Temporal trends in the incidence of molecular subtypes of breast cancer

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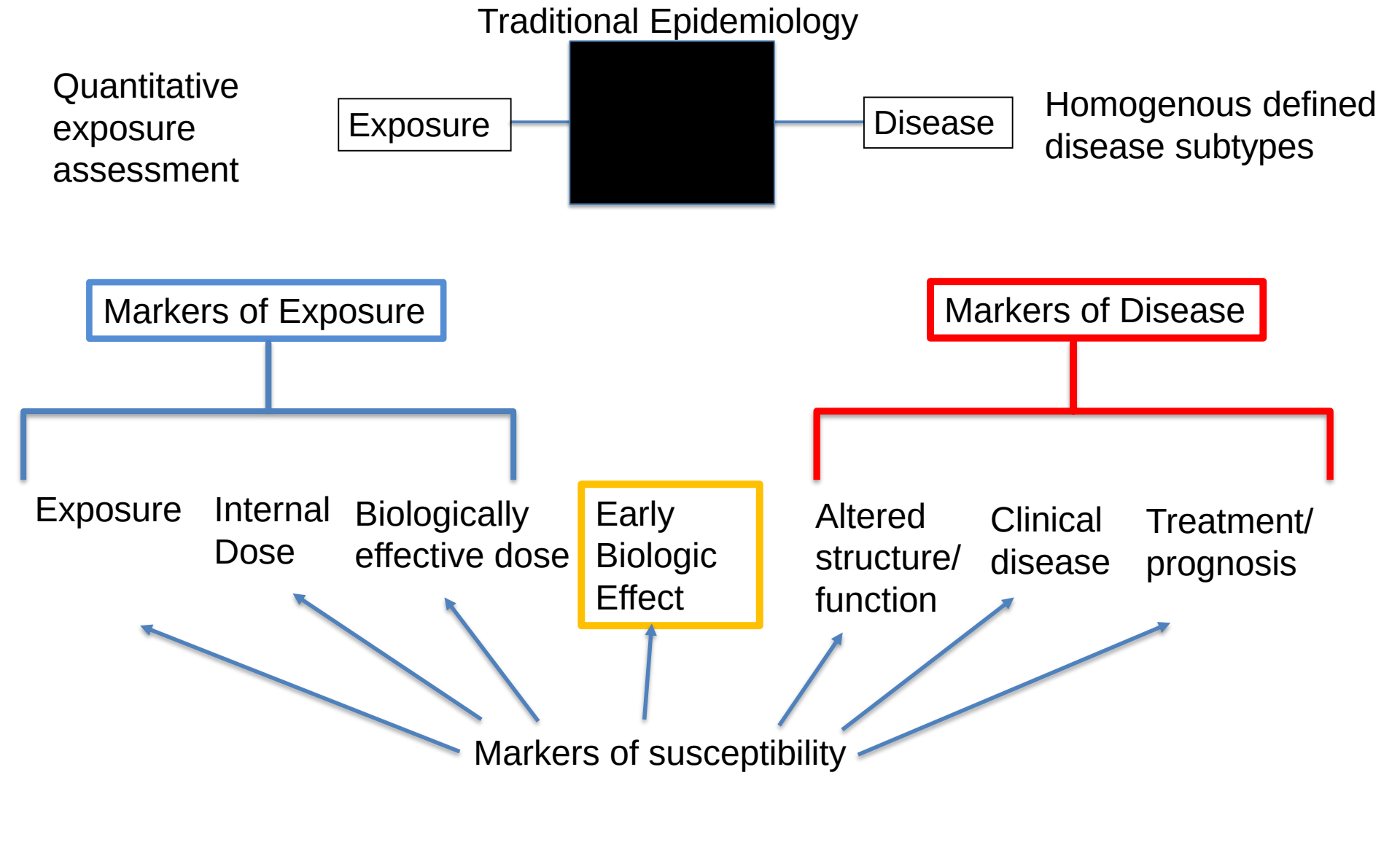
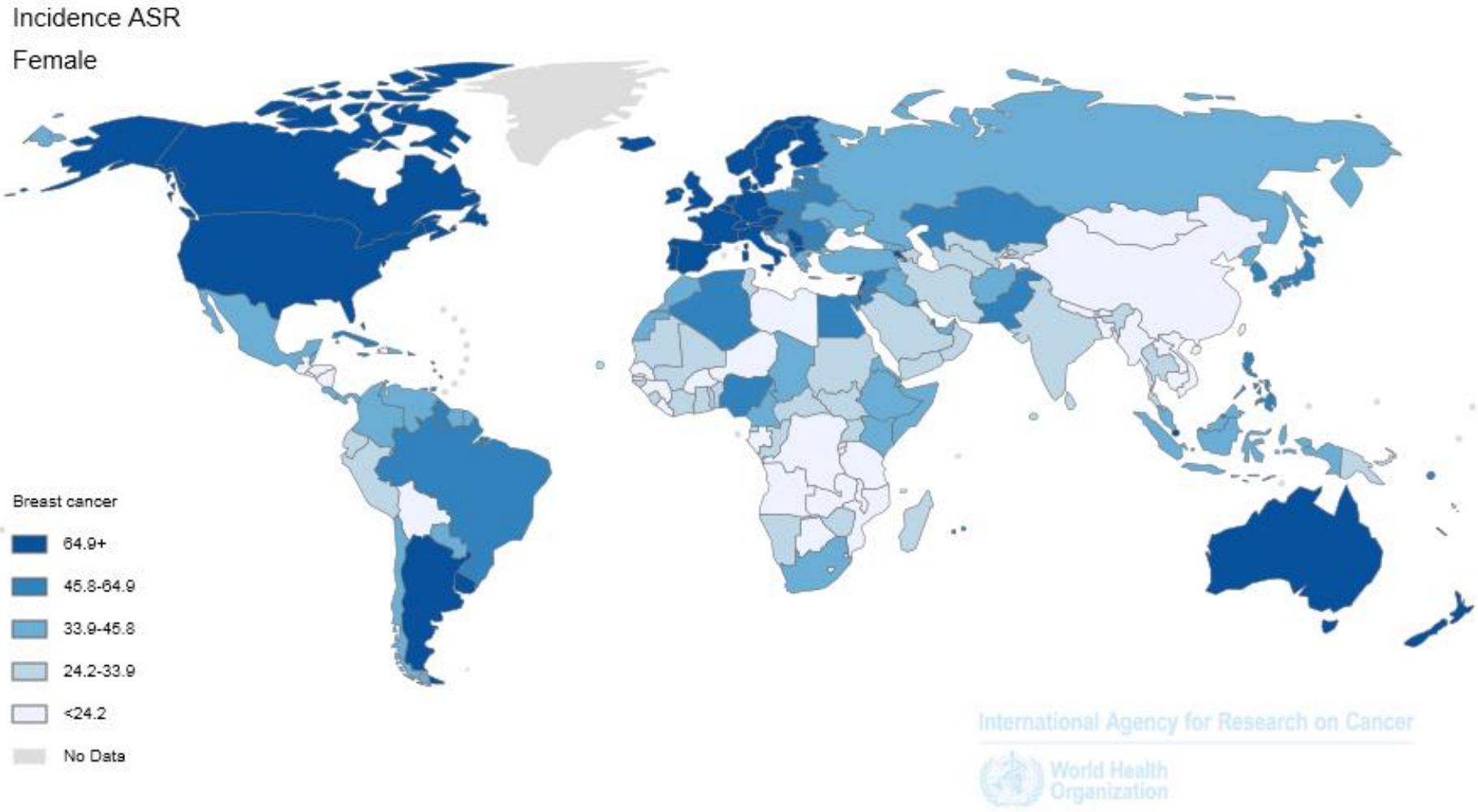
Epidemiology: Health data science

