

The Impact of Cancer Treatment on Female Fertility: Achieving Pregnancy and Live Birth

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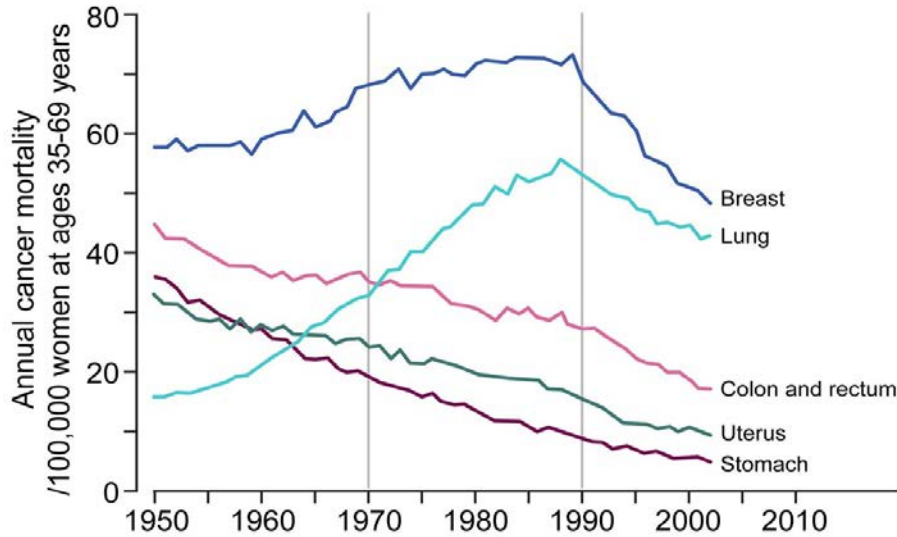


Disclosures

Research support, consultancy, speaker fees from Roche Diagnostics, Ferring Pharmaceuticals, Merck

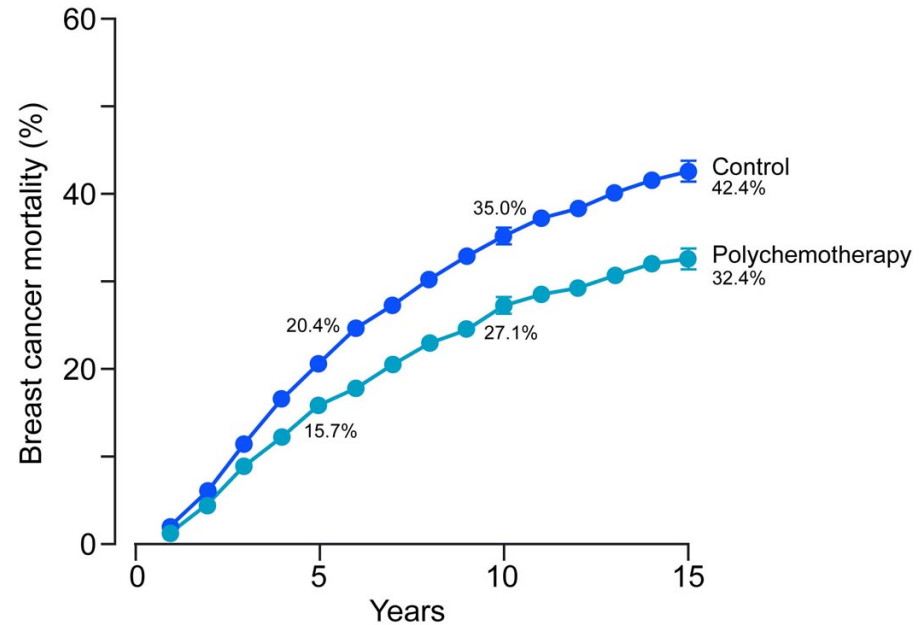
Research support from Beckman Coulter, Ansh labs

Improving survival: minimising 'late effects'

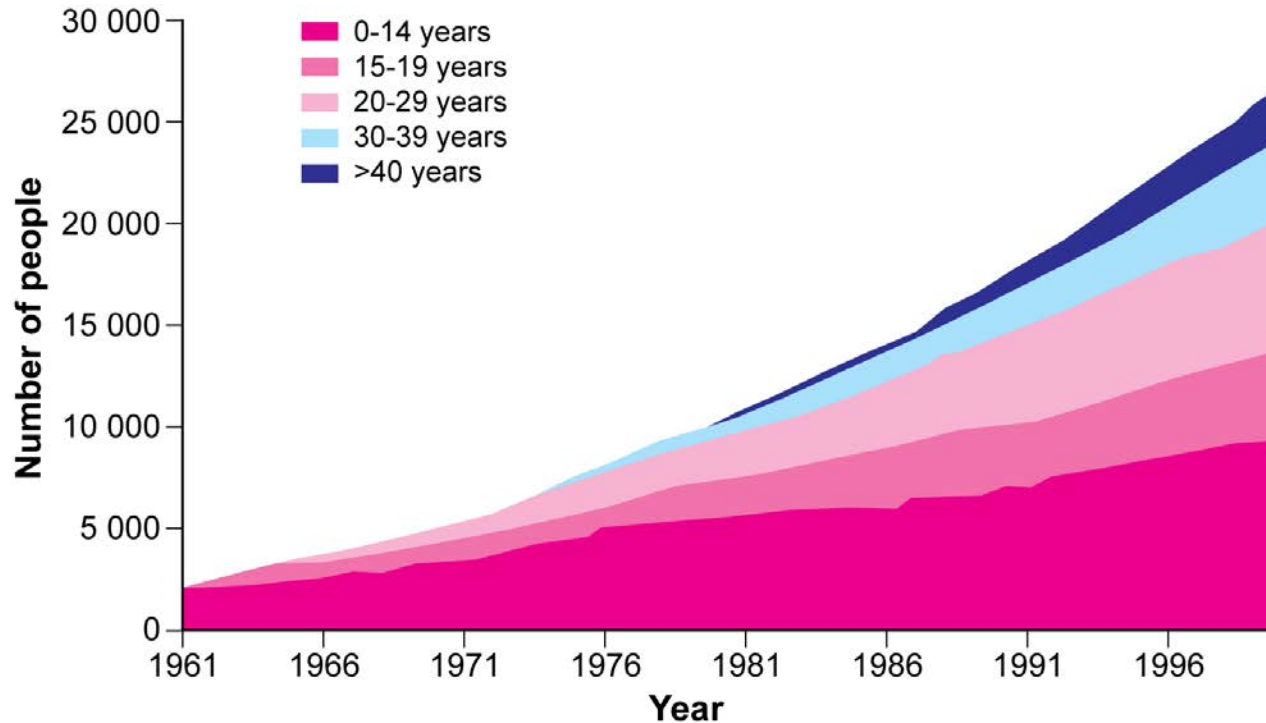


Chemotherapy reduces the annual breast cancer death rate by 38%

We now need to add the 'ageing' delays of endocrine Rx



Childhood cancer survivors by current age



Long-term survival rate from childhood cancer is **80%**
1 in 700 adults is a childhood cancer survivor

The broader 'survivorship' agenda

- Most cancer survivors have significant health issues
 - Oeflinger et al NEJM 2006
- Reduced chance of marriage/cohabitation with brain/CNS cancers
 - Frobisher et al Int J Cancer 2007
- Concerns about bringing up a family after cancer
 - Recurrence, life expectancy
 - Goncalvez et al HRUpdate 2014

Chemotherapy: immediate and late effects on the ovary

- Depletion of growing follicles

Himmelstein-Braw R, Peters H and Faber M (1978)

Morphological study of the ovaries of leukaemic children.

Br J Cancer 38, 82-87

- Premature ovarian failure

Chapman RM, Sutcliffe SB and Malpas JS (1979)

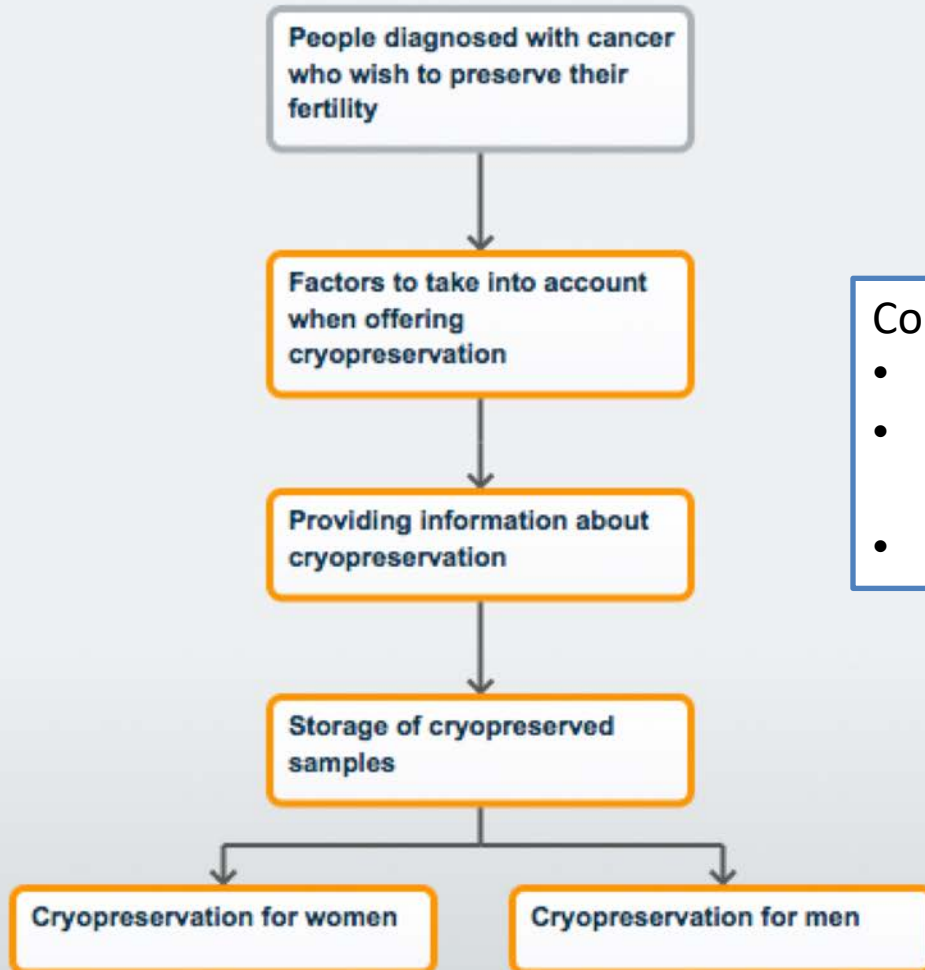
Cytotoxic-induced ovarian failure in women with Hodgkin's disease.

I. Hormone function.

JAMA 242, 1877-1881

Cryopreservation to preserve fertility in people diagnosed with cancer

Fertility ▾



Consider:

- diagnosis / treatment plan
- expected outcome of fertility treatment
- prognosis of the cancer treatment

SIGN 132 • Long term follow up of survivors of childhood cancer

A national clinical guideline

March 2013



Fertility:

‘Good links are required between paediatric oncology units and fertility services’

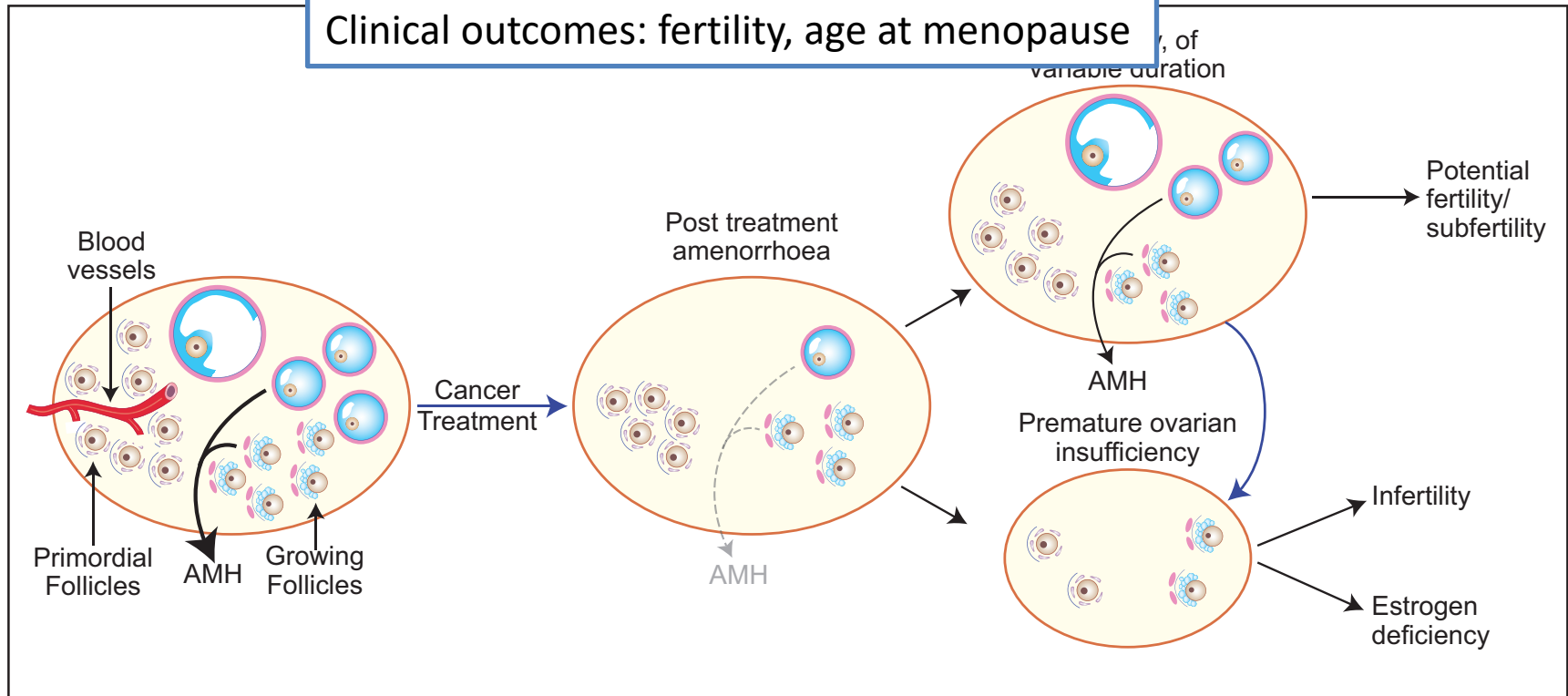
‘Consider ovarian tissue cryopreservation (within the context of a clinical trial) in girls at high risk of premature ovarian insufficiency (D)’

Wallace WH, Thompson L, Anderson RA
Long term follow-up of survivors of childhood cancer:
summary of updated SIGN guidance.
BMJ 2013; **346**: f1190.

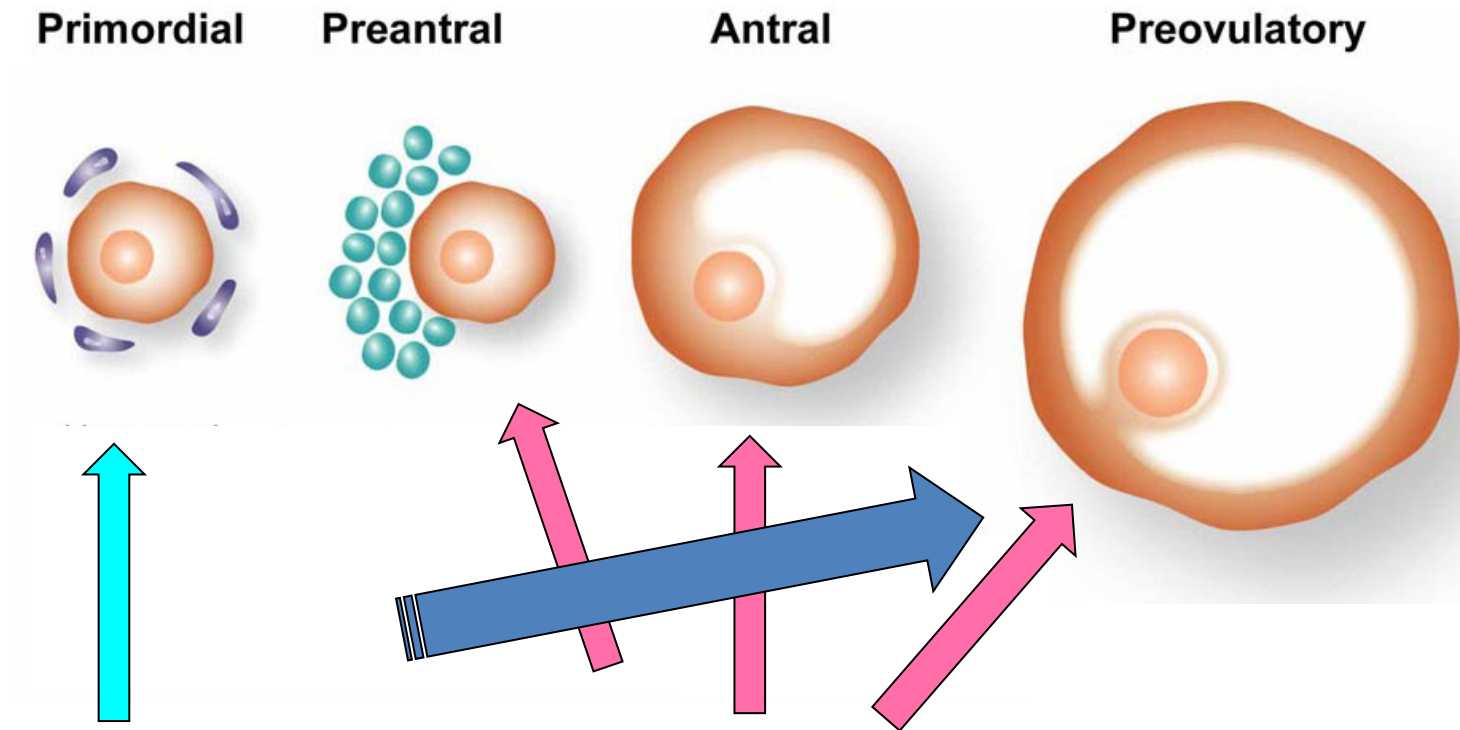
Effects of cancer therapy on the ovary

Biomarkers: AMH, AFC, menses

Clinical outcomes: fertility, age at menopause, of variable duration

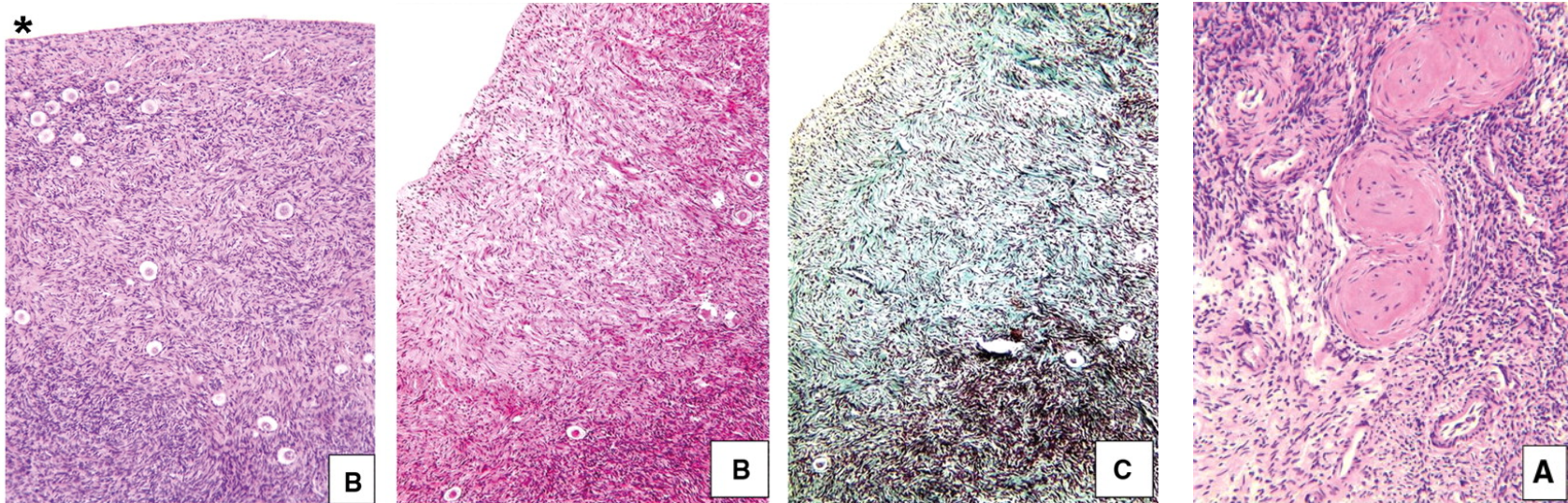


Which stages of follicle growth are key targets of cancer therapies?



