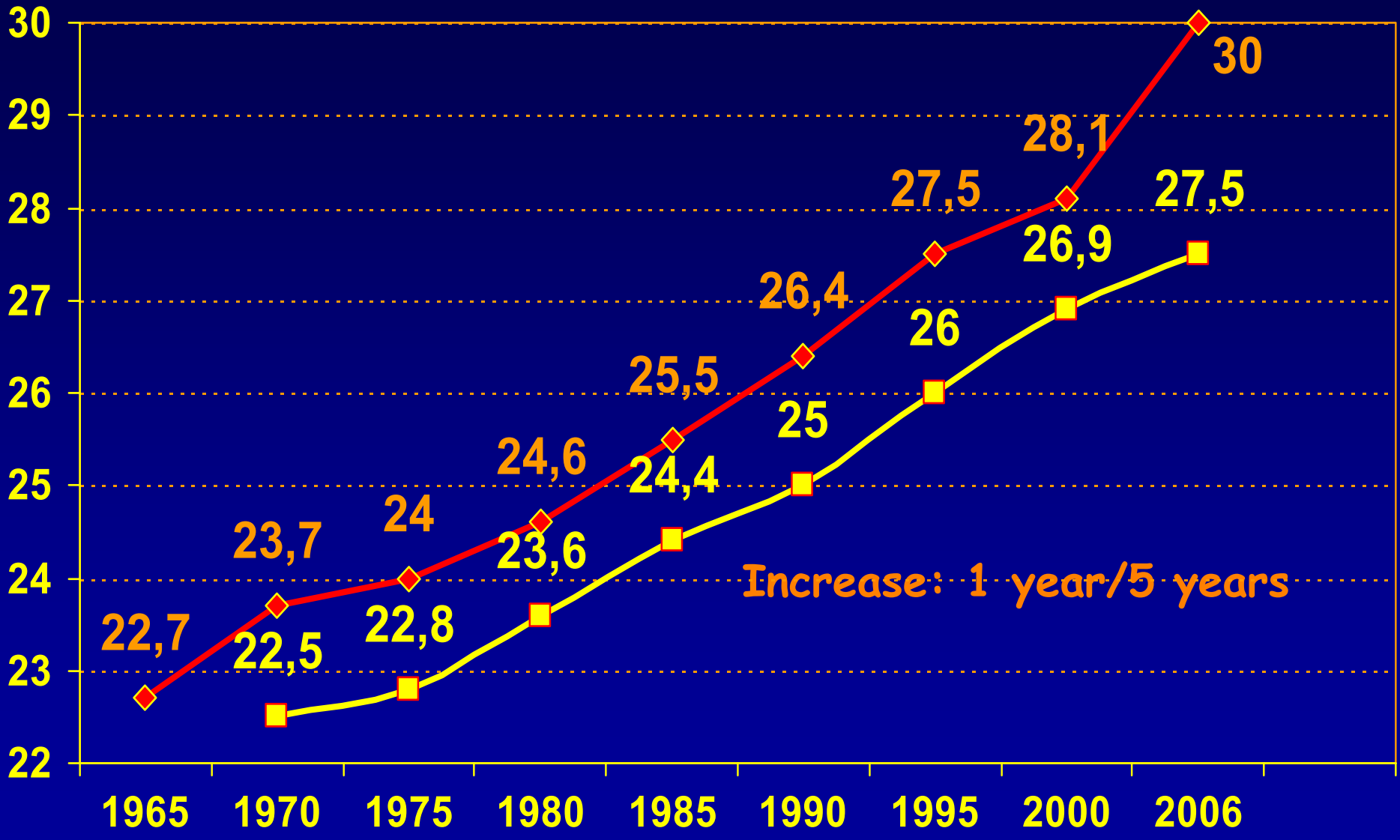
Vatten LJ. Br J Cancer 2002, 86: 89-91

Age at first birth DK 1965-2006



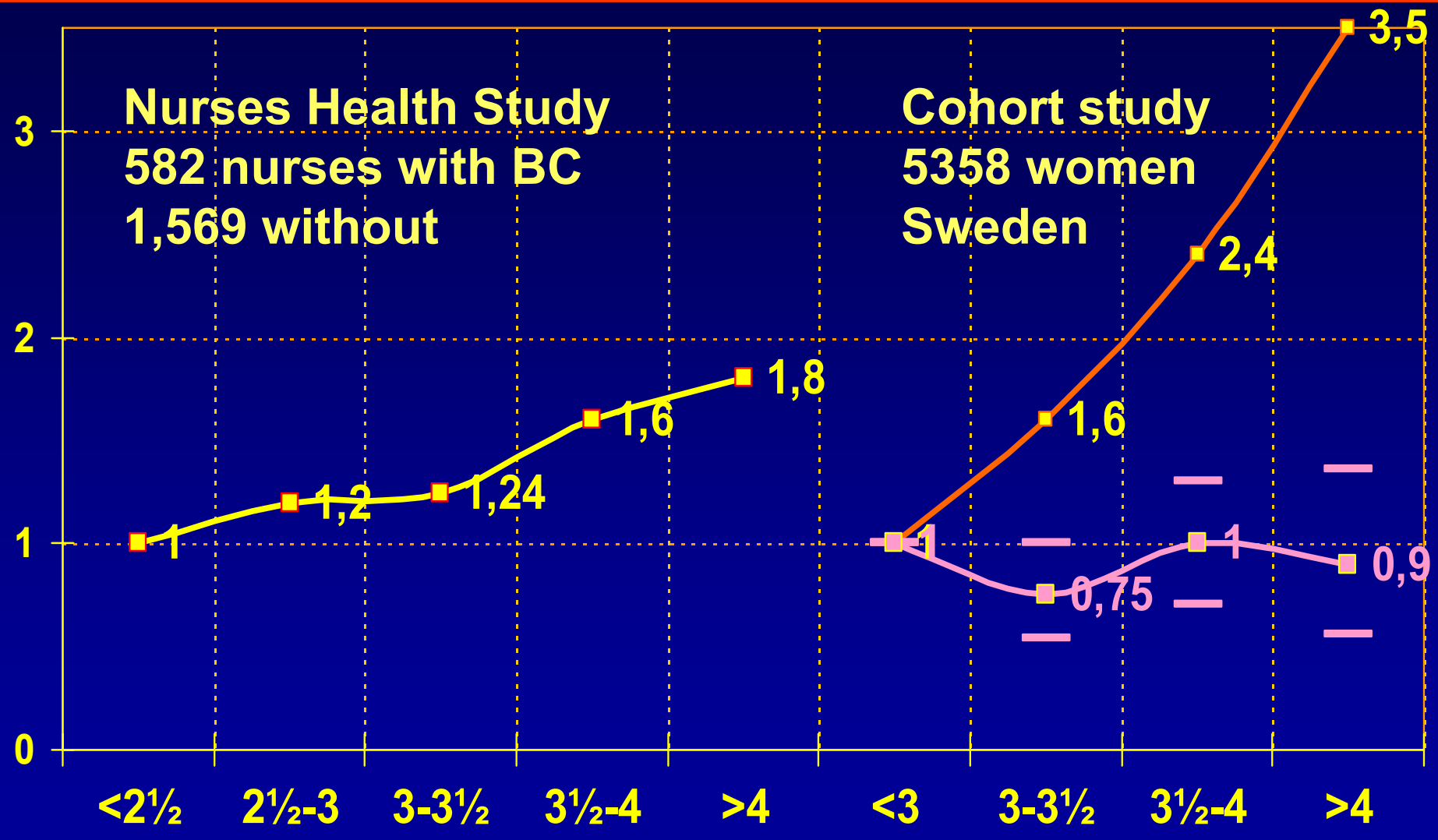
Online statistics: www.dst.dk

Age at first birth DK and No



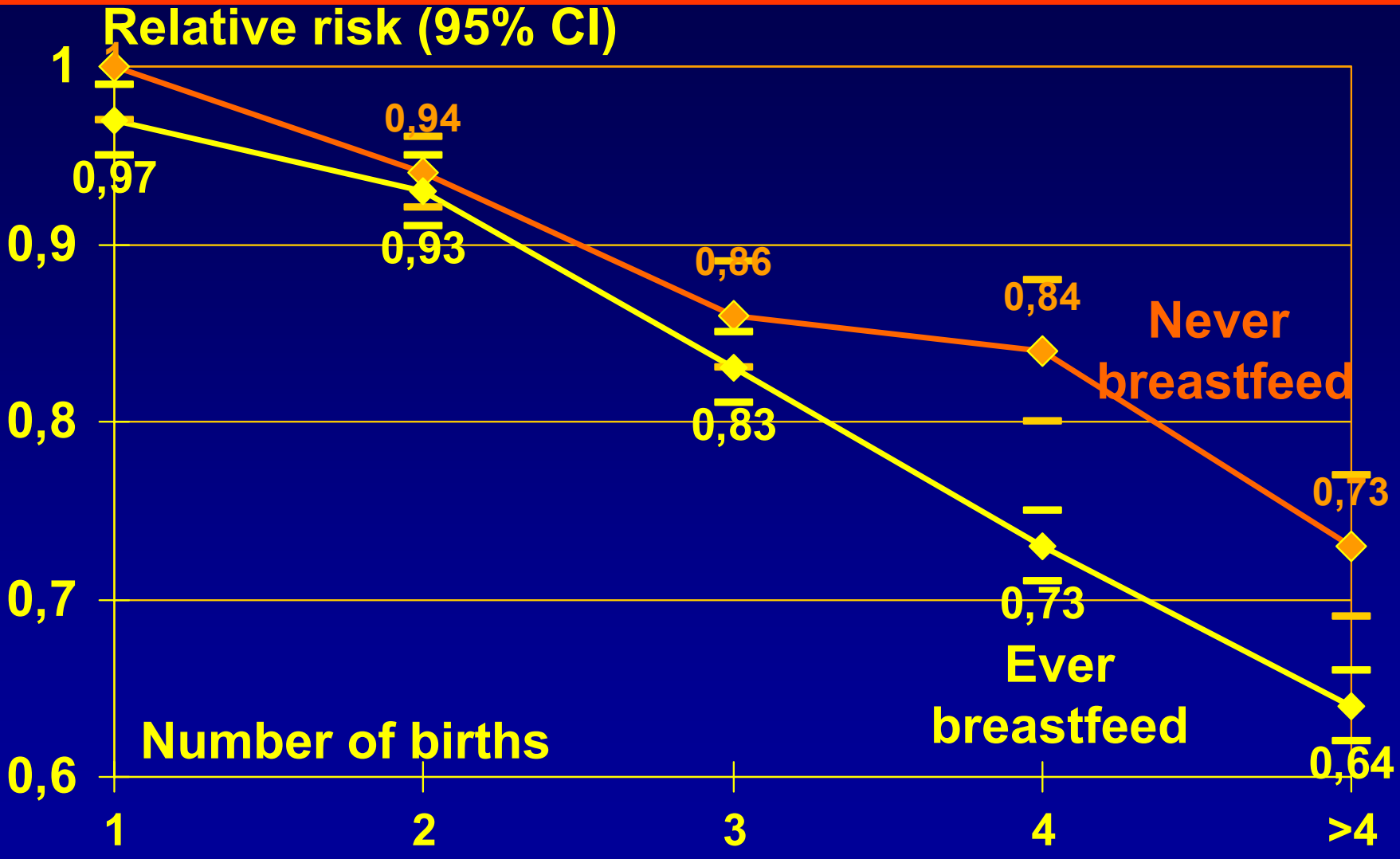
Online statistics: www.dst.dk and www.fhi.no

Breast cancer and birth weight



Lancet 1996; 348: 542-6. BMJ 2003; 326: 248-53.

Breastfeeding, parity and breast cancer



Collaborative group. Lancet 2002; 360: 187-95.

Can we explain the increase?

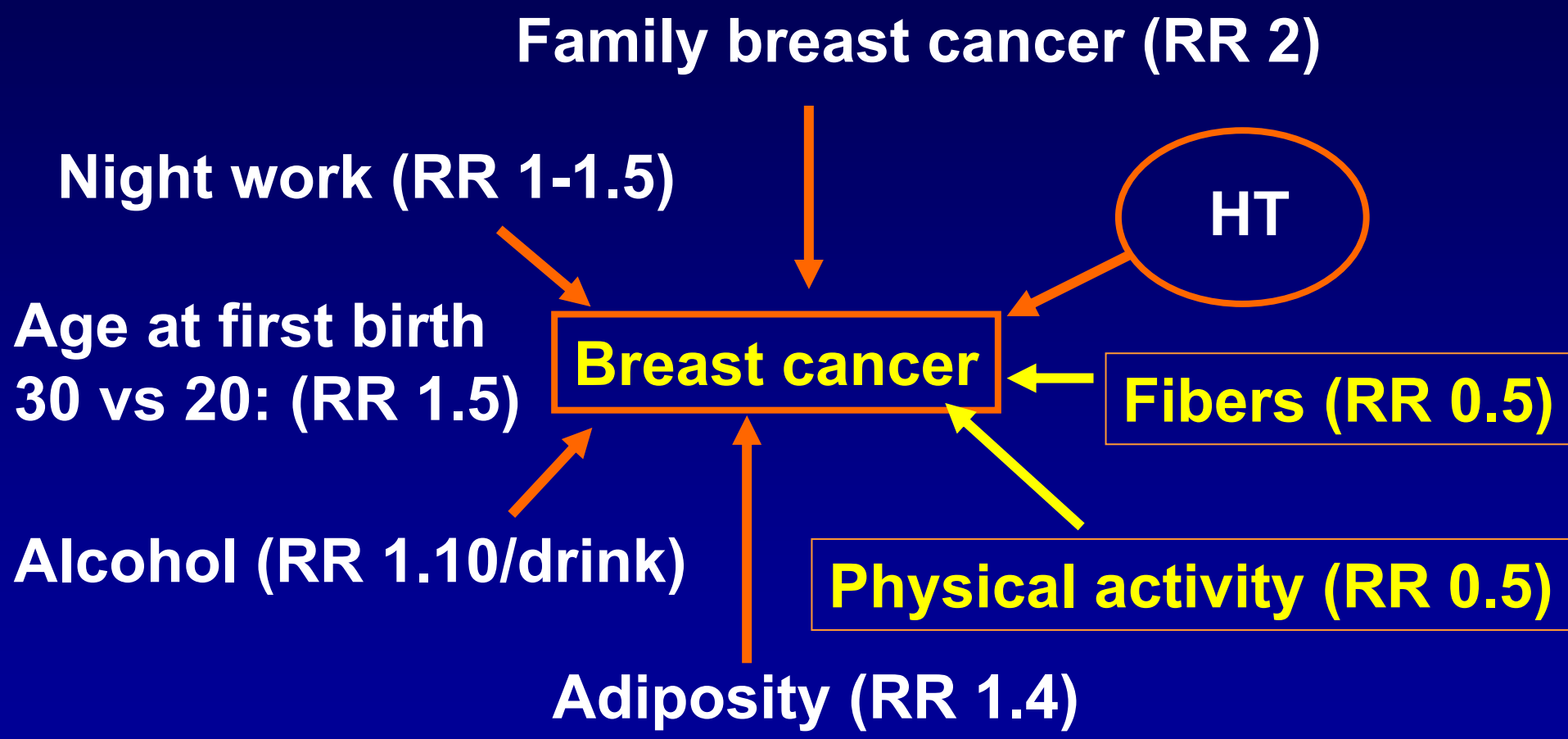
Yes:

- Increase in age at first birth 21→29 years
- Higher birth weight
- Less physical activity
- Fewer children per woman
- Increase in daily alcohol consumption
- Dramatic increase in BMI

These factors fully explain the increase

Lidegaard & Kroman. Eur Clinics Obstet Gynaecol 2005; 1: 24-8

Breast cancer: Risk factors



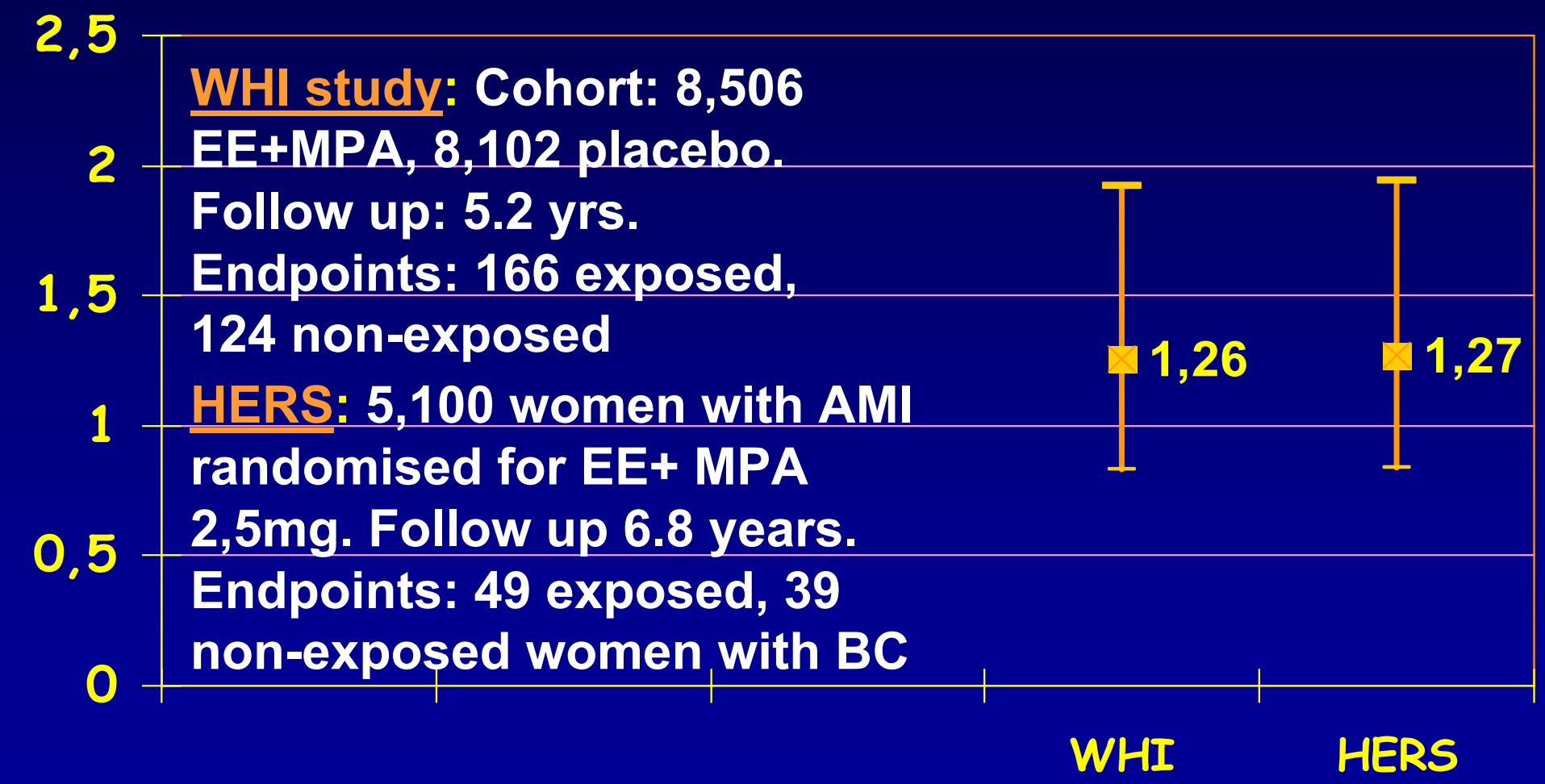
HT and breast cancer (BC) Metaanalysis from 1996

- Current HT increases the risk of breast cancer by 10-30% (5-15 years)
- The risk was 16% higher for comb. HT.
- The risk increased with duration of use
- The risk faded out after cessation
- Women with BC and previous HT have a better survival than BC patients without previous HT => no increased risk of death

Metaanalysis: 52,705 cases, 108,411 controls. Lancet 1997

HT and BC: Randomised studies

Risk after 5.2 and 6.8 years MPA+EE



Rossouw et al. JAMA 2002; 288: 321-33.
Hulley et al. JAMA 2002; 288: 58-66

WHI results

	EPT	ET	50-59
• Coronary heart disease	1.3	0.9	0.6
• Stroke	1.4	1.4	1.1
• Venous thromboembolism	2.1*	1.3	1.2
• **Breast cancer**	**1.3**	**0.8**	**0.7**
• Endometrial cancer	0.8	hysterect.	
• Colorectal cancer	0.6	1.1	0.6
• Hip fracture	0.7	0.6	NA
• Vertebral fracture	0.7	0.6	NA
• All cause mortality	1.0	1.0	0.7

Rossouw et al. JAMA 2002; 288: 321-33.