- Study of the distribution and determinants of health and disease
- All findings must relate to a defined population
- Study designs
  - Descriptive (Ecologic; e.g. cancer incidence and mortality rates)
  - Analytic (Case-control, cohort; e.g. mobile phone use and brain cancer)
  - Interventional (Random control trial e.g. of tamoxifen vs aromatase inhibitors and breast cancer recurrence)

Molecular epidemiology

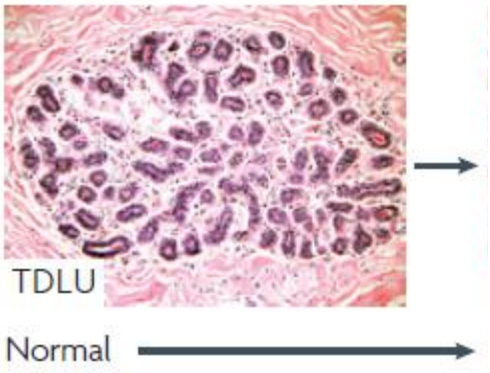


Estimated Age-standardized Incidence Rate per 100,000, Breast Cancer, All Ages, GLOBOCAN 2012

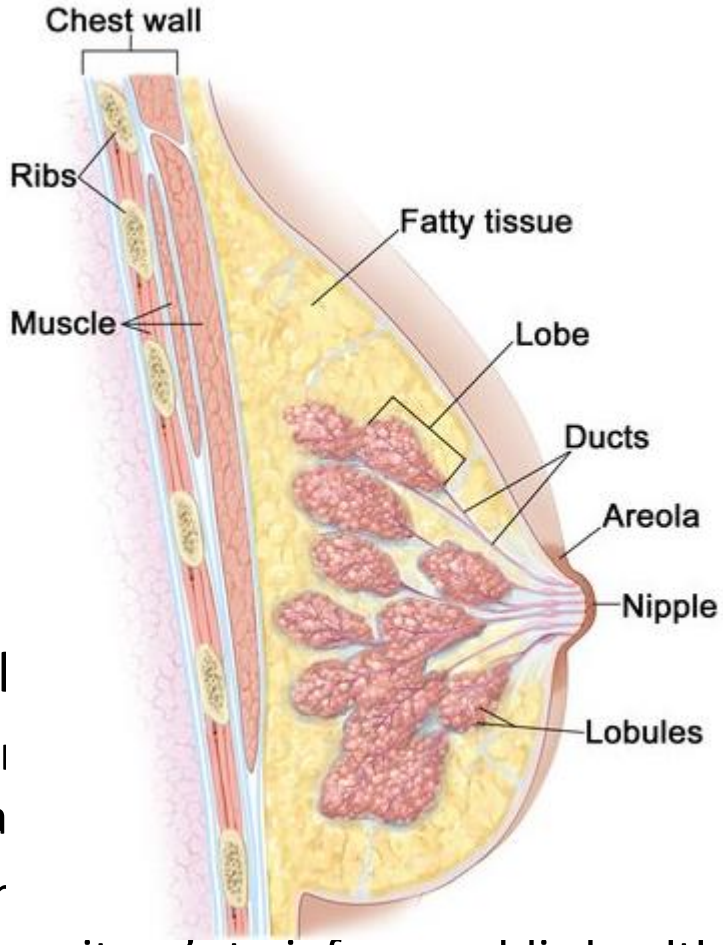


Source: GLOBOCAN 2012 (IARC)

Natural history of breast cancer: transformation of the TDLU



Terminal duct lobular unit (TDLU)



…a *in* …)

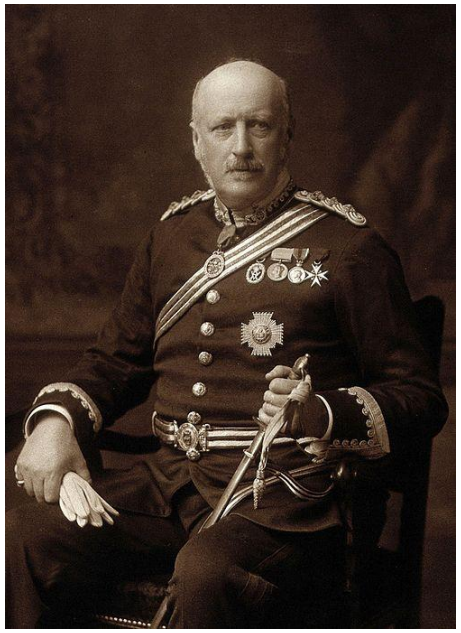
Invasive breast cancer (IBC)

Aim of current researc

- Evaluate tissue bioma… the aetiology and treatment and surviva…ions
- To develop a high-dim…tish e-health records and tumour tissue from repository's to inform public health, policy and prevention

Hormone hypothesis: Oestrogen and breast cancer

1896 1958 1968 1971 1973 1998



Sir George Beatson- Observation of regression of breast cancer after oophorectomy

Elwood Jensen
1958- discovers estrogen.
1968- discovers estrogen receptor
1971- ER rich breast cancers respond better to endocrine ablation

Tamoxifen and breast cancer treatment.

EBCTCG Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet*, **35 1***:* 1451-1467,

Multiple factors affect breast cancer risk

Pre-natal	Childhood	Adolescence	Adulthood pre-menopause	Adulthood post-menopause
Genetics	?	Age at 1st period	Age at first birth	Age at menopause
			Breast-feeding	
			Oral contraceptives	Menopausal therapy
			Density, BBD	
			Height	
			Weight	
			Physical activity	
			Alcohol	
			Smoking	

