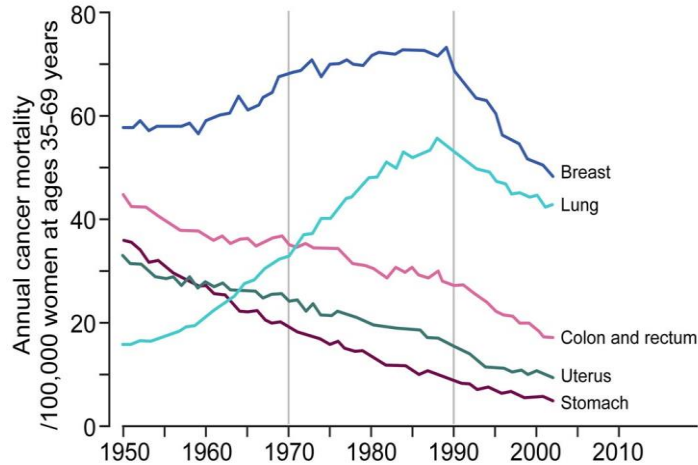# The effects of cancer treatment on female fertility
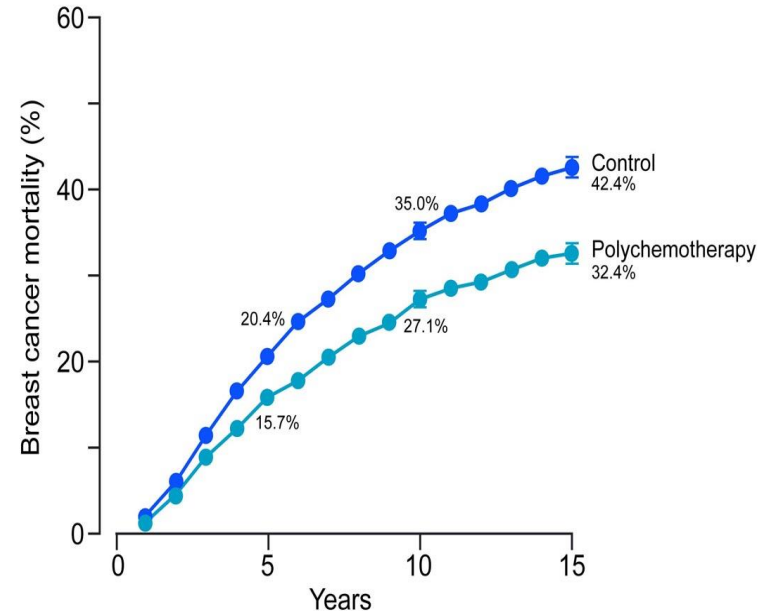
Richard A Anderson

Elsie Inglis Professor of Clinical Reproductive Science

Improving survival, minimising 'late effects'

polychemotherapy reduces the annual breast cancer death rate by 38%

EDITORIALS

Preserving fertility in girls and young women with cancer

Awareness of and access to services remains poor in the UK

Richard A Anderson *professor of clinical reproductive science*[1], Melanie C Davies *consultant gynaecologist*[2]

Who gets fertility preservation? – and how?

**Offer to all
'Insurance policy'**

**Offer to those
with clear need**

**Issues of costs, equality of access,
informed decision making at a time of
extreme stress etc etc**

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: early and late effects on the ovary

- ## Depletion of growing follicles

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

Morphological study of the ovaries of leukaemic children.
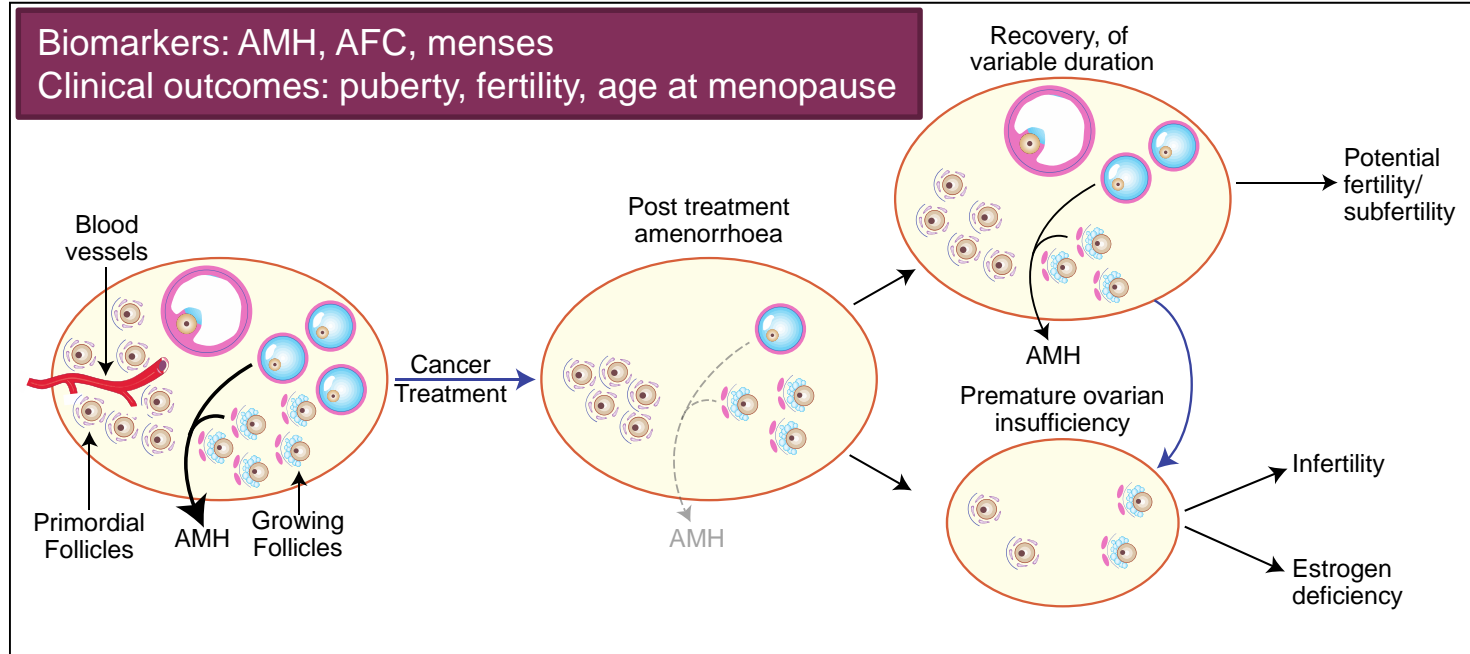Br J Cancer 38, 82-87

- ## 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

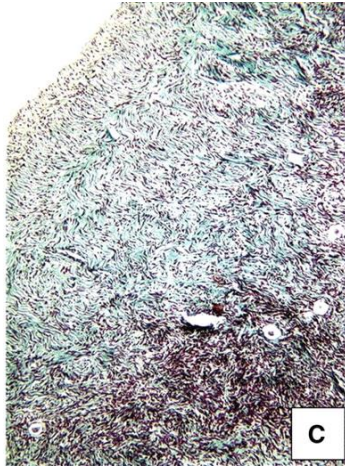# Effects of cancer therapy on the ovary

Biomarkers: AMH, AFC, menses
Clinical outcomes: puberty, fertility, age at menopause

Blood vessels

Primordial Follicles

AMH

Growing Follicles

Cancer Treatment

Post treatment amenorrhoea

AMH

Recovery, of variable duration

Potential fertility/ subfertility

AMH

Premature ovarian insufficiency

Infertility

Estrogen deficiency

Risks of chemo agents to 'fertility'

Degree of Risk	Treatment Protocol	Patient and Dose Factor	Common Usage
High Risk >70% amen	Any alkylating agent + TBI/pelvic radiation		Conditioning for HSCT; sarcoma inc Ewings, ovarian
	Total cyclophosphamide dose	5 g/m^2 age > 40 7.5 g/m^2 age <20	Multiple cancers: breast cancer, NHL, HSCT
	Procarbazine: MOPP, BEACOPP		Hodgkin lymphoma
Intermediate 30-70% amen	Total cyclophosphamide	5 g/m^2 in women age 30- 40	Multiple cancers, breast
	AC for breast cancer	x4 + Paclitaxel or Docetaxel in women age <40	Breast
Lower Risk <30% amen	nonalkylating agents or lower levels of alkylating (e.g., ABVD, CHOP, COP; leukemia)		Hodgkin lymphoma, NHL; leukemia
	for breast cancer with cyclophos (CMF, CEF, CAF)	Women < 30	Breast
	Anthracycline + cytarabine		AML
Very Low/No Risk	Multi-agent with vincristine		Leukemia, Lymphoma