Million women study

Design:

- A prospective cohort study

Cohort:

- Women invited with invitation to breast cancer screening. 75% accepted screening,

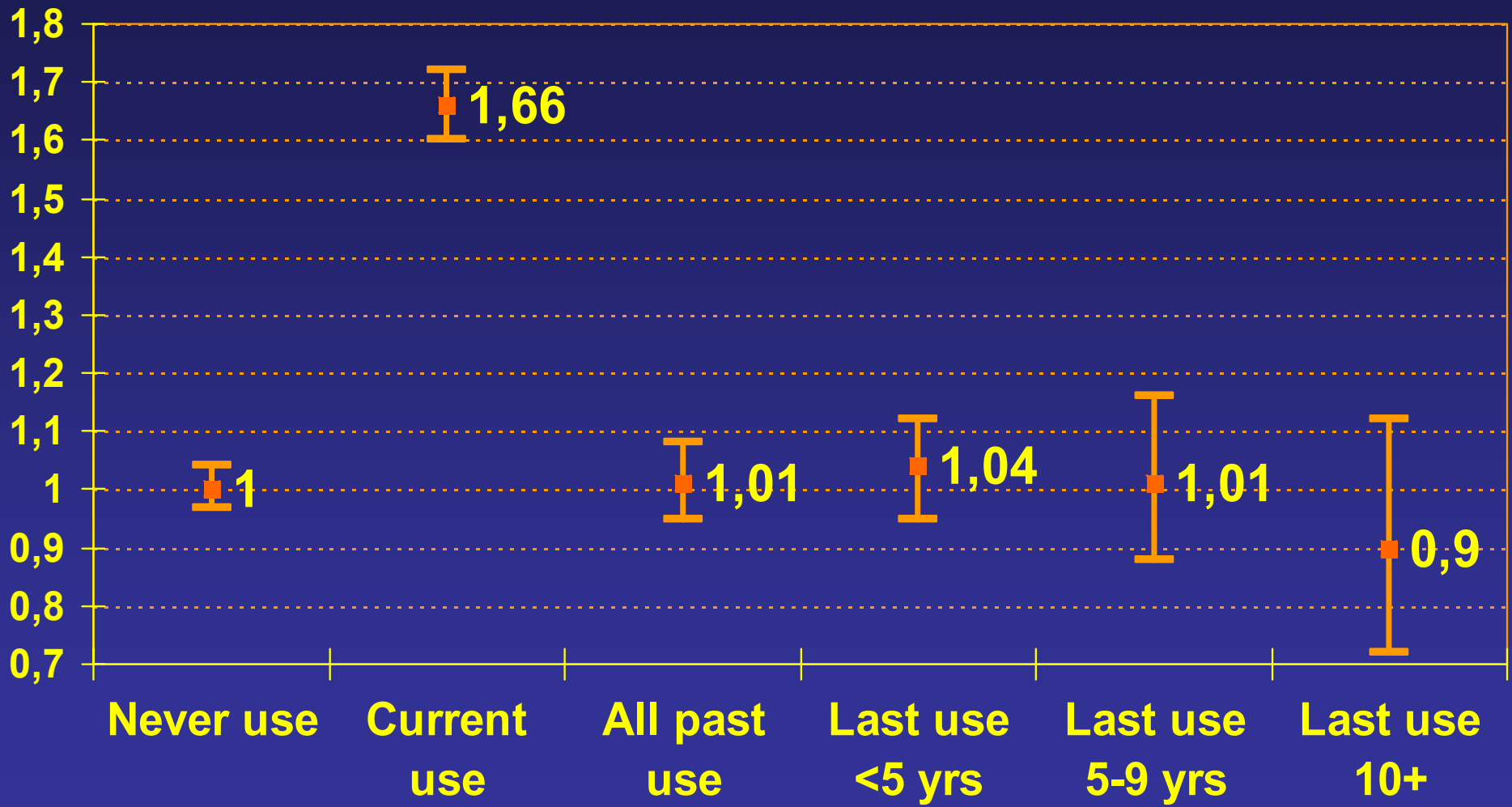
  71% of screened (53% of all) accepted participation in the study.
- Age: 50-64 years at baseline
- Recruitment: May 1996 – March 2001

Follow up

- Incidence: Dec 2000 or 2001; 2.6 years
- Mortality: December 2002; 4.1 years

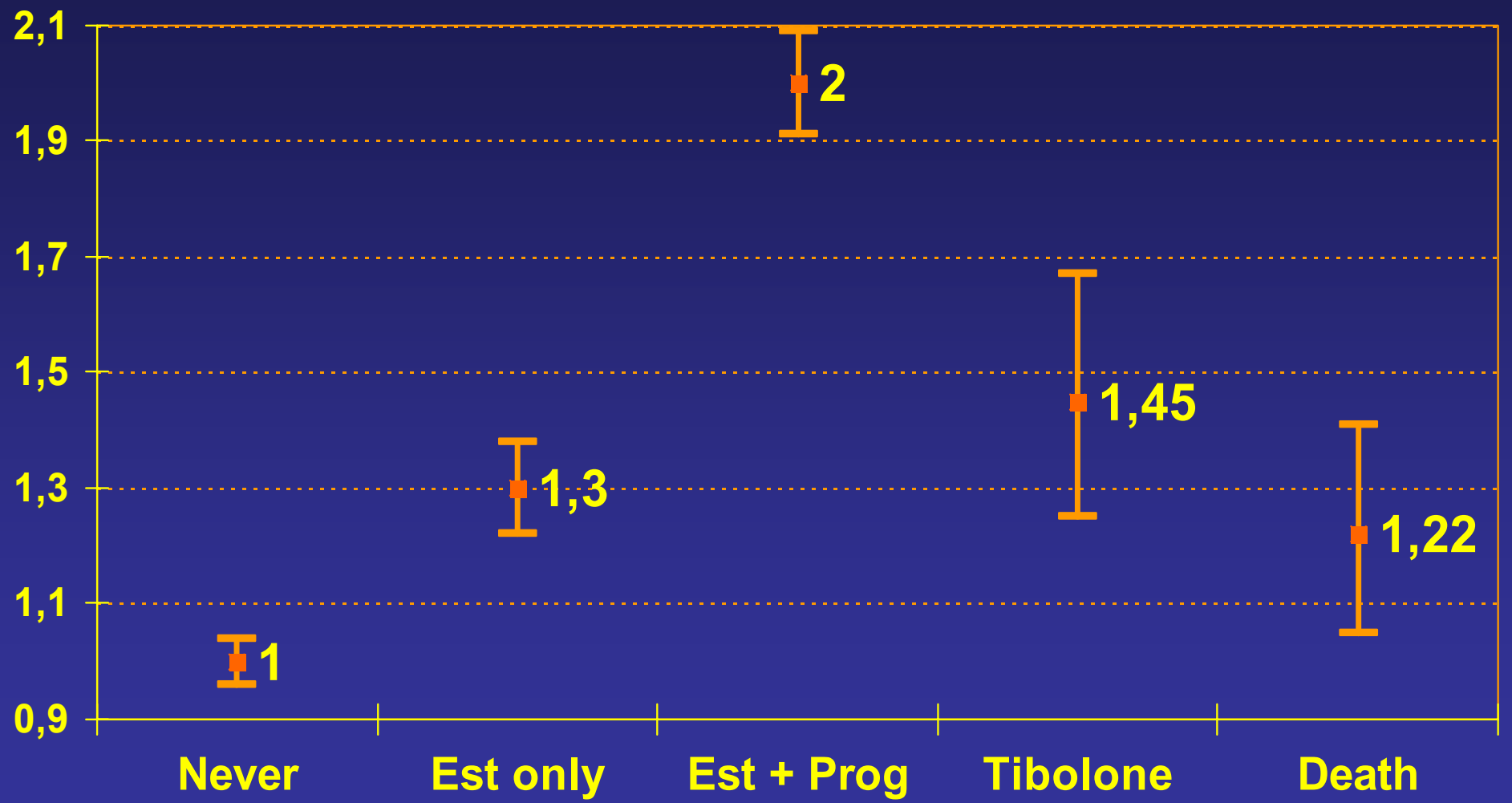
Lancet 2003; 362: 419-27

Risk in women currently on HT

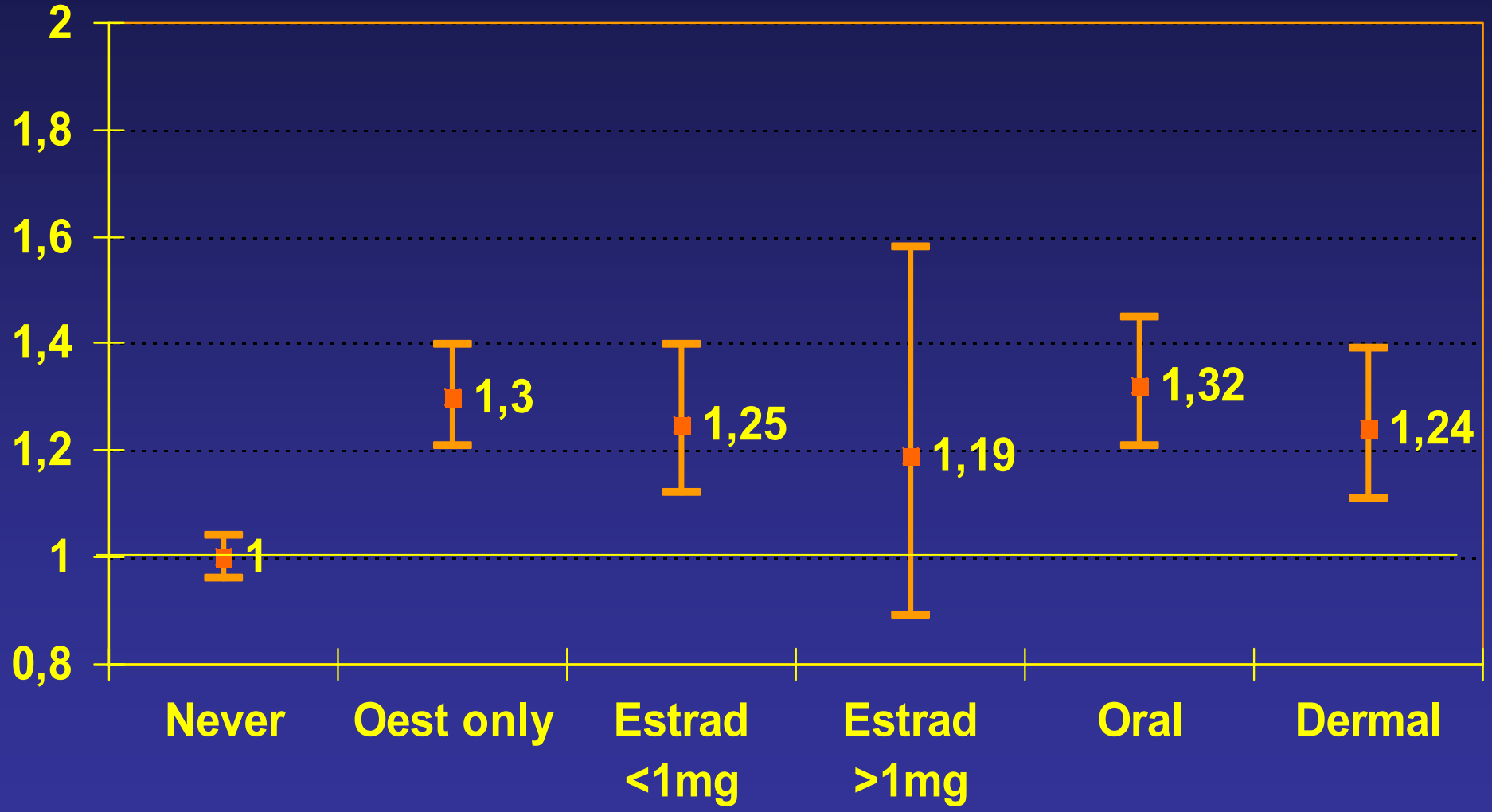


Lancet 2003; 362: 419-27

Risk on different regimens

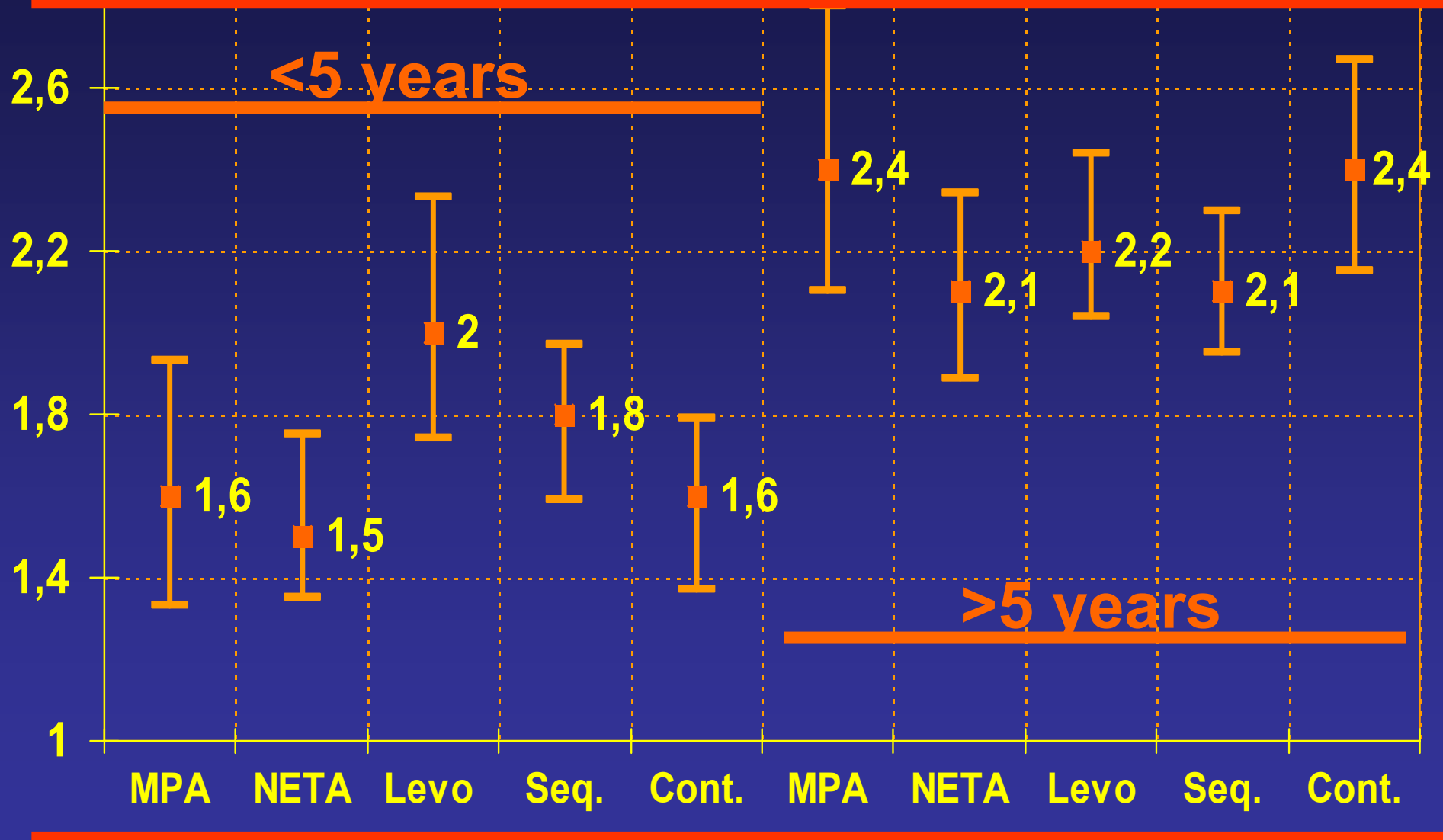


Oestrogen only therapy



Oestrogen-progestagen therapy

Influence from different progestagens



Danish sex Hormone Register Study
DaHoRS (1.8 mio women study)

Hormone therapy and breast cancer

Øjvind Lidegaard
Ellen Løkkegaard
Lisbeth Møller
Carsten Agger
Anne Helms Andreasen