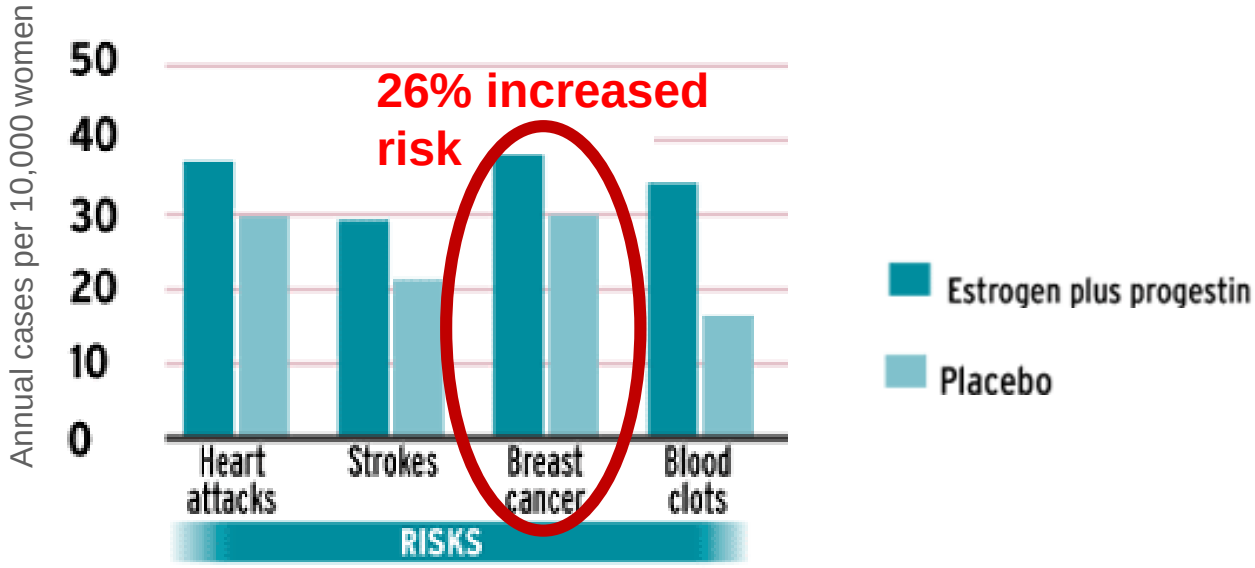
Selected factors associated with breast cancer by ER status

Exposure	ER+	ER-
Younger age at menarche	++	++
Multiparity	-	+
Older age at first birth	++	unknown
Breastfeeding	-	-
Older age at menopause	++	+
Obesity		
Premenopausal	-	+
Postmenopausal	+	unknown
Family history of bc	+++	+++
HRT	++	unknown

+++ consistent evidence of a positive association, ++ probable positive association, + possible positive association. Minuses indicate similar consistency of inverse associations. Colditz et al (2004) , Ma et al (2006), Brinton et al (2017)

- Reproductive factors are more consistently associated with ER+
- Fewer factors found for ER- tumours
- Risk factors association with distinct subtypes not fully understood

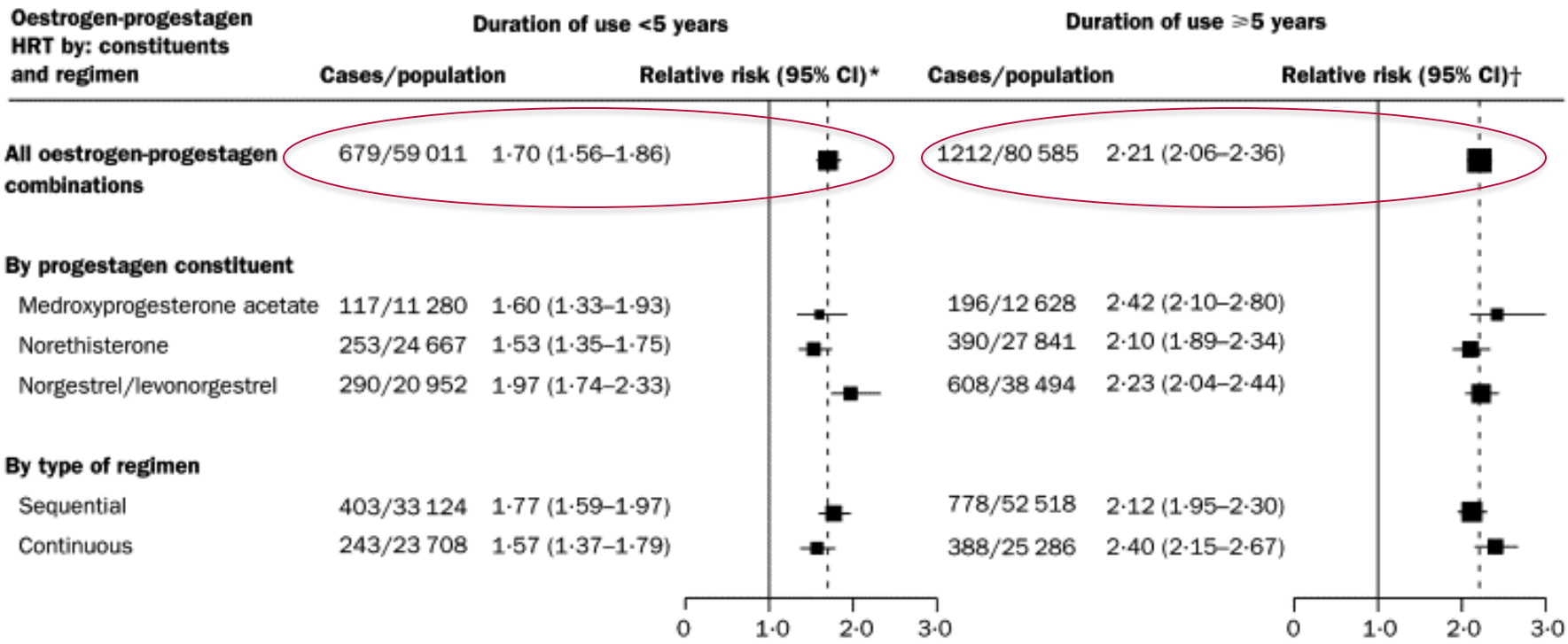
Women's Health Initiative investigating hormone replacement therapy (HRT) finds significant increased breast cancer risk



Source: Women's Health Study (United States)