The ovarian stroma and vasculature are also targets

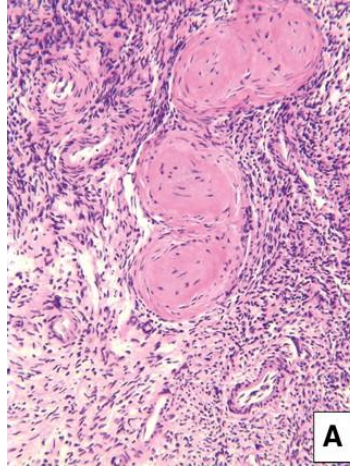Focal cortical fibrosis in ovaries exposed to chemotherapy

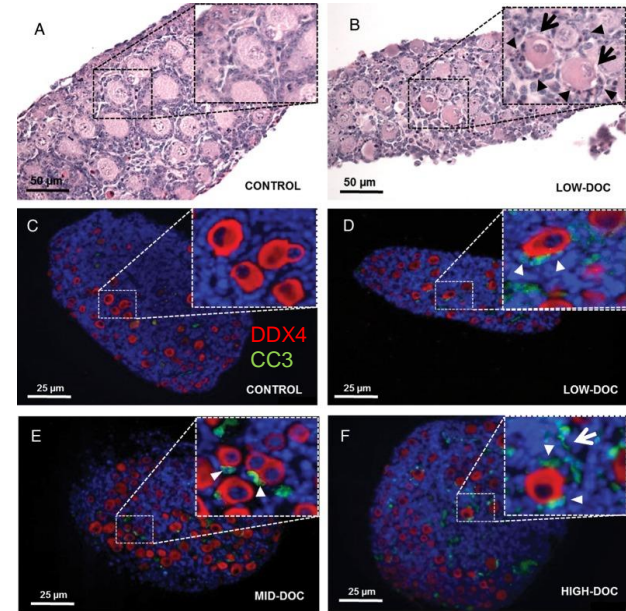Hyalinization, narrowing, obliteration of lumen

Doxorubicin induces stromal cell apoptosis
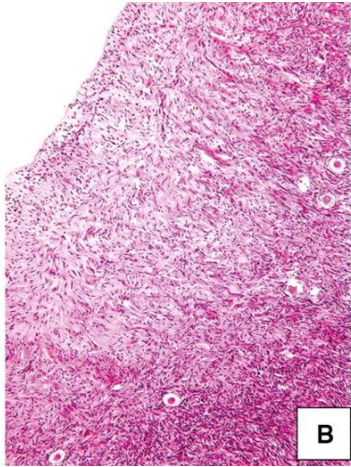
After chemotherapy

Green: Masson stain for collagen

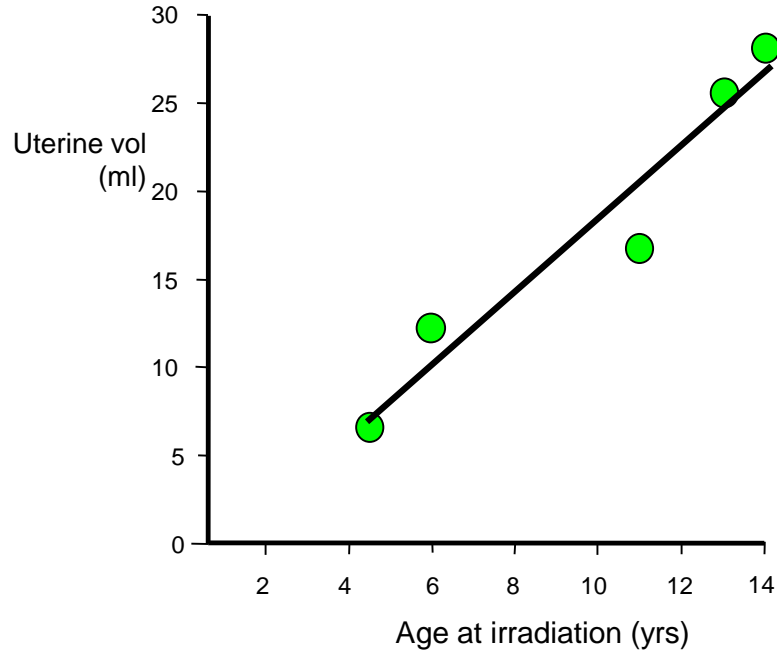DDX4
CC3

Meirow D et al. Hum. Reprod. 2007;22:1626-1633

Lopes F et al Mol HR 2014, 20, 948-959
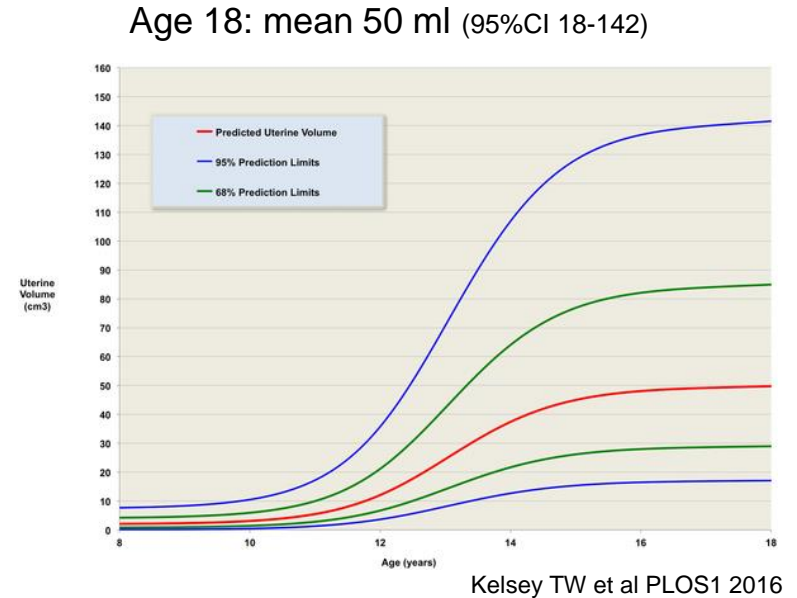
Adverse effect of radiotherapy to uterus

Miscarriage

Percent

TBI: 5/8 (~62%)
Cyclophos: 8/44 (~16%)
Expected: ~8%

Premature delivery

TBI: 6/16 (~37%)
Cyclophos: 4/56 (~7%)
Expected: ~11%
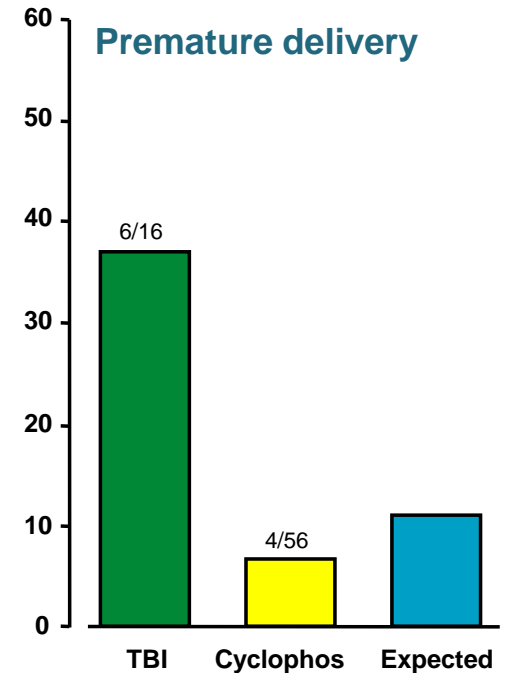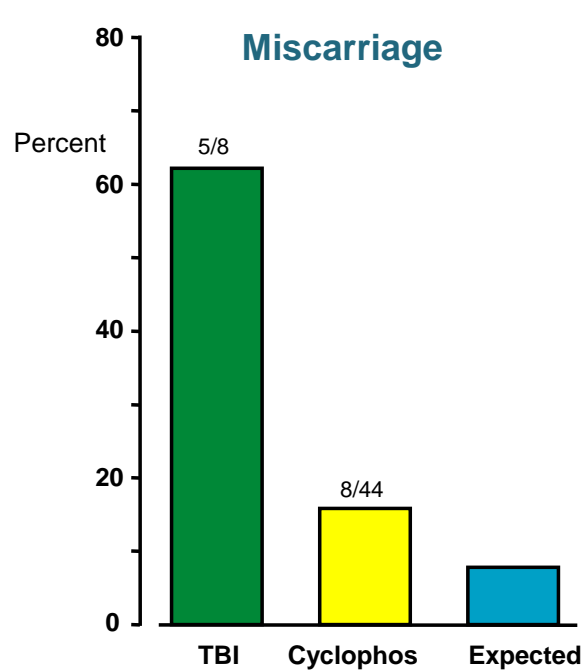
Effect of age at irradiation on adult uterine volume

Bath LE et al BJOG 1999

Age 18: mean 50 ml (95%CI 18-142)

Kelsey TW et al PLOS1 2016

Treatment effects are superimposed on the variable and age-related changes in the ovarian reserve

Can we individualise based on ovarian reserve?

n = 325
r² = 0.81

NGF population (log₁₀ scale)