DaHoRS: Principal study design

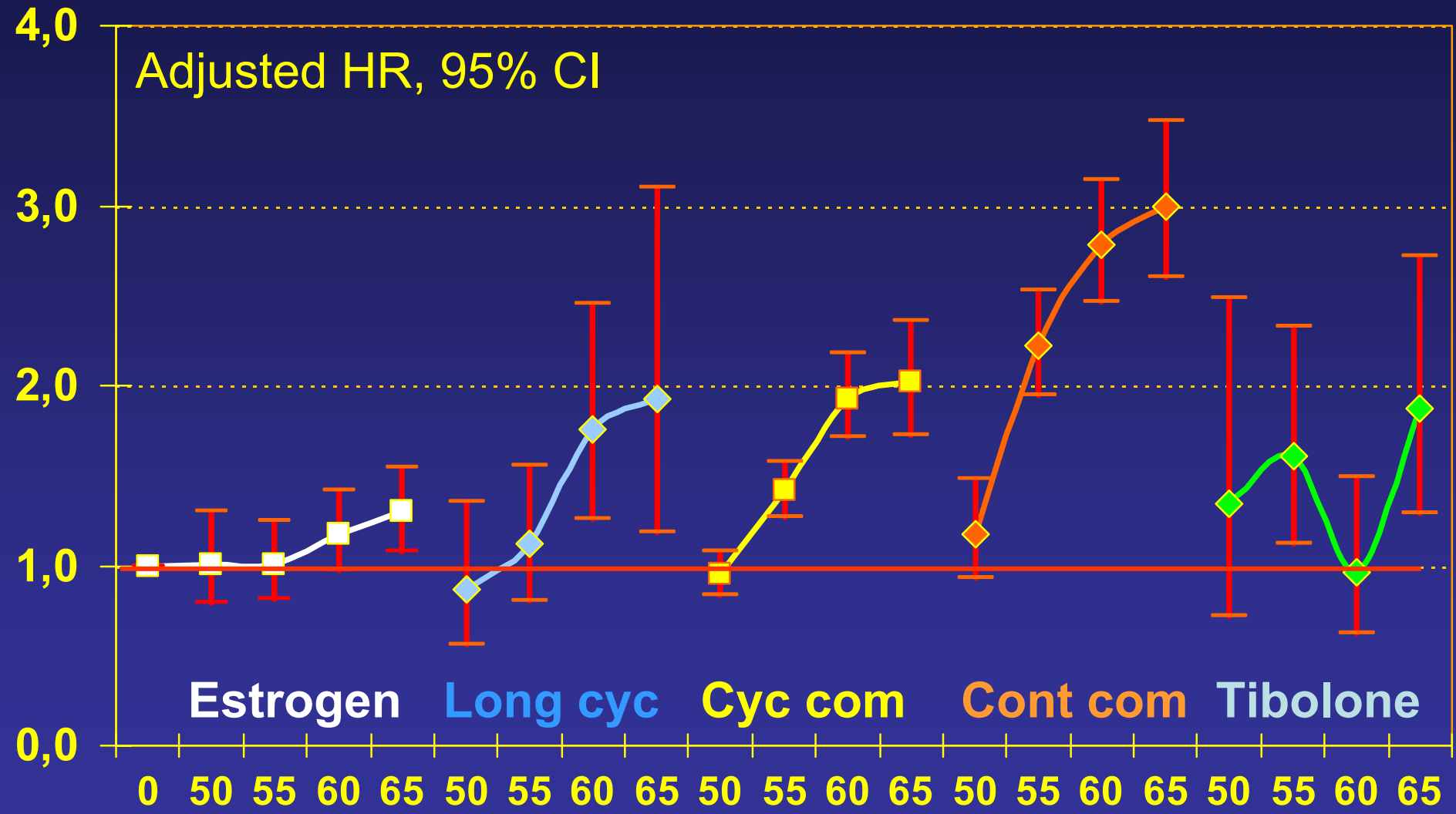
- A National cohort of women
- 15-69 years old per January 1, 1995
- Followed from January 1995 through 2002
- Exposures and outcomes from national registers
- Assessing the influence of OC and HT on the risk of cardiovascular diseases and cancer
- Details on www.dachre.dk

Hormone therapy and breast cancer

• Cohort: Included women 50-69:	785,397	
• Exposed women (current+prev):	234,955	
• Control women (never users):	550,442	
• Women currently on HT with BC:	3,010	2.5
• Women previously on HT w BC:	1,957	1.7
• Women never on HT with BC:	7,864	1.4
• Included with BC:	12,831	

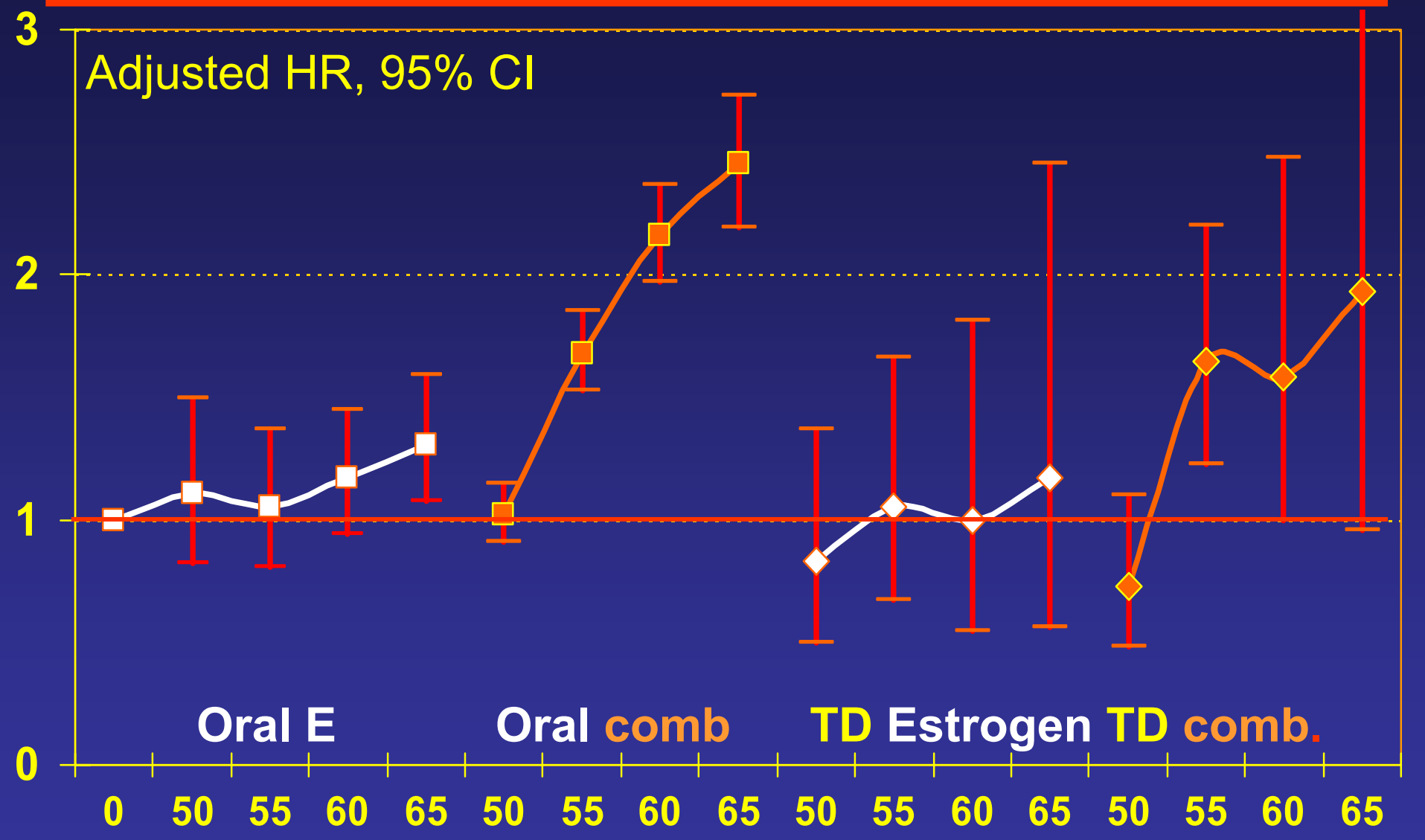
Danish Sex Hormone Register Study (DaHoRS): www. dachre.dk

BC risk according to HT regimen



DaHoRS/07

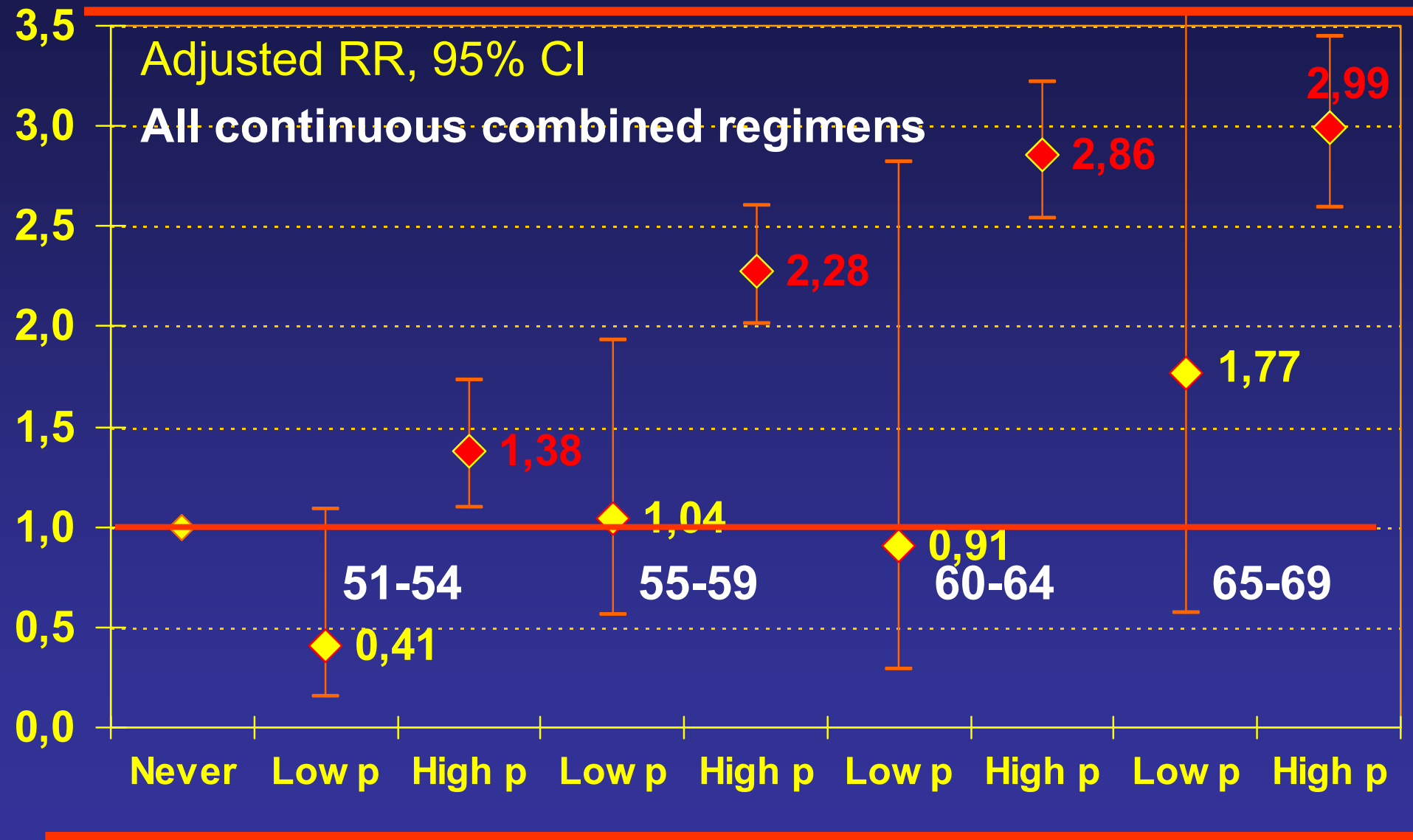
BC risk according to route



DaHoRS/07

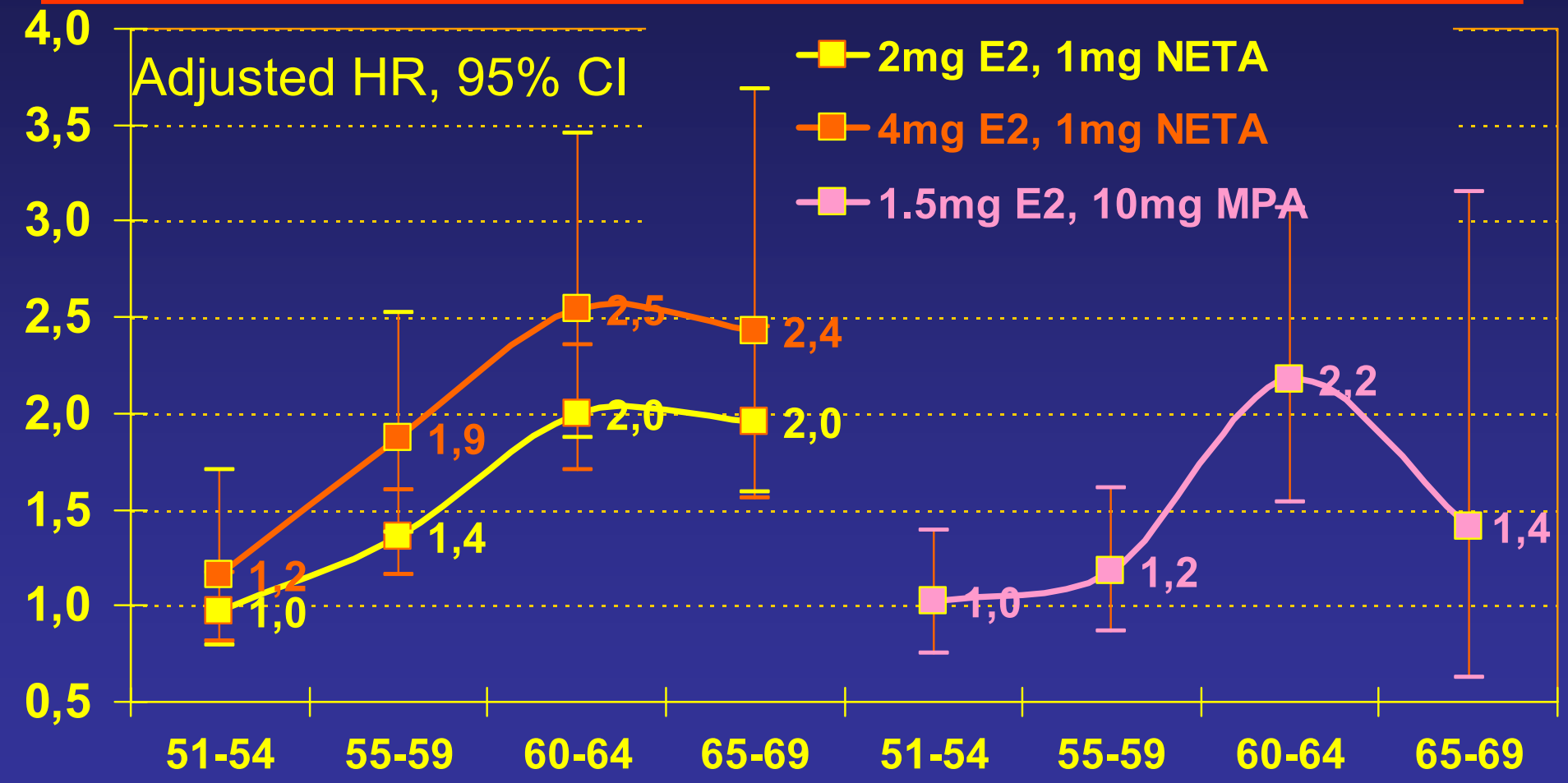
The impact of progestagen dose

Low = 0.5mg NETA or 2.5mg MPA. High = 1mg NETA or 5mg MPA

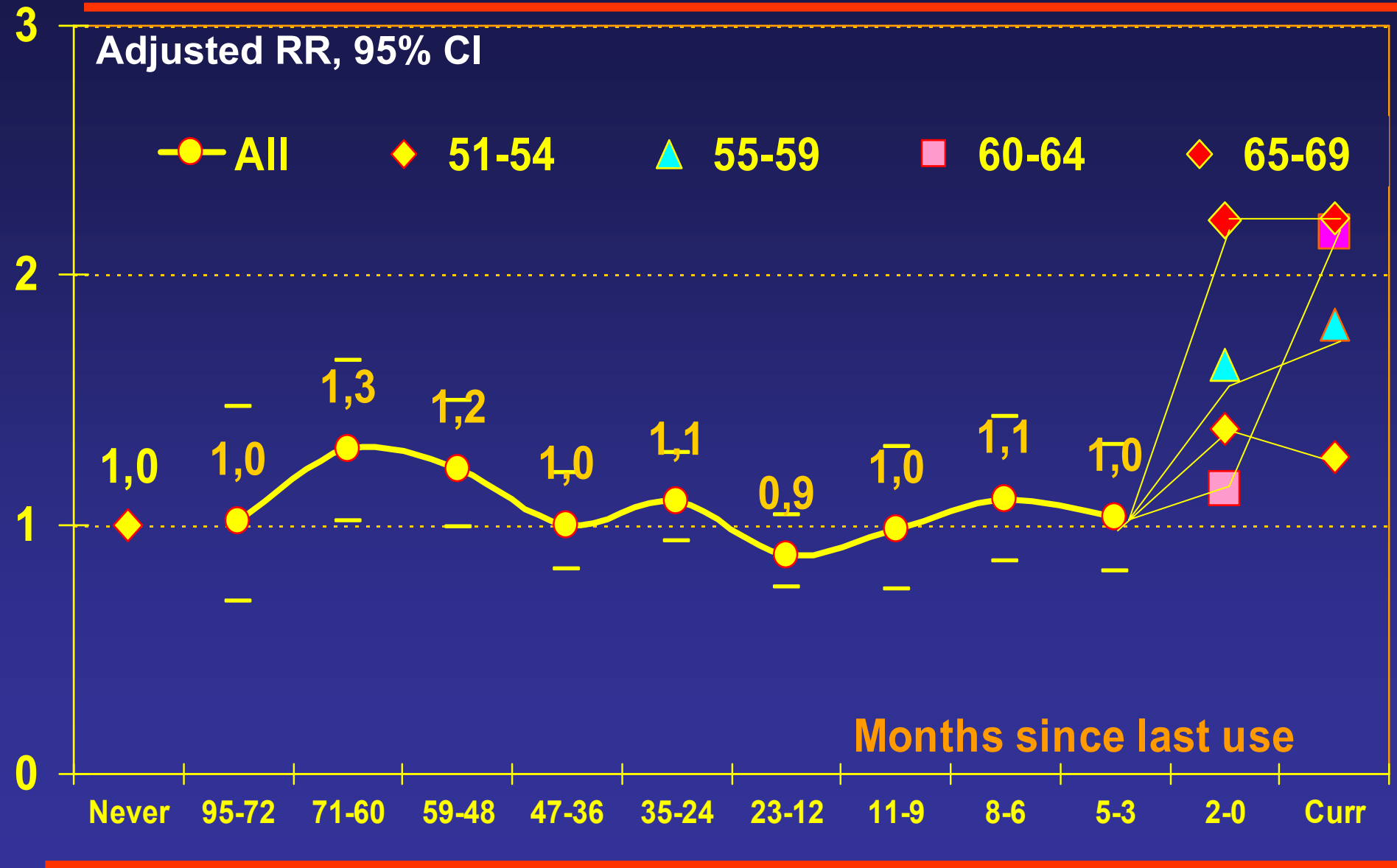


BC risk acc to progestagen type and estrogen dose.