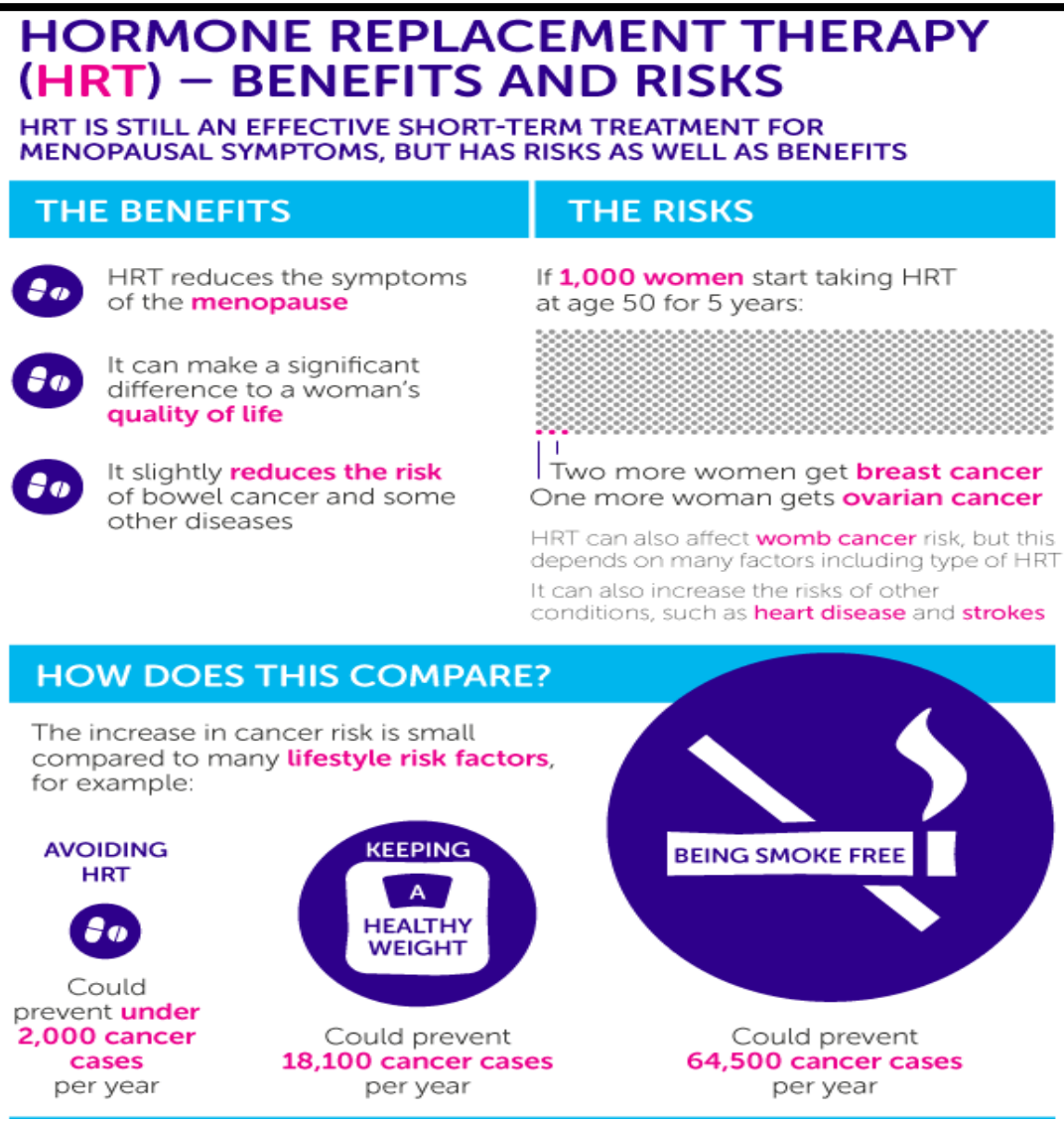
JAMA 2002; 288:321-33.

Million women's study and HRT use and breast cancer risk



Lancet 2003

Hormone replacement therapy and cancer risk



https://scienceblog.cancerresearchuk.org/2015/10/20/no-hrt-isnt-harmless-there-are-risks-as-well-as-benefits/

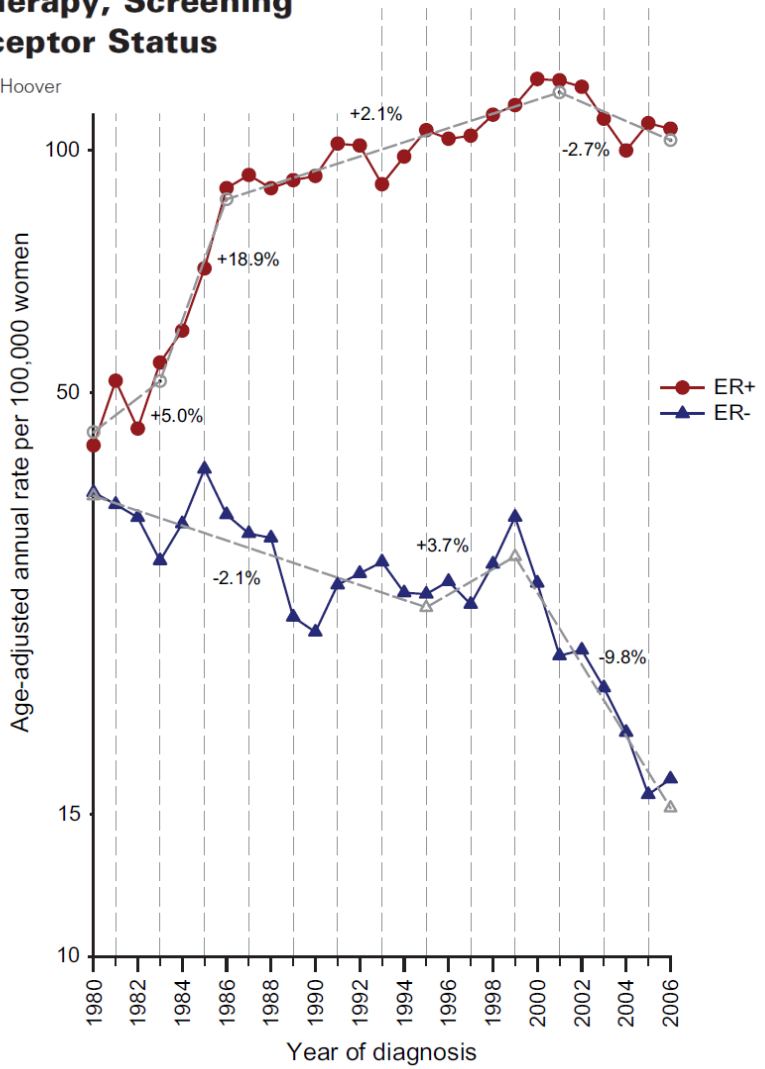
JNCI Journal of the National Cancer Institute Advance Access published July 24, 2007

ARTICLE

Breast Cancer Incidence, 1980–2006: Combined Roles of Menopausal Hormone Therapy, Screening Mammography, and Estrogen Receptor Status

Andrew G. Glass, James V. Lacey Jr, J. Daniel Carreon, Robert N. Hoover

- Don Berry and Peter Ravdin: 'An anomalous finding is the 50% decrease in the incidence of ER- cancers from 2002-2006, … possibly due to a statistical fluctuation' (*JNCI 99: 1152-61, 2007*)
- Validate in other datasets