Loss of growing follicles may increase growth activation

The ovarian stroma and vasculature are also targets



Normal control

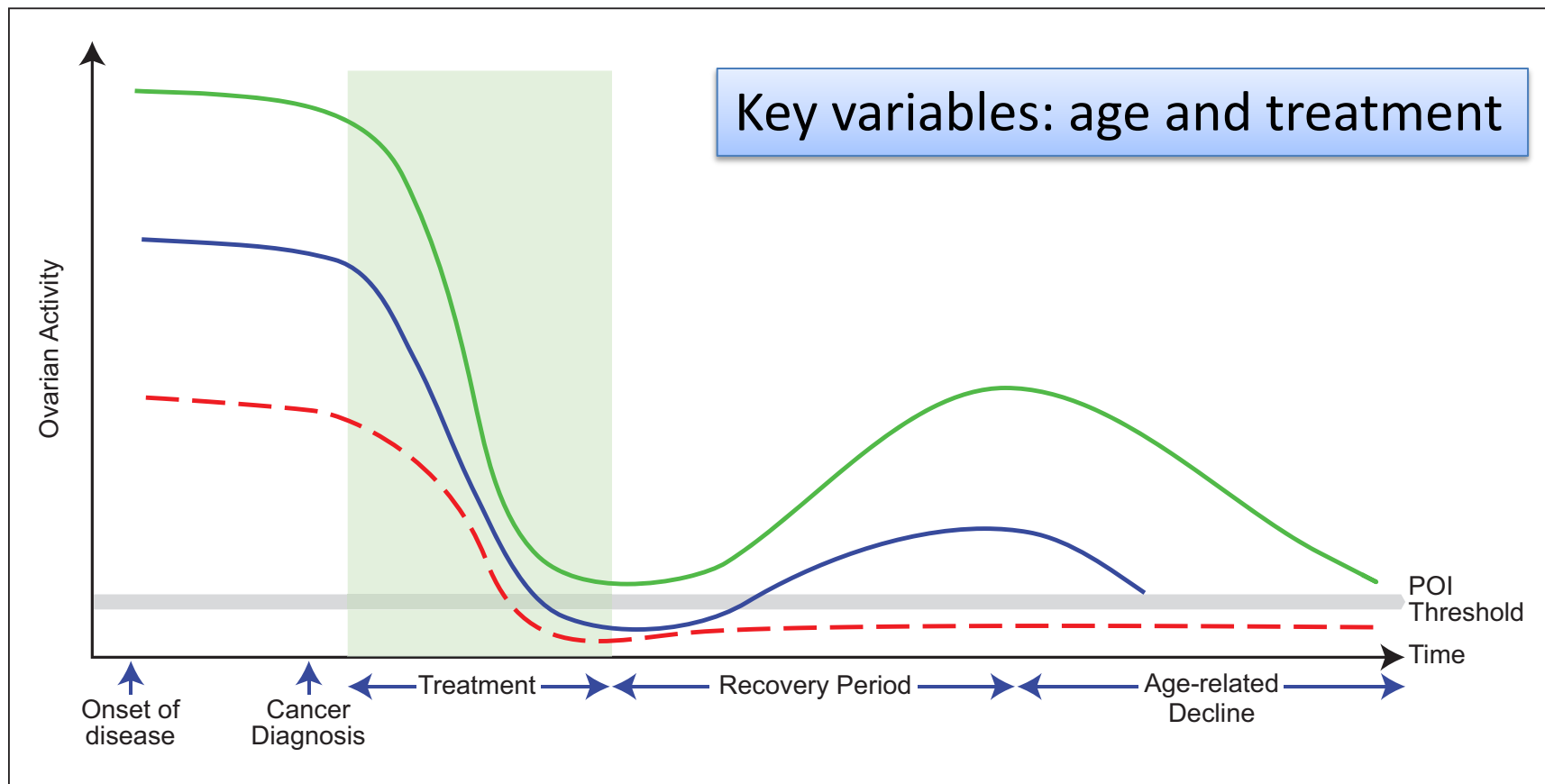
After chemotherapy

Green: Masson stain for collagen

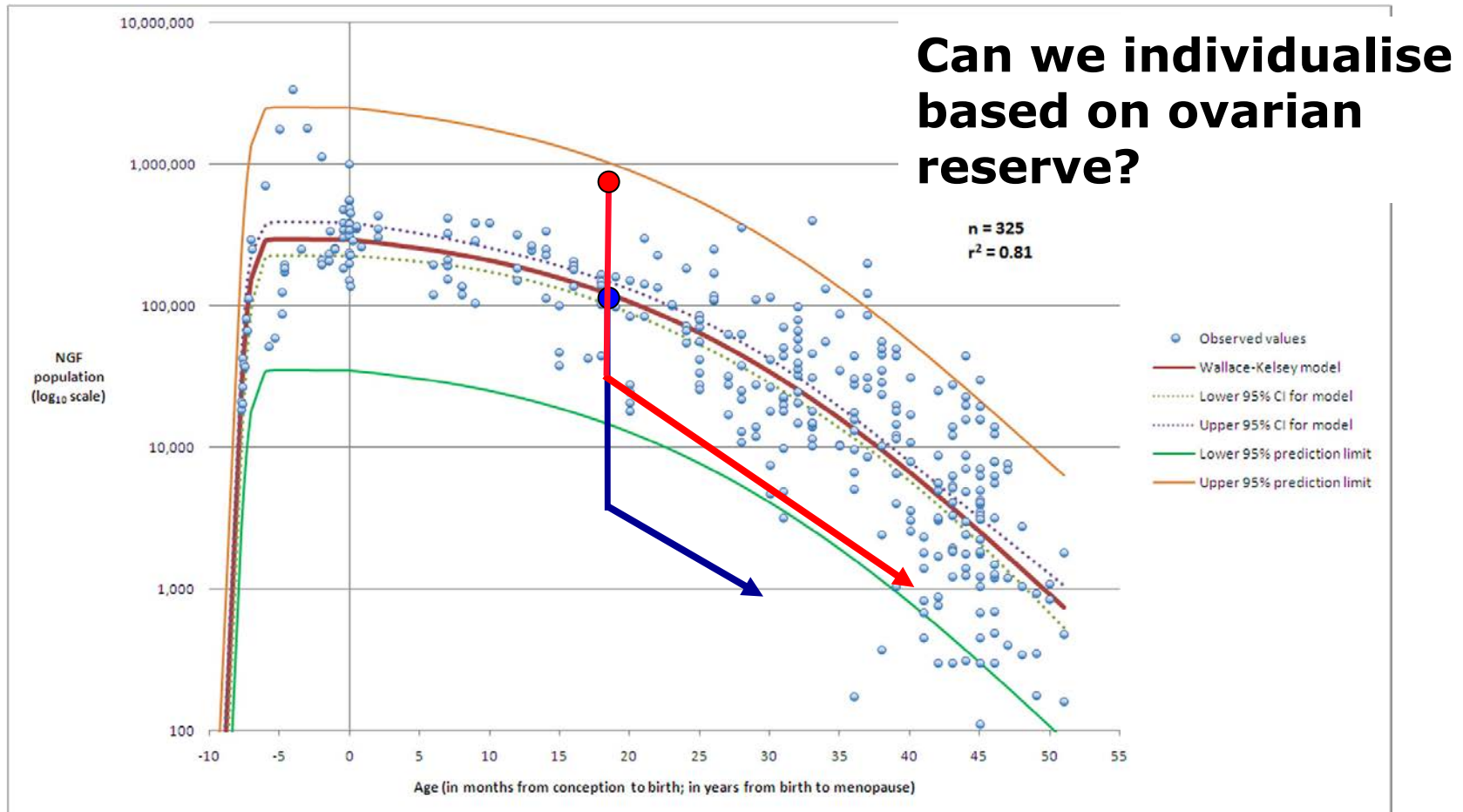
Focal cortical fibrosis in ovaries exposed to chemotherapy

Prominent thickening and hyalinization, with narrowing /obliteration of the lumen

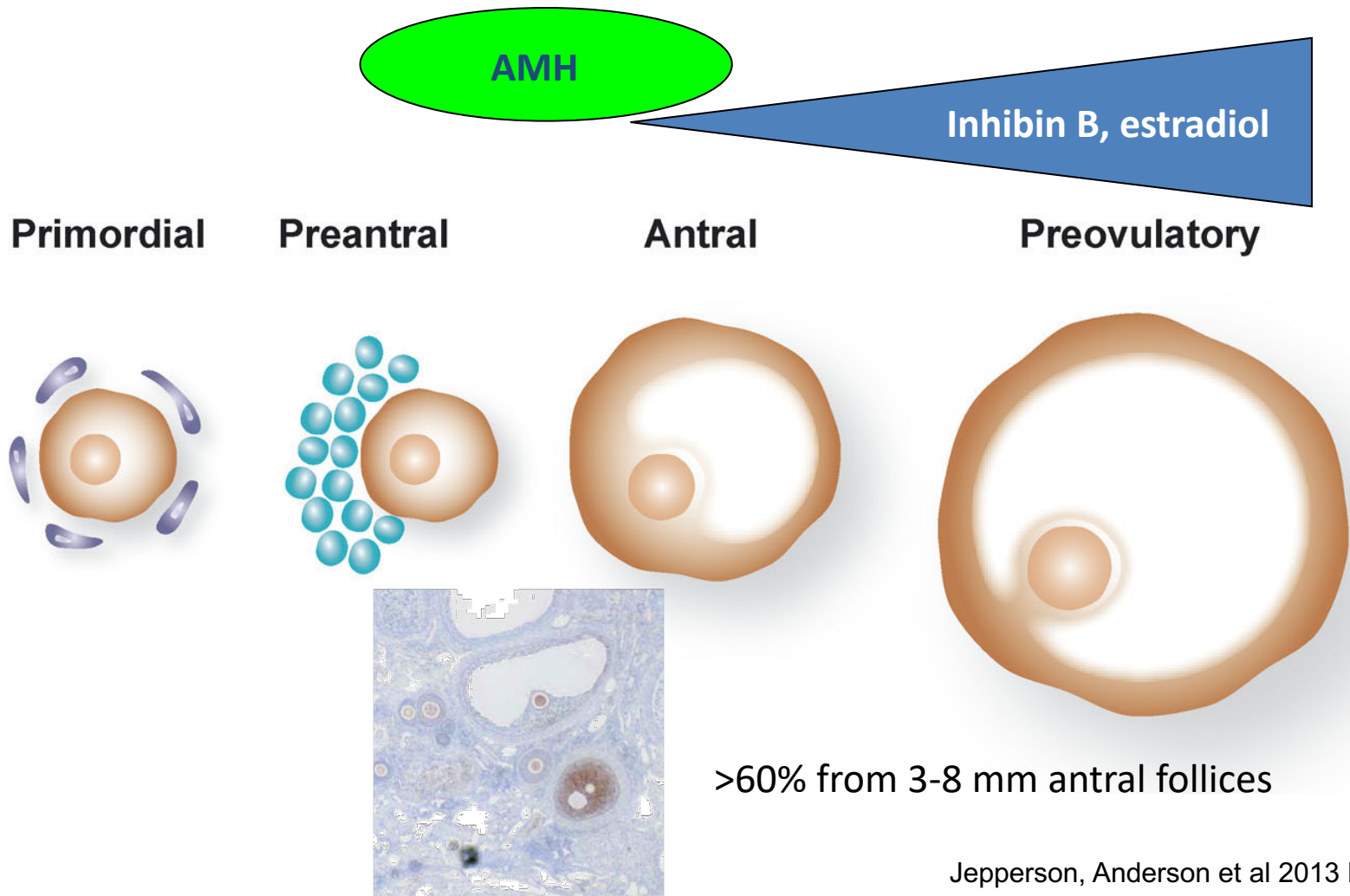
The variability in ovarian activity after cancer treatment



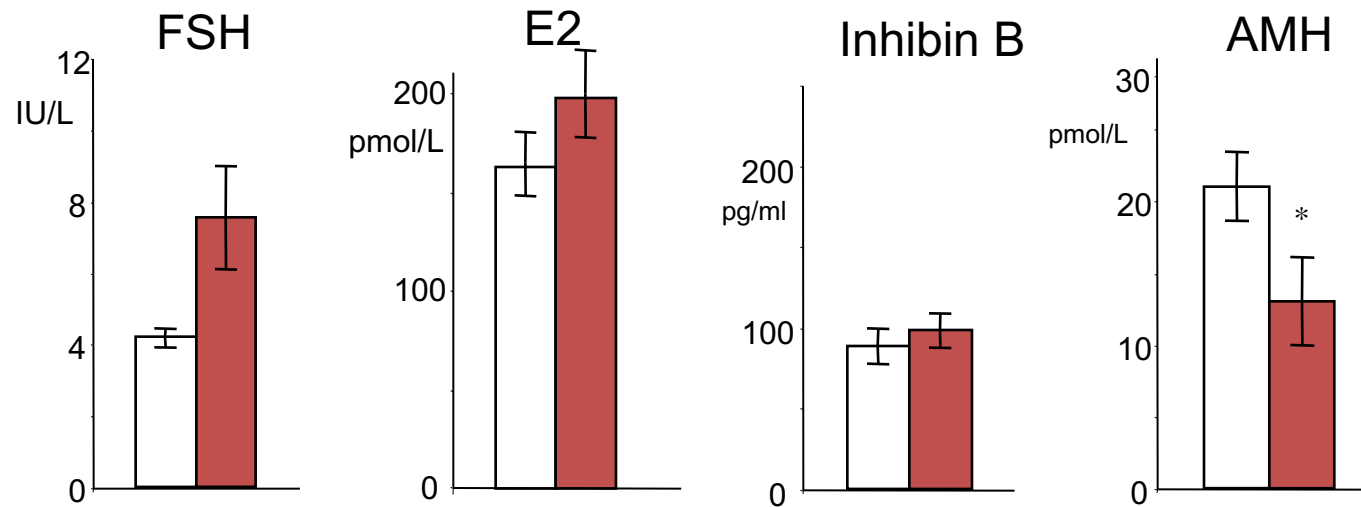
Age-related changes in the ovarian reserve



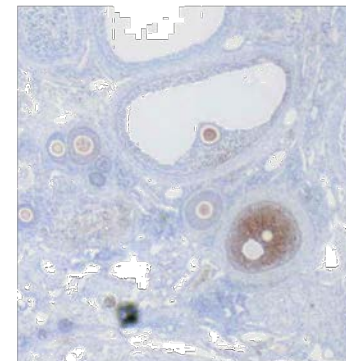
AMH reflects the number of small growing follicles



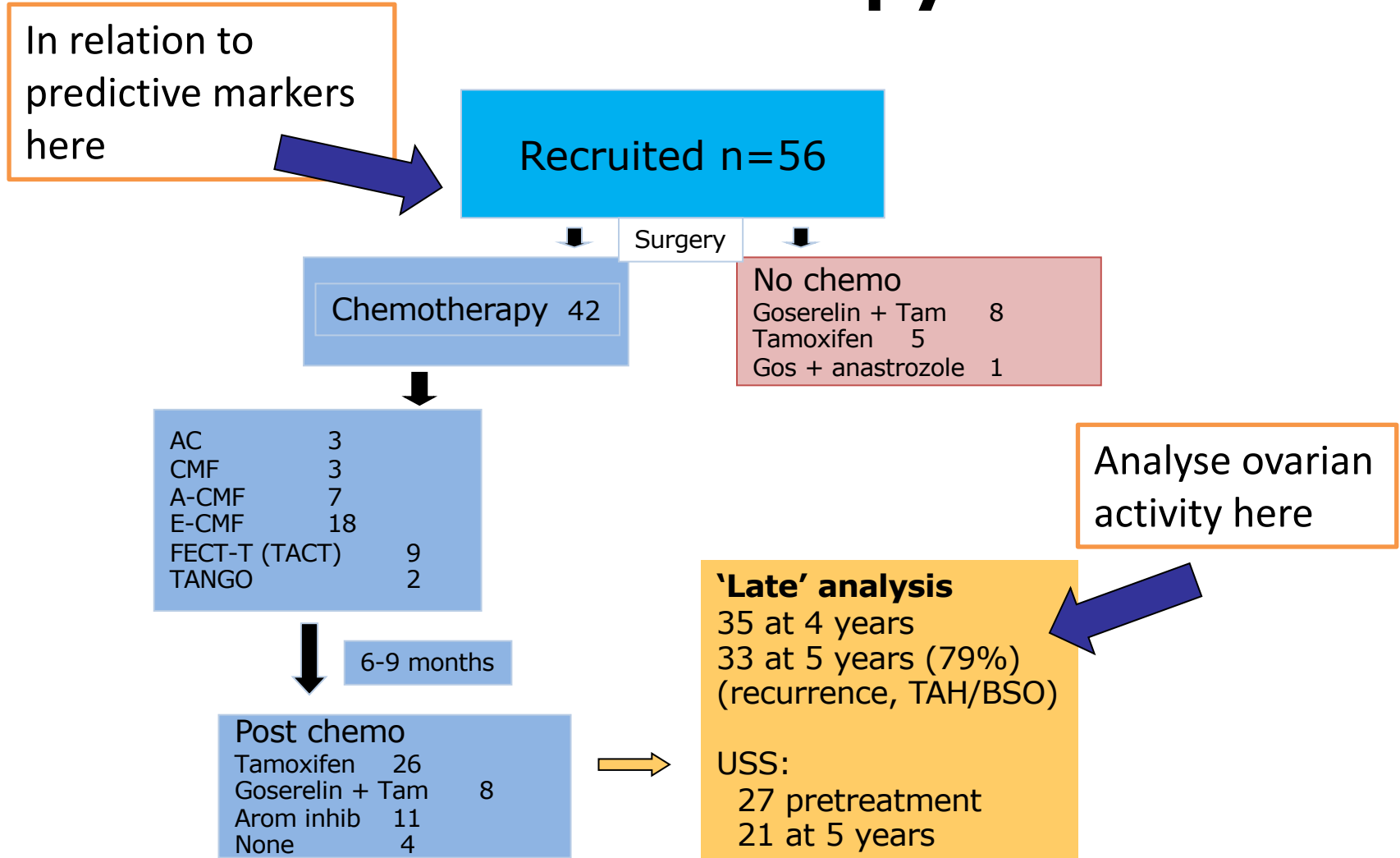
AMH identifies ovarian damage in childhood cancer survivors despite regular cycles



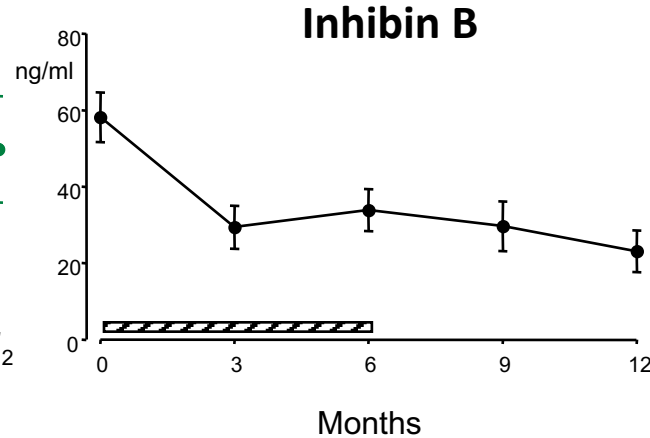
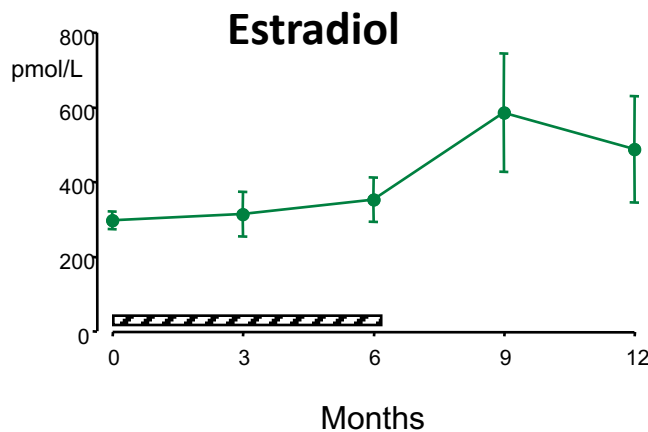
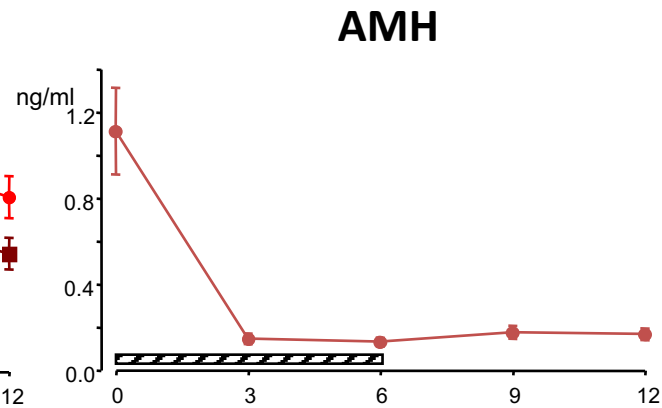
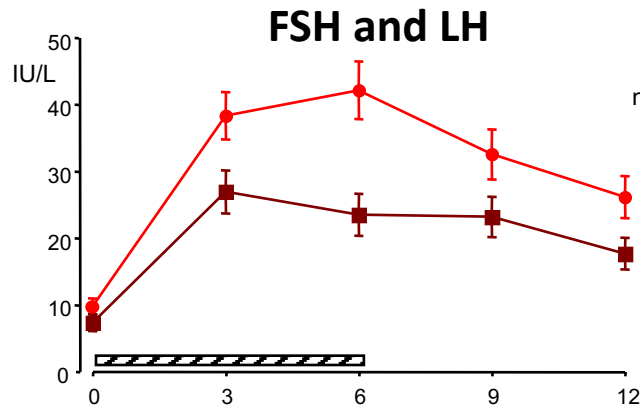
□ Controls
■ Cancer survivors