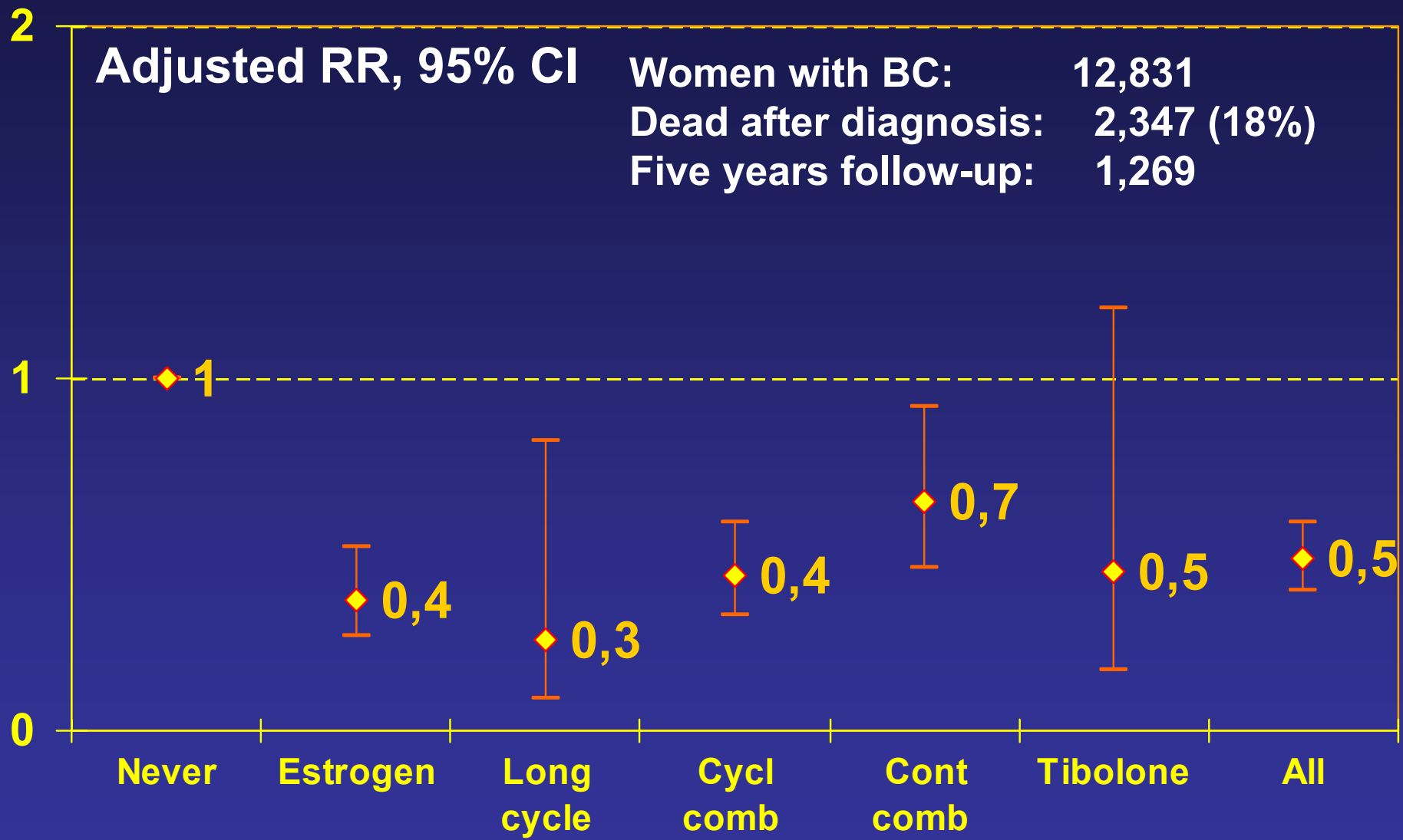
Cyclic combined regimen



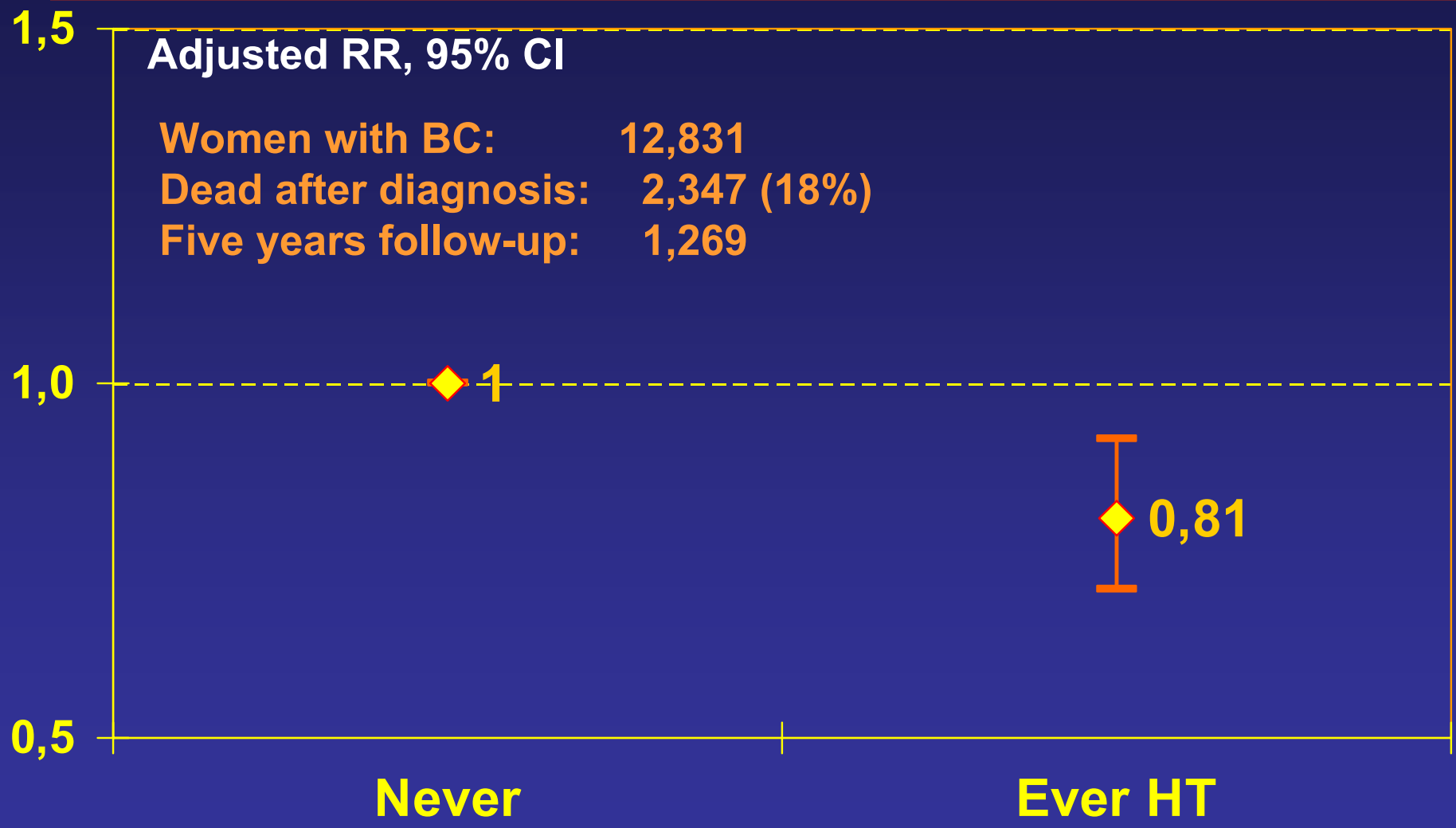
Previous systemic use and BC risk



Case-fatality rate 5 yrs after diagnosis



Risk of lethal BC with hormones within five years after diagnosis



BC screening, HT and BC

- Cohort study among screening participants
- Enrolment period: 1995-2004
- Questionnaire at enrolment
- Follow-up 2 years (up to next BC screening)
- Included: 296,651 women.
- Detection of screening BC: 1,512
- Detection of interval BC: 814
- Confounders: menarche, education, number of births, family history, alcohol, menopause

Hofvind S et al. Int J Cancer 2006; 118: 3112-7.

Hofvind: Results

	Screen BC	Interval BC
Never HT	ref	ref
HT <1 year	1.1 (0.9-1.3)	1.2 (0.9-1.6)
HT 1-4 years	1.5 (1.3-1.7)	1.8 (1.5-2.2)
HT 5-9 years	1.7 (1.4-2.1)	2.8 (2.2-3.5)
HT ≥10 years	1.9 (1.5-2.5)	2.9 ((2.1-4.0)
Ever HT	1.5 (1.3-1.6)	1.9 (1.6-2.2)
+HT, grade III	14%	27%
- HT, grade III	17%	36%

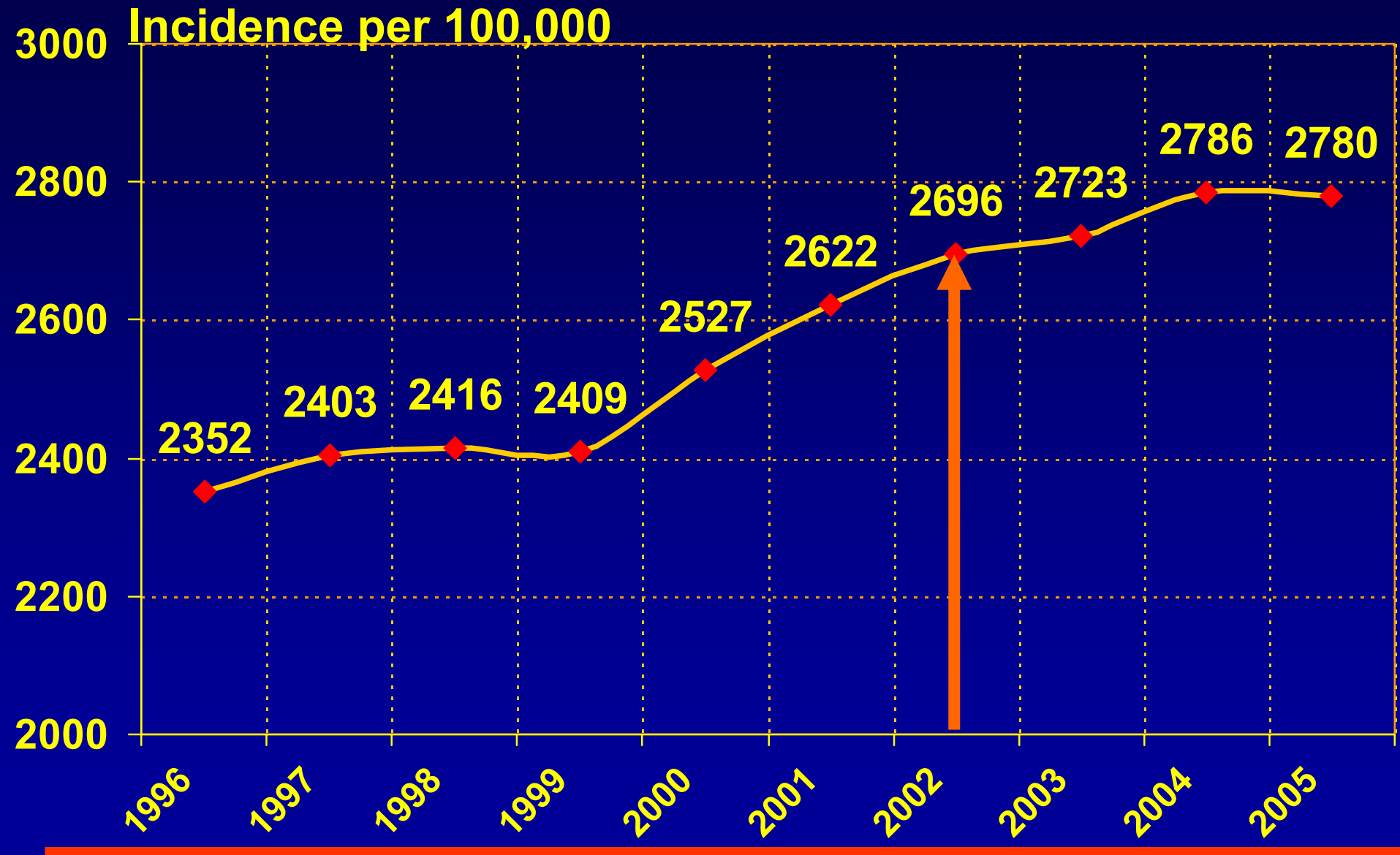
Hofvind Solveig et al. Int J Cancer 2006; 118: 3112-7.

Hofvind: Comments/questions

- Overall risk ratio of 1.6 with HT as in MWS
- Expected that interval BC are more aggressive and more advanced than screening cancers (with and without HT)
- BC after HT are less aggressive than BC in women never on HT (lower grade)
- Survival data missing
- We have to expect fewer BC events from 2003 as compared with 2002.

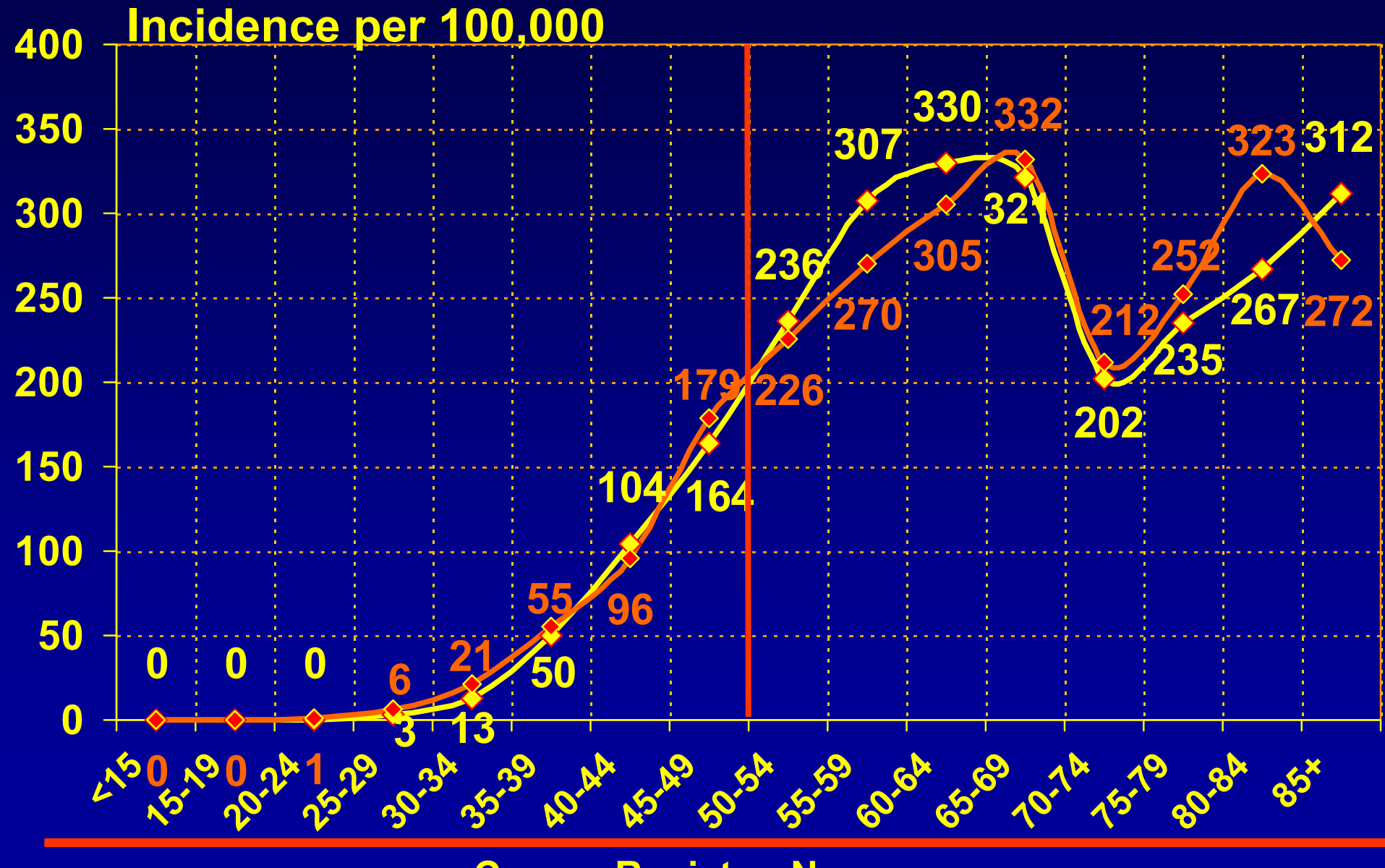
Hofvind S et al. Int J Cancer 2006; 118: 3112-7.

BC incidence in Norway 1996-2005



Cancer Registry, Norway

BC incidence rate Norway 2002 and 2005



Cancer Registry, Norway

Latest news

Oral contraceptives – HT – breast cancer

- Cohort study
- OC and HT history at baseline in 1996/97/98
- Follow up in cancer registry until end of 2004
- Follow up time: On average 7 years.
- Cohort size: 30,118 women born 1927-57
- Incident BC: 540 during 209,661 person yrs.
- Confounders: Family history, BMI, menarche, age at first birth, parity.
- Ever OC: 38%. Ever HT: 45%

Lund Eiliv et al. Int J Cancer 2007; Early view.

Lund et al: Results

HT	Never OC	Ever OC	All
Never HT	ref	1.1 (0.8-1.5)	
Prev. HT	0.9 (0.5-1.4)	0.9 (0.4-1.6)	
Current HT	1.5 (1.2-2.0)	2.3 (1.8-3.0)	1.95
Current ET	0.9 (0.5-1.6)	2.6 (1.7-4.2)	
Current EPT	2.0 (1.5-2.6)	2.6 (1.9-3.4)	

Conclusion: Women previously on OC have a higher risk of BC with HT that women never on OC.

Lund E et al. Int J Cancer 2007; Early view.

Lund et al: Comments/questions

- No update on exposure since enrolment
- Same risk for ET and EPT
- Previous OC no HT: No↑BC risk
- Previous OC and previous HT: No↑BC risk.
- Length of use ?
- Cyclic / continuous combined HT ?
- New studies generally have a high per cent of previous OC users.

Lund E et al. Int J Cancer 2007; Early view.

Risk measures

Relative risk:

- Express an instant risk
- No cumulated aspect
- No idea of the absolute risk

Life-time risk

- The best and easiest measure to understand
- Expresses the cumulated risk
- Expresses the absolute risk

Hormoner fordobler risikoen for kræftdød

Flere hundrede tilfælde af brystkræft hvert år skyldes hormoner i overgangsalderen.

Af Inge Methling

En kvinde, som tager hormoner efter overgangsalderen, fordobler sin risiko for at dø af brystkræft i forhold til den kvinde, der aldrig har taget hormoner.

Det viser en ny, dansk undersøgelse, som for første gang ikke alene har set på sammenhængen mellem hormonbehandling i overgangsalderen og udvikling af brystkræft, men også på risikoen for at dø af sygdommen.

En lang række videnskabelige undersøgelser har i de senere år dokumenteret, at hormonbehandling i overgangsalderen øger risikoen for flere alvorlige sygdomme. Især har der været fokus på brystkræft, som i 2003 ramte 4.044 danske kvinder.