Age-incidence rates and etiologic heterogeneity Denmark and the US

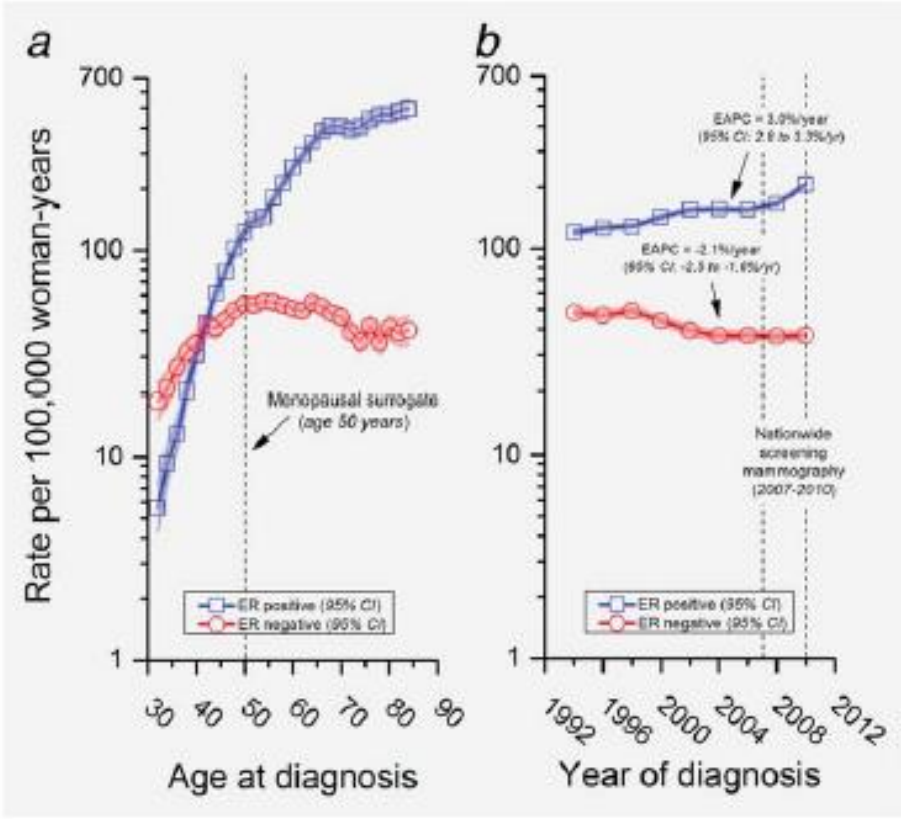
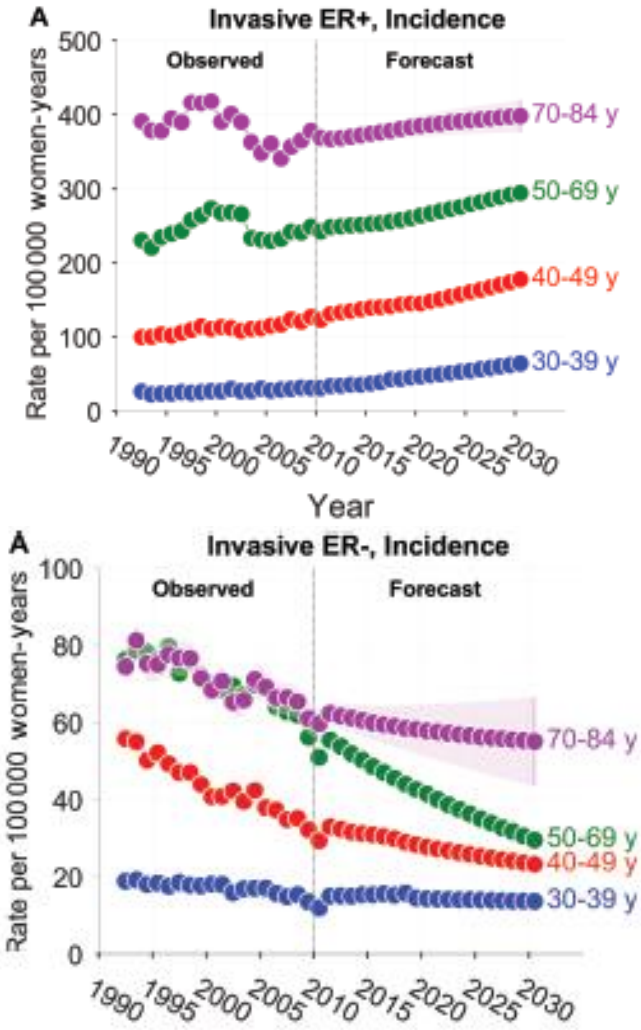
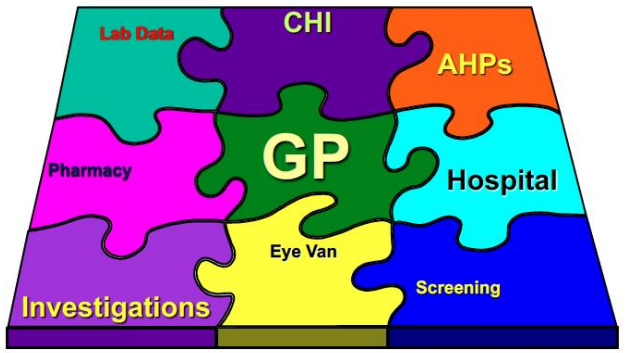


Figure 1. Longitudinal fitted age at onset curve (*a*) and age-standardized incidence rates (*b*) by estrogen receptor (ER)-positive and -negative expression. The fitted age at onset curve provides a summary measure of the longitudinal age-specific incidence by birth cohort and is adjusted for period and cohort effects.



Andersen et al IJE 2013; Rosenberg et al JNCI 2015

Temporal trends of molecular subtypes of breast cancer in Scotland



- Scotland unique in the UK as ER data collected since 1997-present with good coverage (e.g. England started collection from 2009)
- With access to other electronic medical records an important resource to understand trends of molecular subtypes of breast cancer

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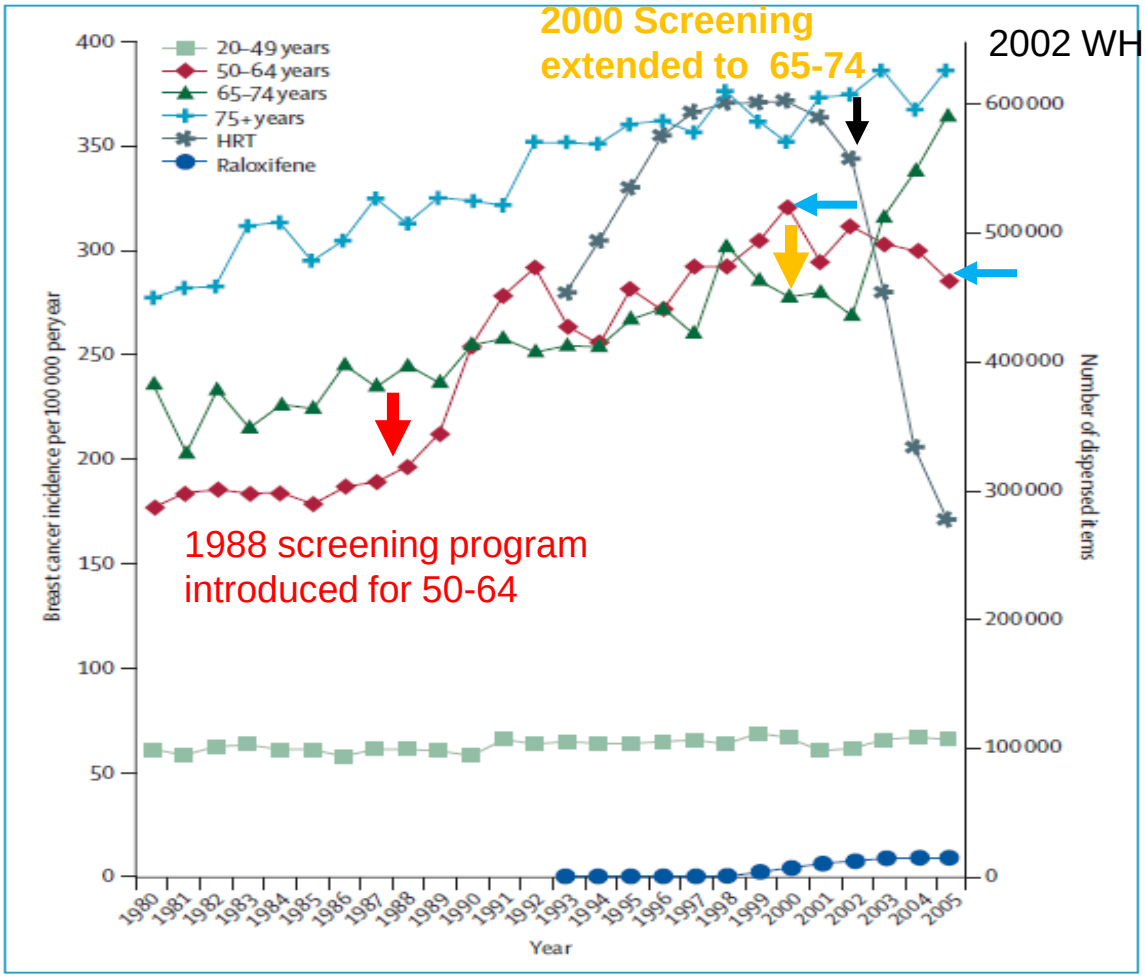
Age-standardized incidence rates in Scotland from 1980-2005