Age (in months from conception to birth; in years from birth to menopause)

- Observed values
- Wallace-Kelsey model
- Lower 95% CI for model
- Upper 95% CI for model
- Lower 95% prediction limit
- Upper 95% prediction limit
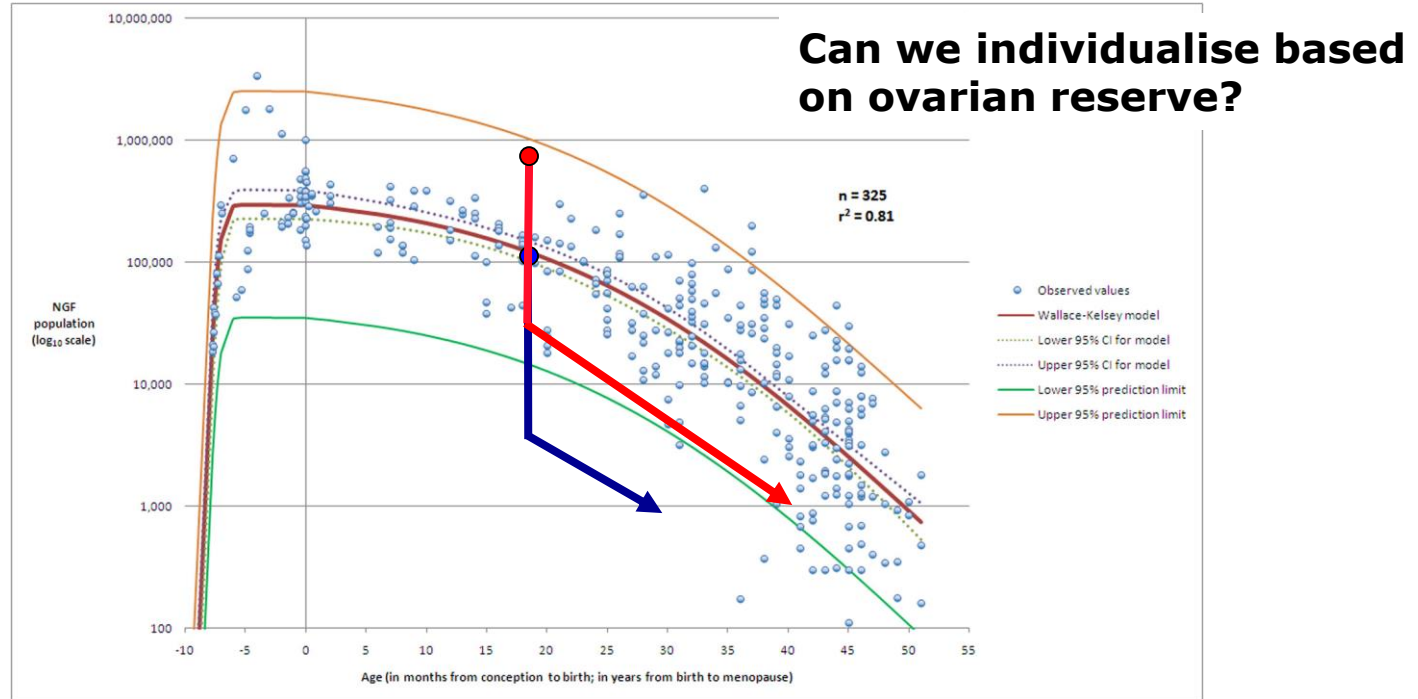
The variability in ovarian activity before and after cancer treatment

Jayasinghe, Wallace and Anderson 2018 Expt Rev Endo Metab

Eg Hodgkin Lymphoma

Infertility despite menses resuming after chemotherapy

- Breast (n = 169)*
- HD (n = 128)*
- NHL (n = 123)*
- GI (n = 50)*
- Leukemia (n = 60)

Proportion of women (y-axis)

Age at diagnosis (x-axis)
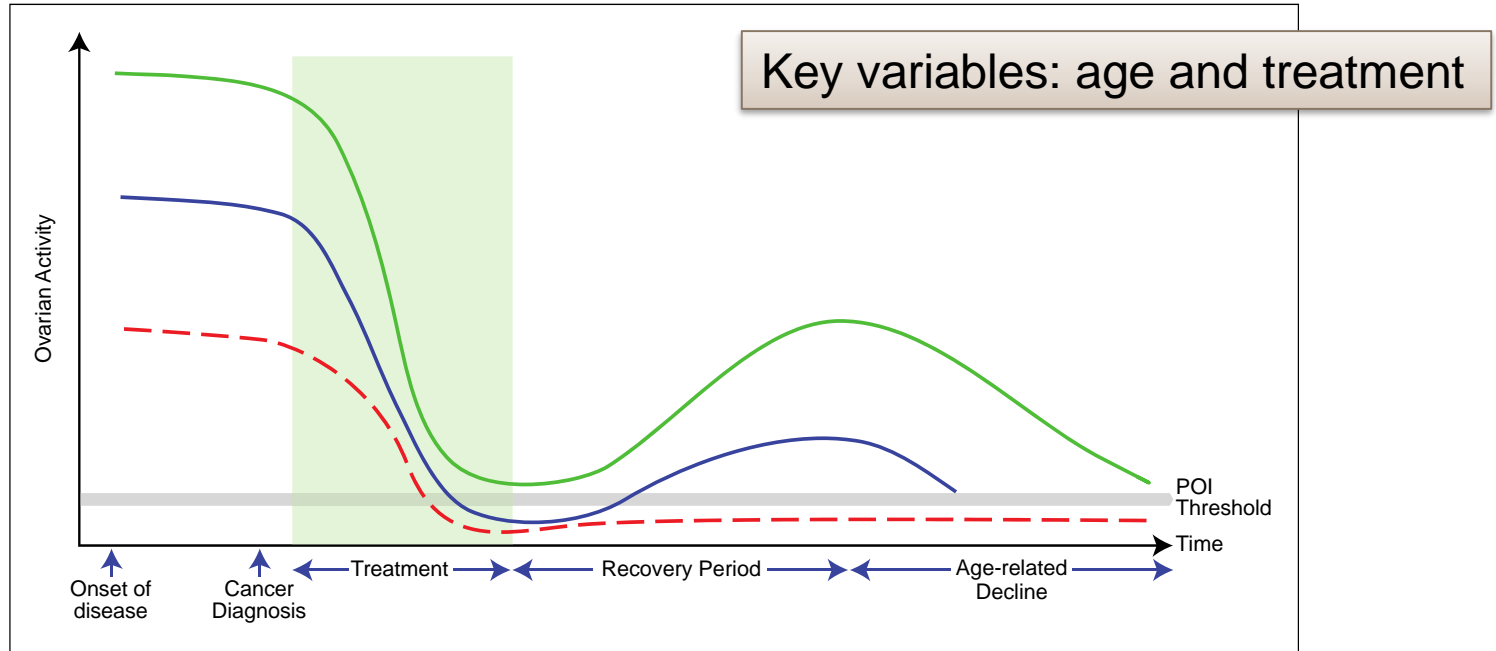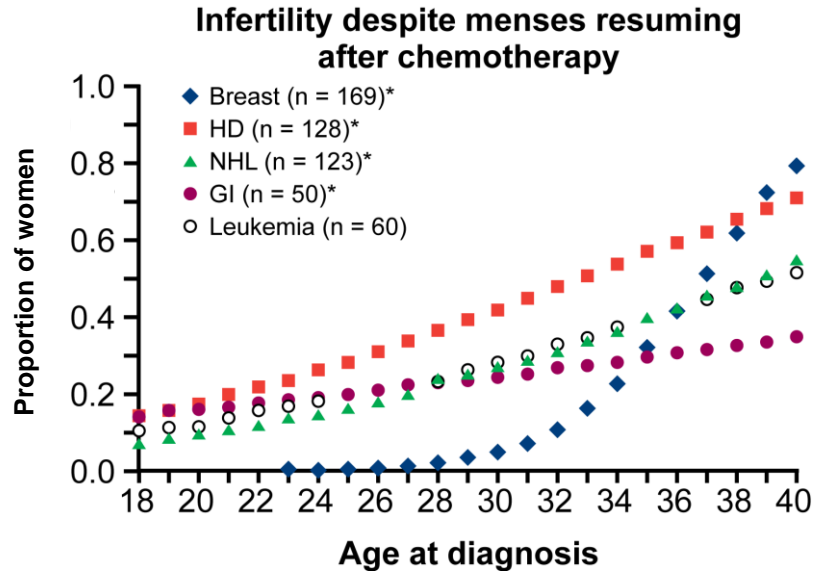
Letourneau et al 2012 Cancer 118, 1710