»Mange – herunder medicinalindustrien – har været ude med beroligende meldinger om, at hormonerne kun øger risikoen for den hormonfølsomme type brystkræft, som er lettere at behandle end den ikke-hormonfølsomme«, siger læge, ph.d. Claudia Stahlberg, som står bag undersøgelsen.

»Det er også rigtigt ifølge vores undersøgelse. Men man har en tilbøjelighed til at overse, at kvinderne i første omgang måske slet ikke havde fået brystkræft, hvis det ikke var for hormonerne«.

Undersøgelsen bygger på 11.000 kvinder fra en dansk gruppe sygeplejersker, som er fulgt over 11 år. Den viser to og en halv gange flere tilfælde af brystkræft i den gruppe, som var i hormonbehandling – målt i forhold til den gruppe, der aldrig havde taget hormoner.

Når der alligevel »kun« var dobbelt så mange kvinder, der døde af sygdommen i hormongruppen, hænger det sammen med, at disse kvinder hyppigere udvikler den type brystkræft, som har bedre behandlingsmulighed.

»Selvfølgelig er det ikke sådan, at bare fordi man spiser hormoner, så får man brystkræft. Der er også andre årsager til sygdommen«, siger Claudia Stahlberg.

»Men baseret på tallene i vores undersøgelse ville man undgå 26 procent af brystkræfttilfældene i aldersgruppen 55-70 år, hvis hormonerne slet ikke fandtes på det danske marked. Det svarede i 1997 til 320 tilfælde af sygdommen i den aldersklasse«.

Undersøgelsen viser også en let forøget risiko både for at udvikle sygdommen og for at dø af den i den gruppe, som en overgang har taget hormoner, men er stoppet med dem.

»Normalt regner man med, at risikoen er nede på det, der svarer til normalbefolkningens, fem år efter, at man er ophørt med hormonerne«, siger Claudia Stahlberg.

Andre videnskabelige undersøgelser har tidligere vist, at hormonbehandling efter overgangsalderen også øger risikoen for en række andre sygdomme. Det gælder for eksempel kræft i æggestokkene, blodpropper i hjerne, ben og lunger, demens og astma. Samtidig er myten dementeret om, at hormonbehandling efter overgangsalderen har en positiv virkning på livskvaliteten i form af almindeligt velbefindende, vitalitet, nattesøvn og seksuel tilfredshed.

Derimod kan hormonerne forebygge knogleskørhed. Men på grund af risikoen for de øvrige bivirkninger anbefales kvindelige kønshormoner ikke længere som førstevalg til det formål.

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Hormonforbruget næsten halveret

Mange danske kvinder har droppet hormonerne, efter at rapporter om risiko for alvorlige bivirkninger i de seneste år er væltet ind. Siden 2002 er salget af hormoner faldet med 40 procent, viser tal fra Lægemiddelstyrelsen.

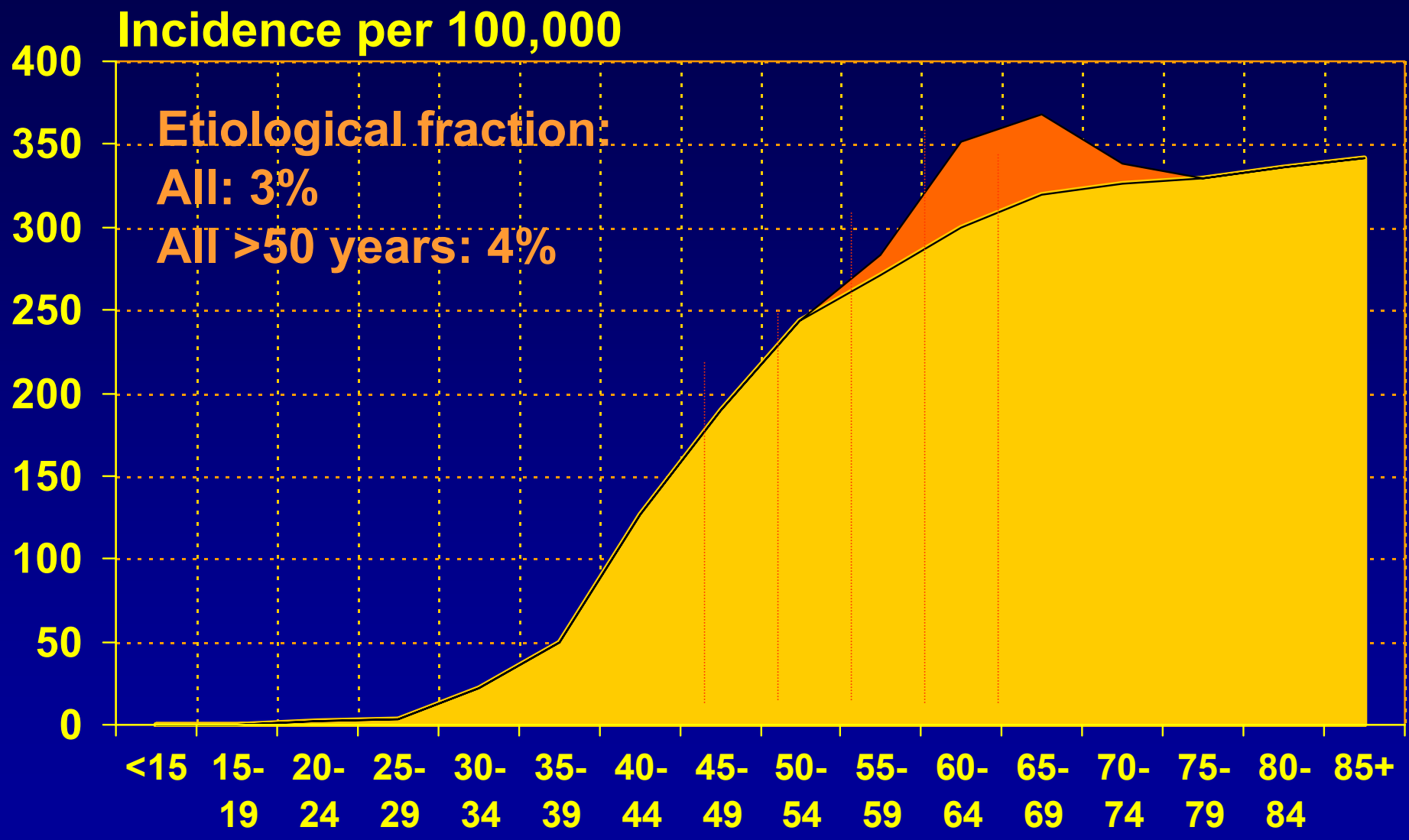
Størst har faldet været for præparater med en kombination af østrogen og gestagen, som ser ud til at have de værste bivirkninger.

I USA har omkring en fjerdedel af de kvinder, som droppede hormonerne af frygt for bivirkninger, genoptaget deres hormonbehandling. En tilsvarende udvikling kan ikke spores i Danmark.

Både Lægemiddelstyrelsen og gynækologernes videnskabelige selskab anbefaler i dag, at hormonbehandling kun bruges i tilfælde af alvorlige gener i forbindelse med overgangsalderen.

Helst kun i et år, og under alle omstændigheder i kortest mulige tid med lavest mulige dosis. (meth.)

Breast cancer: Etiologic fraction of HT



Health Statistics, National Board of Health, Denmark

Li/07

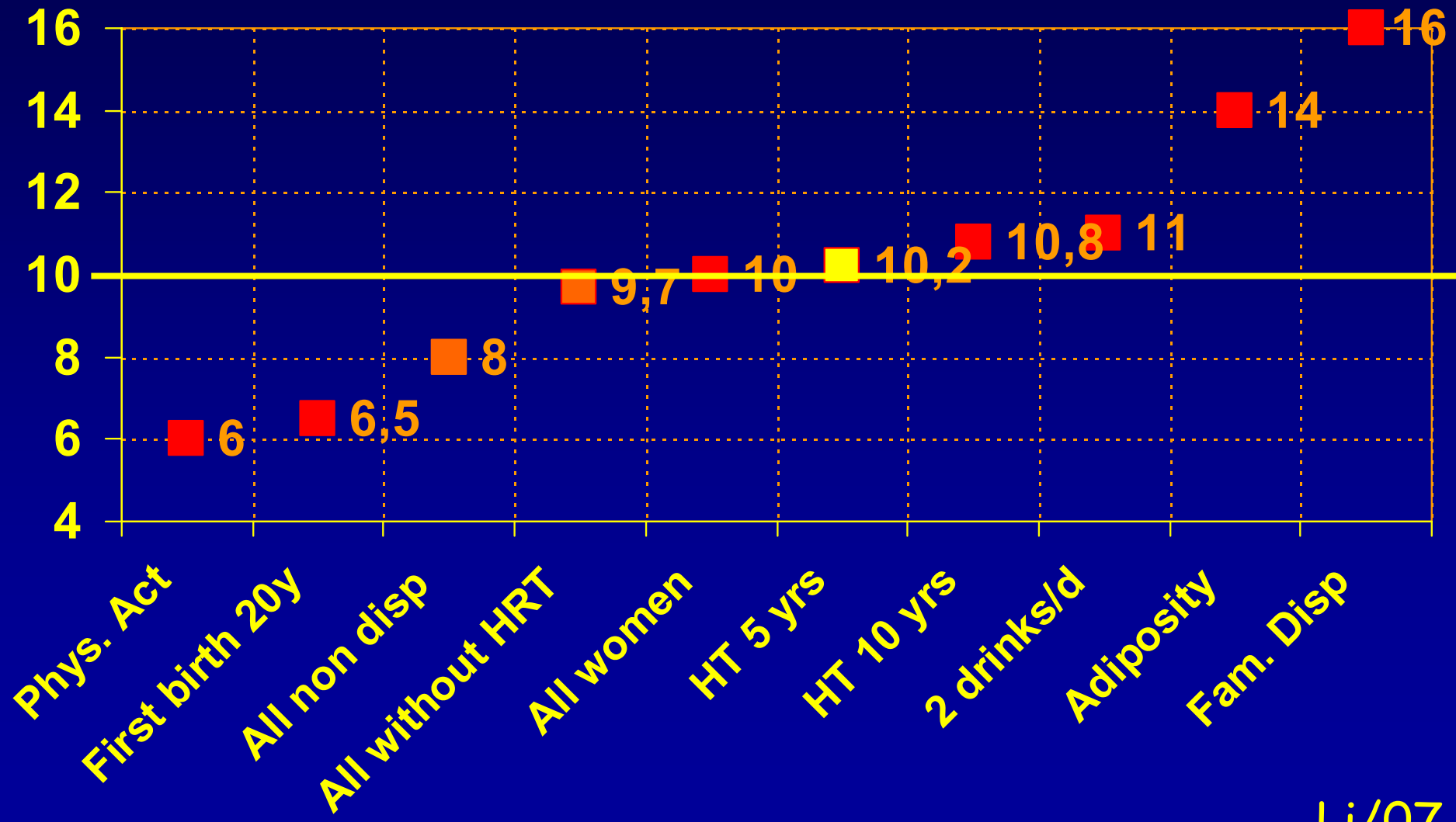
HT and breast cancer: Conclusion

Breast cancer	Life-time risk
All women	10%
No family BC, no HT	8%
Mother or sister BC, no HT	16%
All women without HT	9.7%
ET in five years	9.8% (+0.1)
ET in 10 years	10,2% (+0.5)
EPT in five years	10.2% (+0,5)
EPT in 10 years	10,8% (+1,1)

Concl: About 1 more/100 wom 10 yrs on HT

DSOG guidelines 2005

Lifetime risk of breast cancer after dif. exposures from 50 years



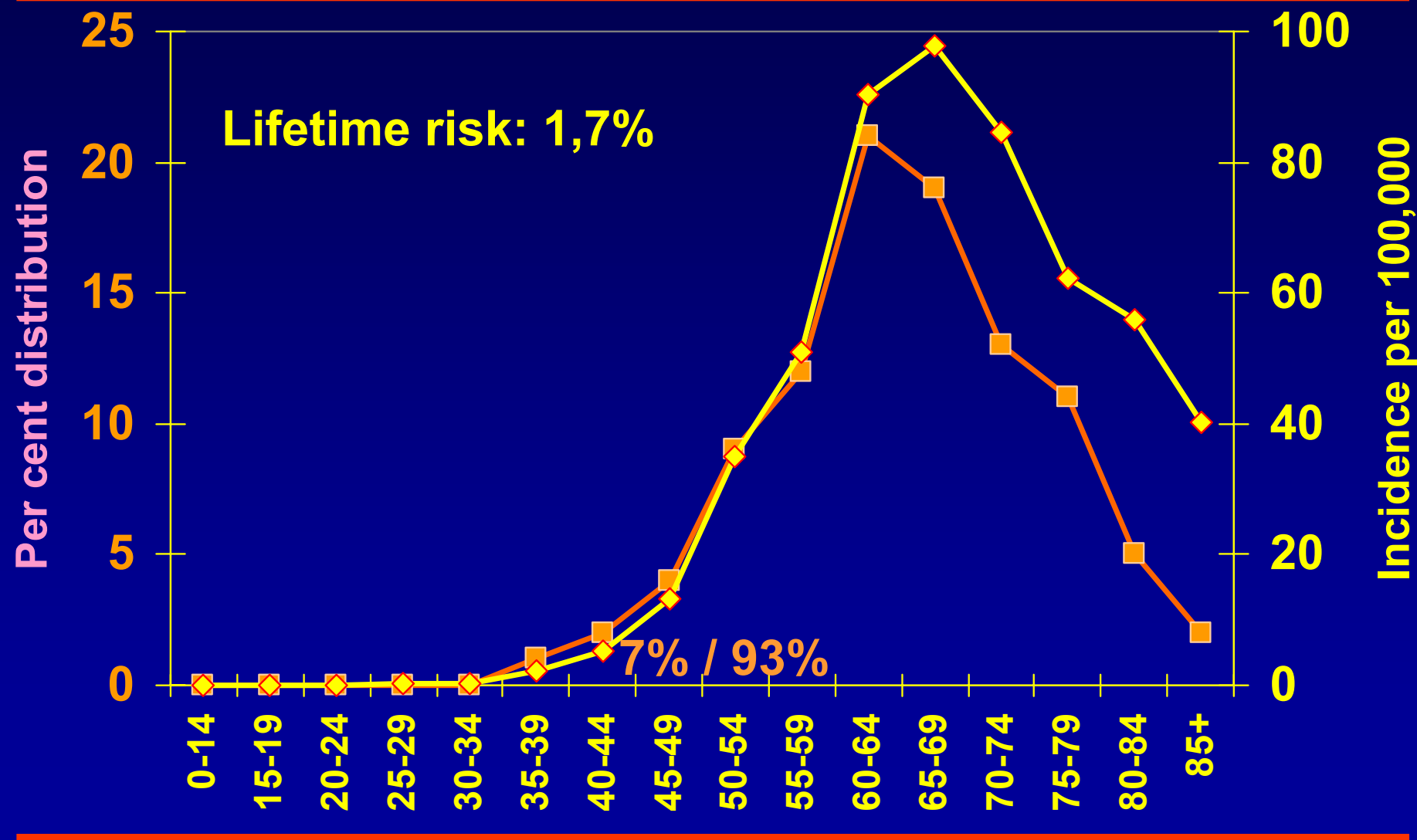
Li/07

Hormone therapy; an update

- Hormone use
- HT - breast cancer
- **HT - endometrial cancer**
- HT - ovarian cancer
- HT - colo-rectal cancer
- HT - heart and circulation
- HT - death
- Conclusion