Prediction of ovarian function after chemotherapy

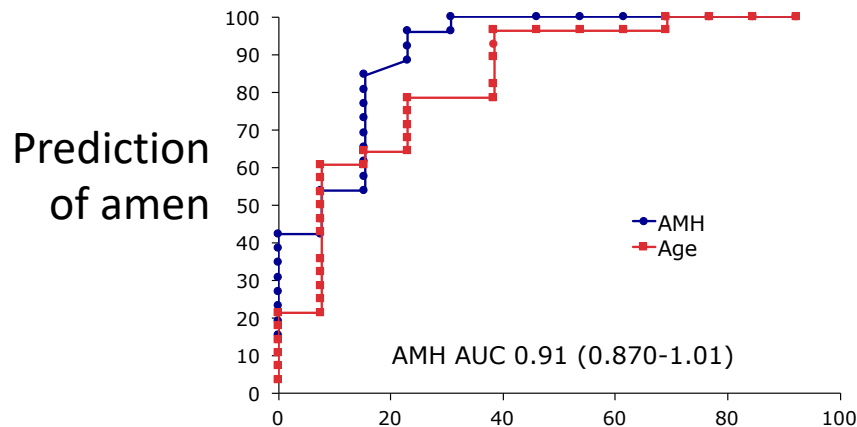
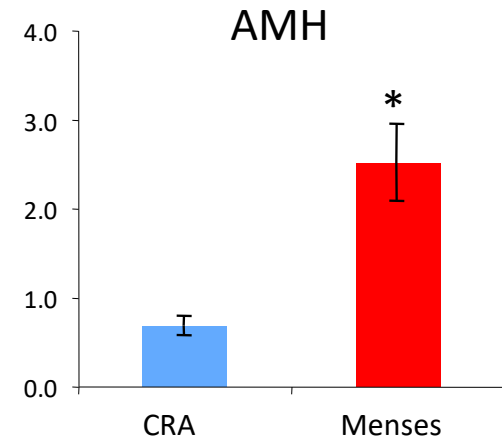
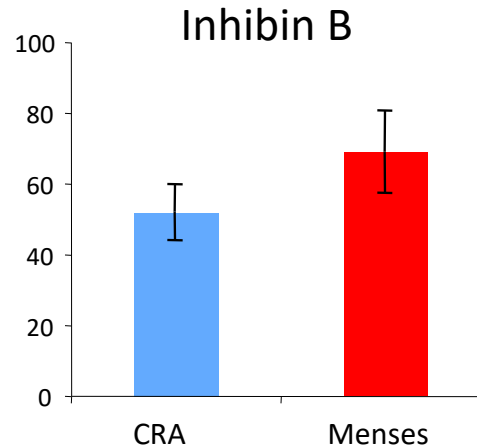
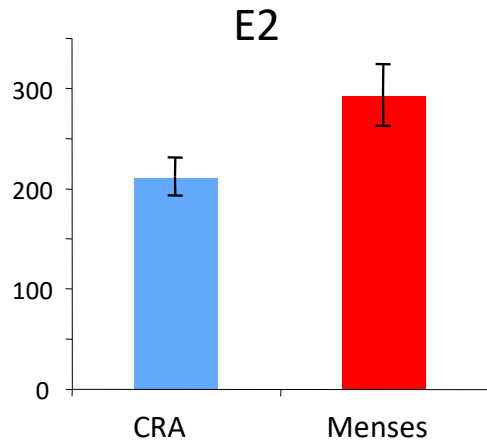


Effect of chemotherapy in eBC acute toxicity and long-term prediction



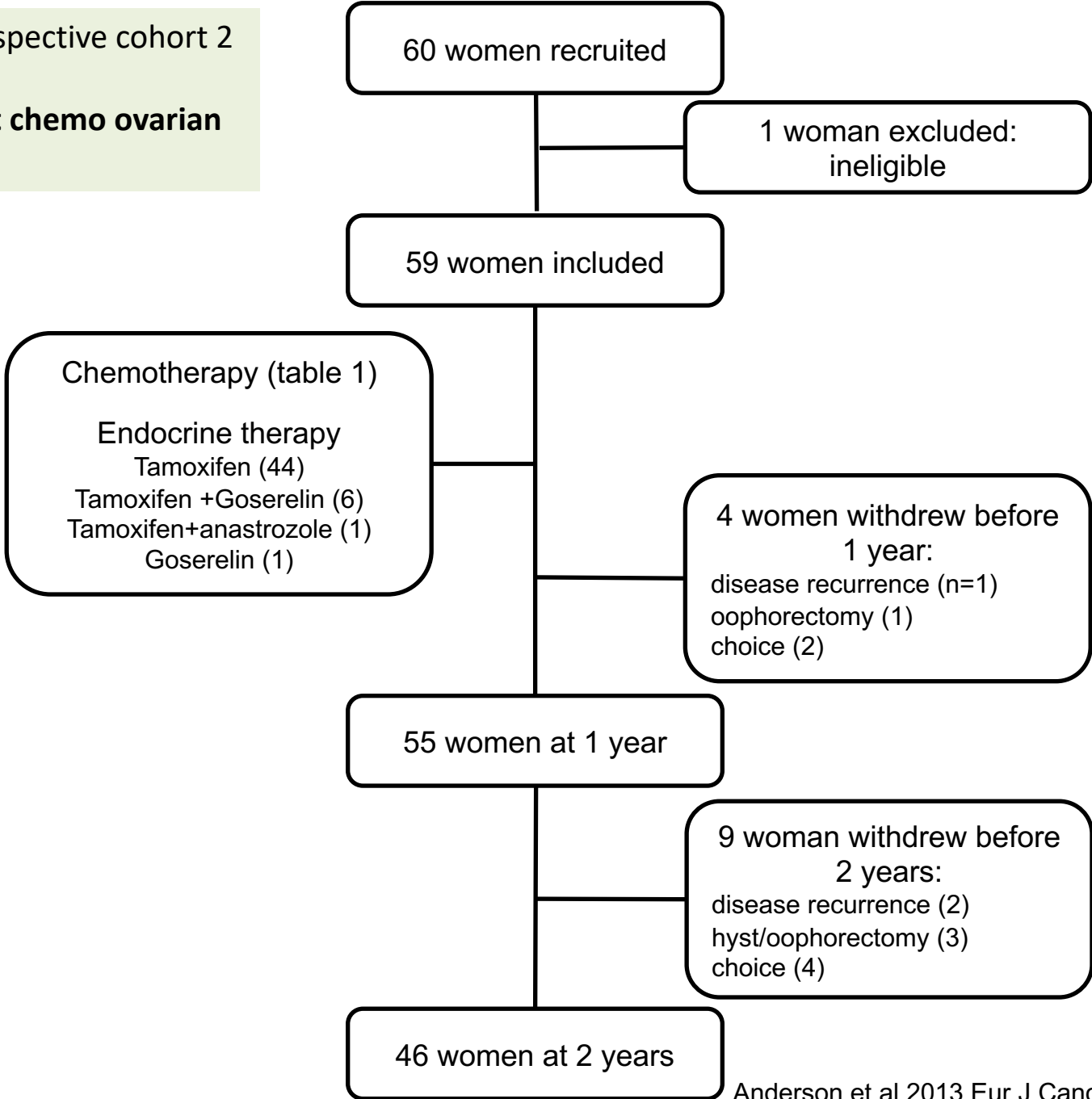
n=42

Prediction of long-term ovarian function: pretreatment assessment

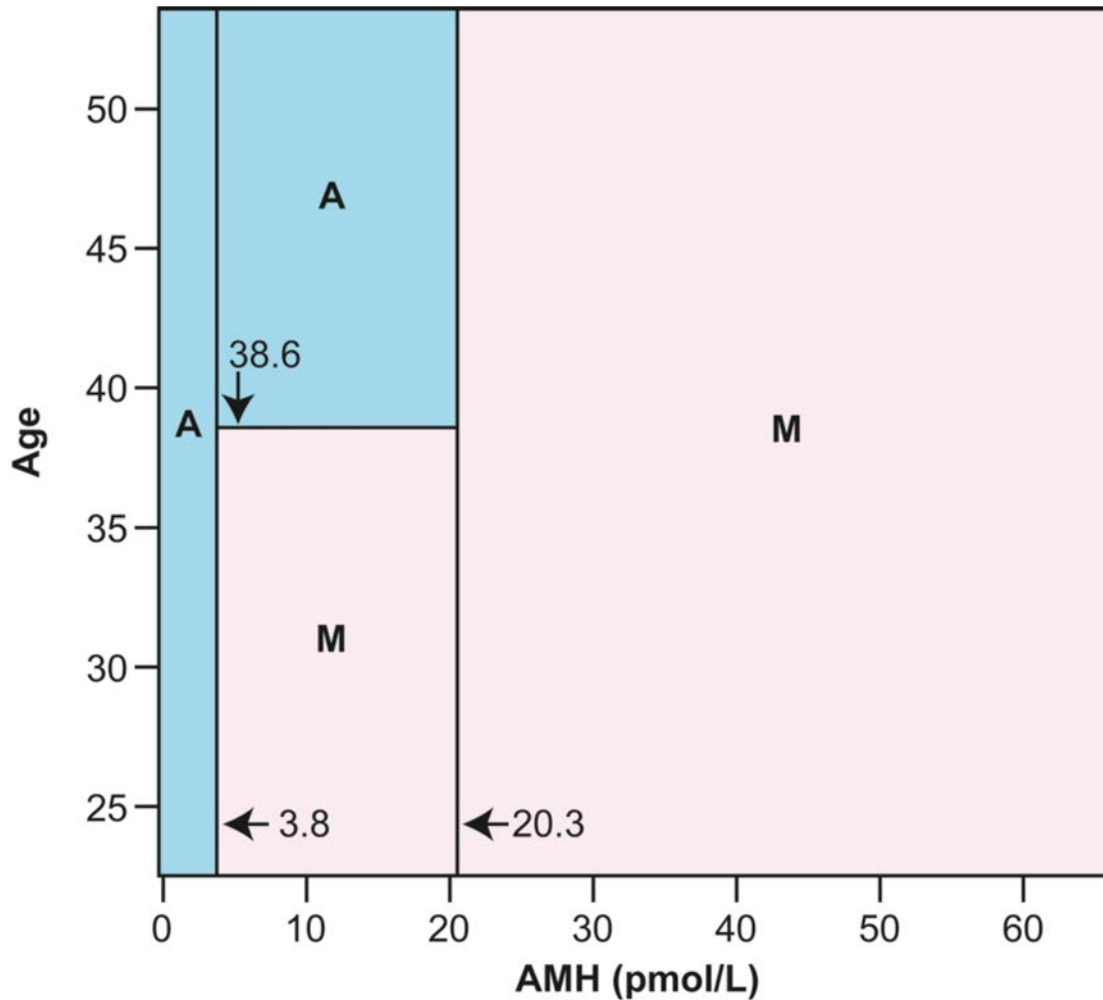


AMH at diagnosis of early breast cancer is higher in those women who will still be having menses 5 years later

Breast cancer prospective cohort 2
Prediction of post chemo ovarian function



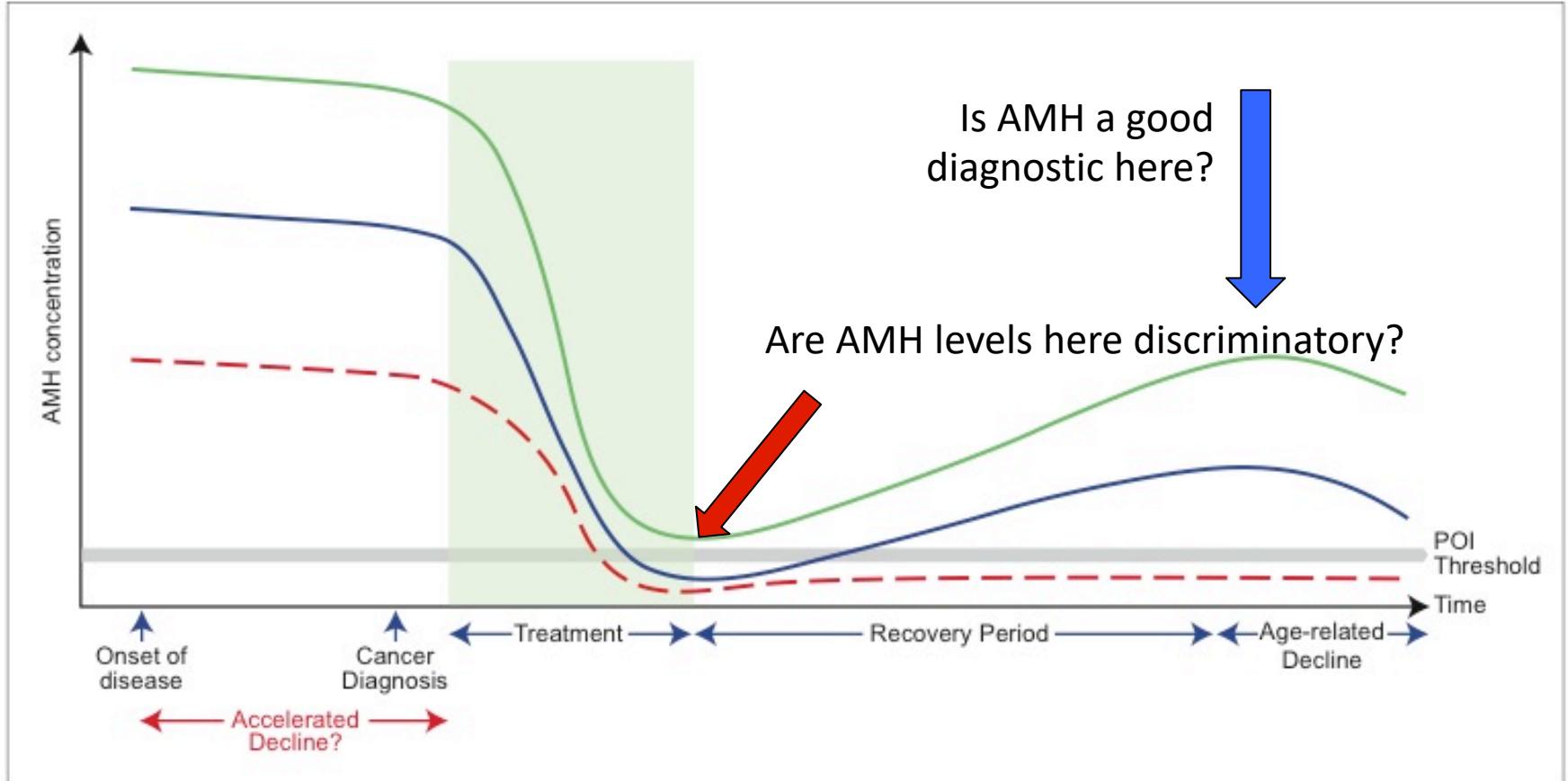
Clinical application: predictive mosaic chart in eBC



sensitivity 98.2%
specificity 80.0%
for correct classification of
amenorrhoea

n=75

AMH profiles after chemotherapy



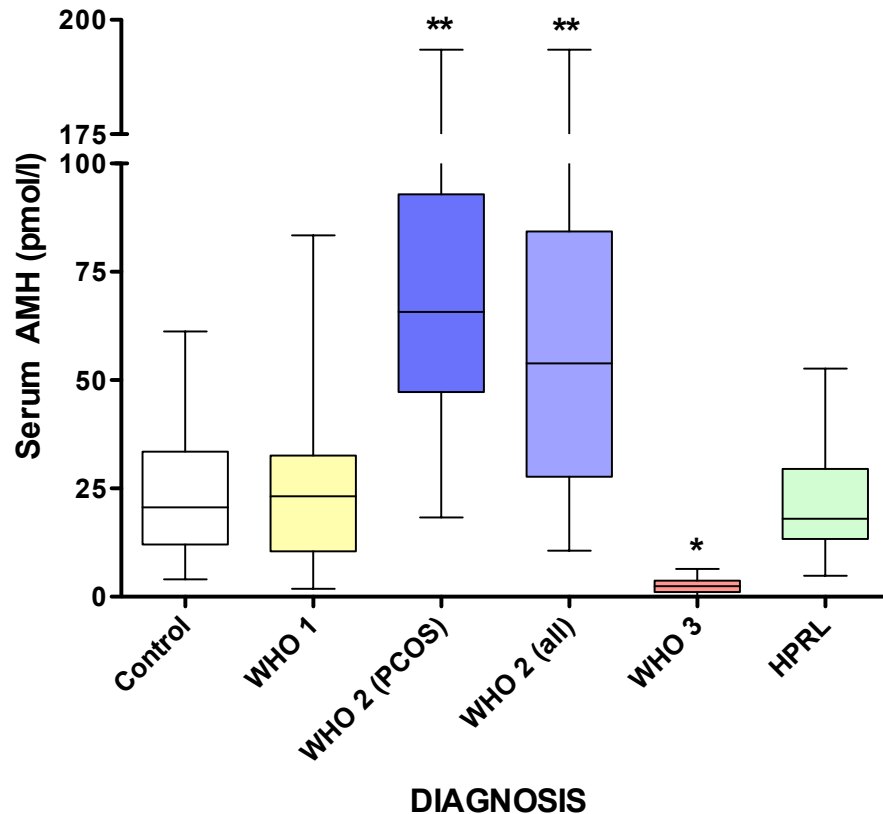
ORIGINAL ARTICLE

GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial

R. C. F. Leonard^{1*}, D. J. A. Adamson², G. Bertelli³, J. Mansi⁴, A. Yellowlees⁵, J. Dunlop⁶, G. A. Thomas¹, R. E. Coleman⁷ & R. A. Anderson⁸, for the Anglo Celtic Collaborative Oncology Group and National Cancer Research Institute Trialists

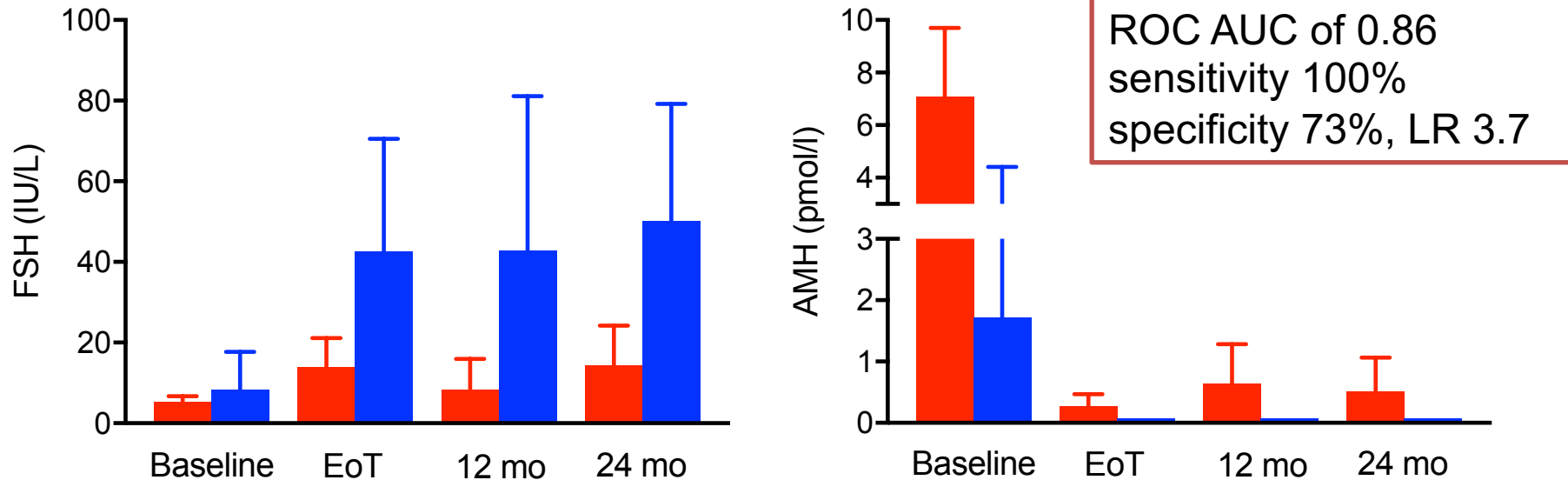
227 women with breast cancer, randomised to \pm goserelin during chemotherapy

AMH as a diagnostic test in POI?



- Not part of the diagnosis at present
- Will increased assay sensitivity help?
- Useful in 'fluctuant' stage of condition when E2 and FSH very variable?

Can AMH diagnose POI after chemo?



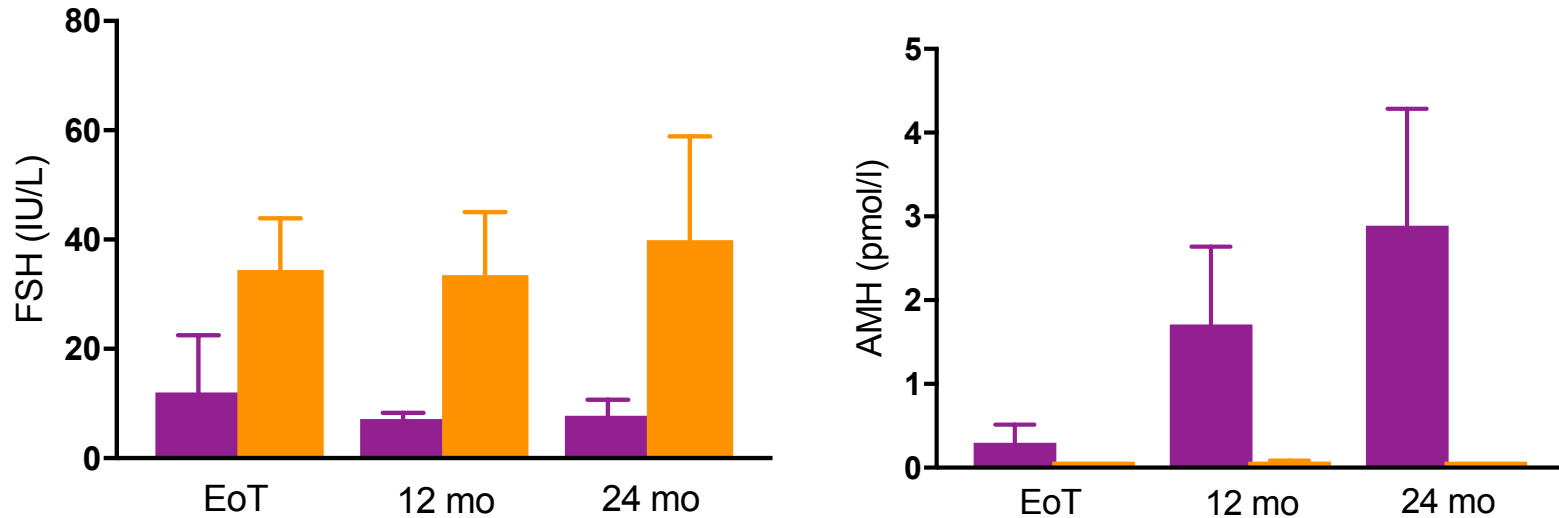
Serum FSH and AMH by POI at 24 months. Data from all women from OPTION Roche automated AMH assay

Red, not POI

Blue: POI (amenorrhoea plus FSH >25IU/L).