Hazard ratio for menopause <40 yrs

- ABVD with pelvic RT
- ABVD
- Alkylating, pelvic RT
- Alkylating, no pelvic RT
- Pelvic RT
- No alkylating, no pelvic RT
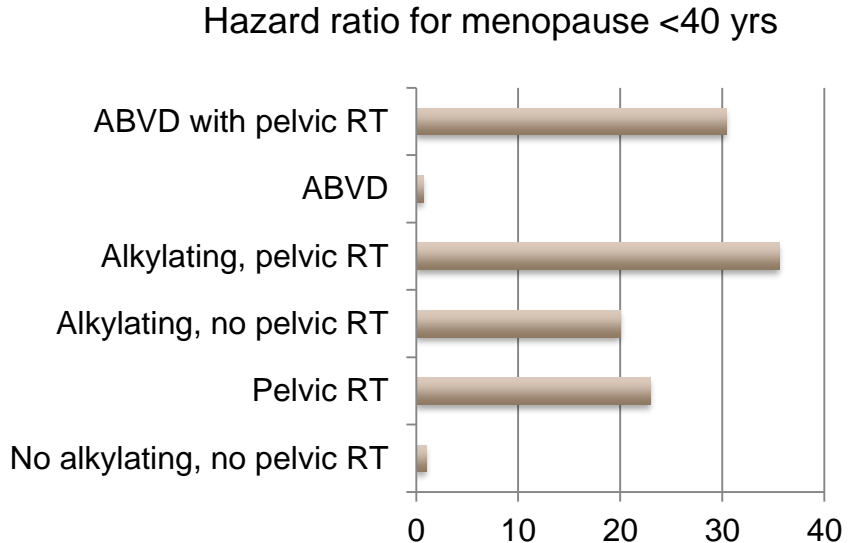
Adjusted for age
Overall n=2127 (though data only from 50%)

Swerdlow AJ et al 2014, J Natl Cancer Inst

Population analysis: Hodgkin Lymphoma

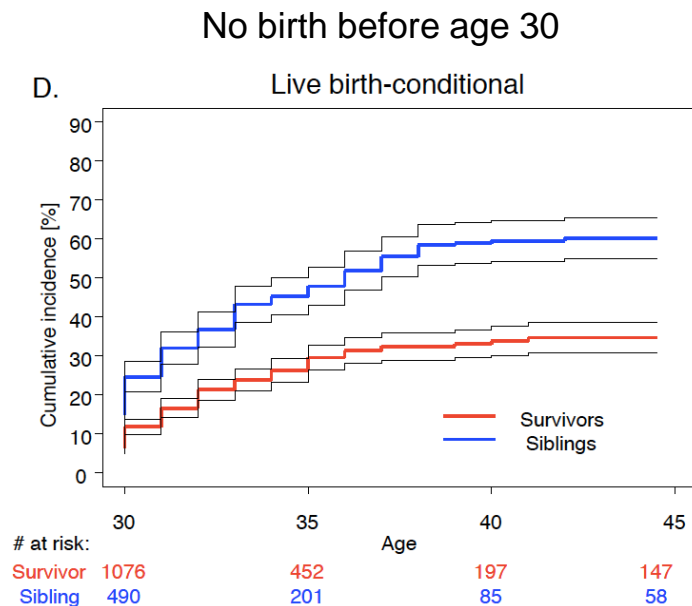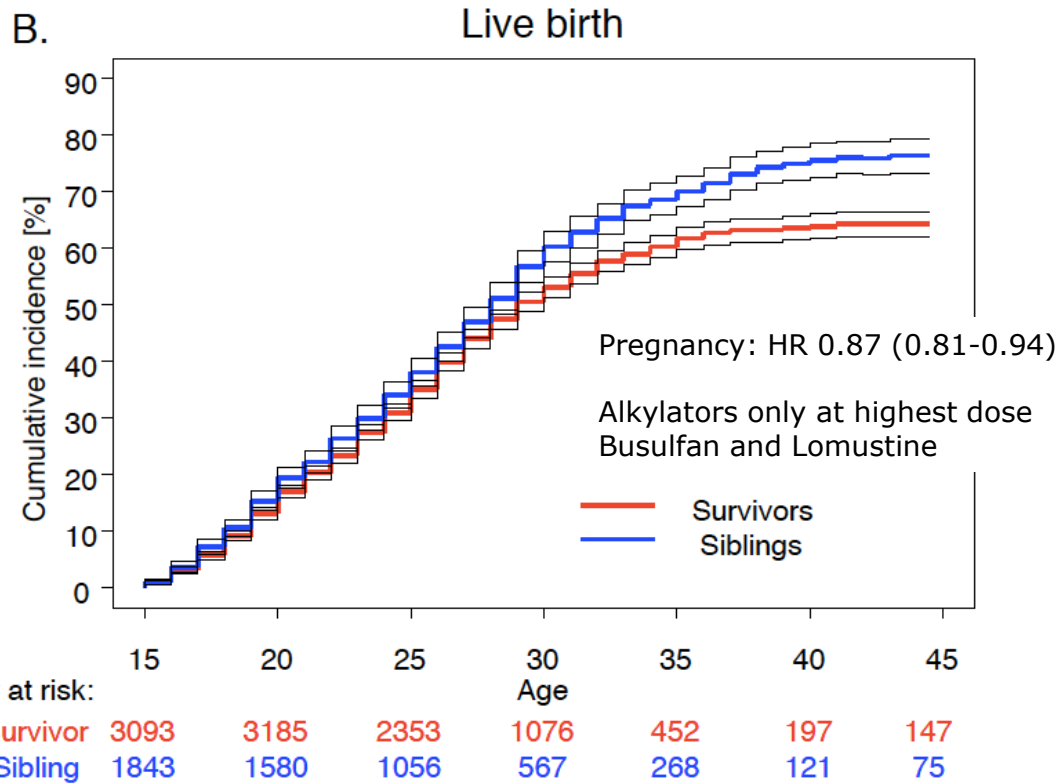Parenthood in female survivors <18 at diagnosis
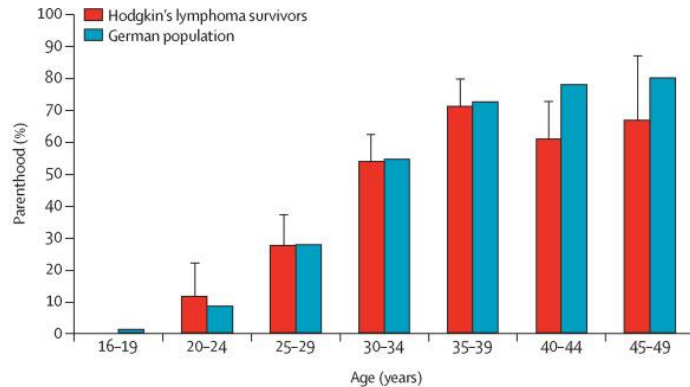
N=590
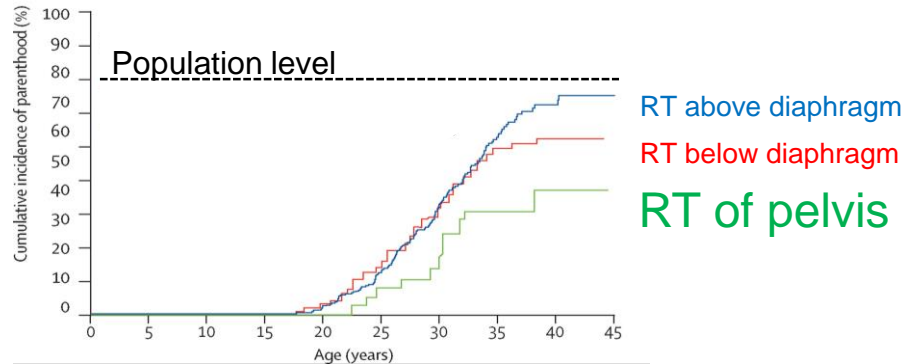
Non significant or only minor effects of:
- procarbazine (to 11400 mg/m^2)
- cyclophosphamide (to 6000 mg/m^2)
- alkylating agent dose scores of 1–5
- treatment protocol
- age at treatment

Brämswig et al 2015 Lancet Oncol 16, 557-675

Live birth to female childhood cancer survivors: chemo only

B. Live birth

Pregnancy: HR 0.87 (0.81-0.94)

Alkylators only at highest dose
Busulfan and Lomustine

Survivors
Siblings

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

No birth before age 30

D. Live birth-conditional

Survivors
Siblings

at risk:

	30	35	40	45
Survivor	1076	452	197	147
Sibling	490	201	85	58

Chow et al Lancet Oncol 2016

The impact of cancer on subsequent chance of pregnancy: a population-based analysis

Richard A. Anderson[1,*], David H. Brewster[2], Rachael Wood[3],
Sian Nowell[4,5], Colin Fischbacher[3], Tom W. Kelsey[6],
and W. Hamish B. Wallace[7]