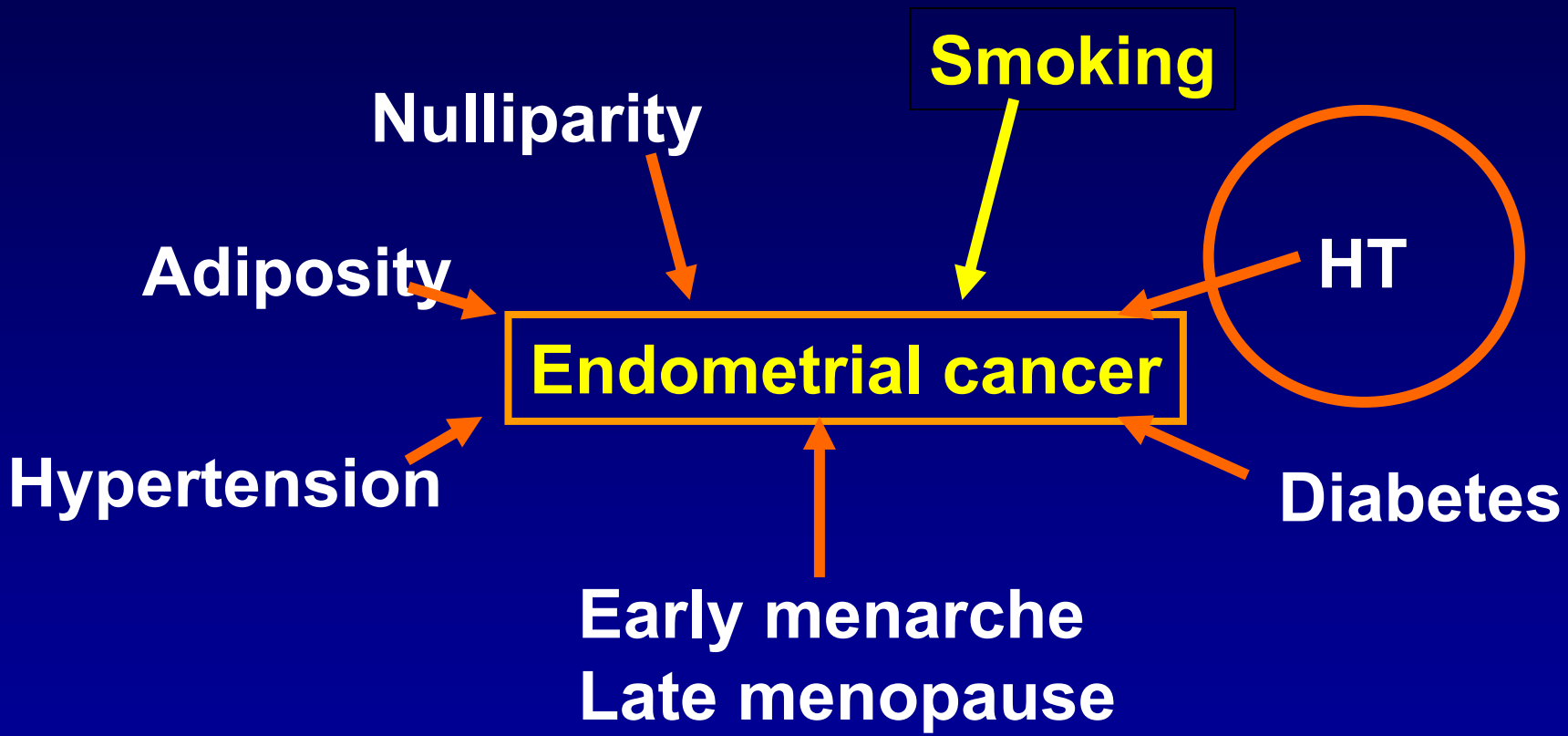
Endometrial cancer in DK

Incidence: 600/year, deaths: 80 per year



Danish Cancer Society, Division of Cancer Epidemiology

Endometrial cancer: Risk factors



Endometrial cancer in DK

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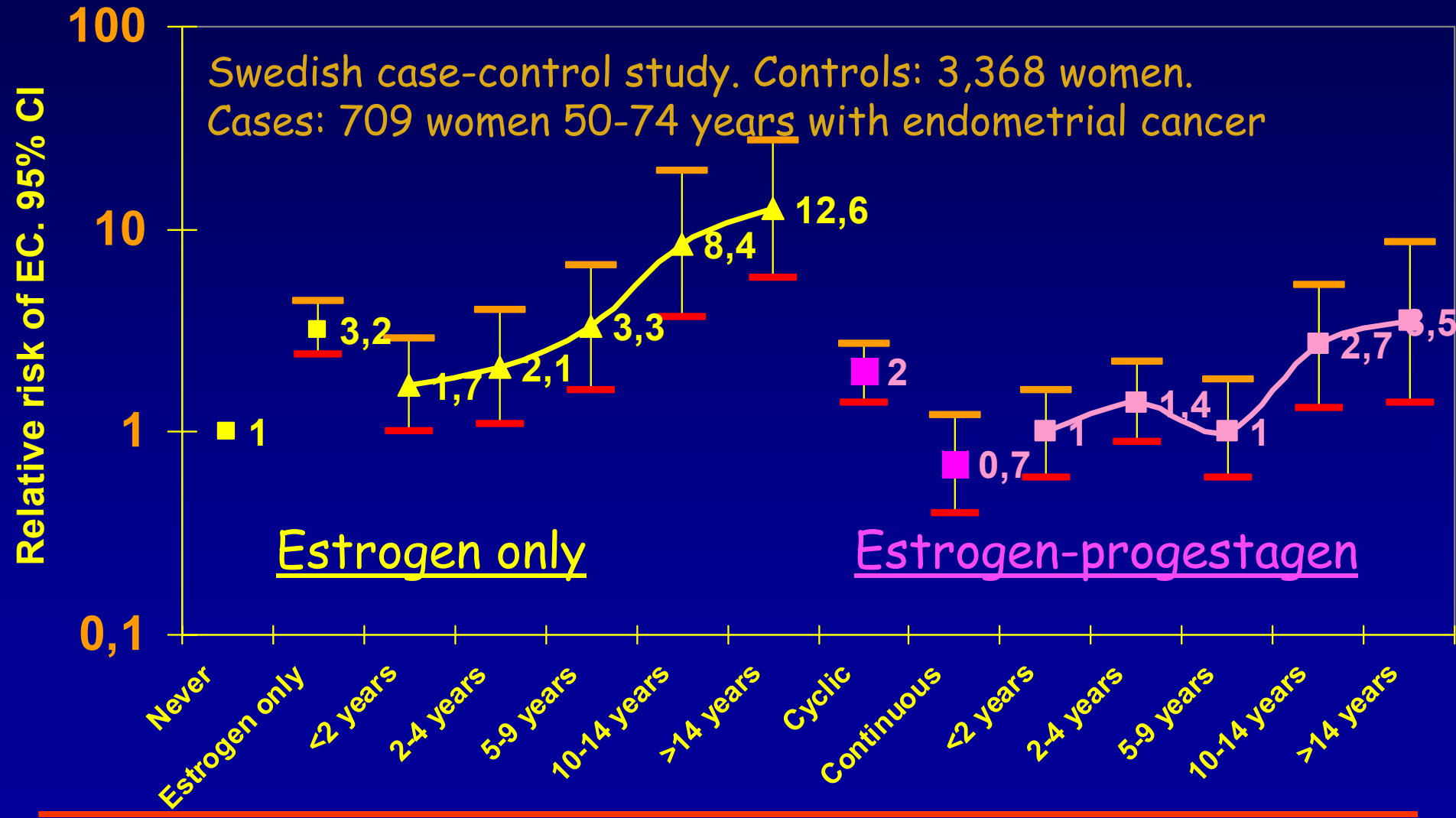
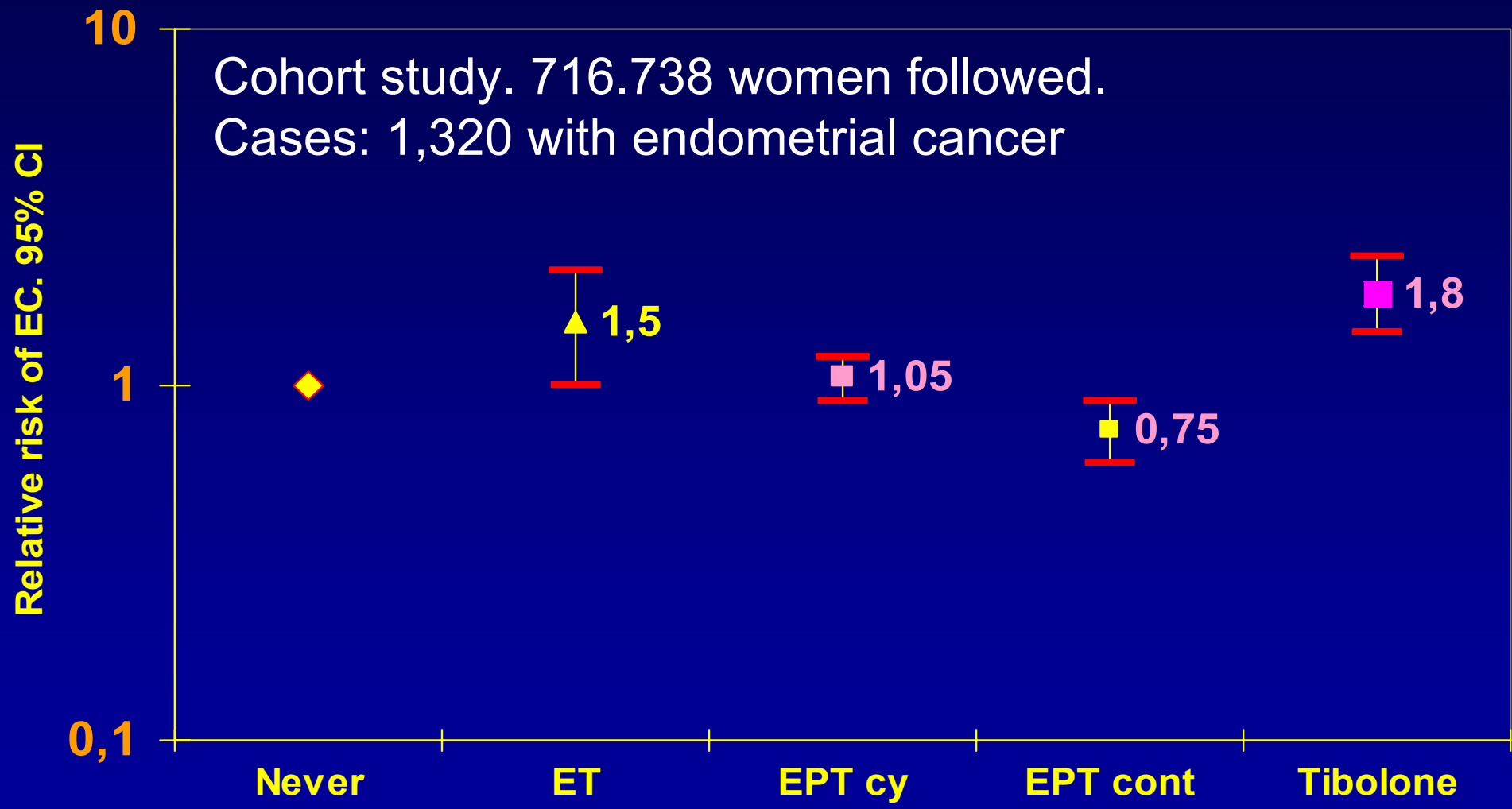


Weiderpass et al. J Natl Canc Inst 1999; 91: 1131-7

HT and endometrial cancer

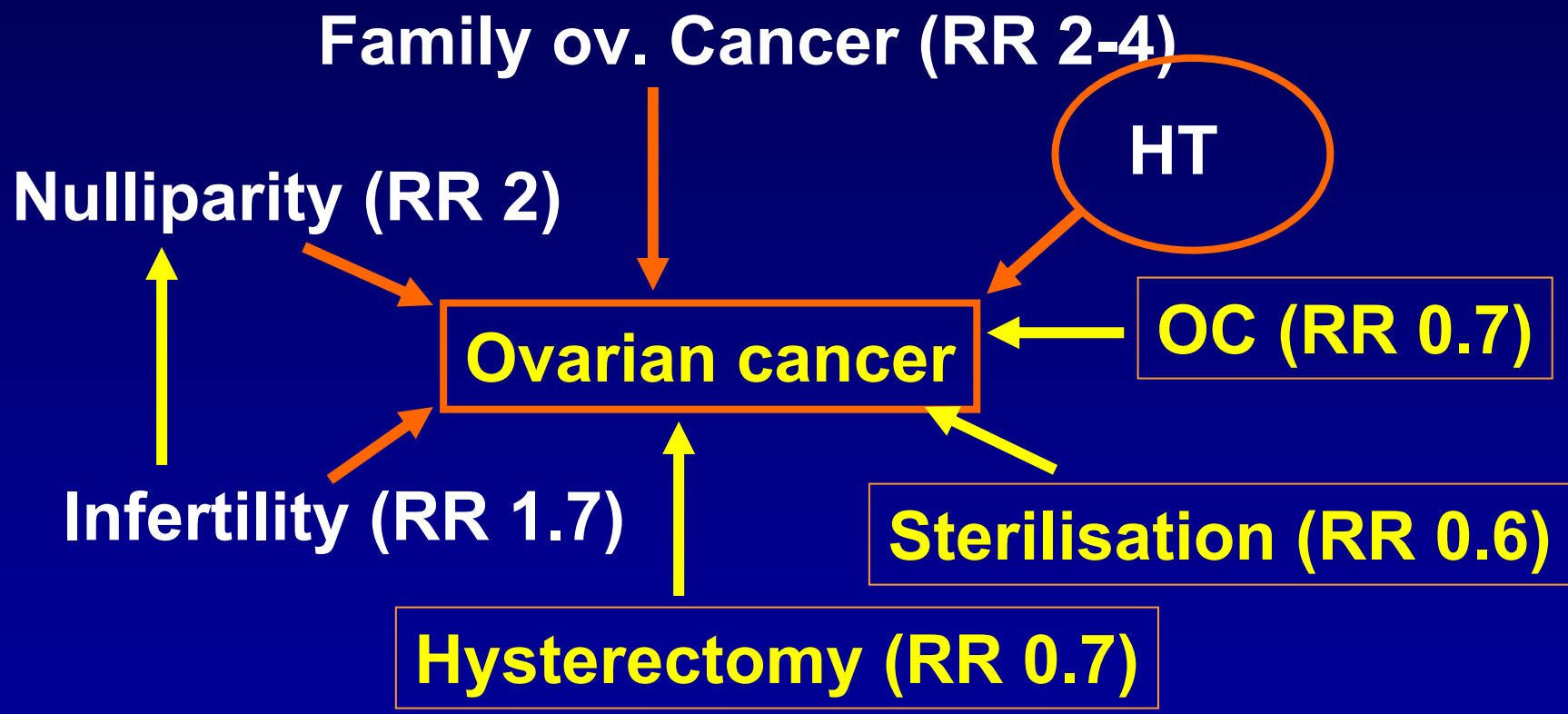


MWS. Lancet 2005: 365: 1543-51

Hormone therapy; an update

- Hormone use
- HT - breast cancer
- HT - endometrial cancer
- **HT - ovarian cancer**
- HT - colo-rectal cancer
- HT - heart and circulation
- HT - death
- Conclusion

Ovarian cancer: Risk factors

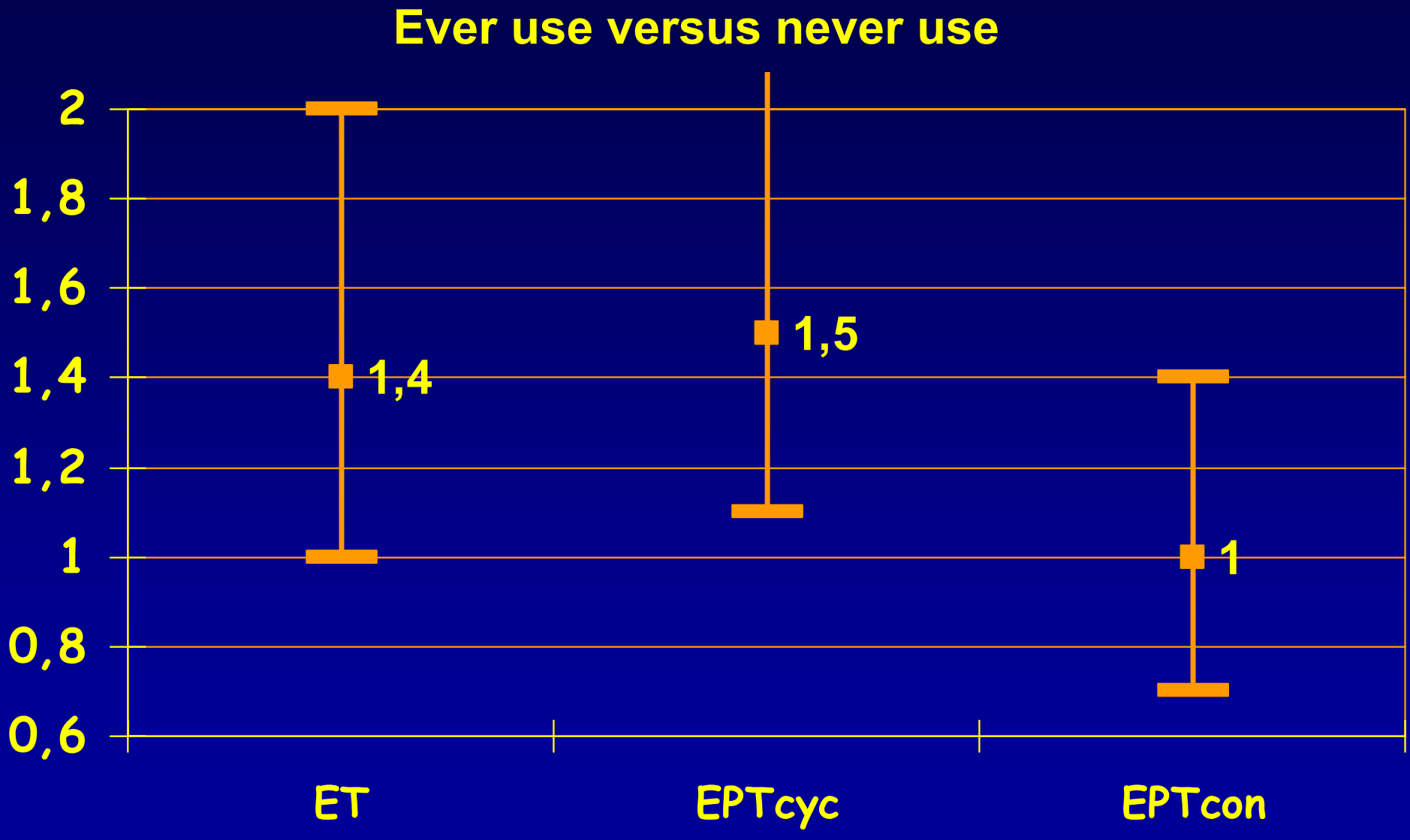


HT and ovarian cancer

- Case-control study, Sweden 1993-95
- 655 women with epithelial ovarian cancer
- 3,899 population controls 50-74 years old
- Included variables: HT, OC use, age at menarche, age at menopause, parity, age at first birth, breastfeeding, abortions, BMI, tubal ligation, hysterectomy, family ovarian cancer, family breast cancer, infertility.

Riman et al. Am J Epidemiol 2002; 156: 363-73

HT and ovarian cancer



Riman et al. J Natl Canc Inst 2002; 94: 497-504

HT and cancer of ovary (CO)

Conclusion

- Epidemiologic findings may be explained by retrograde transportation of contaminants
- HT implying bleeding may thus extend the period during which the ovaries are exposed to contaminants.
- A regimen on 1-2 years cyclic HT followed by continuous HT don't confer risk of CO.