N=96 and 28 respectively; median \pm 95% confidence intervals.

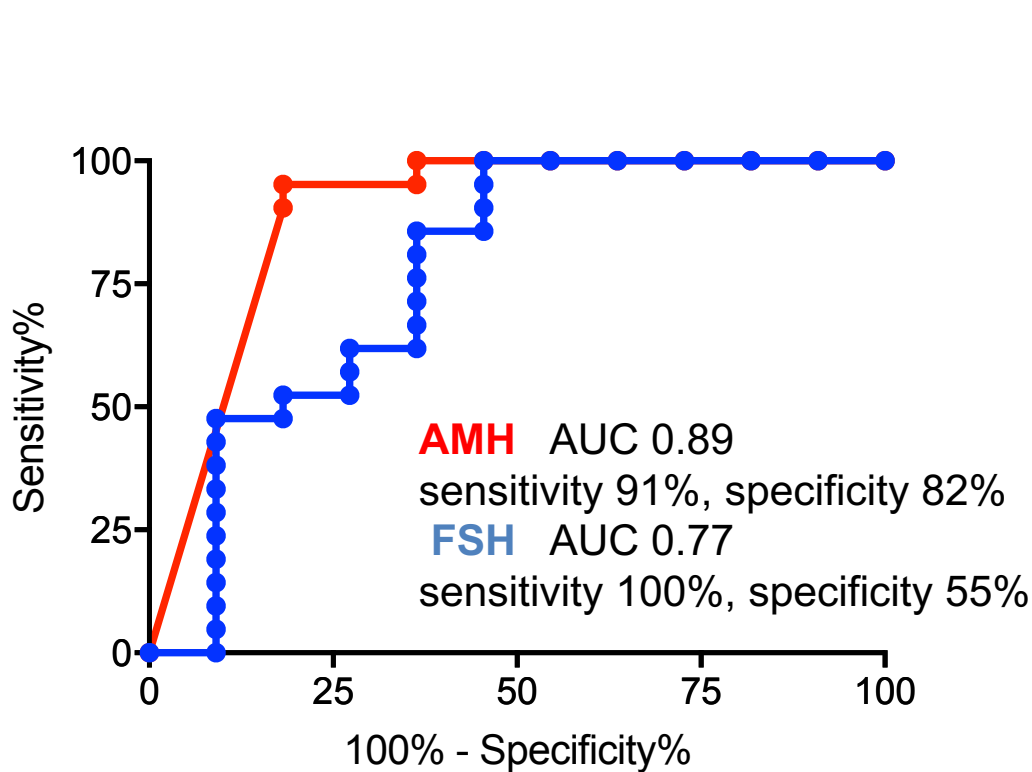
Importance of age for recovery of ovarian function after chemotherapy



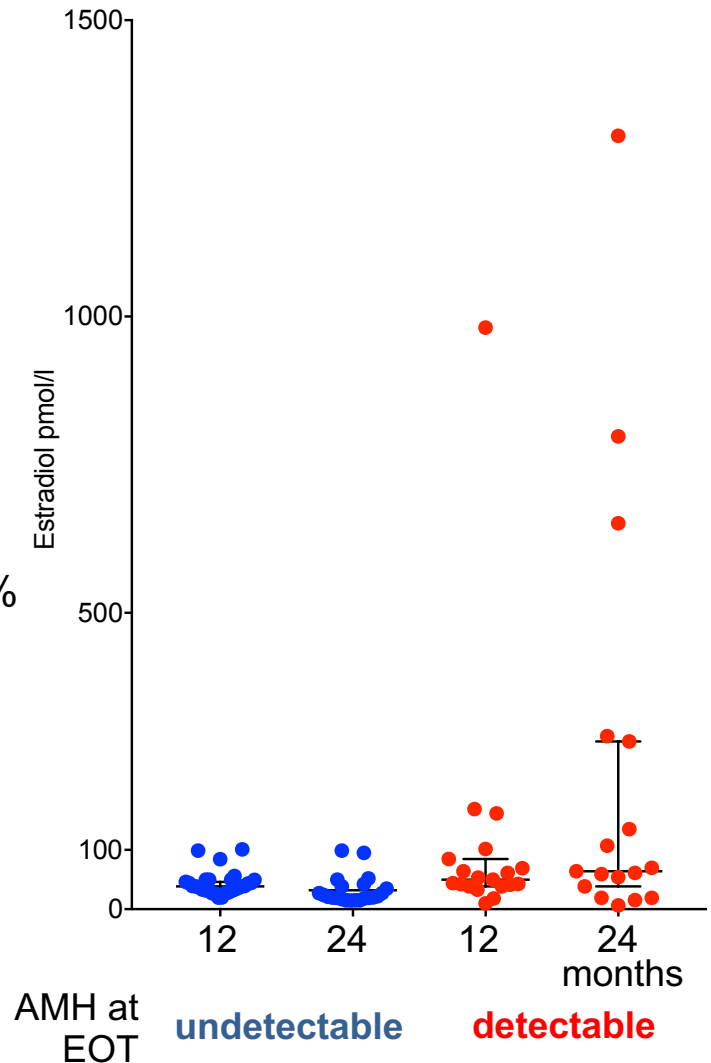
Women aged ≤ 40 (purple) vs >40 years (orange)
n=62 and 81, median \pm 95% CI.

Data from OPTION trial

EOT predictive analysis in women >40 yrs

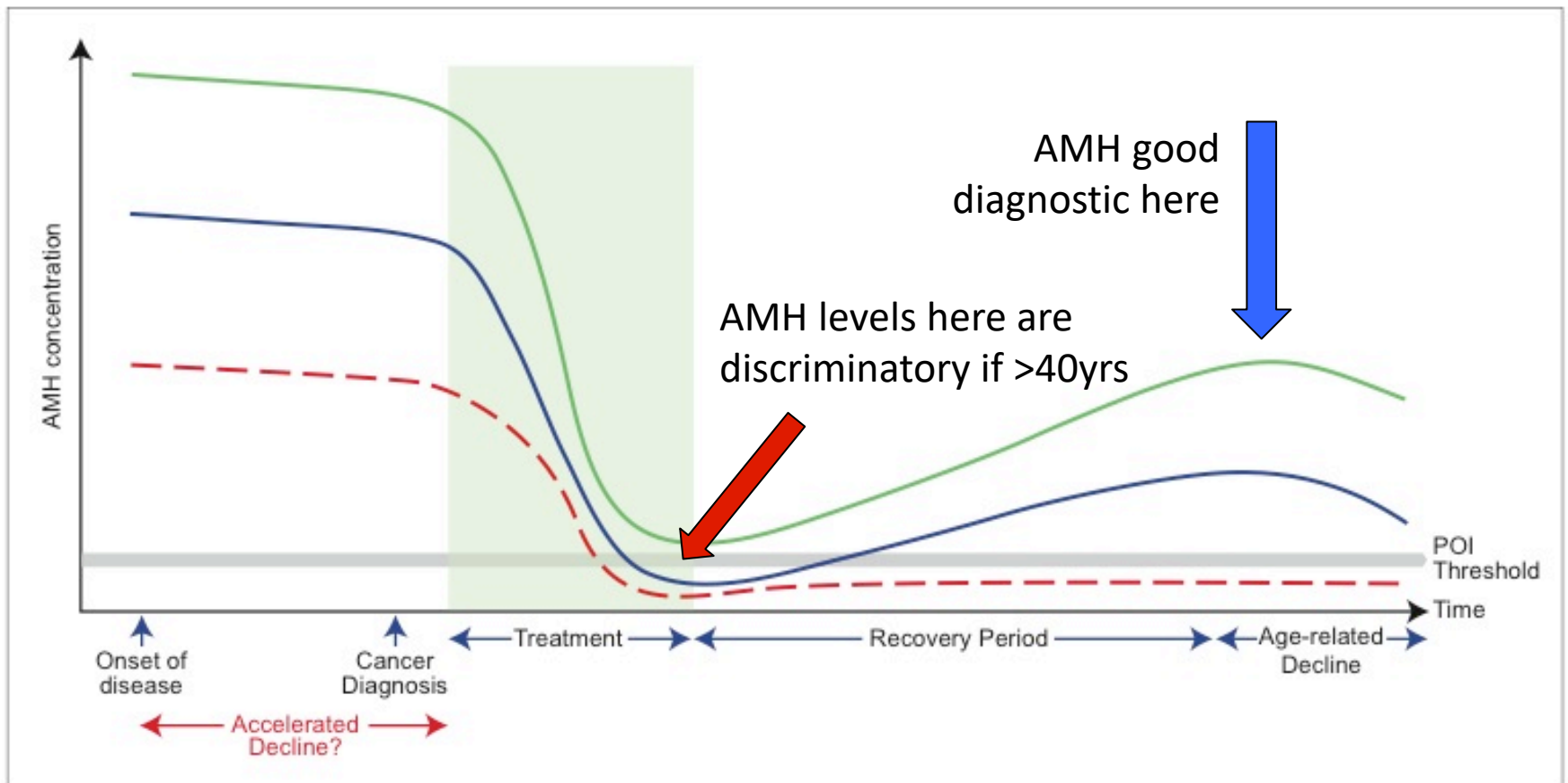


AMH and **FSH** at end of treatment for prediction of POI at 24 months
OPTION control group, n=32

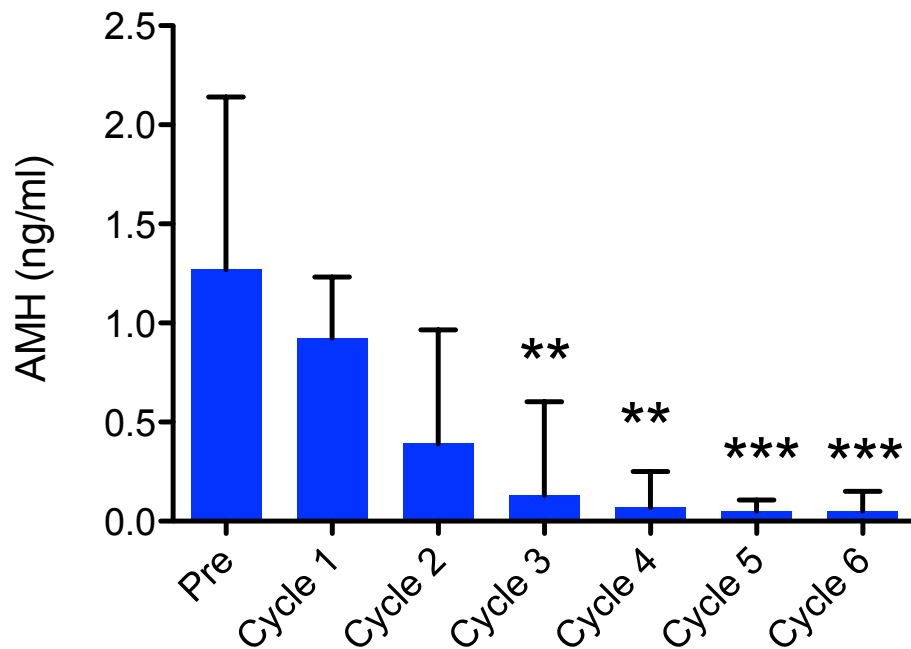


AMH profiles after chemotherapy

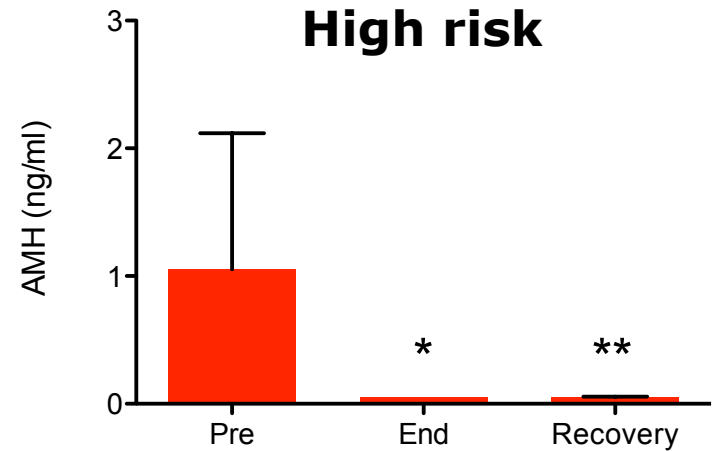
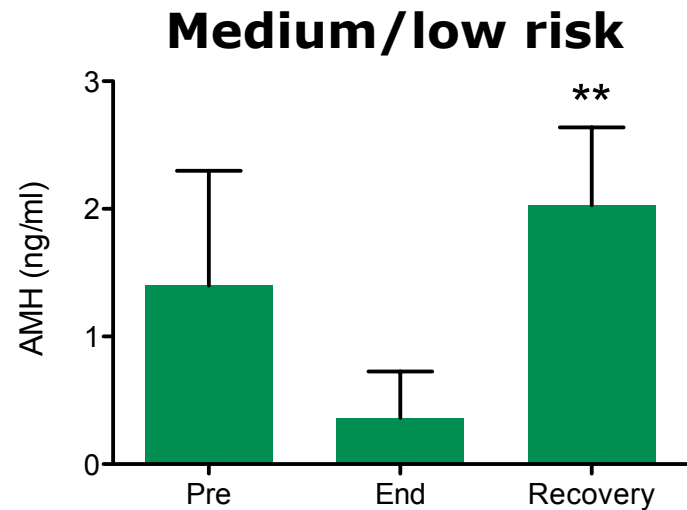
Clinical importance: identification of permanent POI may allow optimisation of endocrine treatment post chemo



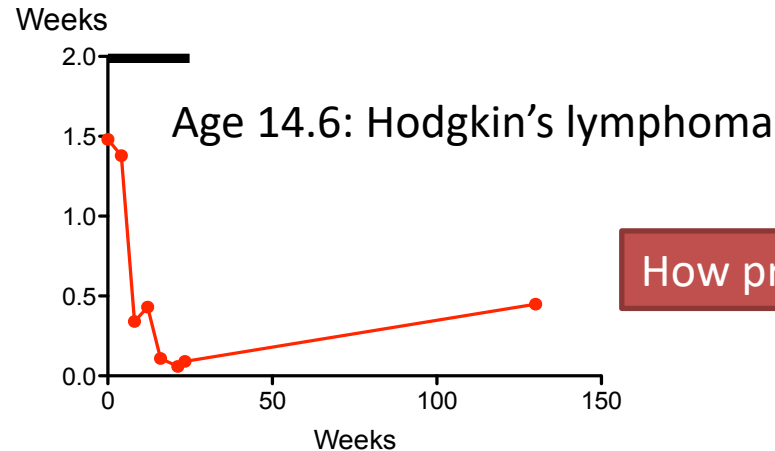
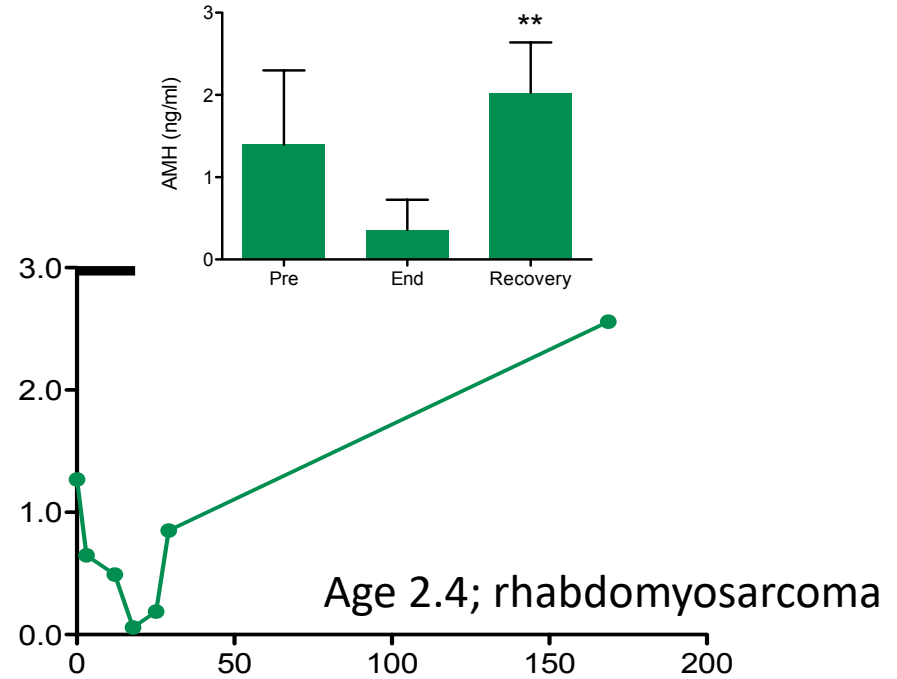
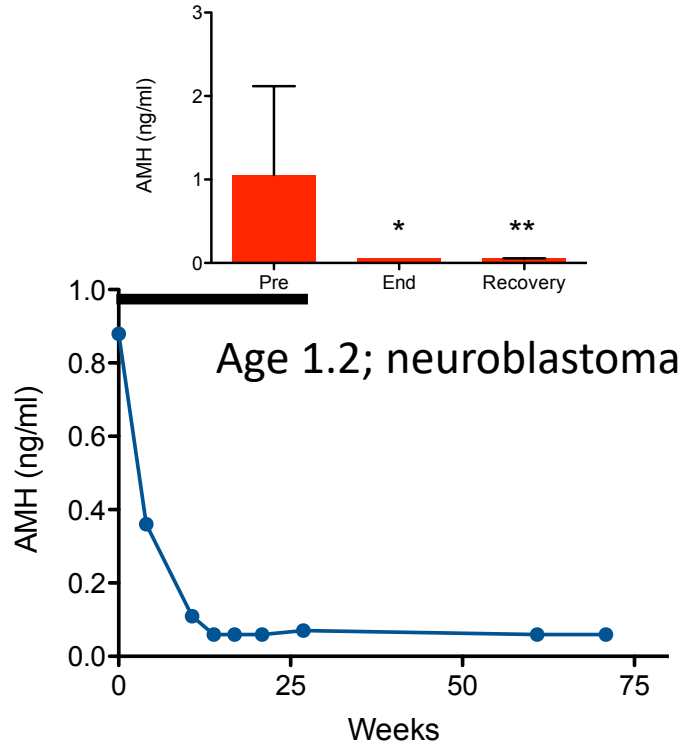
AMH: application in childhood cancer



22 girls age 0.3-15yr
17 prepubertal



AMH in 3 girls with cancer



How predictive is this?

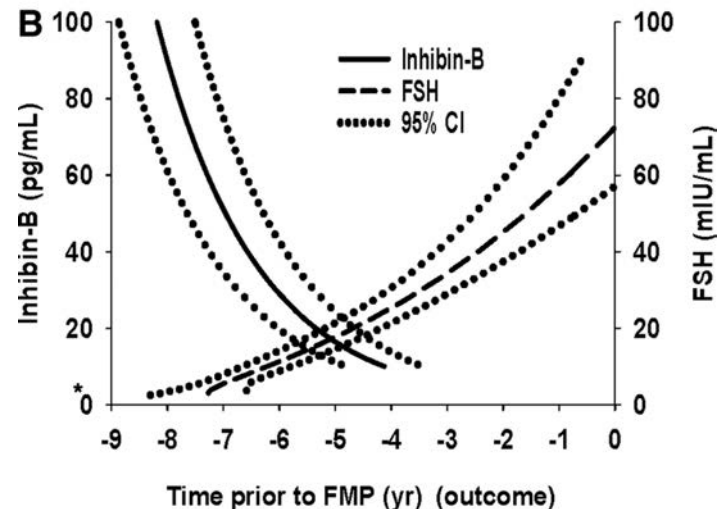
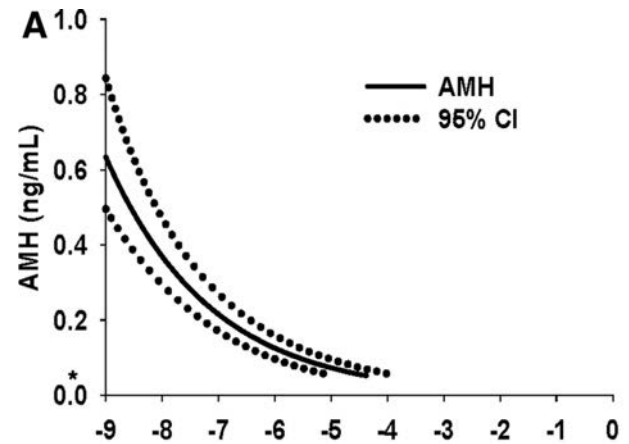
Does AMH predict natural menopause

50 women followed prospectively
(Michigan Bone Health and Metabolism Study)
6 annual assessments