[1]MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, 47 Little france Crescent, Edinburgh EH16 4 TJ, UK [2]Scottish Cancer Registry, Information Services Division, NHS National Services Scotland, 1 South Gyle Crescent, Edinburgh EH12 9EB, UK [3]Information Services Division, NHS National Services Scotland, 1 South Gyle Crescent, Edinburgh EH12 9EB, UK [4]eData Research & Innovation Service (eDRIS), Information Services Division, NHS National Services Scotland, Edinburgh, 1 South Gyle Crescent, Edinburgh EH12 9EB, UK [5]Farr Institute Scotland, Nine Edinburgh Bioquarter, Little France Road, Edinburgh EH16 4UX, UK [6]School of Computer Science, University of St. Andrews, North Haugh, St. Andrews KY16 9SX, UK [7]Department of Oncology and Haematology, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF, UK
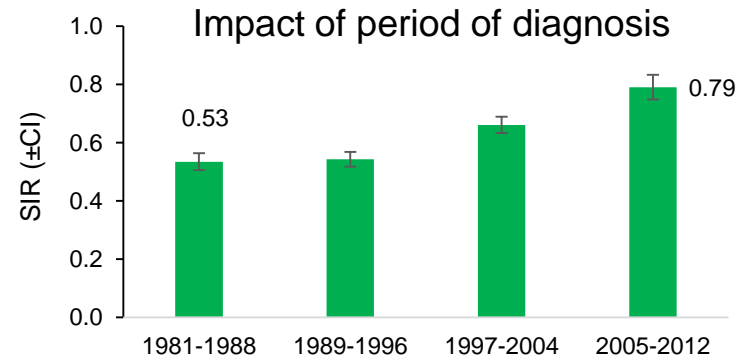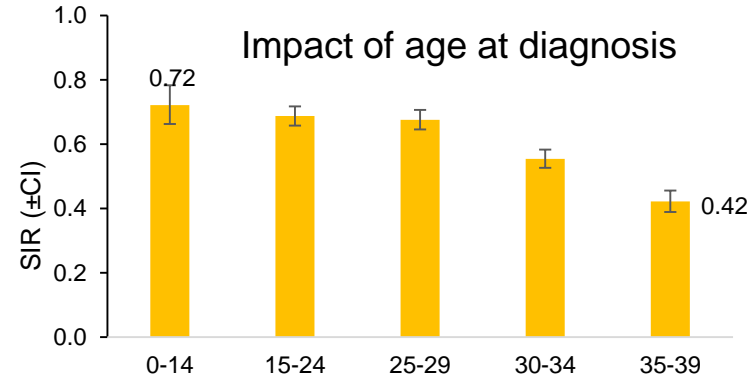
Population-based analysis of pregnancy after cancer

1981-2012, aged 0-40
23,201 cancer survivors

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

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

-across all diagnostic groups

Impact of age at diagnosis

Impact of period of diagnosis

RA Anderson et al 2018 Human Reprod

Population-based analysis of pregnancy after cancer

1981-2012, aged 0-40
23,201 cancer survivors

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

	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

Chance of a first pregnancy after cancer
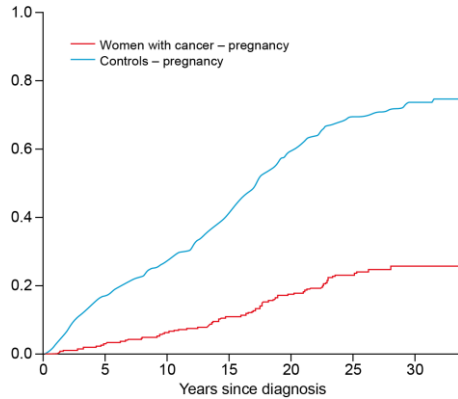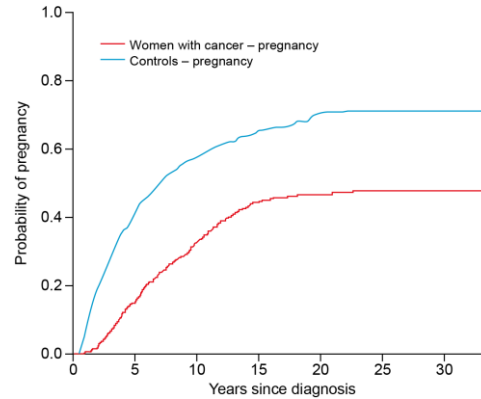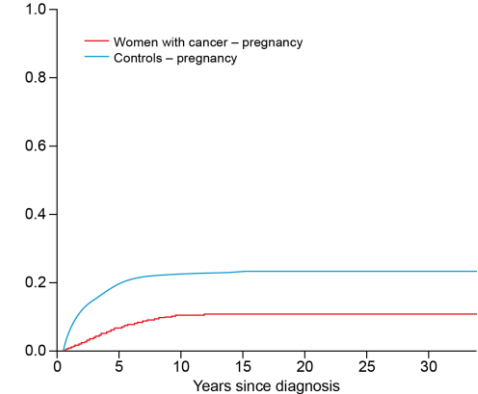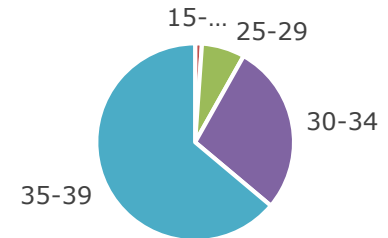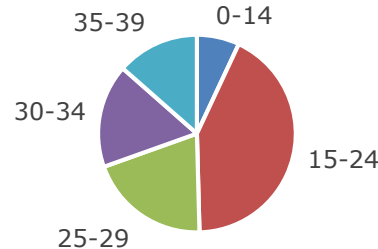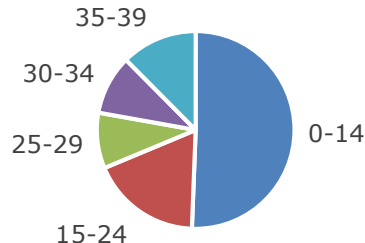
Scottish population based analysis

RA Anderson et al 2018 Human Reprod
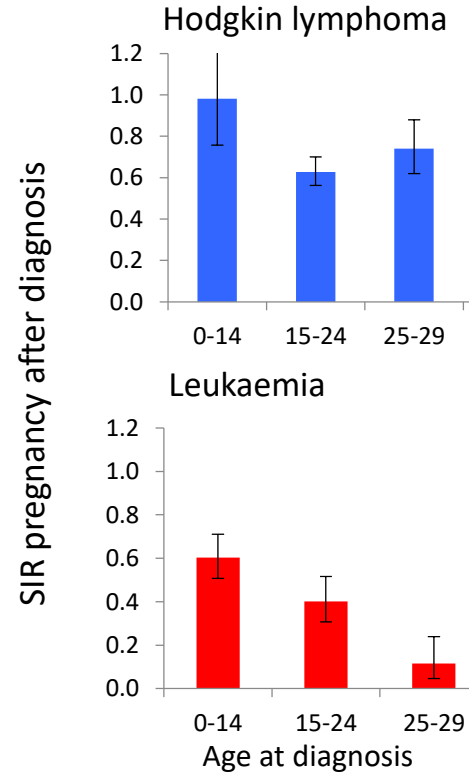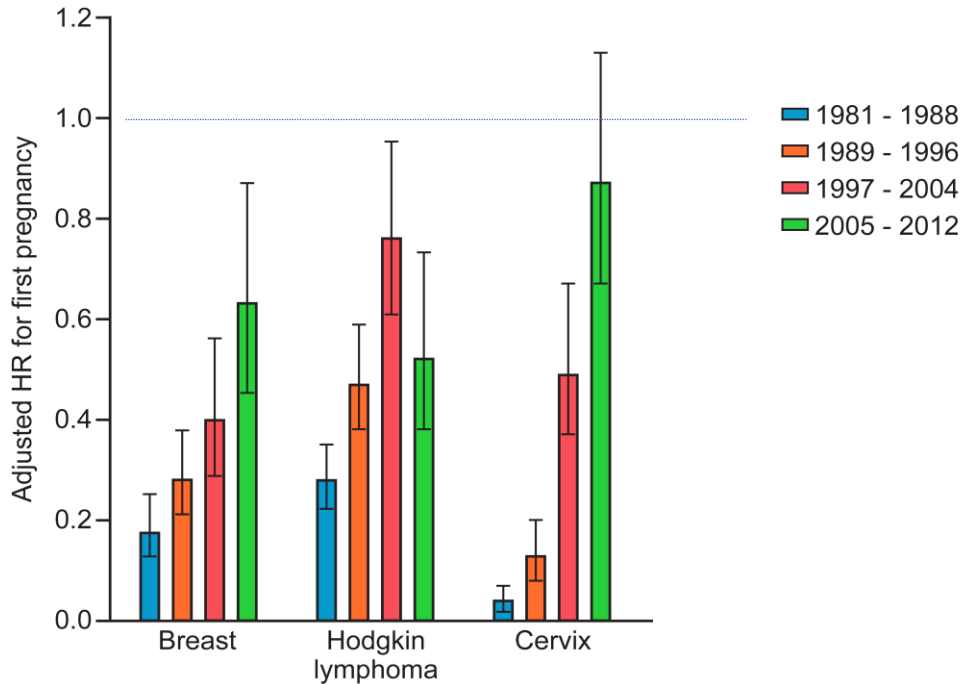
Outcome of singleton first pregnancies