Incidence dropped from 1470 to 1387 cases from 2000-2005

Figure: **Age-standardised incidence of invasive breast cancer by age-group in Scottish women (1980–2005), and numbers of dispensed items of HRT and raloxifene (1993–2005)**
Within each age-group, incidences of breast cancer have been age-standardised to the European standard population.

Sharpe et al. Eur J Cancer, 2010

Age-standardized incidence rates by ER

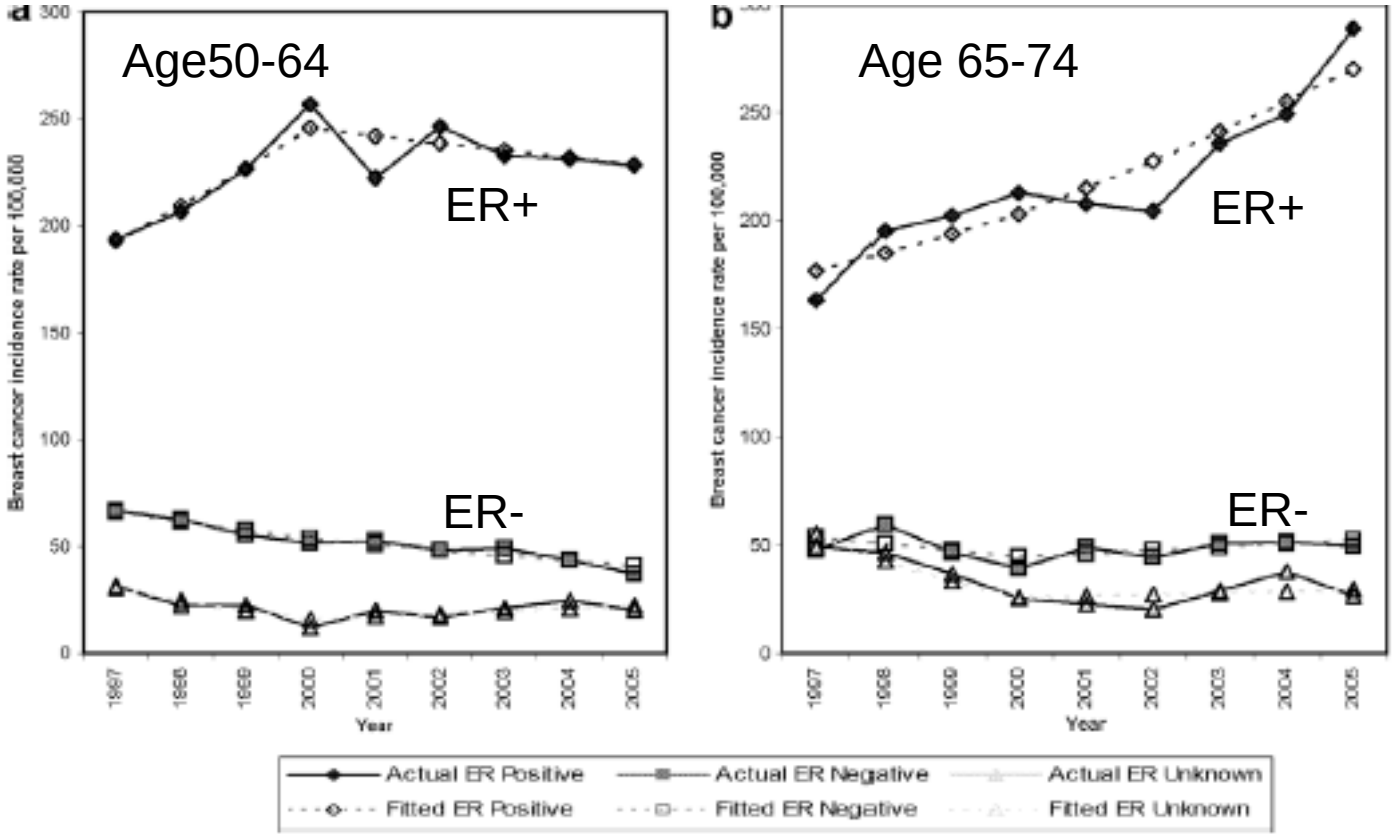


Fig. 4 – (a) Fitted and actual age-standardised incidence rates of invasive breast cancer by oestrogen receptor status in Scottish women aged 50–64 years (1997–2005). (b) Fitted and actual age-standardised incidence rates of invasive breast cancer by oestrogen receptor status in Scottish women aged 65–74 years (1997–2005).

Sharpe et al. Eur J Cancer, 2010

Tumour characteristics for 73,827 cases registered in Scotland

	Total cases	ER +	ER-	ER unknown
Sample size	73827	56163 (76%)	11863 (16%)	5805 (8%)
% total cases	100	76.07	16.07	7.86
Median age category	60-64	60-64	55-59	70-74

- ER+ breast cancers are more common and diagnosed among women between age 60-64 years
- Relatively good completeness of data on ER (only 8% missing with later years (<5% missing 2008 on)

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Tumour characteristics for 73,827 cases registered in Scotland

Variable	Category	ER+ (%)	ER- (%)	P
Menopause	<50	18.01	25.75	
	50+	81.99	74.25	<0.0001
Grade	Well differentiated/Moderately	61.58	17.00	
	Poorly	25.67	69.75	<0.0001
Method of detection	Clinical presentation	64.46	78.88	
	Screening examination	29.74	16.35	
	Other	4.50	3.12	<0.0001
Tumor size	≤20mm	48.95	38.57	
	>20mm	31.98	42.50	<0.0001
Node status	Negative	52.53	51.72	
	Positive	30.80	35.02	<0.0001