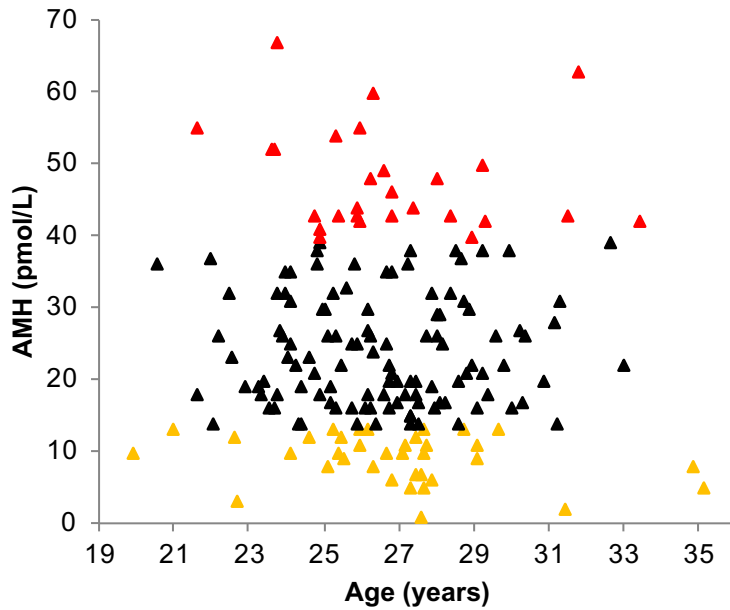
Mean initial age 42 yr

AMH related to both time to and age at FMP

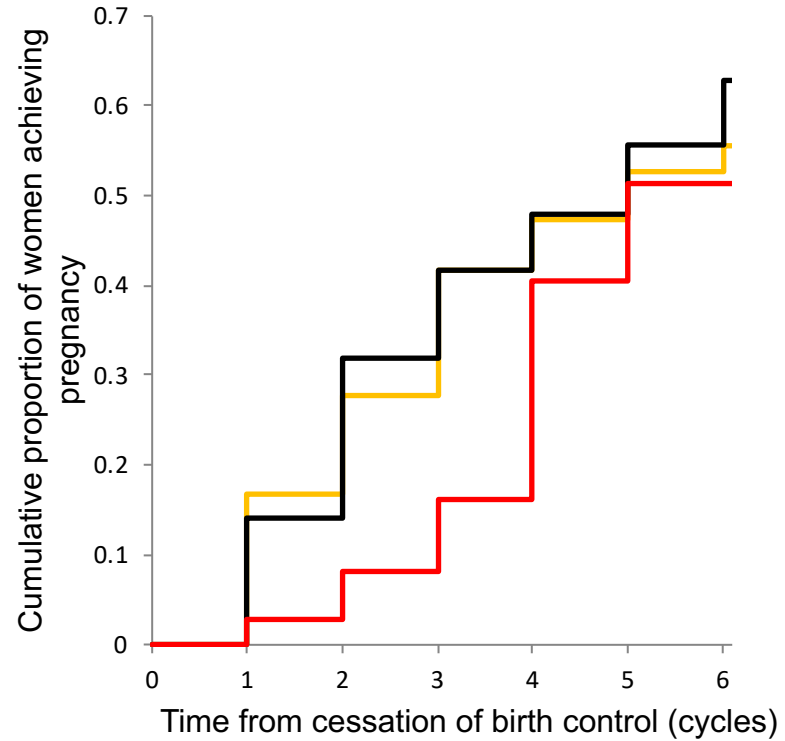
Inhibin B less predictive of both



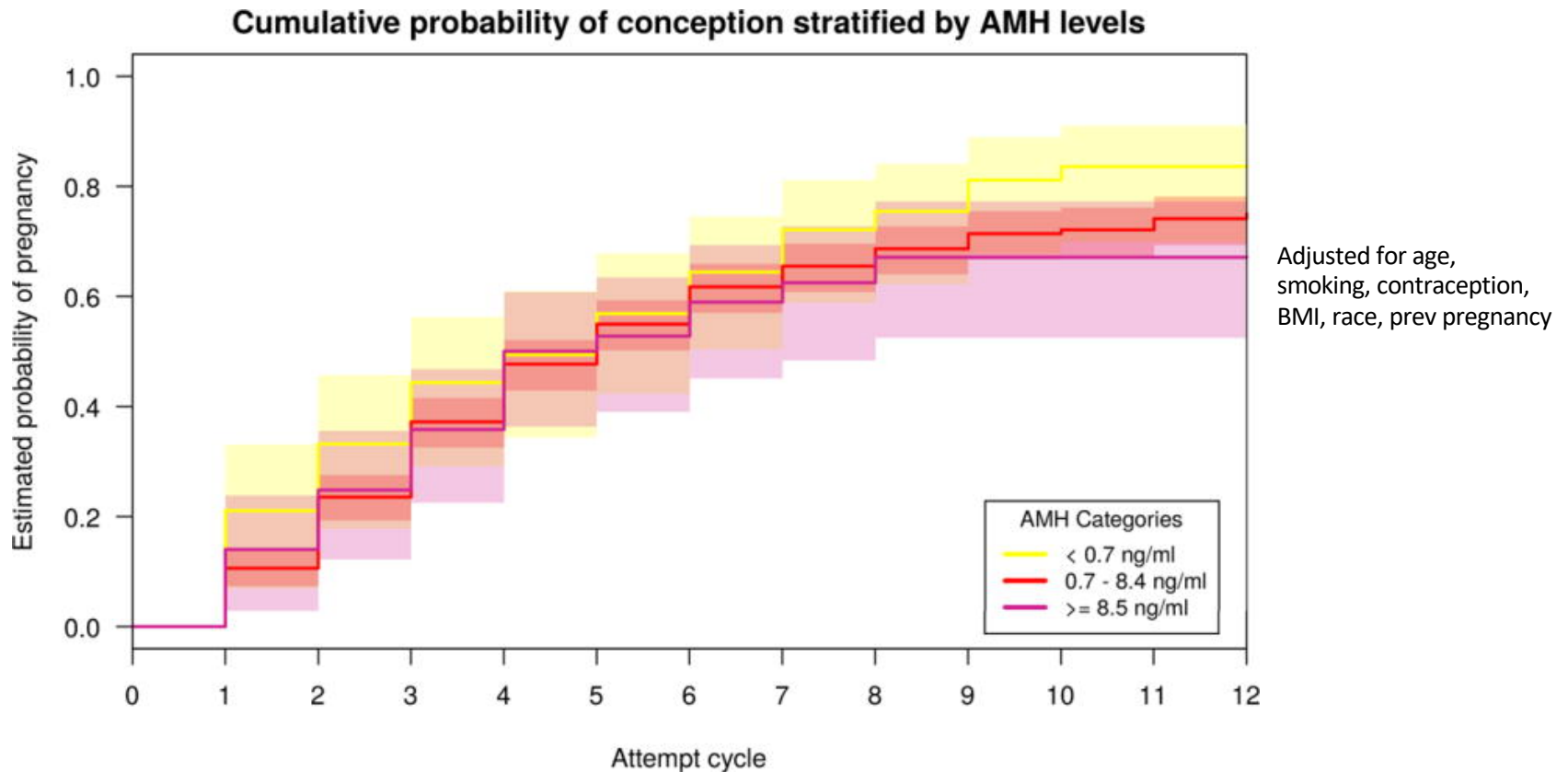
AMH and fecundability



AMH quintiles, middle 3 combined

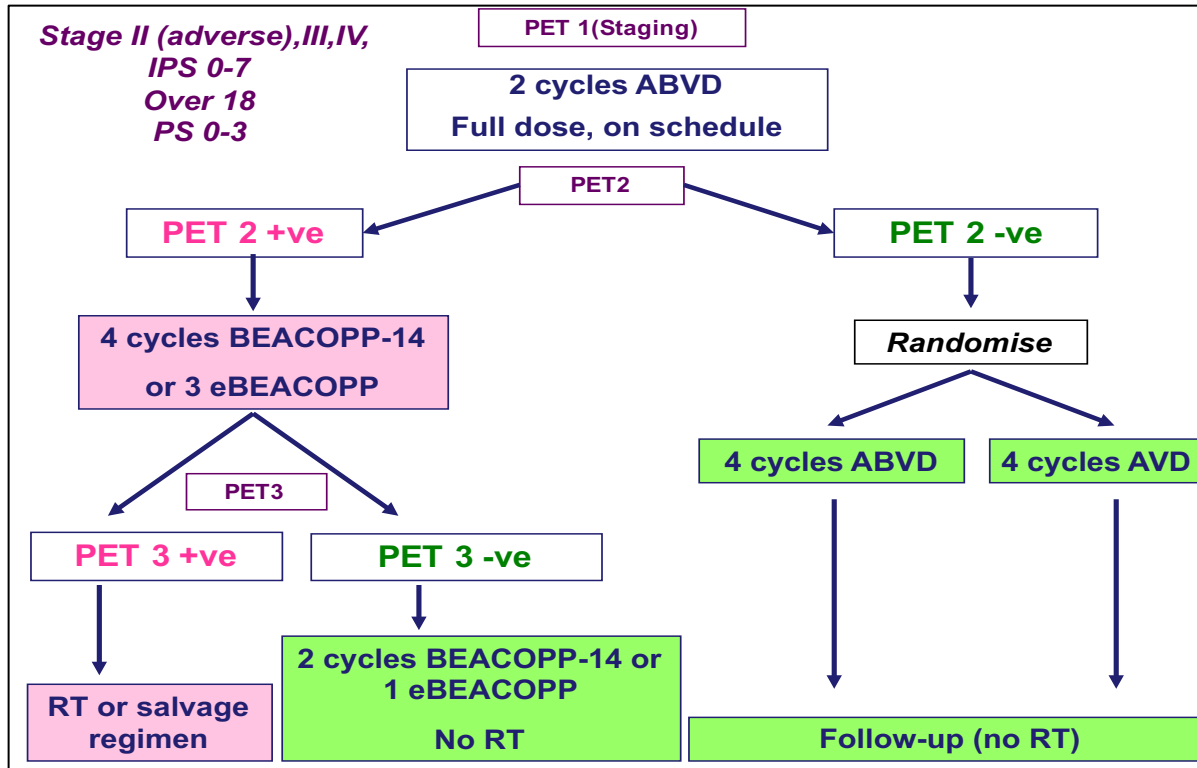


AMH and fertility in older women



981 women aged 30 to 44, trying to conceive max 3 months at study entry

What about low toxicity regimens? RATHL trial in Hodgkin Lymphoma



Ovarian substudy method

Women aged 18-45 were recruited (ethics approval/consent)

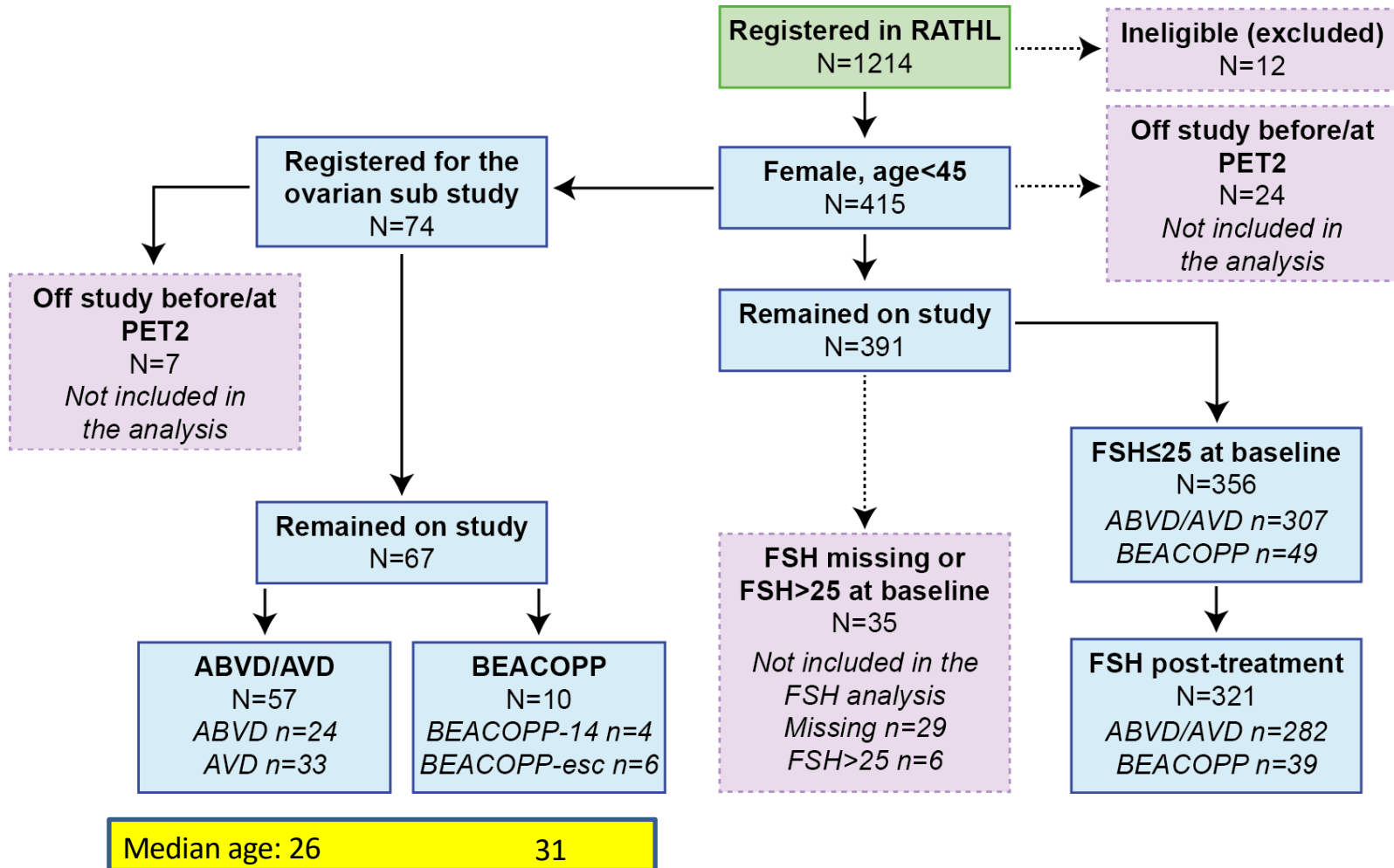
Blood samples:

- Pre-treatment
- After 2 cycles ABVD
- End of chemo
- 1, 2, 3 years later
- Analysed for AMH, FSH (Roche)

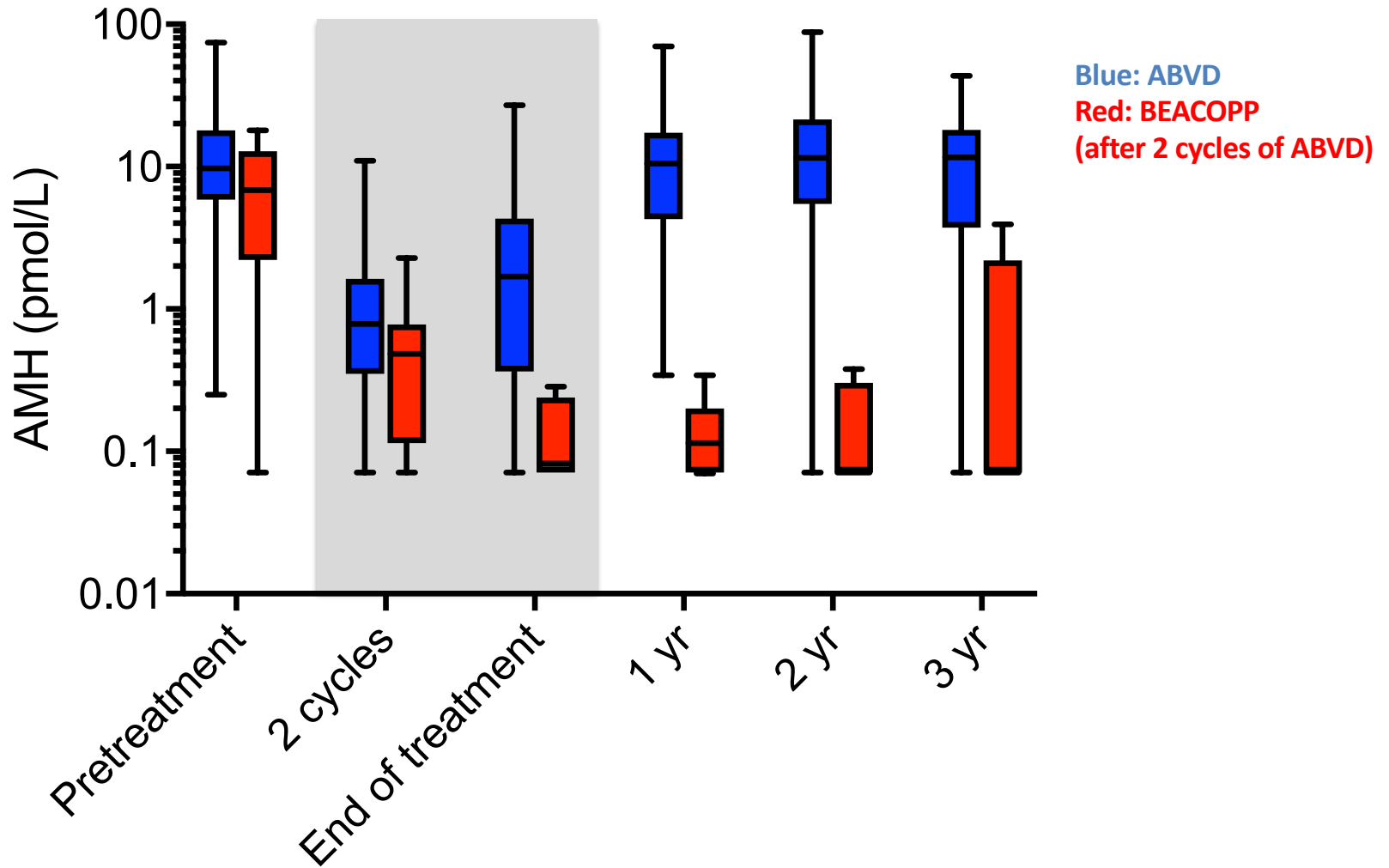
Johnson P et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma.

N Engl J Med. 2016; **374**: 2419-29

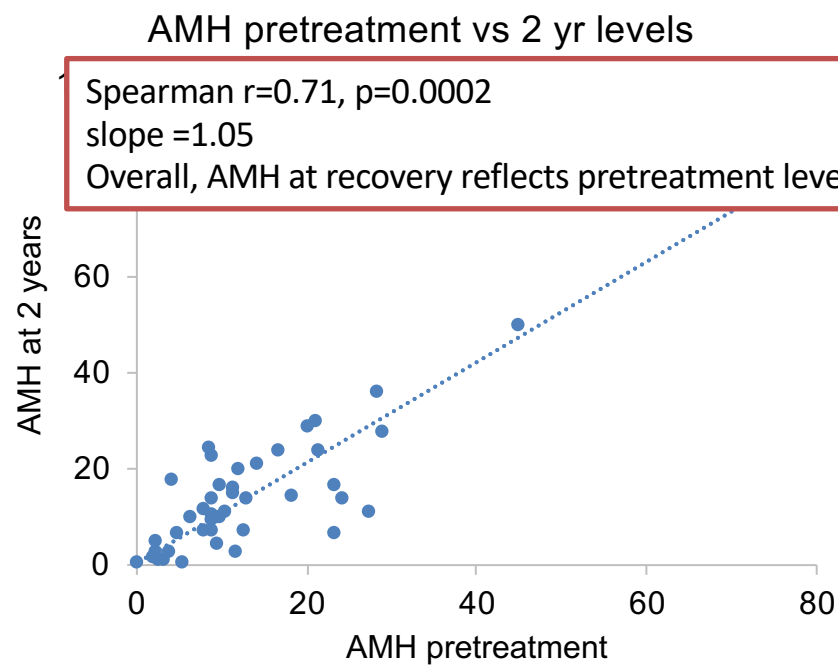
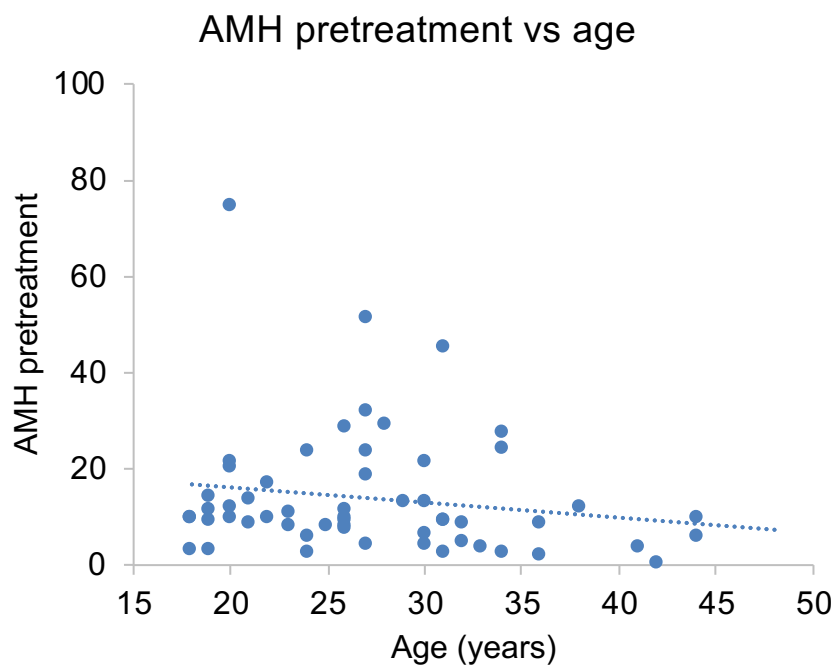
RATHL ovarian substudy



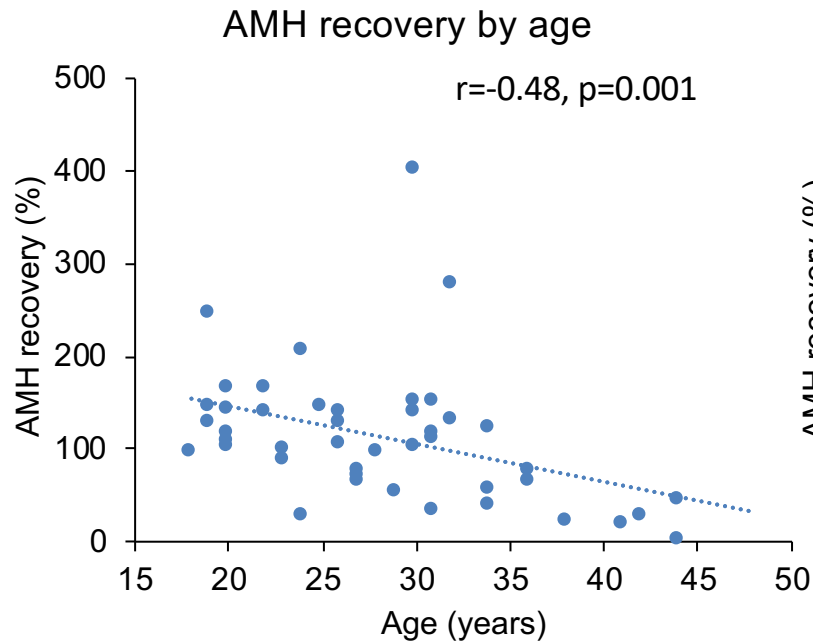
Effects of A(B)VD and BEACOPP on ovarian function



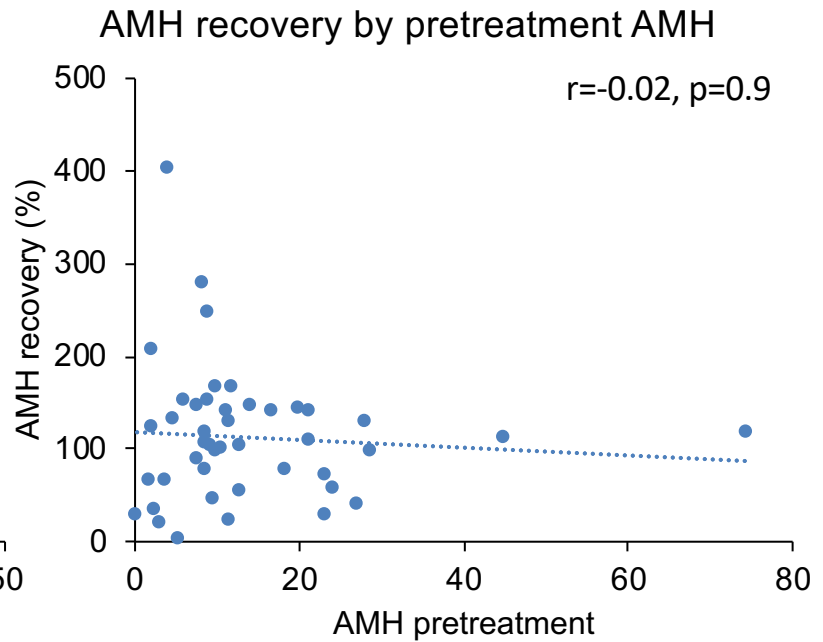
Main relationships: AMH, age, recovery



Is AMH recovery always good?