	Post cancer %	Controls %	Difference (cancer-control)	Lower CI	Upper CI	
Total	n=2071	n=11772				
Miscarriage	9.8	9.3	0.50	-0.9	1.9	
Termination	11.2	14.7	-3.50	-5	-2	Seen in all ages except oldest
Still Birth	0.4	0.5	-0.06	-0.4	0.2	
Live Birth	78.7	75.6	3.06	1.1	5	
Infant Death *	7.4	4.8	2.53	-1.9	6.9	

* Infant deaths: rate per 1,000 live births

Mode of delivery

Elective Caesarean section

Emergency Caesarean section

van der Kooi et al 2018 Plos One
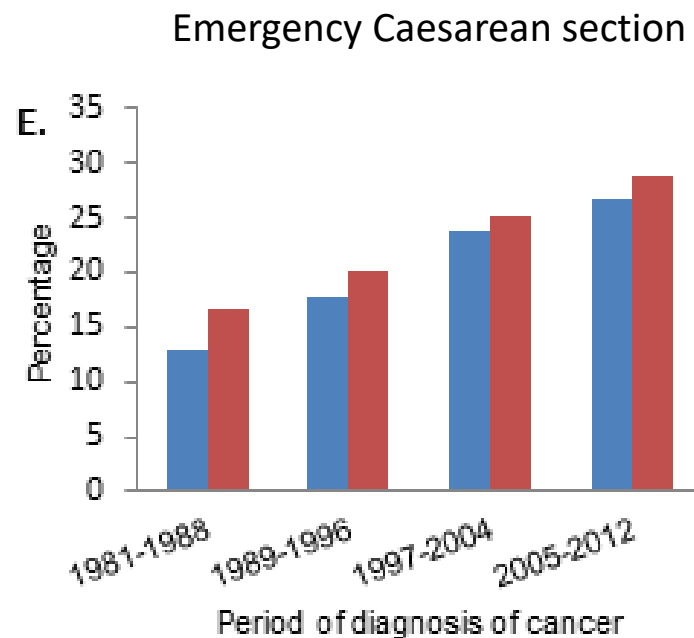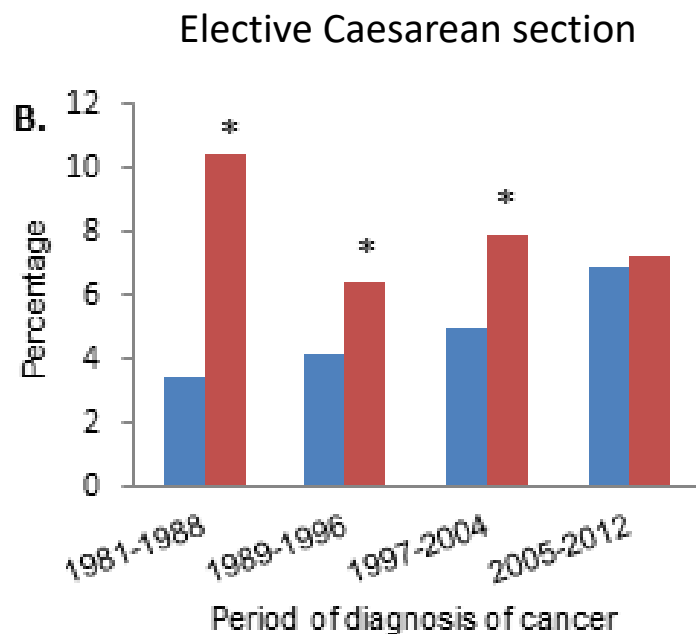
The variability in ovarian activity after cancer treatment

Key variables: age and treatment

Jayasinghe, Wallace and Anderson 2018 Expt Rev Endo Metab
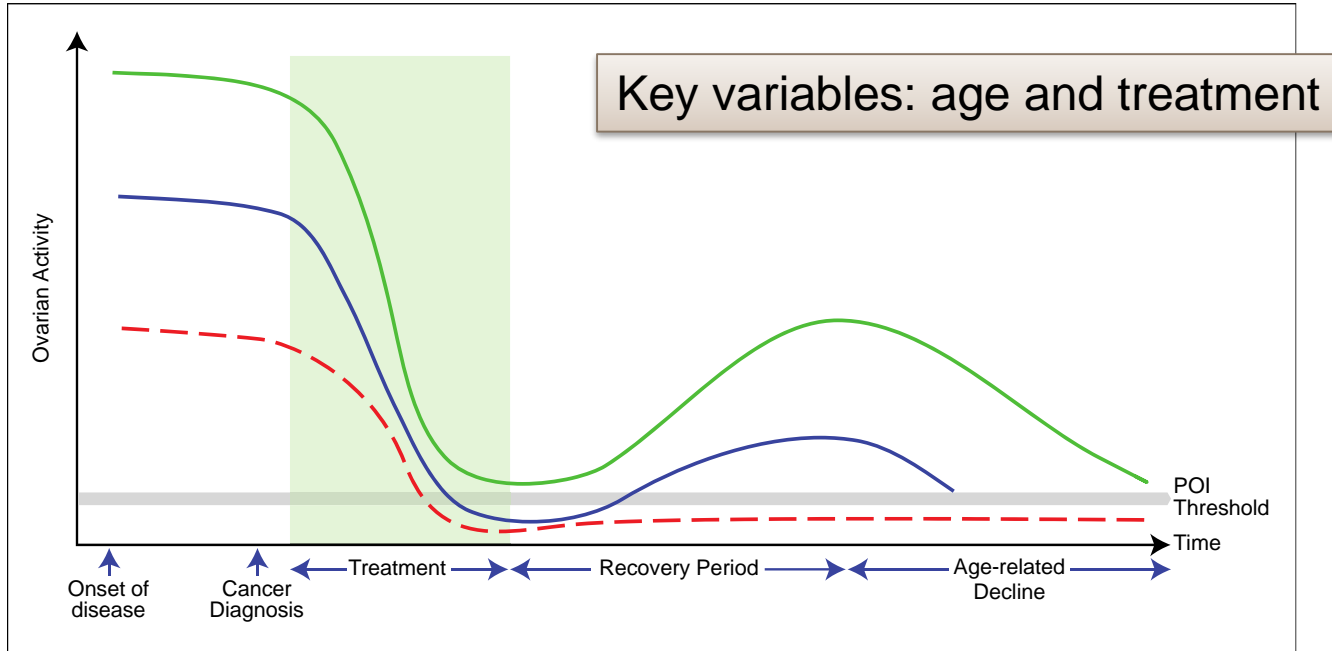
AMH identifies ovarian damage in childhood cancer survivors - despite regular cycles