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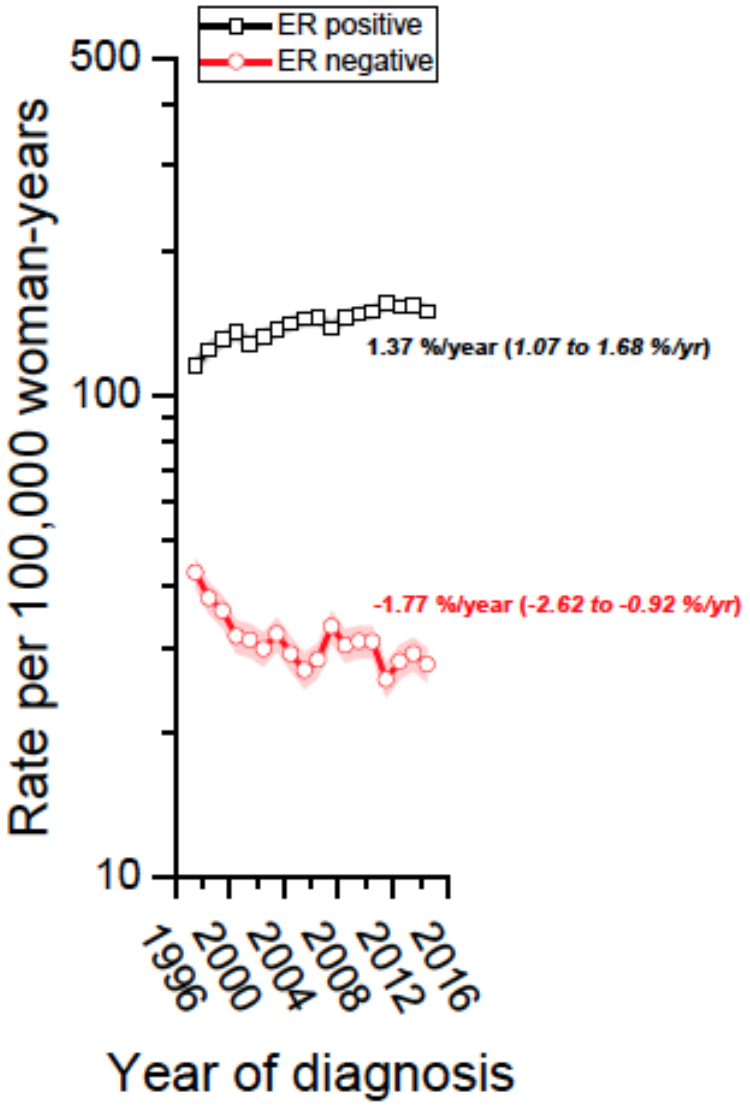
Temporal trends of molecular subtypes of breast cancer in Scotland



- Age standardised incident rates (ASR) by ER status corrected for ER unknown (Anderson JNCI 2011 and IJE 2013)
- Linear trends by ER summarised by annual percentage change of ASR, calculated using a weighted log-linear regression assuming a Poisson distribution (Anderson JNCI 2011 and IJE 2013)

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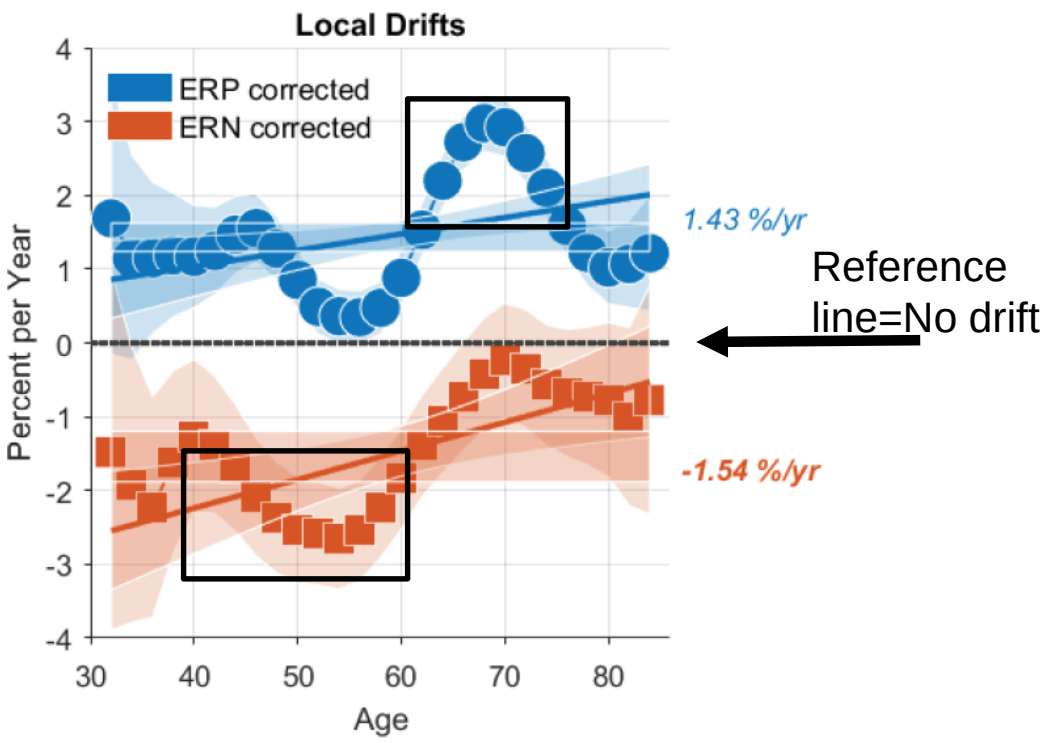
Local drifts = generational or birth-cohort effect



- ER positive breast cancers increasing among older women (60-70 years). Possible factors could be, obesity, reproductive patterns, screening)
- ER negative breast cancers decreasing among younger women (40-60). Possibly due to changes in reproductive patterns.
- Screening age 50-70 every 3 years participation >70%