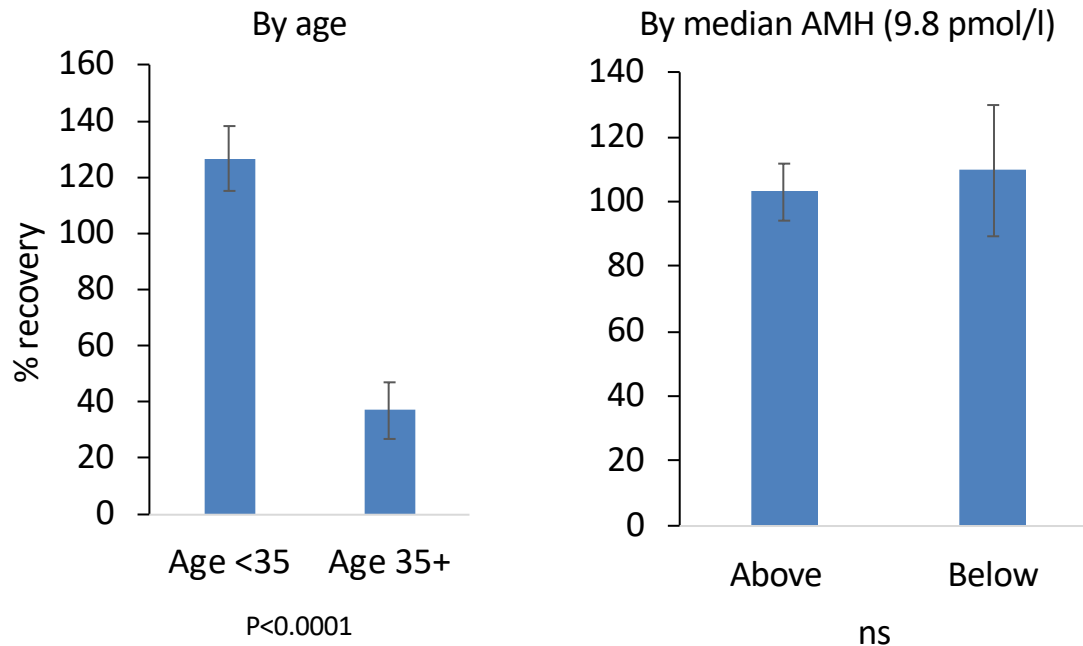


Older women show reduced recovery



Women with low AMH show full recovery

Confirmation of impact of age on recovery

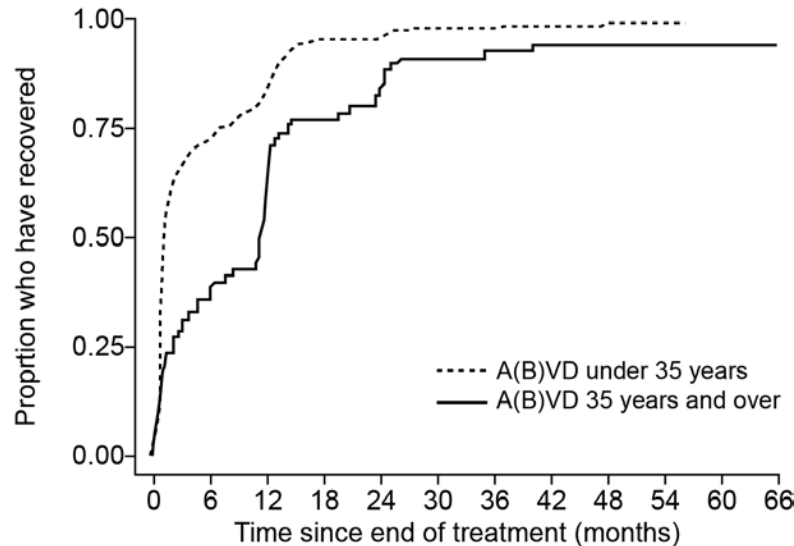


Multiple linear regression analysis vs AMH recovery:
age (beta -0.43, p=0.004)
pretreatment AMH (beta -0.15, p=0.3)

Different to breast cancer data: older population, more toxic treatment

FSH recovery after A(B)VD is also dependent on age

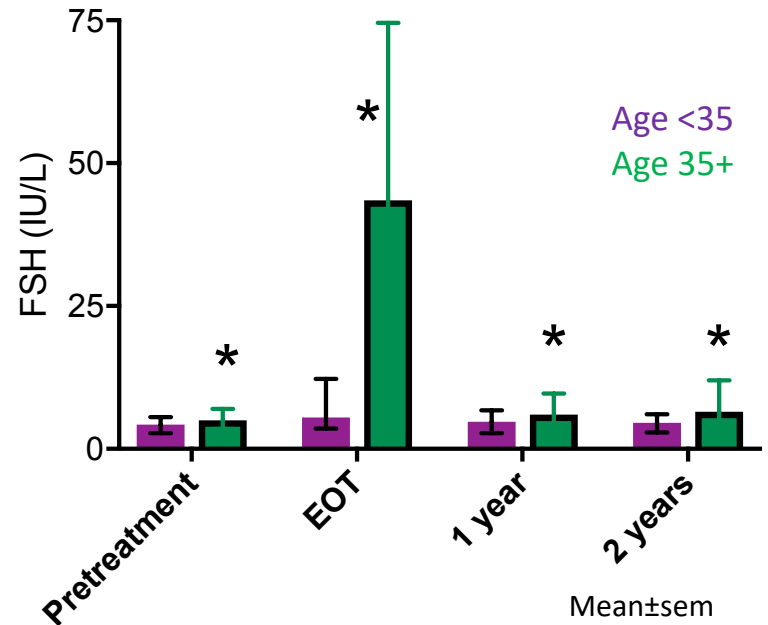
recovery to <25IU/L



Number at risk

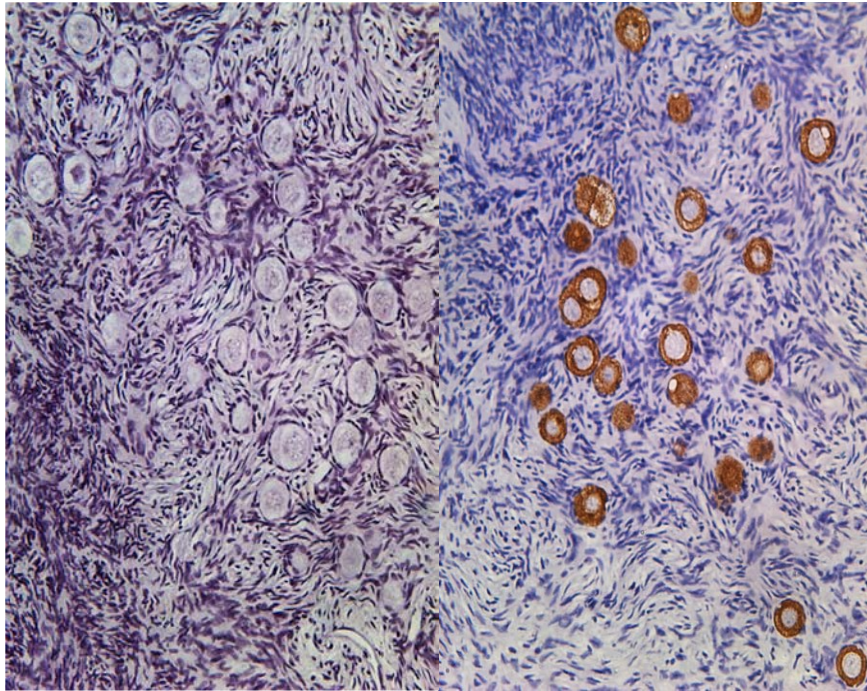
	0	6	12	18	24	30	36	42	48	54	60	66
A(B)VD under 35	208	56	35	9	8	3	3	2	1	1	0	0
A(B)VD 35 and over	74	45	32	16	12	6	5	4	4	4	3	0

% recovered	Age <35	35+
At 1 year	83% (77 – 88)	54% (43 – 66)
At 2 years	96% (93 – 98)	83% (73 – 91)
At 3 years	98% (95-99)	93% (85-97)

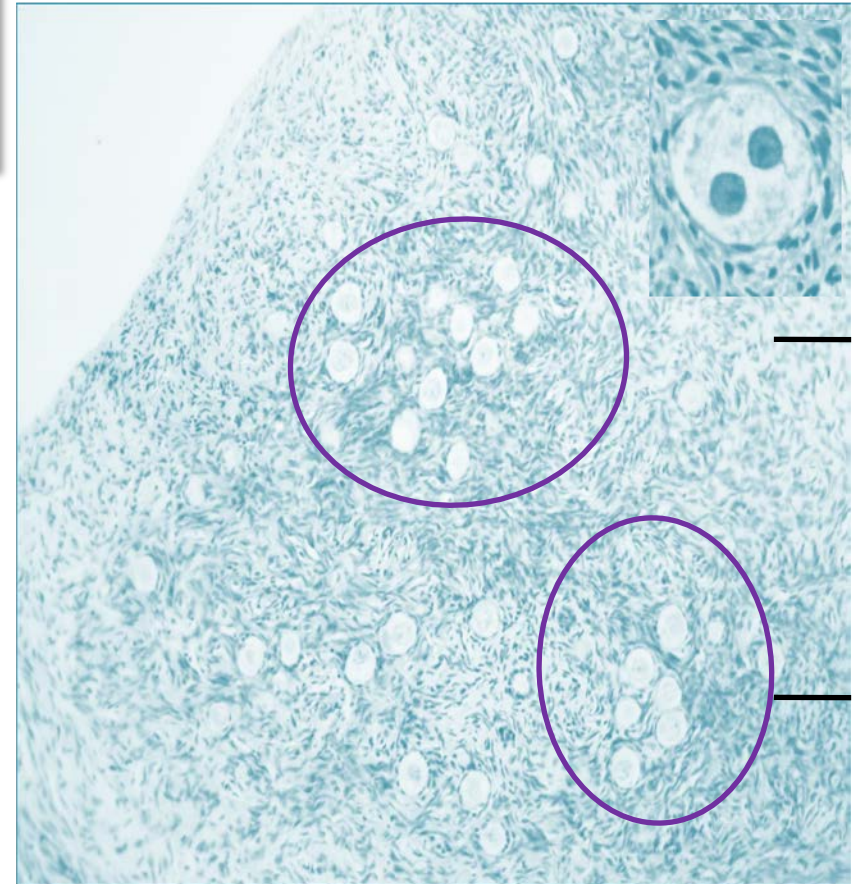


Non-growing follicle density is increased following adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy in the adult human ovary

M. McLaughlin^{1,2}, T.W. Kelsey³, W.H.B. Wallace⁴, R.A. Anderson⁵,
and E.E. Telfer^{1,2,*}



ABVD Tissue immuno-stained for germline marker DDX4

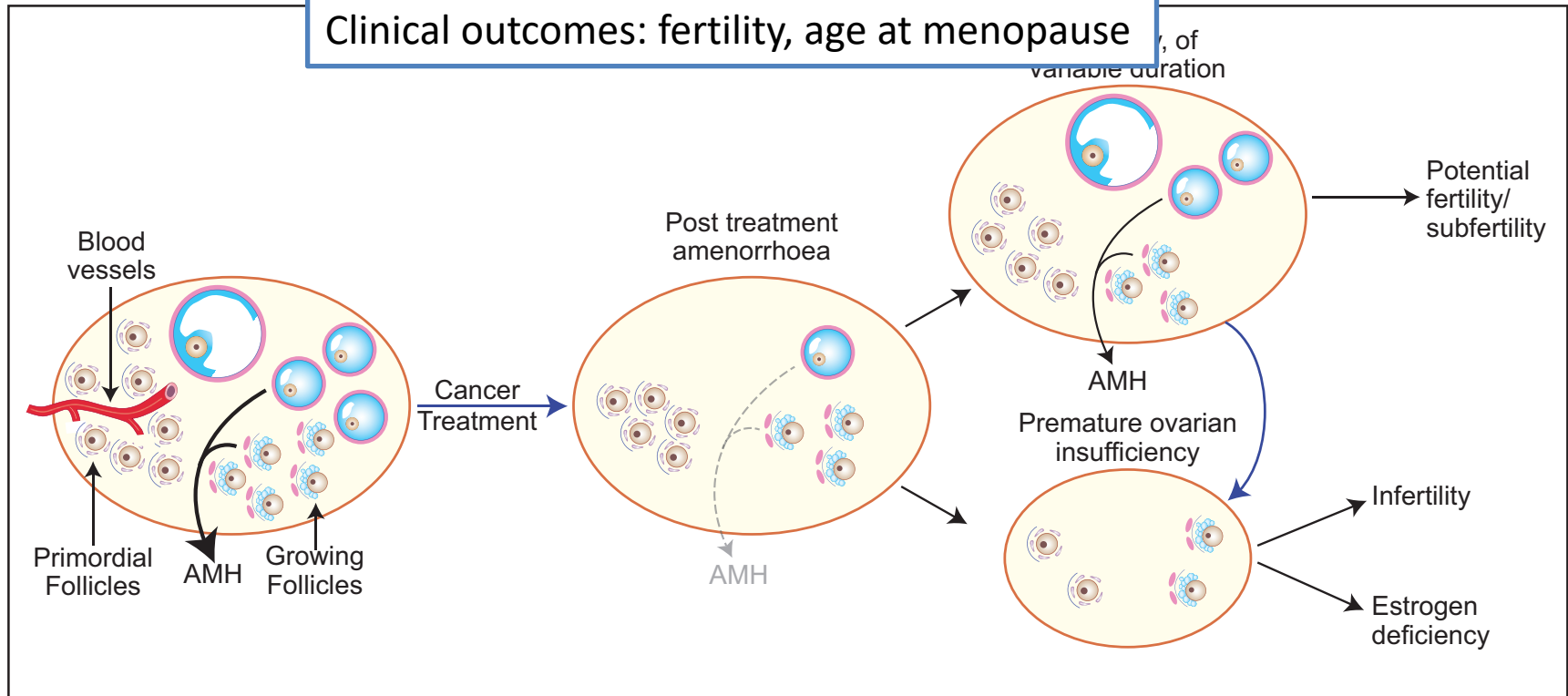


**ABVD Tissue shows clustering of follicles
Also seen in pre-pubertal tissue**

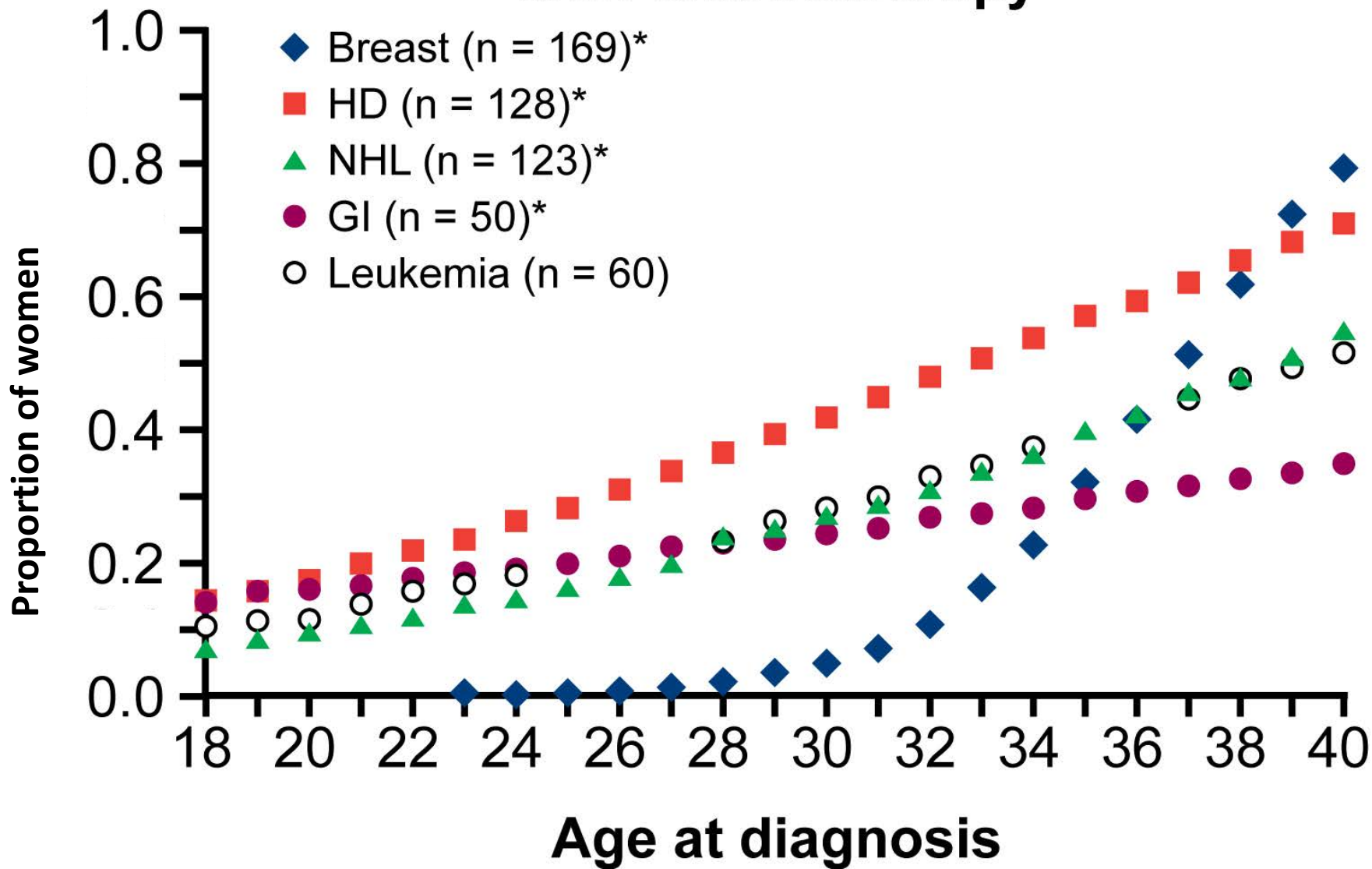
Effects of cancer therapy on the ovary

Biomarkers: AMH, AFC, menses

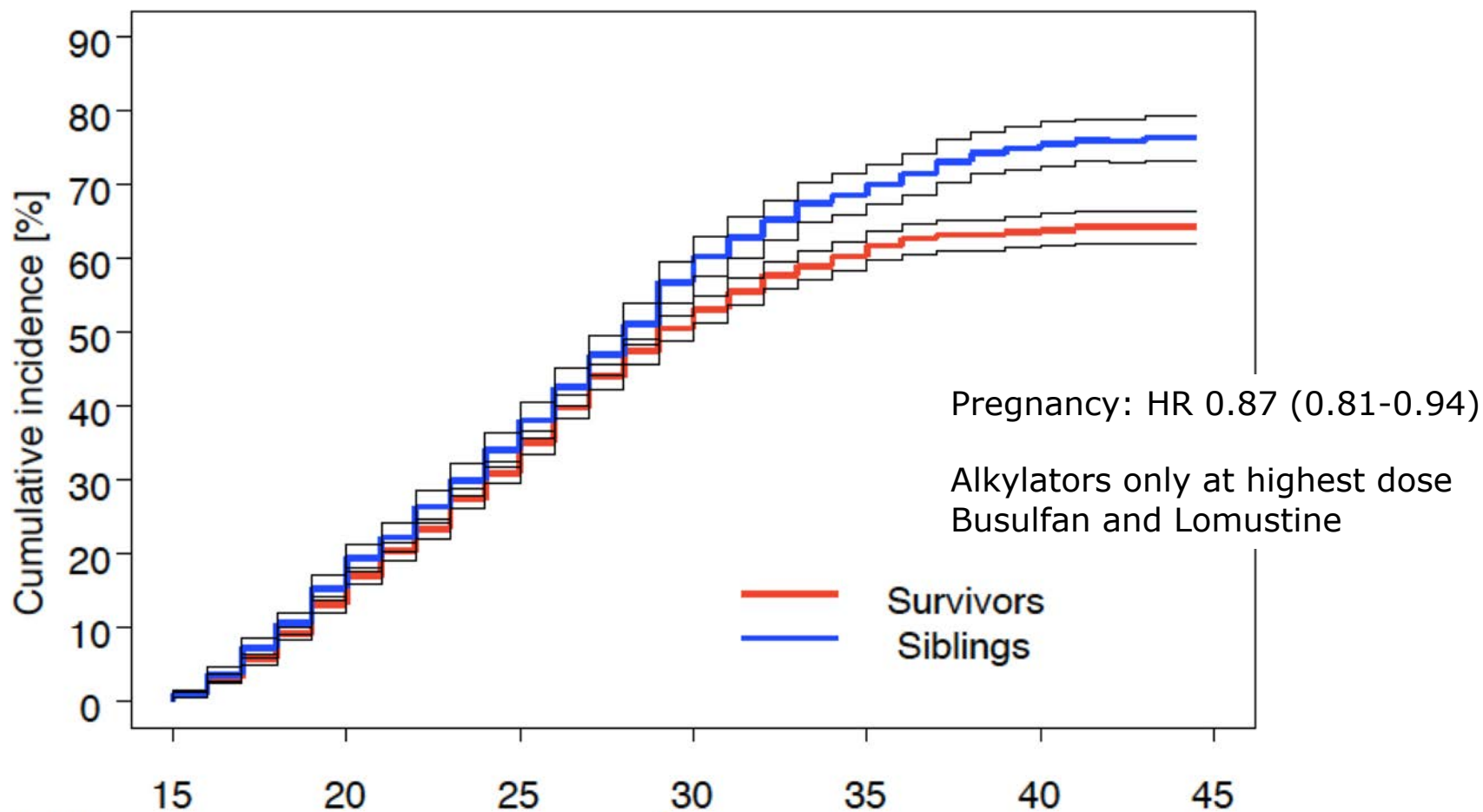
Clinical outcomes: fertility, age at menopause, of variable duration