Riman et al. Am J Epidemiol 2002; 156: 363-73

Hormone therapy; an update

- Hormone use
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- HT - ovarian cancer
- **HT - colo-rectal cancer**
- HT - heart and circulation
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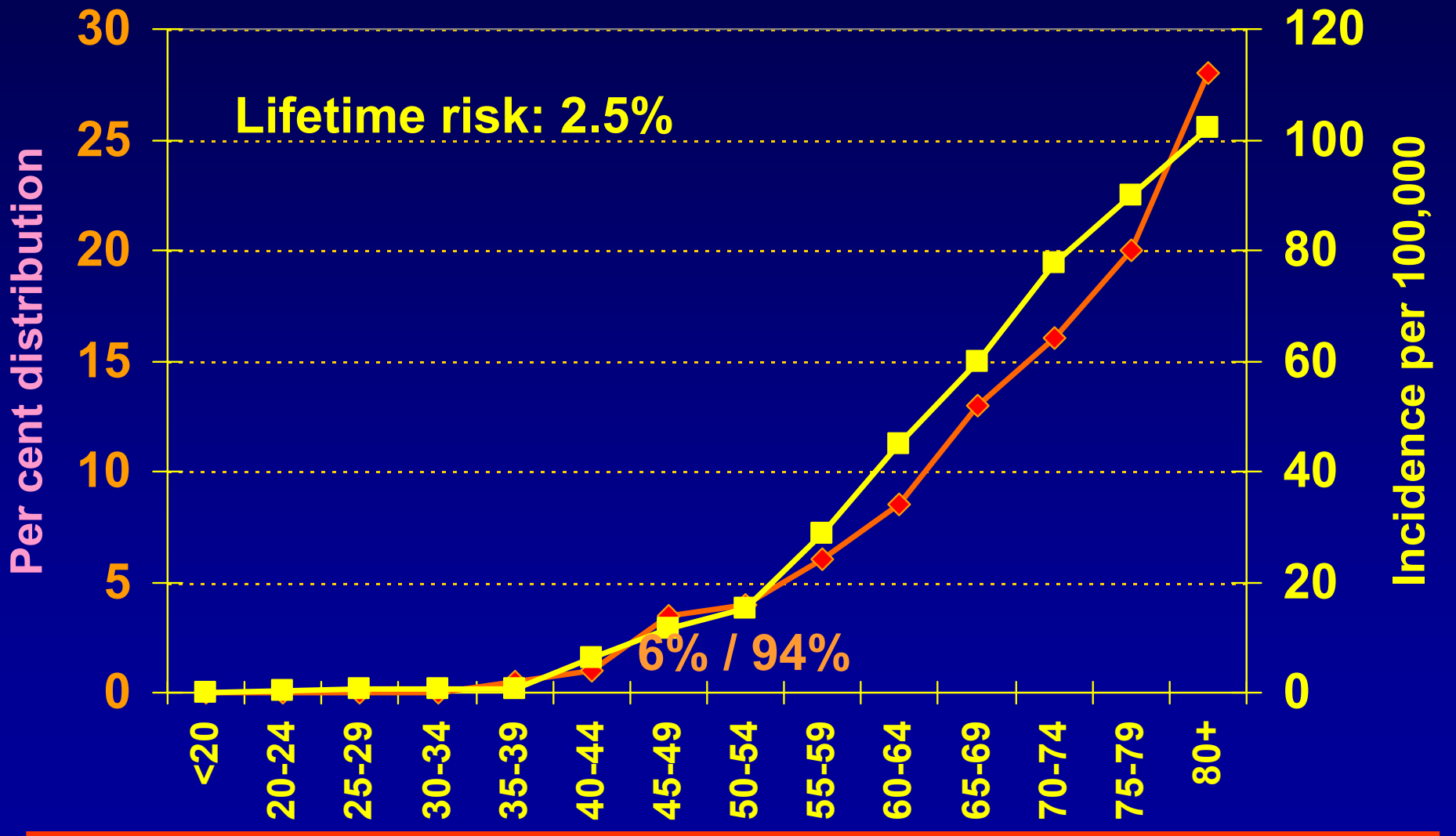
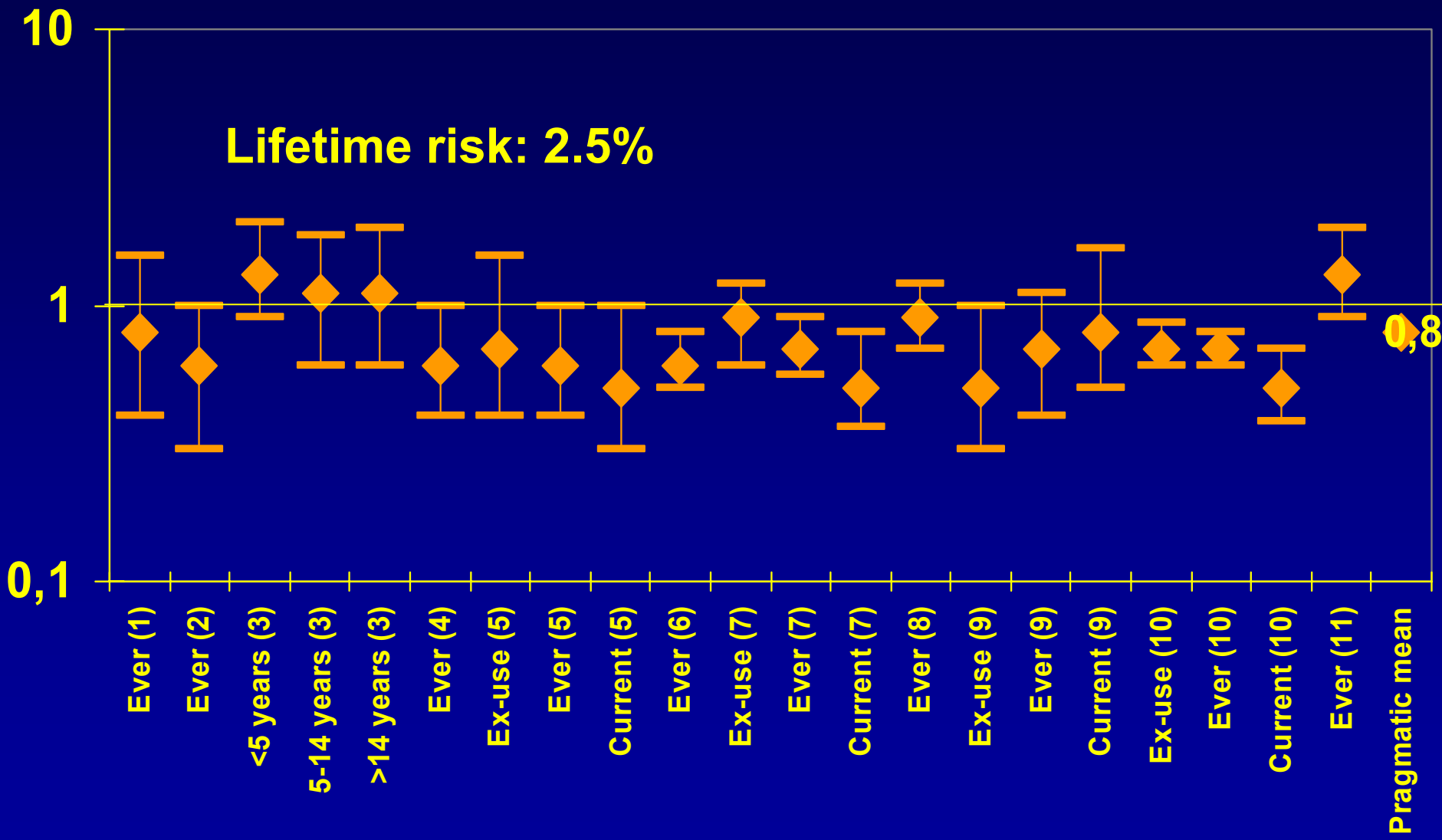
Colo- rectal cancer in DK

Incidence: 1.500/year, deaths: 900/year (60%)

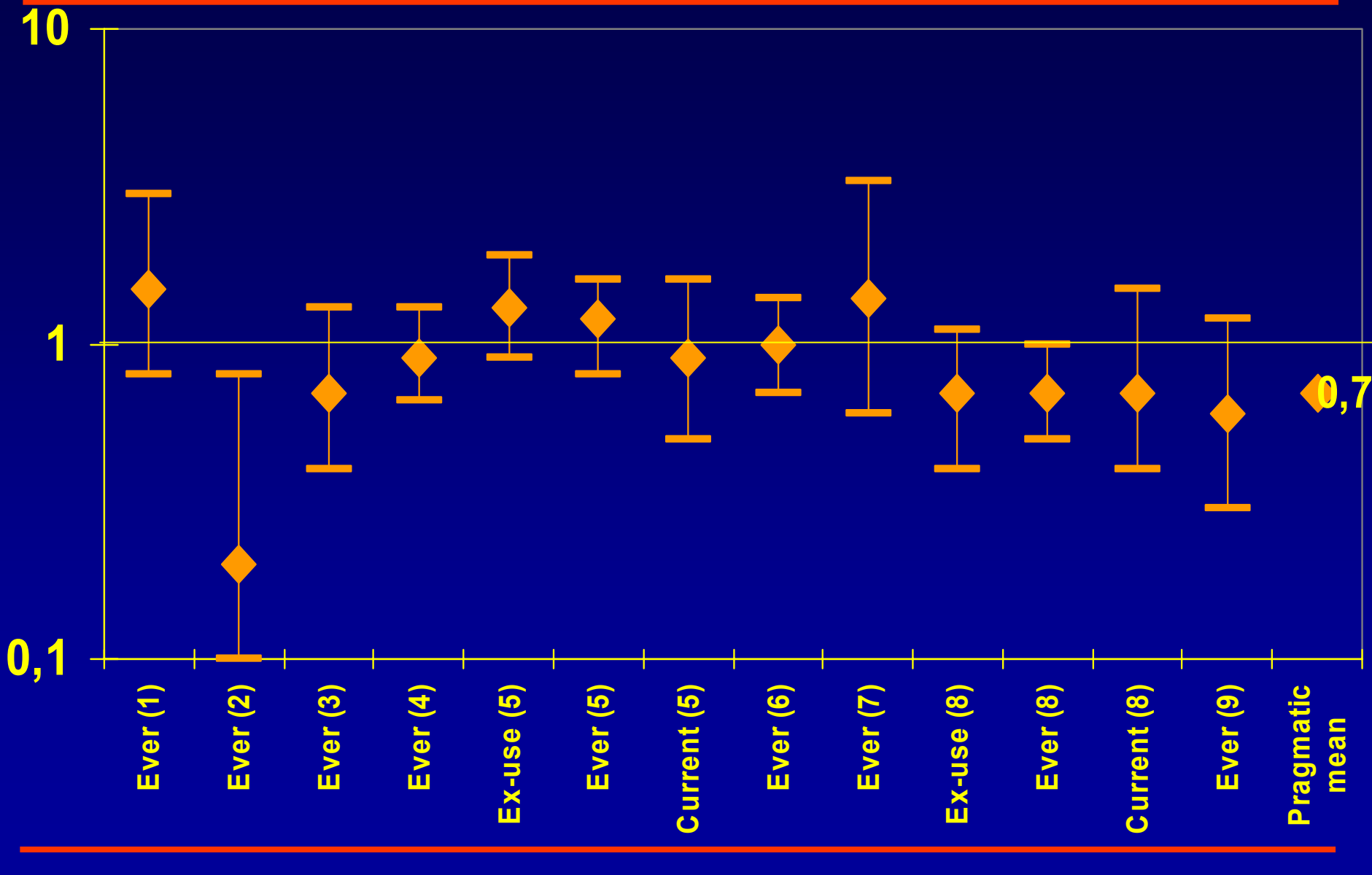


Danish Cancer Society, Division of Cancer Epidemiology

Colon cancer and HT



Rectum cancer and HT



WHI results

	EPT	ET	50-59
• Coronary heart disease	1.3	0.9	0.6
• Stroke	1.4	1.4	1.1
• Venous thromboembolism	2.1*	1.3	1.2
• Breast cancer	1.3	0.8	0.7
• Endometrial cancer	0.8	hysterect.	
• **Colorectal cancer**	**0.6**	**1.1**	**0.6**
• Hip fracture	0.7	0.6	NA
• Vertebral fracture	0.7	0.6	NA
• All cause mortality	1.0	1.0	0.7

HT og colo-rectal cancer

Conclusion

- ET as well as EPT protects against colon and rectum cancer.
- The protection fades out five years after stopping with HT
- The protection is about 30-40%
- No difference in protection between ET and EPT.

HT and cancer: Conclusion

- **Breast:** Increased risk after 5 yrs

  EPT confers higher risk than ET
- **Endometrium**: ET increases the risk EPTcycl a little, EPTcon no increased risk
- **Ovary**: Slightly increased risk after 5 yrs use of ET or EPTcycl, EPTcont. no risk
- **Colon-rectum:** 30-40% protection after five years of use.

  Same influence from ET and EPT.

Hormone therapy; an update

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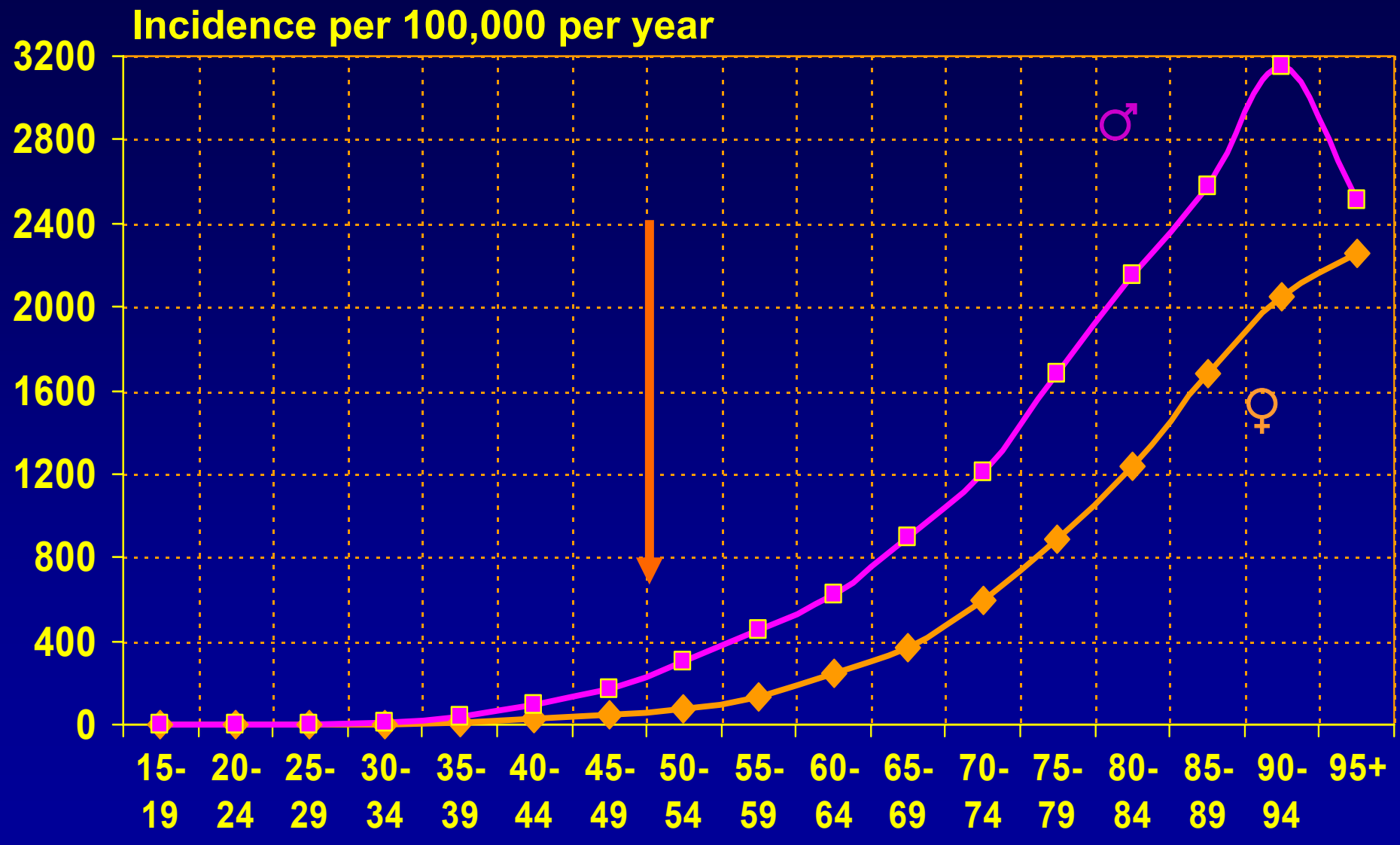
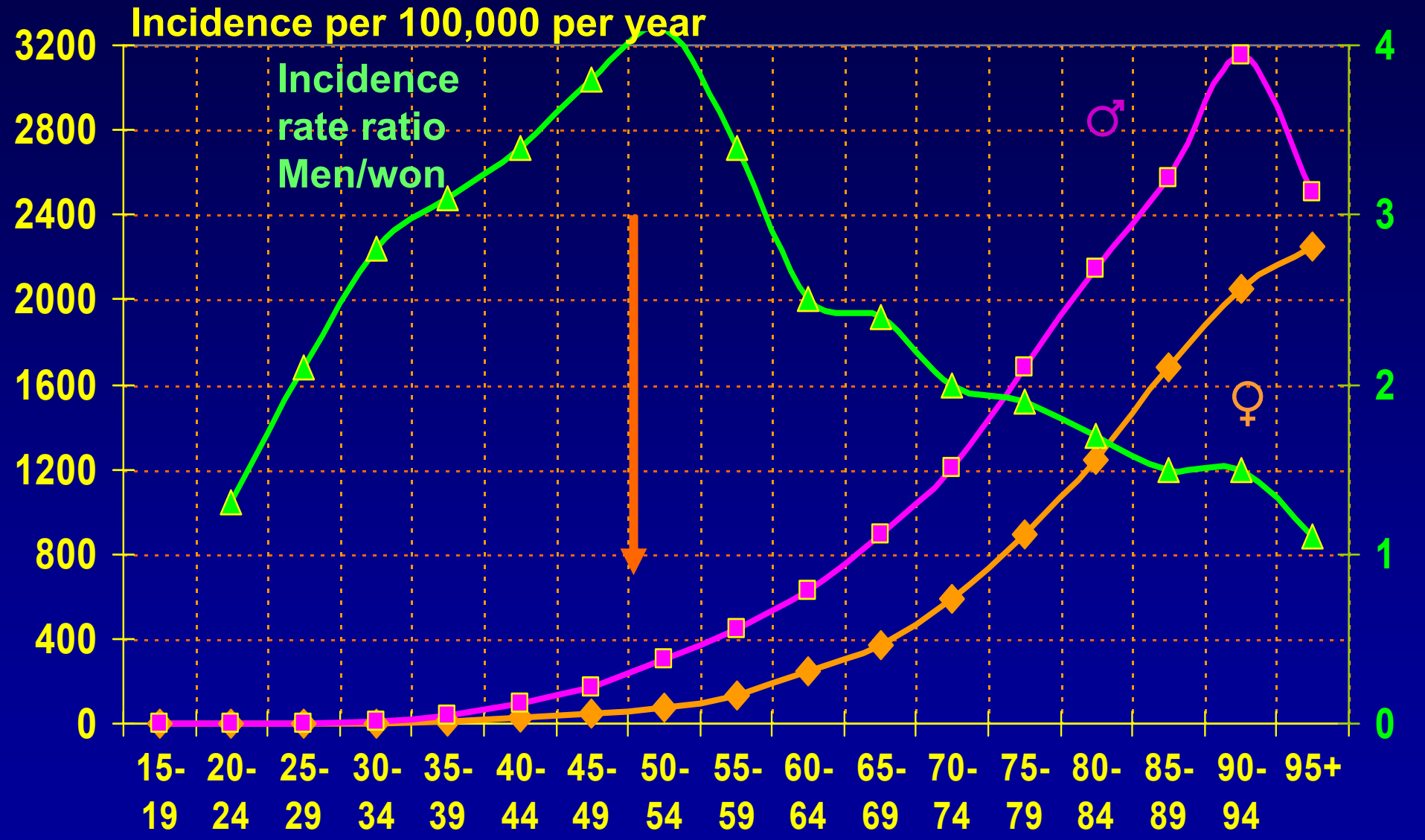
AMI in women and men in DK