□ Controls
■ Cancer survivors
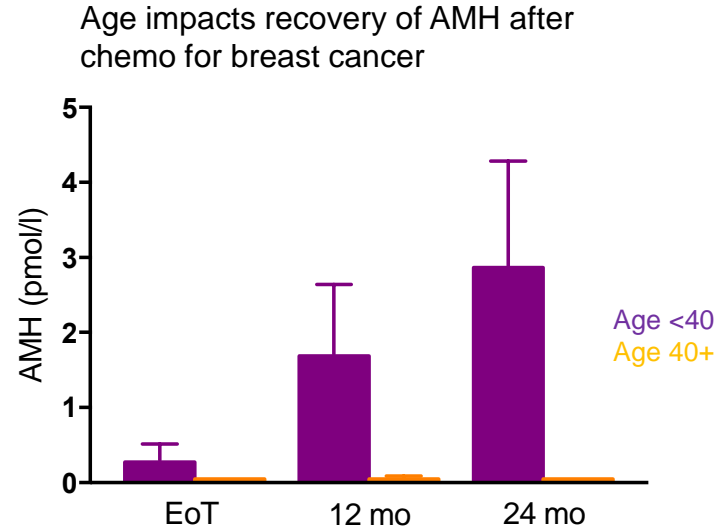
Bath LE et al 2003 Human Reprod 18 2368
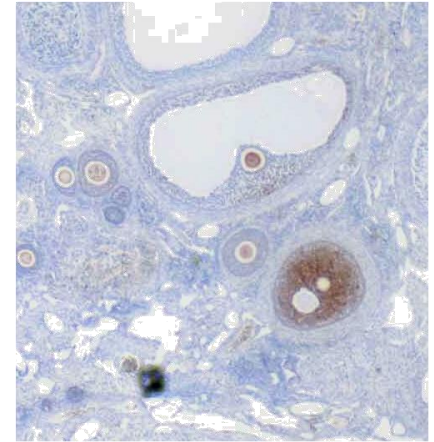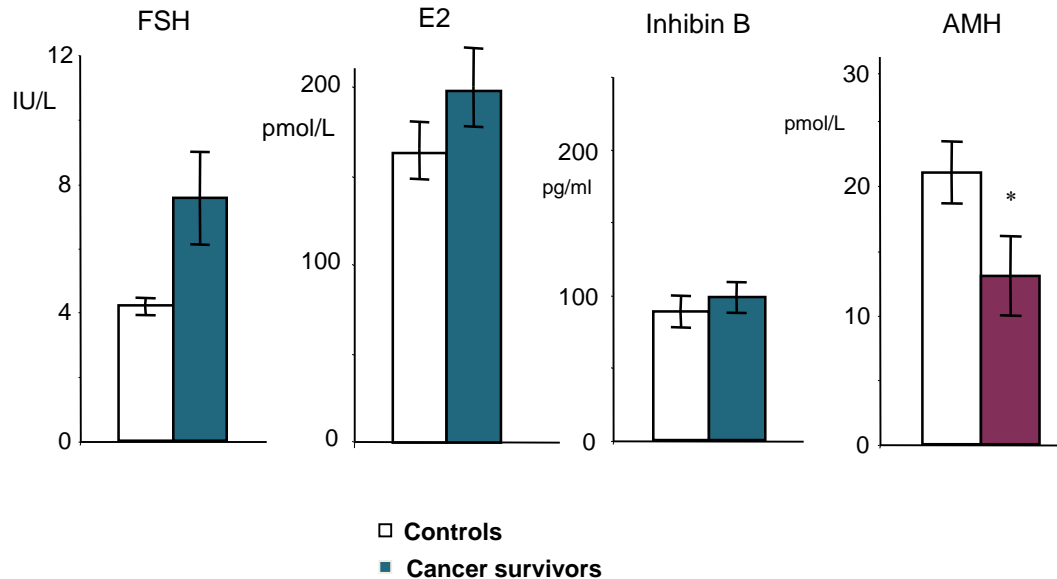
Pretreatment ovarian reserve and age impact on ovarian recovery after chemotherapy for eBC

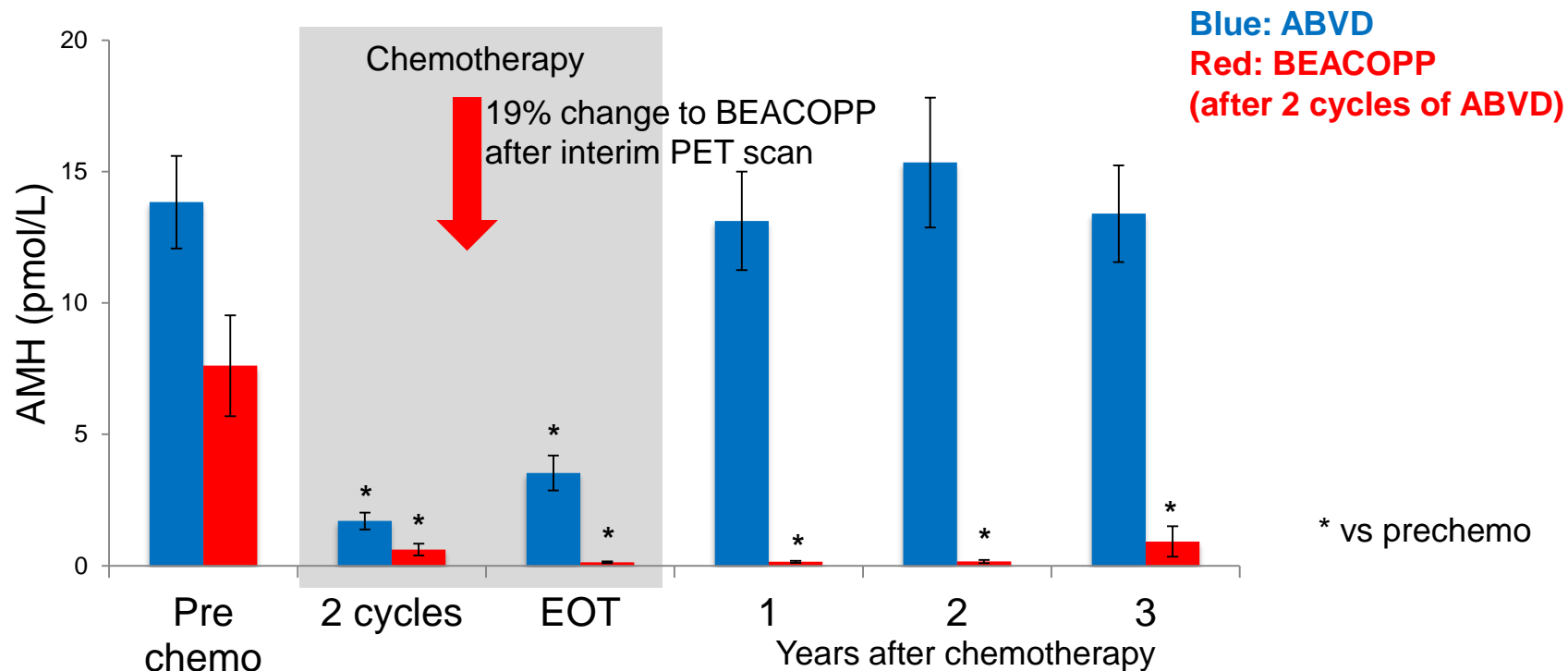AMH is higher at **diagnosis** of eBC in those who will still be having menses **5 years later**

AMH
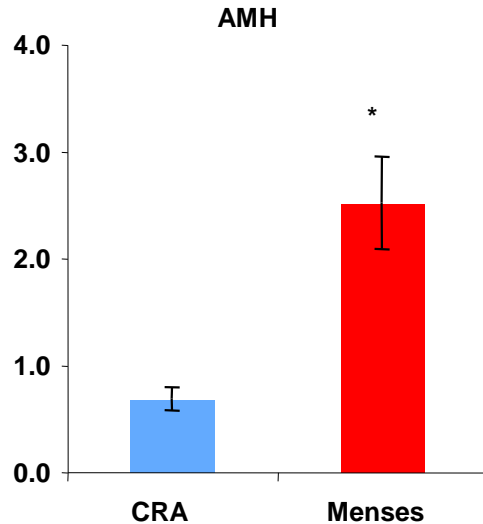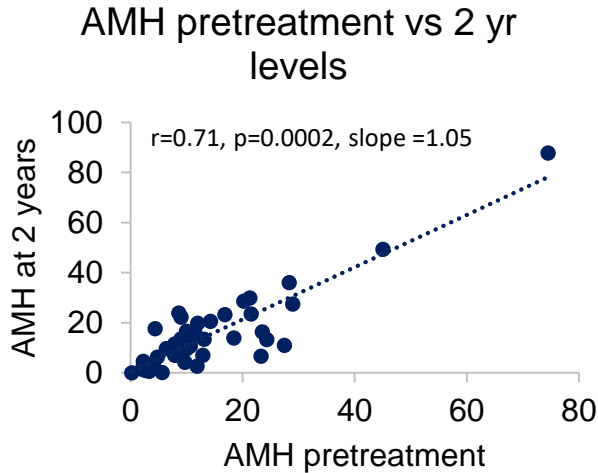

Anderson and Cameron 2011 JCE&M 96, 1336

Age impacts recovery of AMH after chemo for breast cancer

Age <40
Age 40+

Anderson et al 2017 Eur J Cancer

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

Anderson RA et al 2018 Lancet Oncol

After ABVD, age not AMH determines recovery

AMH pretreatment vs 2 yr levels

r=0.71, p=0.0002, slope =1.05

AMH at recovery reflects pretreatment level

AMH recovery by age

r=-0.48, p=0.001
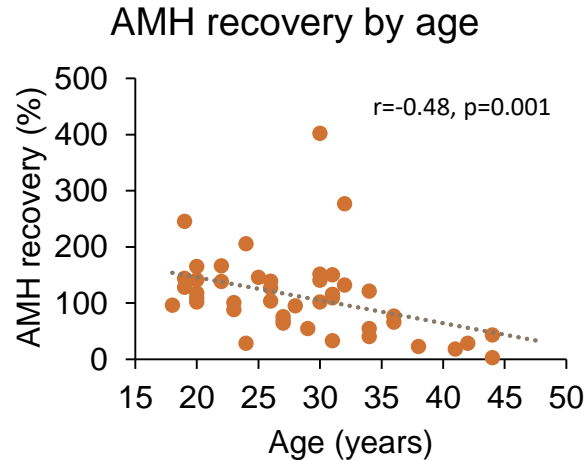
Older women show reduced recovery