Infertility despite menses resuming after chemotherapy



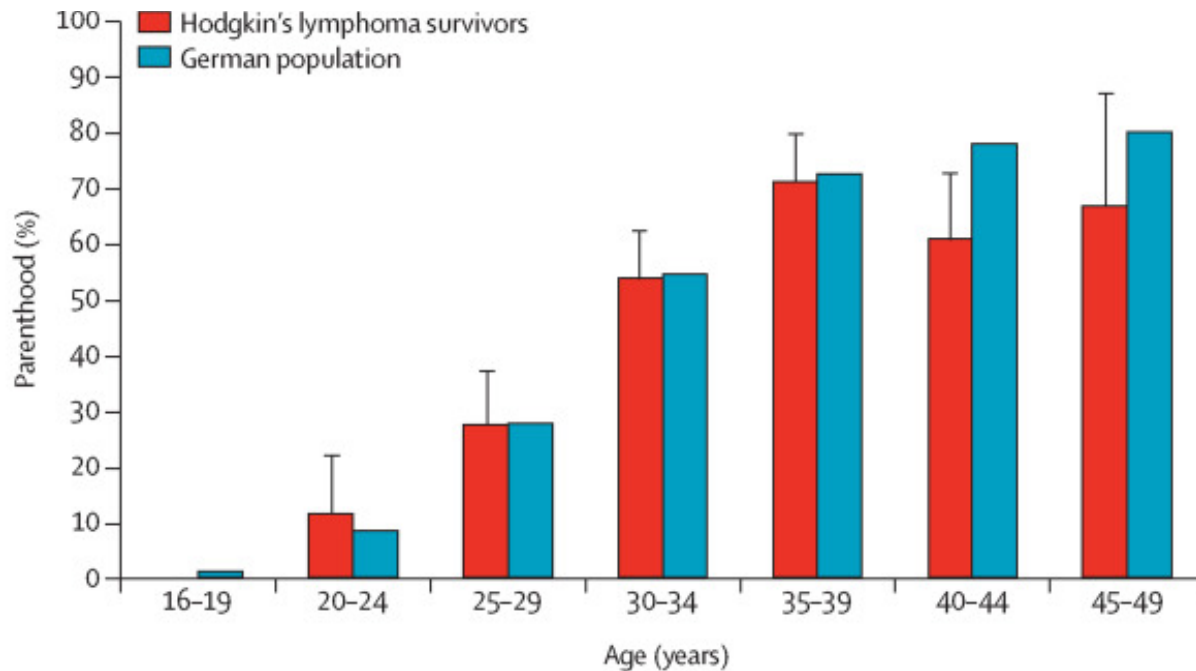
Live birth to female childhood cancer survivors: chemo only



at risk:

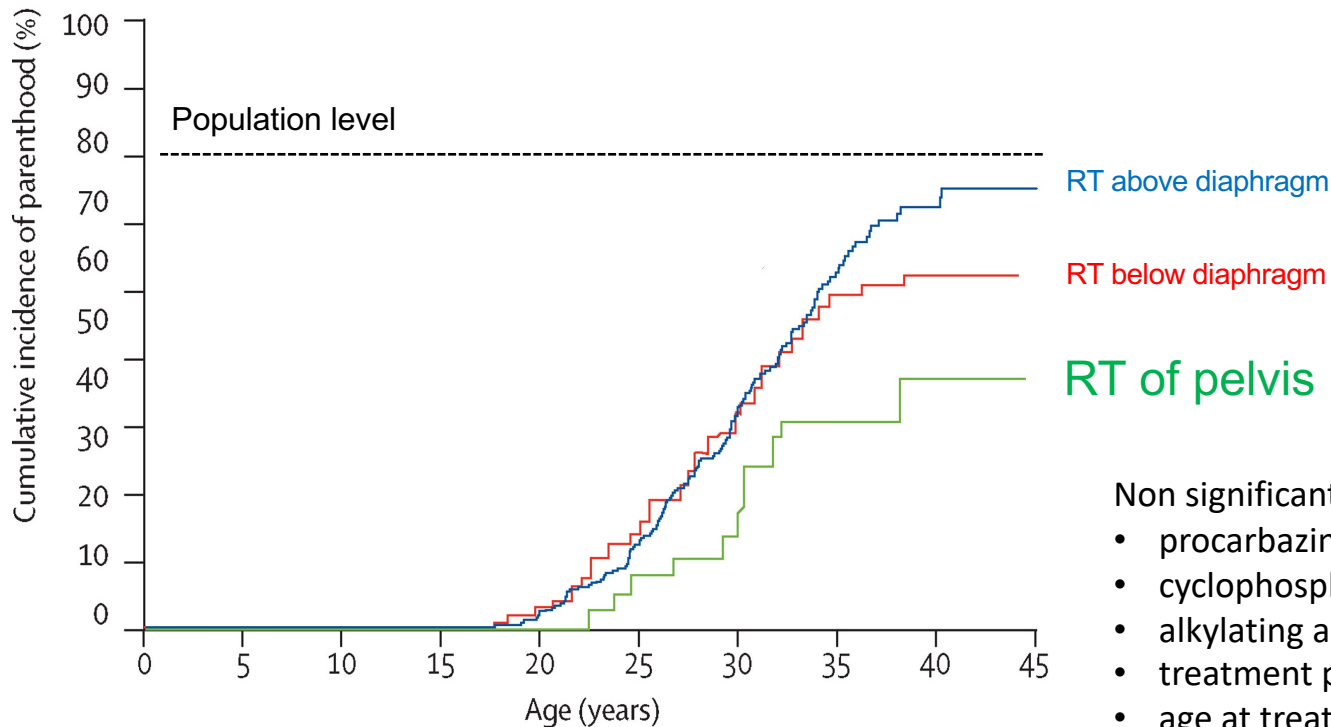
	15	20	25	30	35	40	45
Survivor	3093	3185	2353	1076	452	197	147
Sibling	1843	1580	1056	567	268	121	75

Parenthood in female survivors of Hodgkin lymphoma in childhood and adolescence



Number with first parenthood/number in age group							
Hodgkin's lymphoma survivors	0/19	4/35	23/84	69/129	78/110	40/66	14/21
German population (×1000)	15/1539	190/2246	645/2335	1284/2362	1609/2228	2208/2847	2596/3244
p value		0.53	0.96	0.84	0.76	0.001	0.13

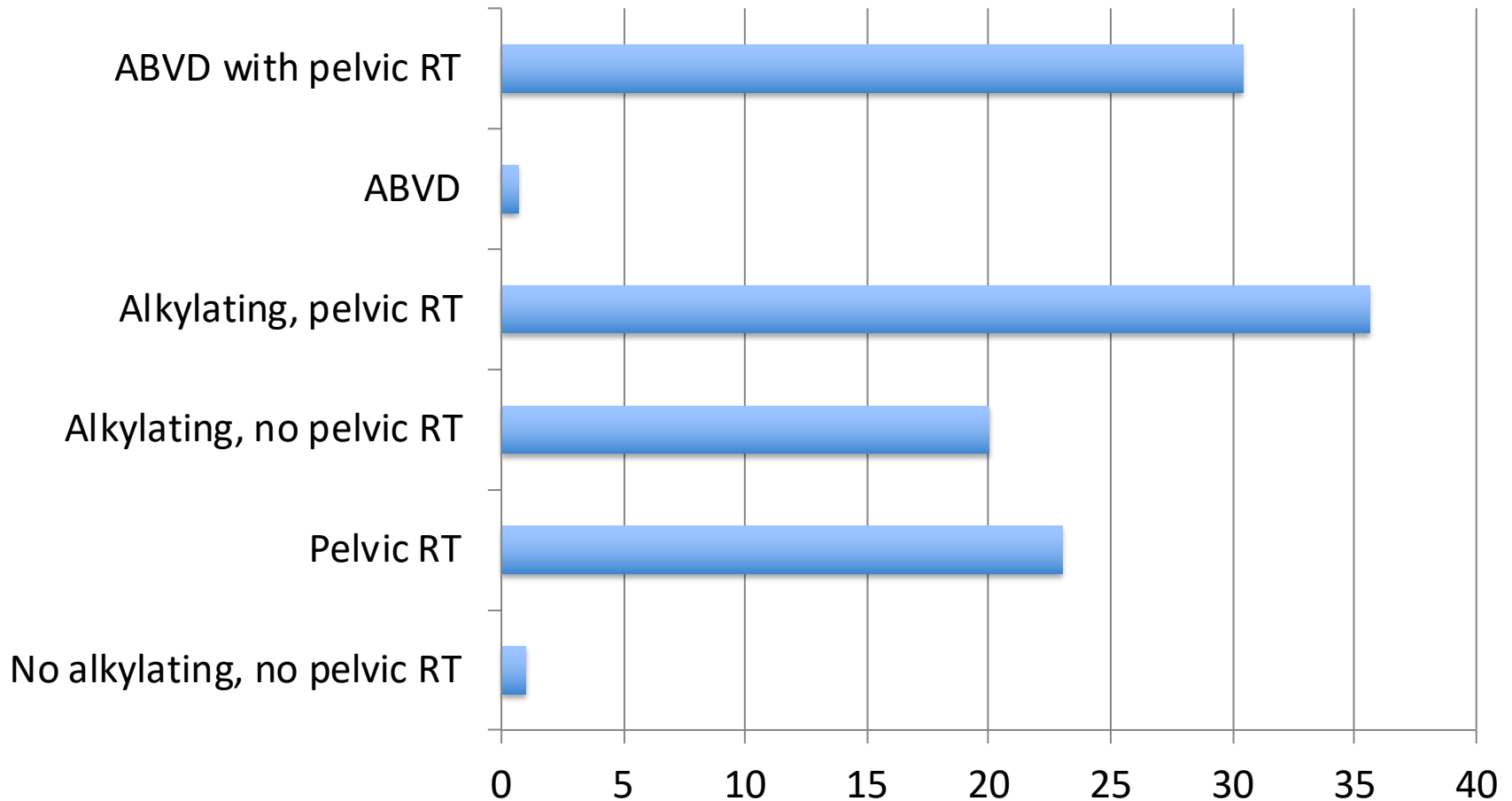
The impact of pelvic radiotherapy in girls with Hodgkin Lymphoma



Non significant or only minor effects of:

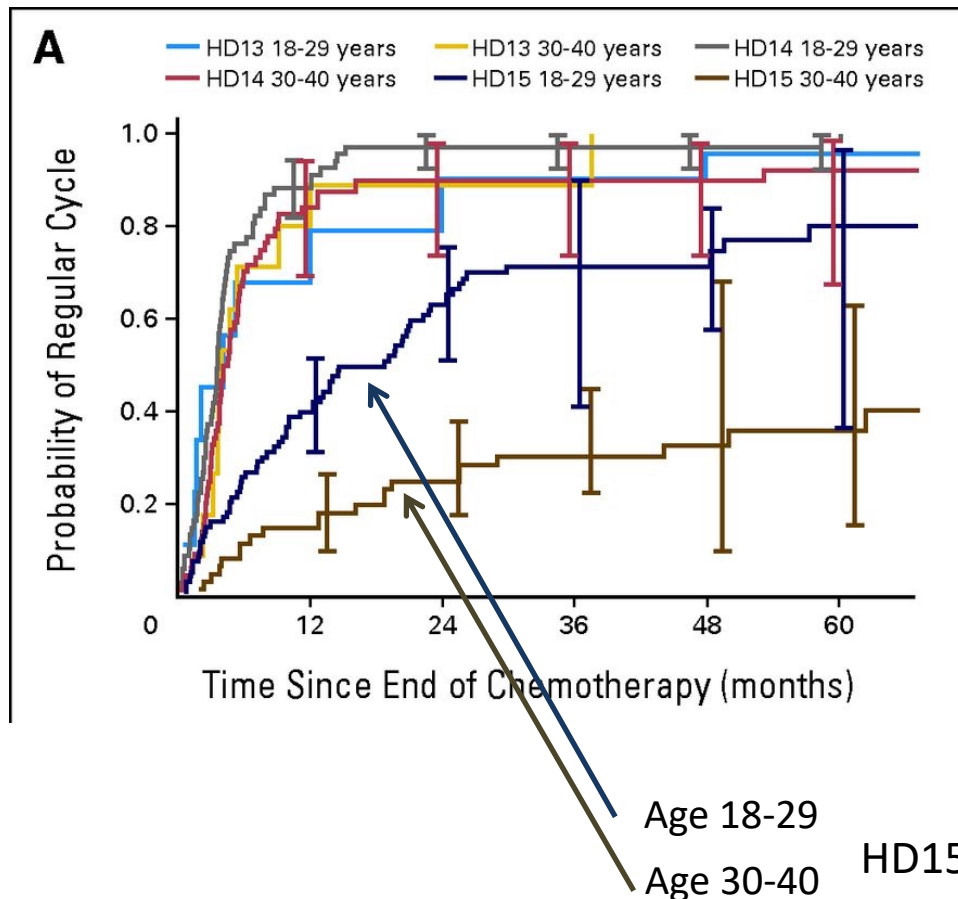
- procarbazine (to 11400 mg/m²)
- cyclophosphamide (to 6000 mg/m²)
- alkylating agent dose scores of 1–5
- treatment protocol
- age at treatment

Hazard ratio for menopause <40 yrs in treatment of HL



All adjusted for age, overall n=2127 (though data only from 50%)

Impact of age on time to regular cycle after treatment for Hodgkin Lymphoma



HD13: early favourable
2xABVD±bleomycin

HD14: early unfavourable
4xABVD or 2xBEACOPP

HD15: advanced
6-8 x BEACOPP esc or -14

Pregnancy after cancer in girls and women in Scotland: a population-based analysis

Richard A Anderson, David H Brewster, Rachael Wood, Sian Nowell, Tom W Kelsey, Colin Fischbacher, W Hamish B Wallace

Scottish Cancer Registry, Information Services Division, NHS National Services Scotland

Information Services Division, NHS National Services Scotland

eData Research & Innovation Service, NHS National Services Scotland and Farr Institute

Department of Oncology and Haematology, Royal Hospital for Sick Children, Edinburgh



THE UNIVERSITY *of* EDINBURGH



MRC

Centre for
Reproductive
Health

Aims

- To provide a population based analysis of the impact of cancer on subsequent pregnancy in females
- All diagnoses
- All ages up to 40

Methods

Study population

- female patients aged 39 years or under at date of first cancer
- on Scottish Cancer Registry
- diagnosed 1981-2012: n=23,201

- Linked to hospital discharge records
 - subsequent pregnancies up until the end of 2014.
 - miscarriage, termination, singleton live or still birth
- Follow-up to the date of death or 31st December 2014.

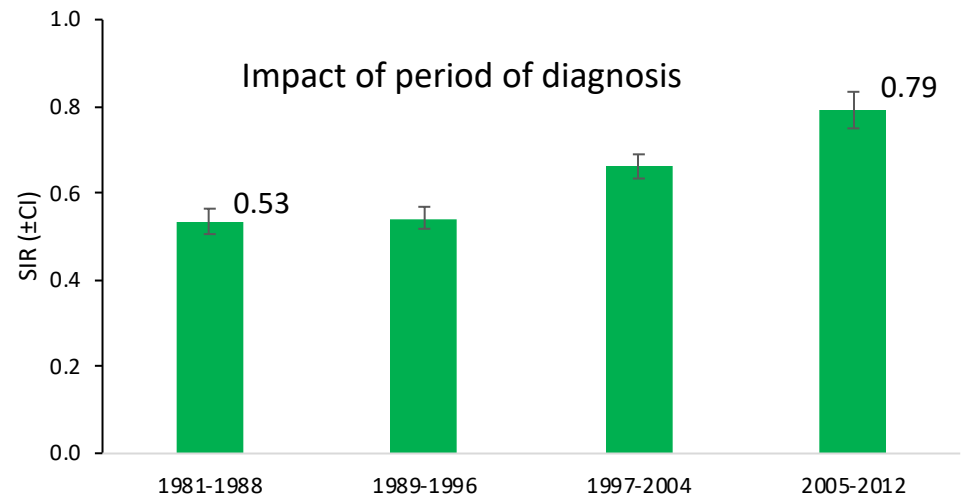
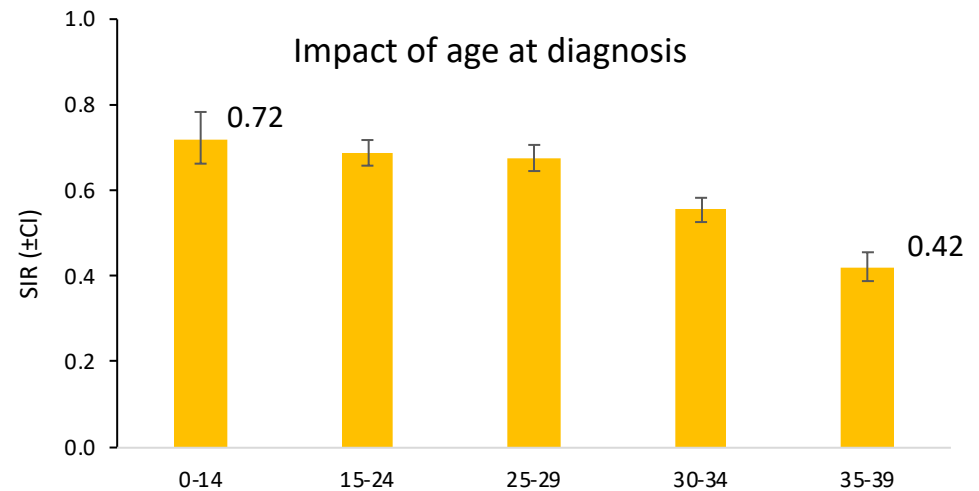
- Controls: population based, age matched
- Not previously pregnant (n=10,271): 3x age matched controls

Population-based analysis of pregnancy after cancer

38% less likely to achieve a pregnancy after diagnosis than women in the general population

28.6% vs 46.4% of women achieve a pregnancy after a cancer diagnosis

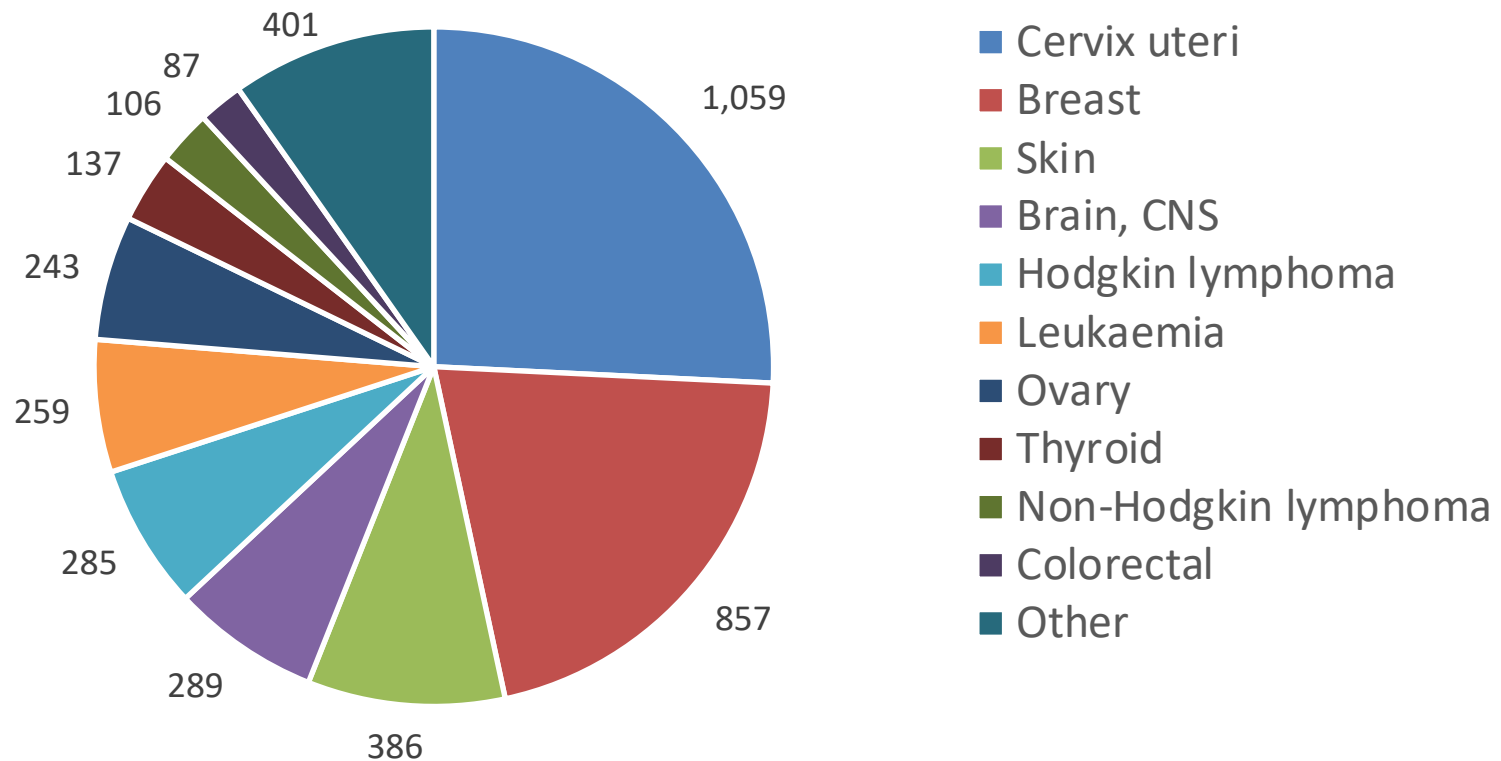
-across all diagnostic groups



Population-based analysis of pregnancy after cancer

	No of women	SIR	95% CI
Cervix uteri	3498	0.34	0.31-0.37
Breast	5173	0.39	0.36-0.42
Brain, CNS	1045	0.42	0.36-0.48
Leukaemia	1077	0.48	0.42-0.54
Ovary	1129	0.63	0.57-0.69
Hodgkin lymphoma	962	0.67	0.62-0.73
Non-Hodgkin lymphoma	673	0.67	0.58-0.77
Thyroid	926	0.79	0.72-0.86
Skin	5252	0.87	0.84-0.90

Overall impact: 'missing' pregnancies



Why is this?