Videbæk J, Madsen M. 2004 Hjertestatistik

AMI in women and men in DK



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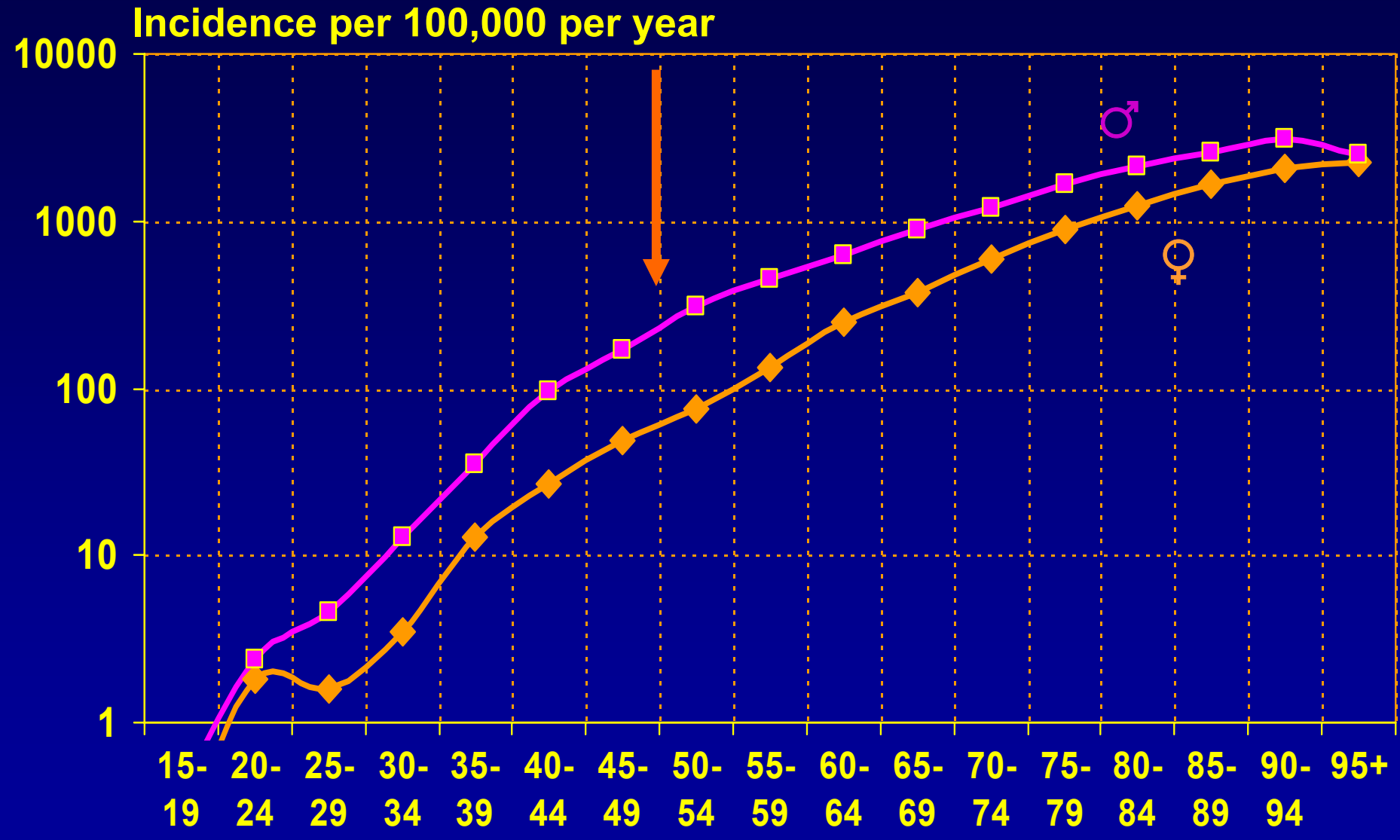
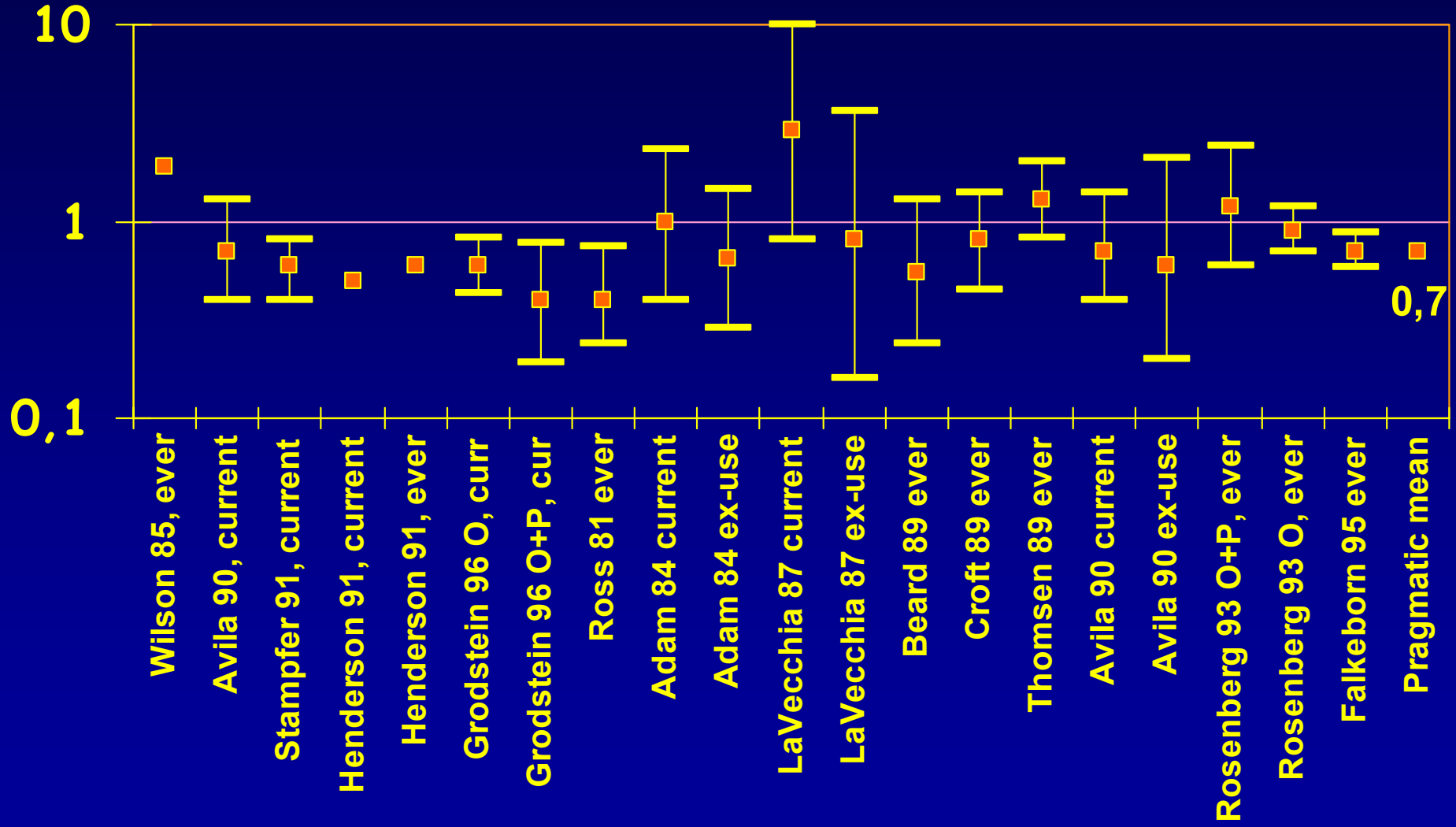


Videbæk J, Madsen M. 2004 Hjertestatistik

HT and myocardial infarction



Heart and oestrogen/progestin replacement study (HERS)

Design: Randomised blinded placebo-controlled secondary prevention trial

Material: 2,763 women with coronary heart disease, younger than 80 years. Mean: 67y

Method: Randomisation between placebo and 0.625mg estrogen + 2.5mg MPA.

HERS I: Follow up 4.1 years (randomised)

HERS II: Follow up 6.8 years (not randomised)

Outcome: Fatal and non-fatal new AMI.

Hulley et al. JAMA 1998; 280: 605-13
Grady et al. JAMA 2002; 288: 49-57

HERS: results

	Estr-prog[1]	Placebo	RR	95% CI
n	1380	1383		
CHD[2] I	179	182	1.0	0.8-1.2
CHD I+II	290	293	1.0	0.8-1.2
Fatal I+II	132	122	1.1	0.9-1.4
Nonfatal AMI	183	196	0.9	0.8-1.2

Conclusion: Comb. HT has no influence on the risk of a new AMI after the first AMI.

1) Oestr-prog = conjugated estrogen 0.625mg + medroxyprogesterone acetate 2.5mg

2) CHD: coronary heart disease (=AMI)

HERS: discussion

- All the women had atherosclerotic vessel walls on which the beneficial influence of oestrogen in preventing these plaque formation may not appear.
- MPA may have counterbalanced a positive influence from oestrogen.
- **Concl:** CHD is not an indication for HT.

WHI results

	EPT	ET	50-59
Coronary heart disease	**1.3**	**0.9**	**0.6**
Stroke	1.4	1.4	1.1
Venous thromboembolism	**2.1***	**1.3**	**1.2**
Breast cancer	1.3	0.8	0.7
Endometrial cancer	0.8	hysterect.	
Colorectal cancer	0.6	1.1	0.6
Hip fracture	0.7	0.6	NA
Vertebral fracture	0.7	0.6	NA
All cause mortality	1.0	1.0	0.7

Rossouw et al. JAMA 2002; 288: 321-33 & 2004: 291: 1701

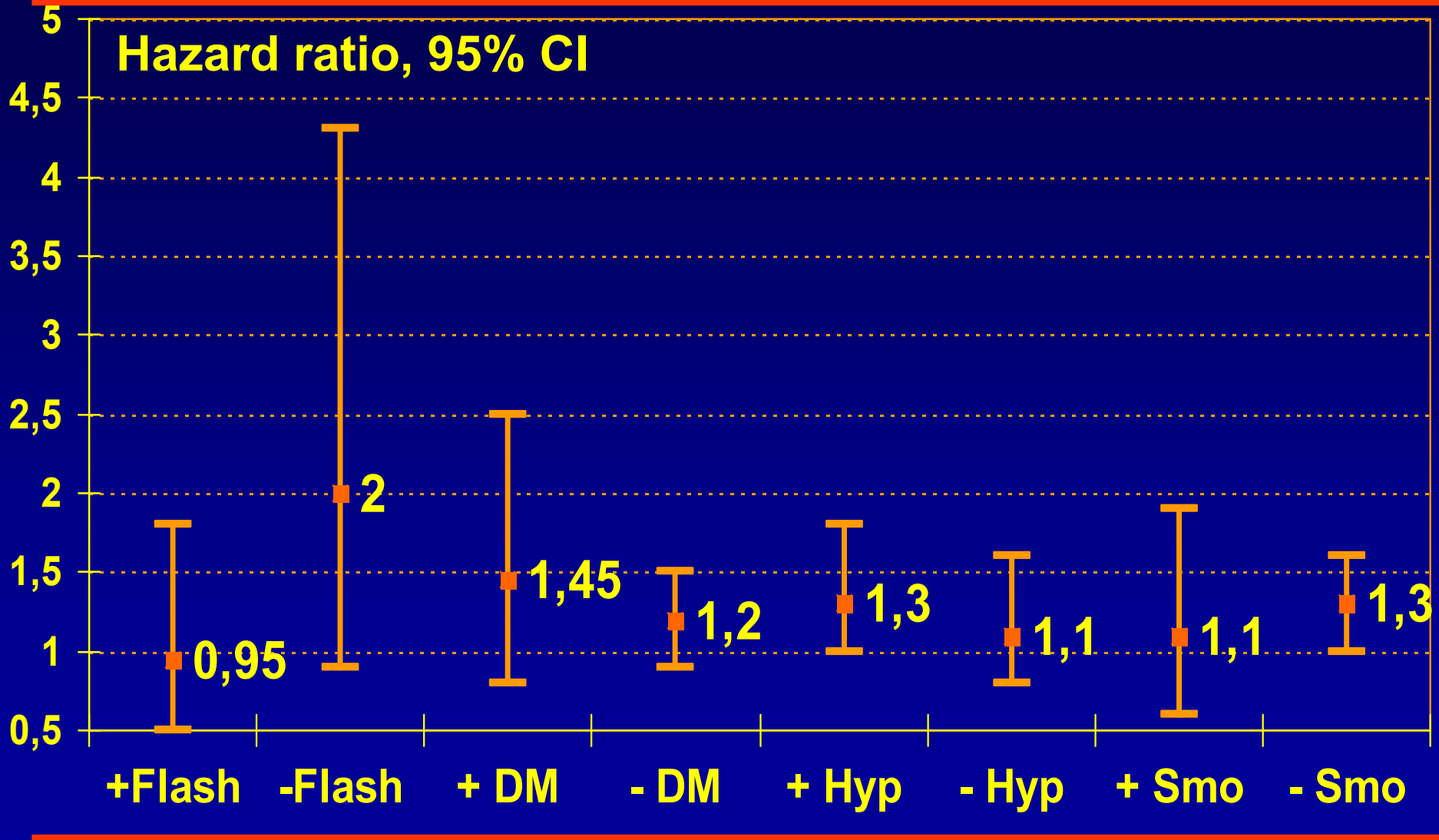
Womens health initiative (WHI)

	EPT vs placebo	ET vs placebo
Age:	50-79	50-79, -uterus
Number:	16,608	10,739
Regimen:	0.6mg CEE/MPA	0.6mg CEE
Follow up:	5.2 yrs,	6.8 yrs
Averag age:	63 years	64 years
>60 years	2/3	70%
Hypertension	36%	48%
BMI ≥25:	70%,	80%
BMI ≥30:	34%	45%

Rossouw et al. JAMA 2002; 288: 321-33 & 2004: 291: 1701

AMI & HT: Sub group analysis

WHI. Oestrogen + progestin



Manson et al. N Engl J Med 2003; 349: 523-34

HT & AMI: Danish nurse cohort

Design:

- 23,178 Danish nurses >45 years were invited to a follow-up study in 1993
- 19,898 (86%) accepted the invitation
- 13,084 (56%) were included in the analysis after exclusion of pre-menopausal women and women with previous thrombosis
- Exposures assessed at inclusion through questionnaires

Løkkegaard E et al. BMJ 2003; 326: 426-30

Ellen Løkkegaard: HT & AMI

AMI: n=108	RR	95% CI
• Never HT	1.0	reference
• Current HT	1.0	0.6-1.7
• Current oestrogen	1.0	0.5-1.9
• Current oestrog-progest.	1.1	0.5-2.2
Stratified according to DM		
AMI: -DM, current vs never	0.8	0.4-1.4
AMI:+DM, current vs never	9.1	2.0-41
IHD: -DM, current vs never	1.2	0.9-1.6
IHD:+DM, current vs never	4.2	1.4-12

HT and AMI: Conclusion

- Observational studies: RR: 0.7-1
  Randomised studies: RR: 0.6-1.3
- Previous AMI is not an indication for HT
- ET may reduce the risk more than EPT.
- It is a long term effect, measurable only after five years.

Most likely mechanism:

- Delayed arteriosclerosis in healthy
- Accelerated thrombosis in atherosclerotic

Hormone therapy; an update

- Hormone use
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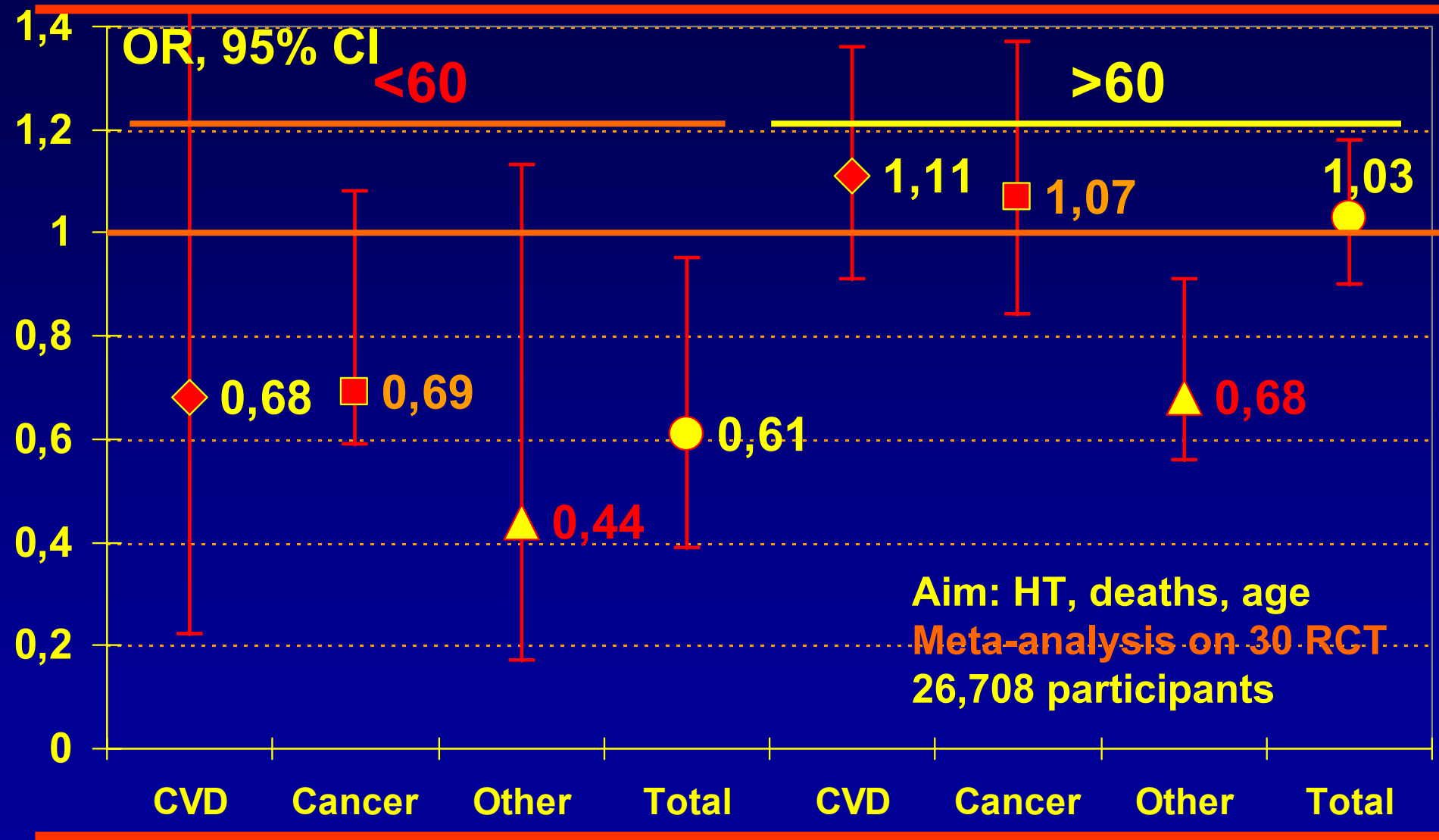
- HT - heart and circulation
- **HT - death**
- Conclusion

Metaanalysis on HT and death



Salpeter et al. J Gen Intern Med 2004; 19: 791-804

Clinical recommendations

- HT demands an indication
- Best documented epidemiological benefit is osteoporosis and colon cancer prevention
- Start on a low dose cyclic comb. therapy
- Shift after 2 yrs to cont. comb. therapy
- Lowest available progestagen dose
- Estrogen dose of less significance
- But low dose of estrogen provides feasibility for a low progestagen dose.

Clinical recommendations

- Best documented risk: BC (incidence)
- Re-evaluation of treatment with few years interval.
- Women on high-dose preparations should be shifted to low-dose preparations.
- A good indication if treatment >5 years


24 HOUR
FITNESS