AMH recovery by pretreatment AMH

r=-0.02, p=0.9

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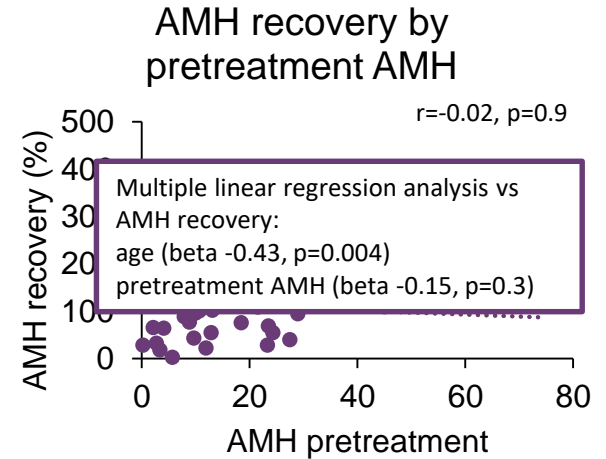
Women with low AMH show full recovery

Anderson RA et al 2018 Lancet Oncol

FSH recovery after A(B)VD is dependent on age
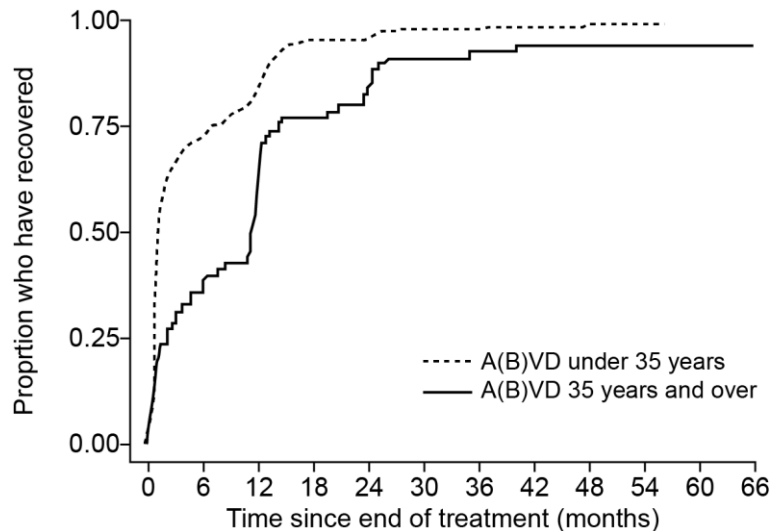
Recovery to FSH <25IU/L

Kaplan-Meier estimates at 1 year
83% (77 – 88) in <35 yrs
54% (43 – 66) in ≥35 yrs

at 2 years
96% (93 – 98) in <35 yrs
83% (73 – 91) in ≥35 yrs

At 3 years: 98% (95-99) vs 93% (85-97)
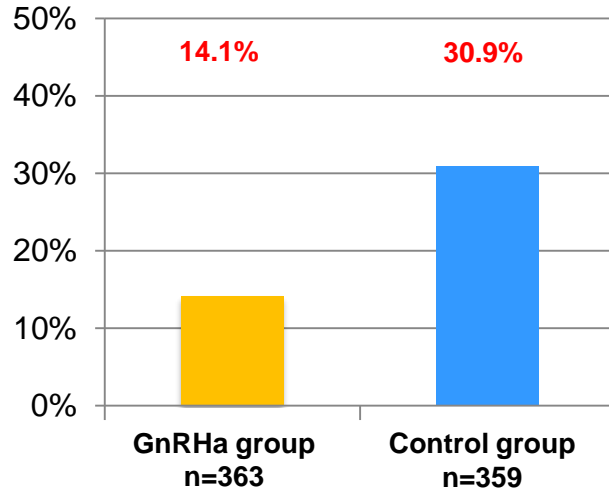
Can we protect the ovary?

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. Adamson[2], G. Bertelli[3], J. Mansi[4], A. Yellowlees[5], J. Dunlop[6], G. A. Thomas[1], R. E. Coleman[7] & R. A. Anderson[8], for the Anglo Celtic Collaborative Oncology Group and National Cancer Research Institute Trialists
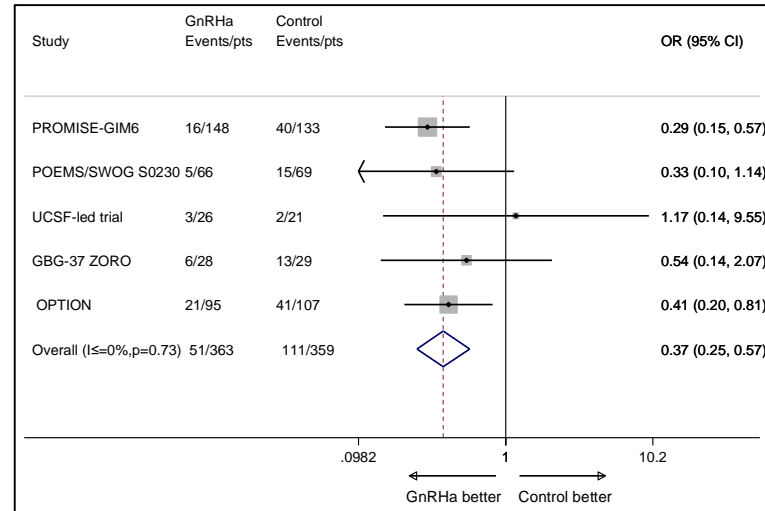
Premature Ovarian Insufficiency Rate

IPD approach
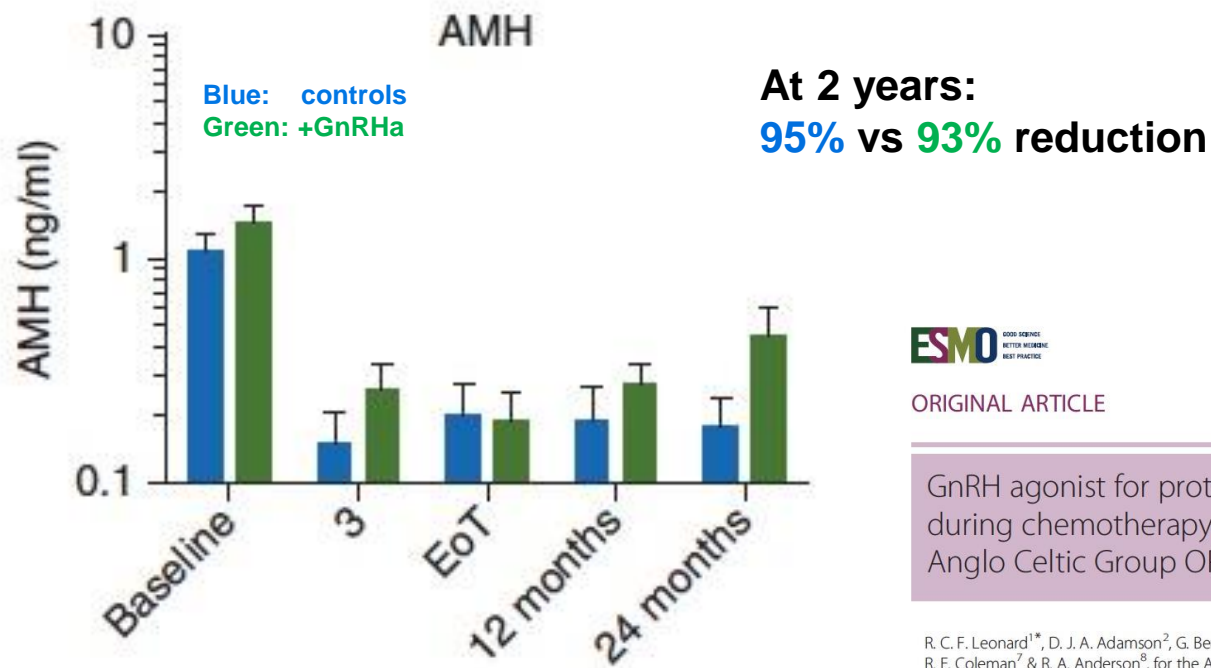
OR* 0.38 (95% CI 0.26-0.57)
p<0.001

Meta-analysis approach

*Odds ratio (OR) adjusted for age, estrogen receptor
status, type and duration of chemotherapy administered

Lambertini M et al 2018 J Clin Oncol

GnRHa: how much ovarian function is preserved?

Blue: controls
Green: +GnRHa

At 2 years:
95% vs 93% reduction

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. Adamson[2], G. Bertelli[3], J. Mansi[4], A. Yellowlees[5], J. Dunlop[6], G. A. Thomas[1], R. E. Coleman[7] & R. A. Anderson[8], for the Anglo Celtic Collaborative Oncology Group and National Cancer Research Institute Trialists

Leonard RCF et al 2017 Ann Oncol

Conclusions

Fertility preservation is now 'main stream' medicine

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

Acknowledgements

Hamish Wallace, Evelyn Telfer

David Cameron, The Edinburgh Breast Unit
Peter Johnson and RATHL investigators
Bob Leonard and OPTION investigators

Hamish Wallace
Paediatric oncologist

Evelyn Telfer