Eg skin cancer:

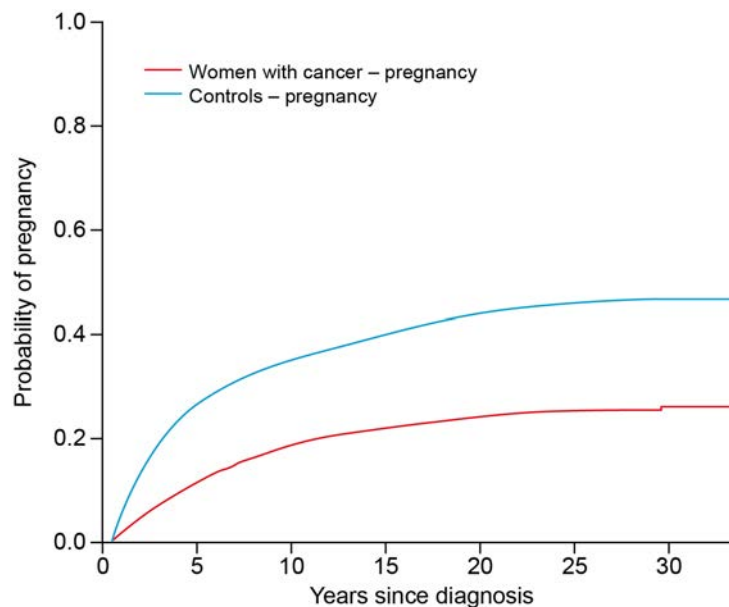
Unlikely to be 'biological'

Possibly 'psychological'

-effect on life choices?

Females not pregnant before cancer

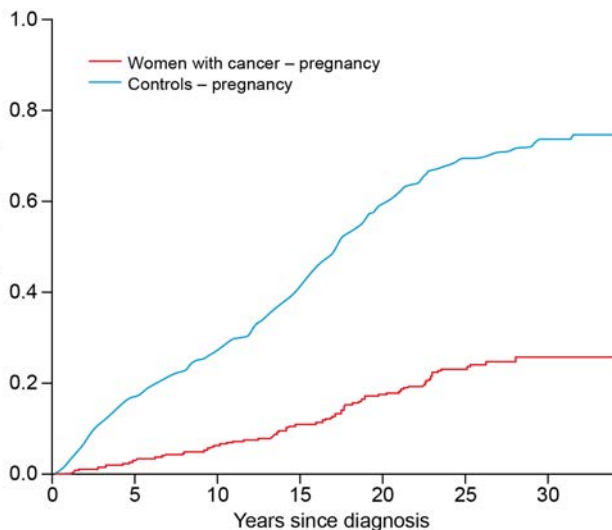
- 10,271 women vs 30,811 age-matched controls
- Competing risk analysis
- Proportion achieving a first pregnancy
 - 20.6% vs 38.7%
- Rate ratio 0.53 (CI 0.51-0.56)



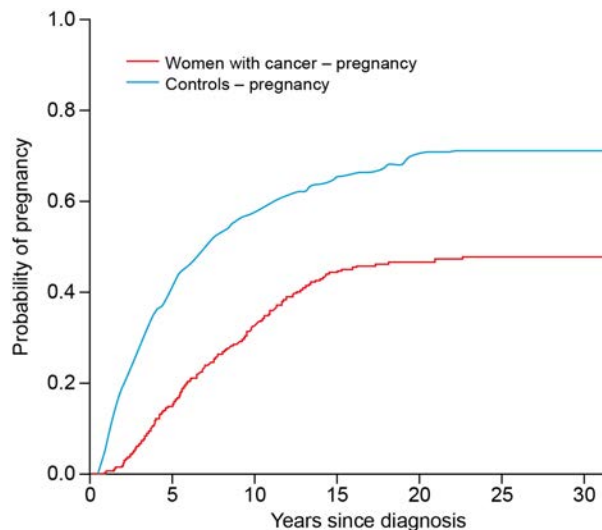
	Number at risk				
	0 yrs	5 yrs	10 yrs	20 yrs	30 yrs
Cancer	10271	6435	4344	2122	570
Controls	30811	20167	14294	6858	1990

Chance of a first pregnancy after cancer

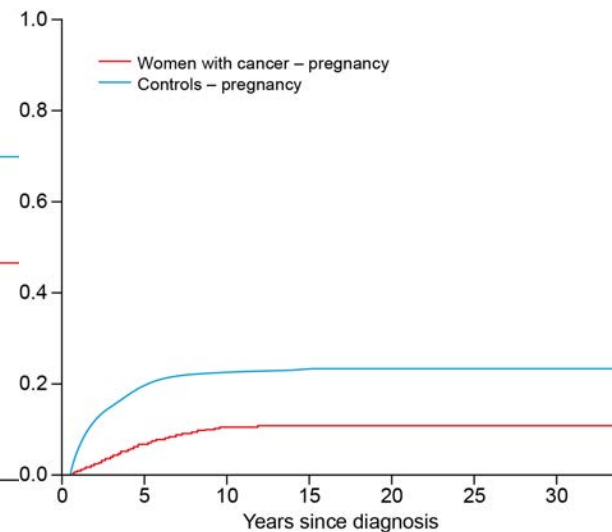
Leukaemia



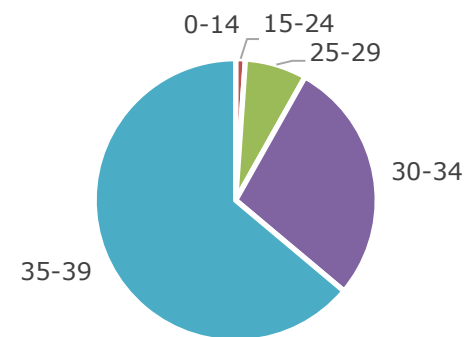
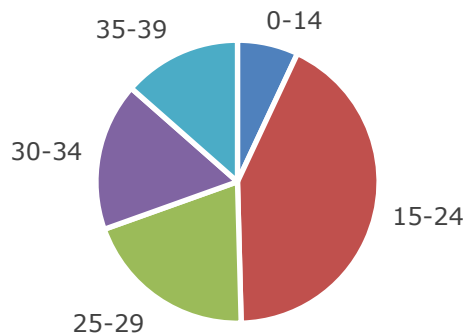
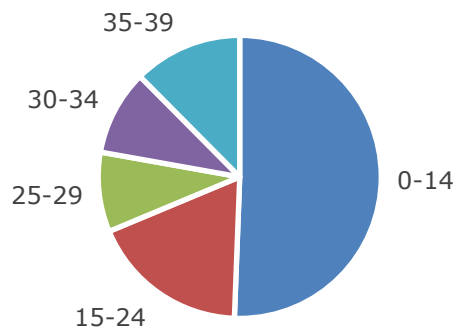
Hodgkin lymphoma



Breast cancer



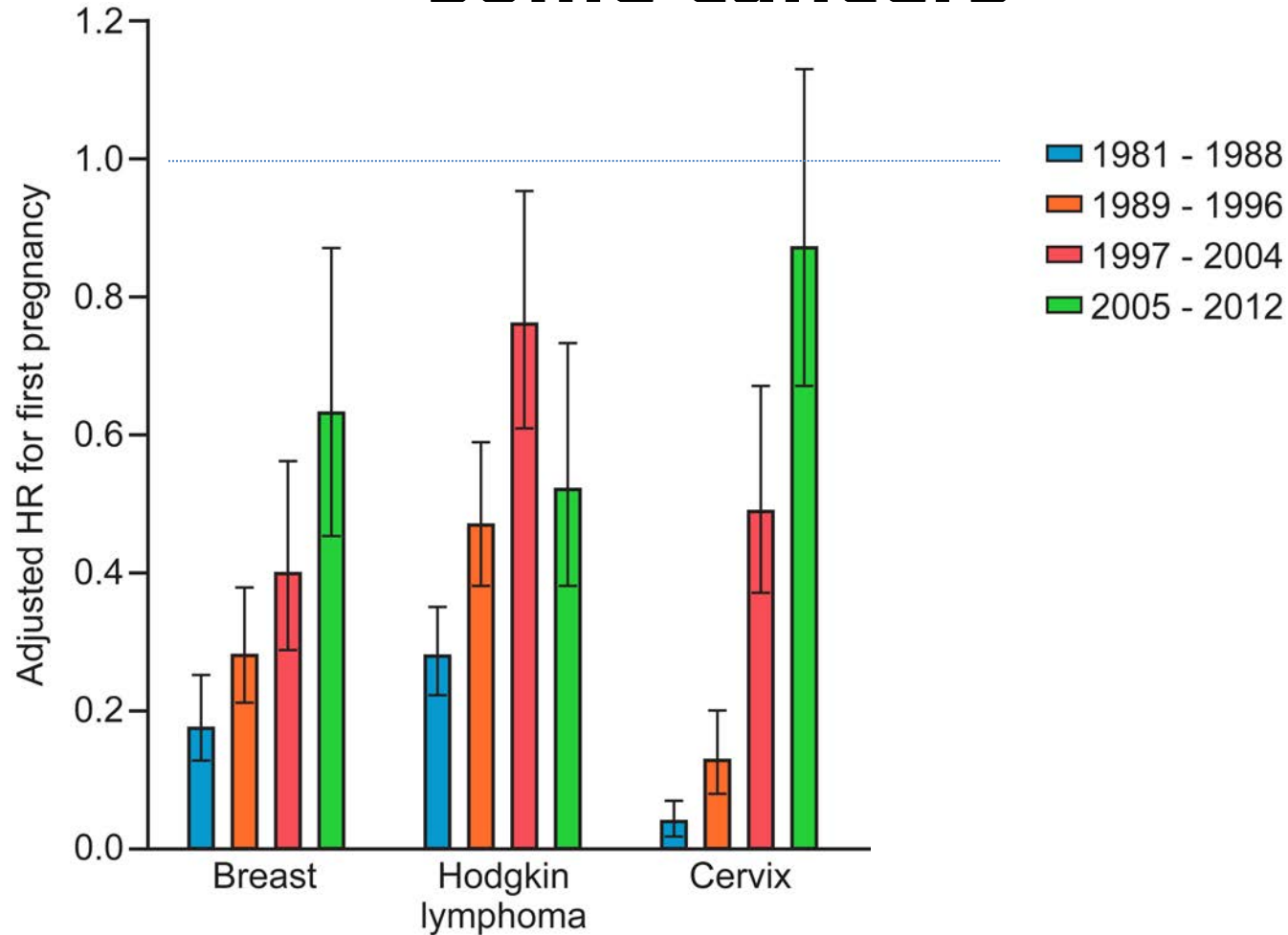
Age at diagnosis



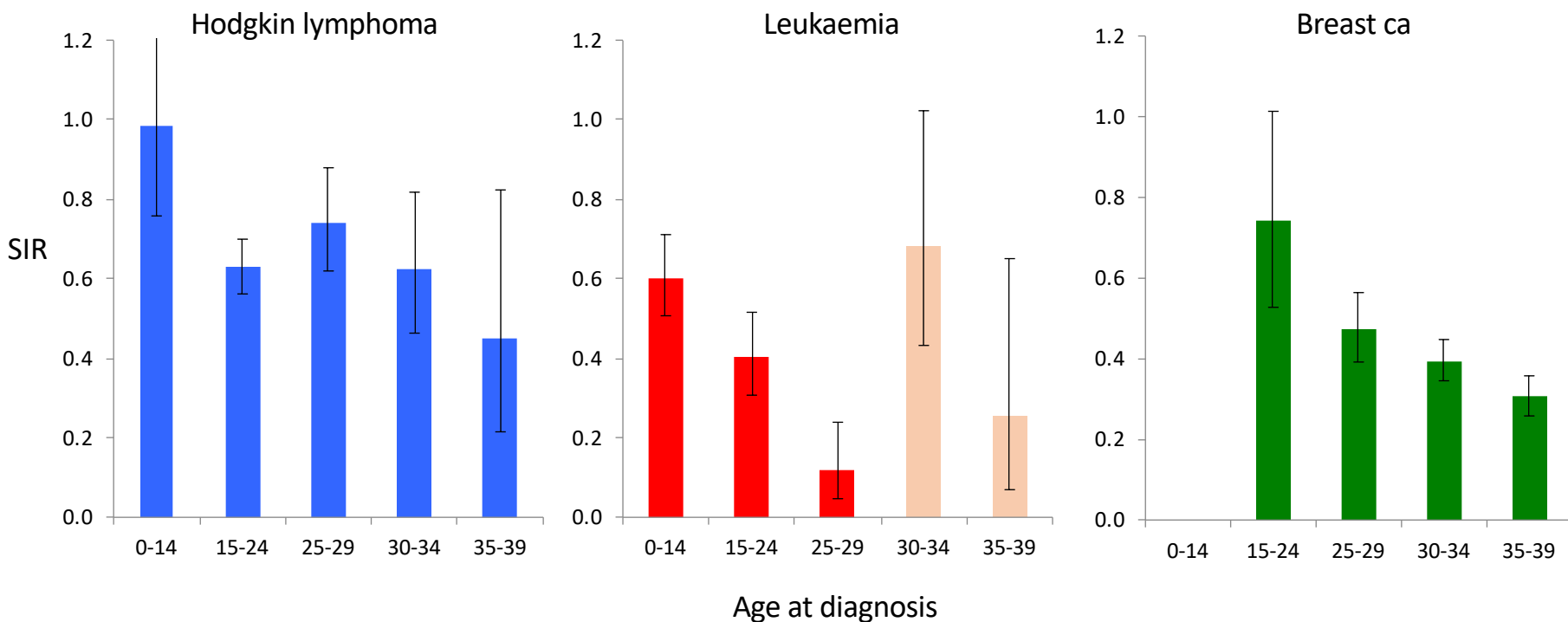
First vs all pregnancies after cancer

	No of women	SIR	95% CI	% pregnant before cancer	% achieving pregnancy after	% achieving first pregnancy after
Cervix uteri	3498	0.34	0.31-0.37	67.4	15.8	12.8
Breast	5173	0.39	0.36-0.42	67.9	10.6	9.7
Brain, CNS	1045	0.42	0.36-0.48	30.3	19.9	11.7
Leukaemia	1077	0.48	0.42-0.54	21.6	21.8	13.3
Hodgkin lymphoma	962	0.67	0.62-0.73	36.1	60.8	38.2
Non-Hodgkin lymphoma	673	0.67	0.58-0.77	46.5	32.2	21.4
Thyroid	926	0.79	0.72-0.86	55.9	53.9	39.0
Skin	5252	0.87	0.84-0.90	57.8	48.8	33.8
Controls						38.7

The changing risk to fertility in some cancers



Changing risk by age



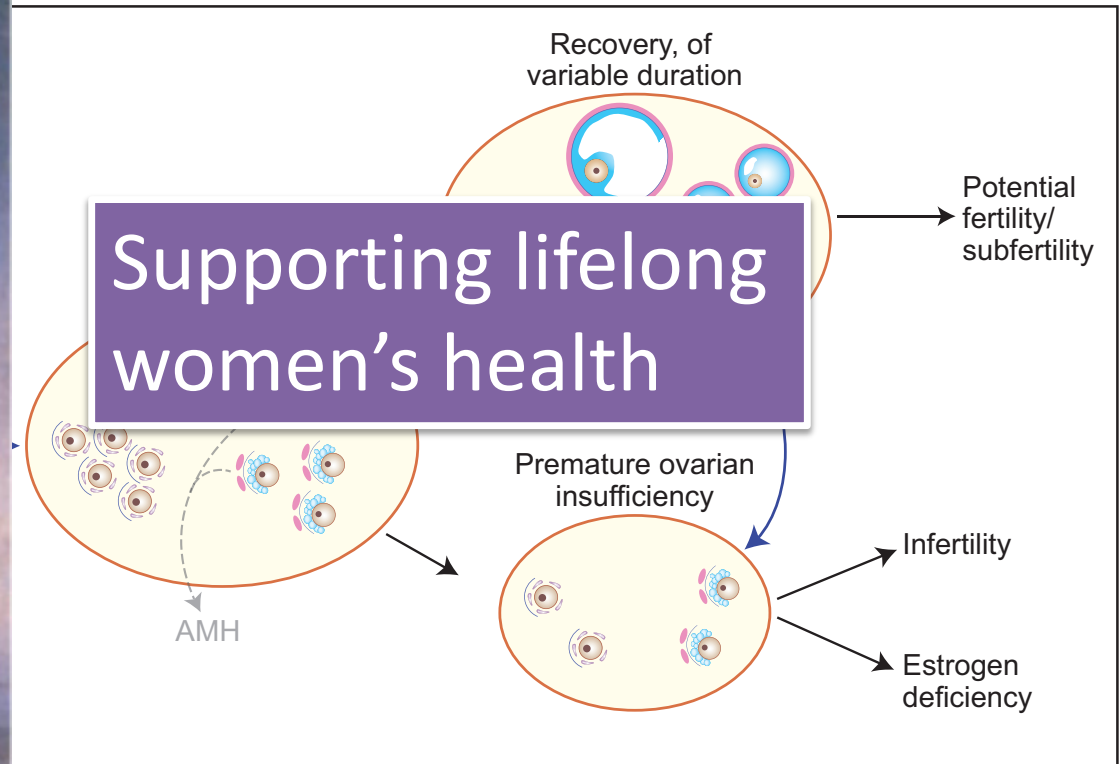
SIR, error bars \pm CI

Outcome of first pregnancies after cancer

Singleton first pregnancies following cancer	Nulliparous women with cancer		Control women		Difference	95% CI	
	Number	% / rate *	Number	% / rate*		Lower	Upper
Total	2071	100	11772	100			
Miscarriage	203	9.8	1095	9.3	0.5	-0.9	1.9
Termination	231	11.2	1725	14.7	-3.5	-5.0	-2.0
Still Birth	8	0.4	53	0.5	-0.1	-0.4	0.2
Live Birth	1629	78.7	8899	75.6	3.1	1.1	5.0
Infant Death	12	7.4	43	4.8	2.5	-1.9	6.9

* % of all first singleton pregnancies apart from for infant deaths which is per 1000 live births

Fertility and women's health: can we link short-term assessment to long term outcomes?



Conclusions

Fertility preservation is now 'main stream' medicine



Oncofertility assessment for all: definitely!

Need for accurate, patient-specific risk to fertility and ovarian function

Extrinsic issues: proposed treatment

Intrinsic issues: age and ovarian reserve

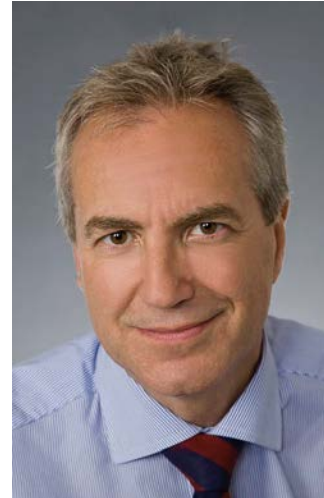
Rational and effective use of FP techniques

Long-term health outcomes from our interventions

Key collaborators and funding



David T Baird



Hamish Wallace
Paed oncologist, Edinburgh



David Cameron and colleagues, Edinburgh Breast Unit
Bob Leonard and OPTION investigators
Peter Johnson and RATHL investigators
David Brewster and Rachael Wood, ISD, NHS Scotland
Tom Kelsey, Mathematician, St Andrews University
Roche Diagnostics for assay reagents