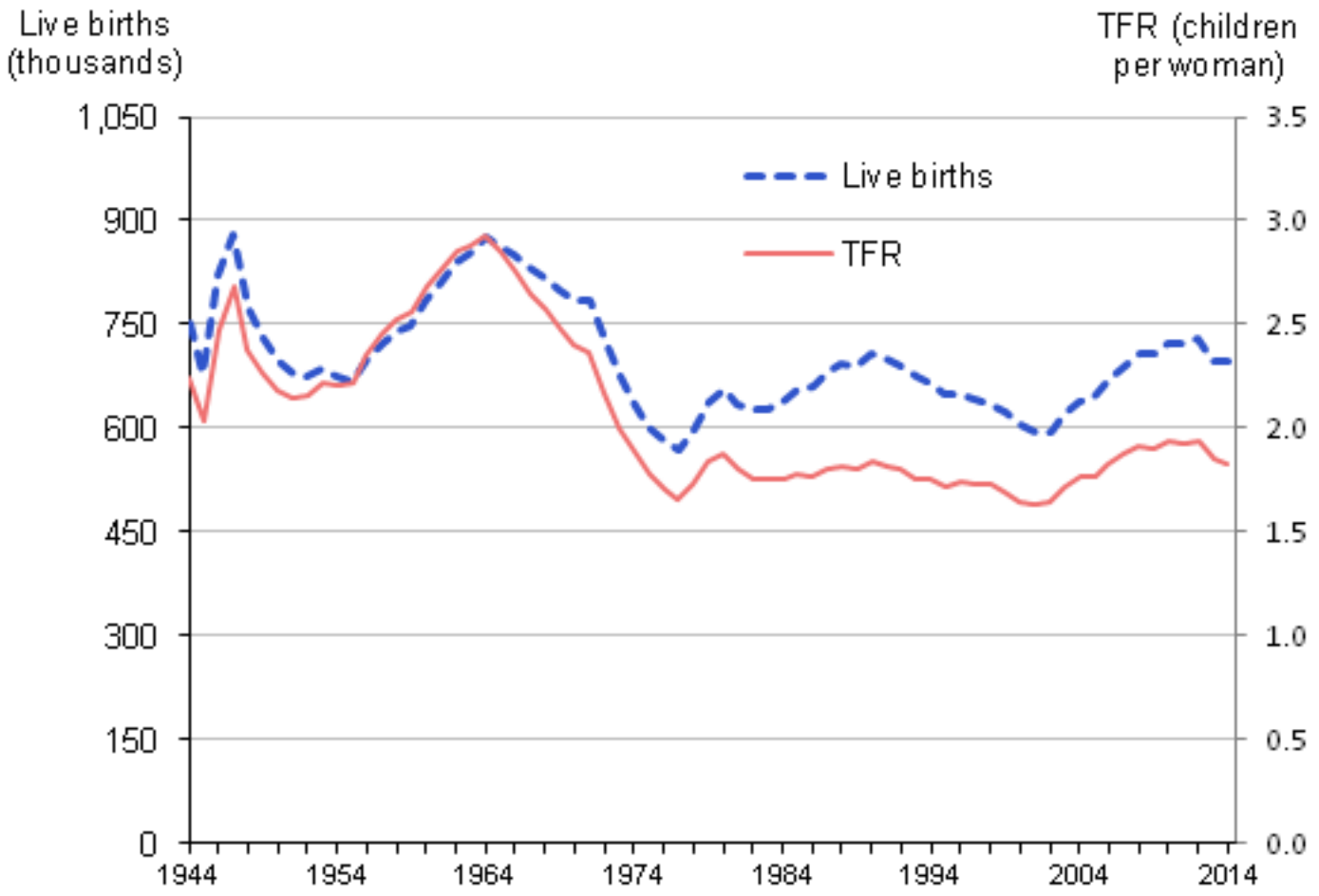
Summary of temporal trends of breast cancer

		ER-positive	ER-negative
Country	**Years**	**Annual % Change**	**Annual % Change**
USA	1992-2008	0.1%	-1.9%
Denmark	1993-2010	3.0%	-2.1%
Ireland	2004-2013	2.2%	-3.4%
Scotland	1997-2014	1.4%	-1.5%

- Variation in the increase of ER+ breast cancers overtime across the four countries, but generally, its increasing.
- ER- breast cancers are consistently decreasing across the cancer registries. Whether declines are similar for basal vs HER2 enriched tumours is not known.

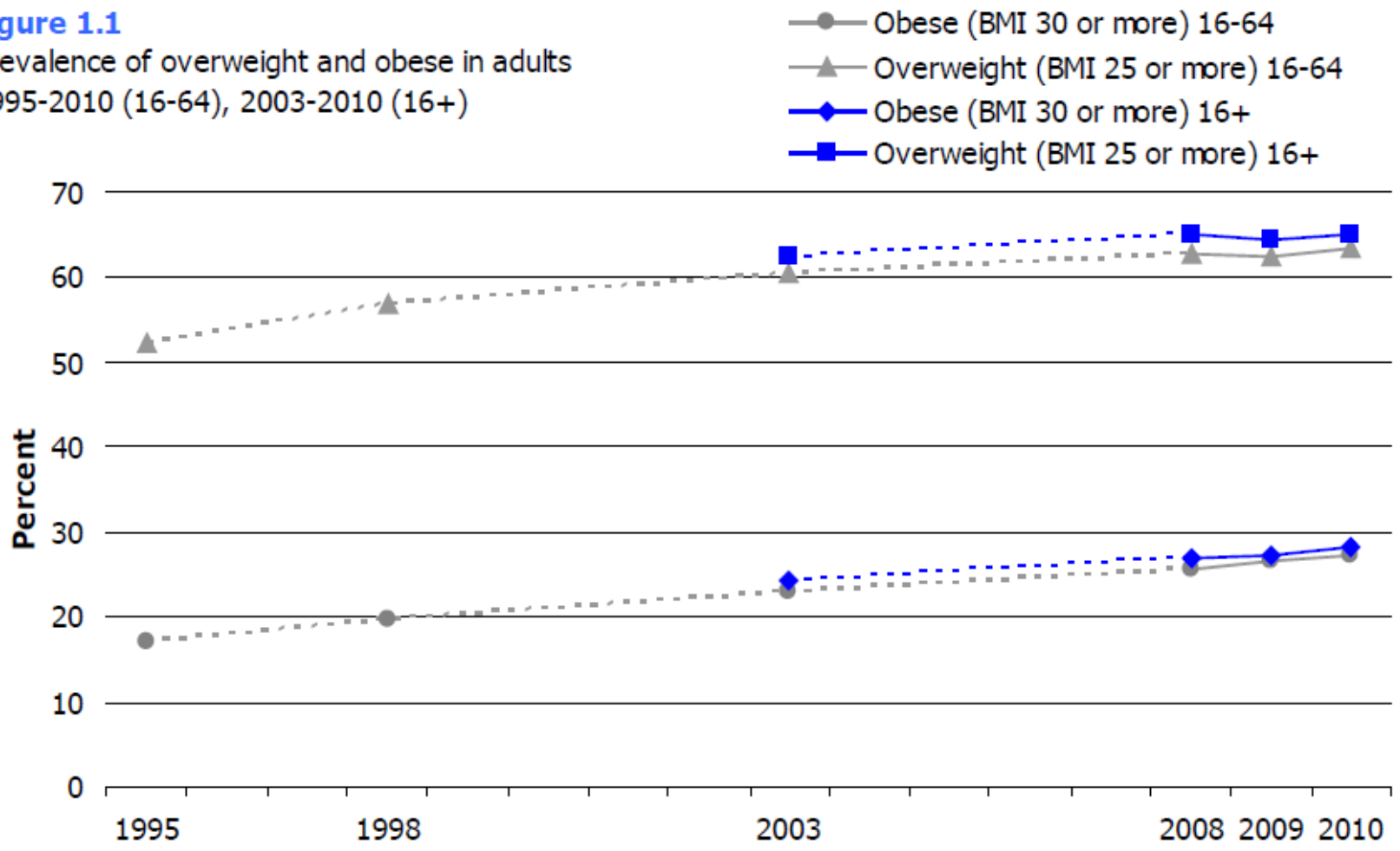
In preparation; Anderson et al. *JNCI* 2011, *IJE* 2013, EJC 2017

Temporal trends in birth rates in UK



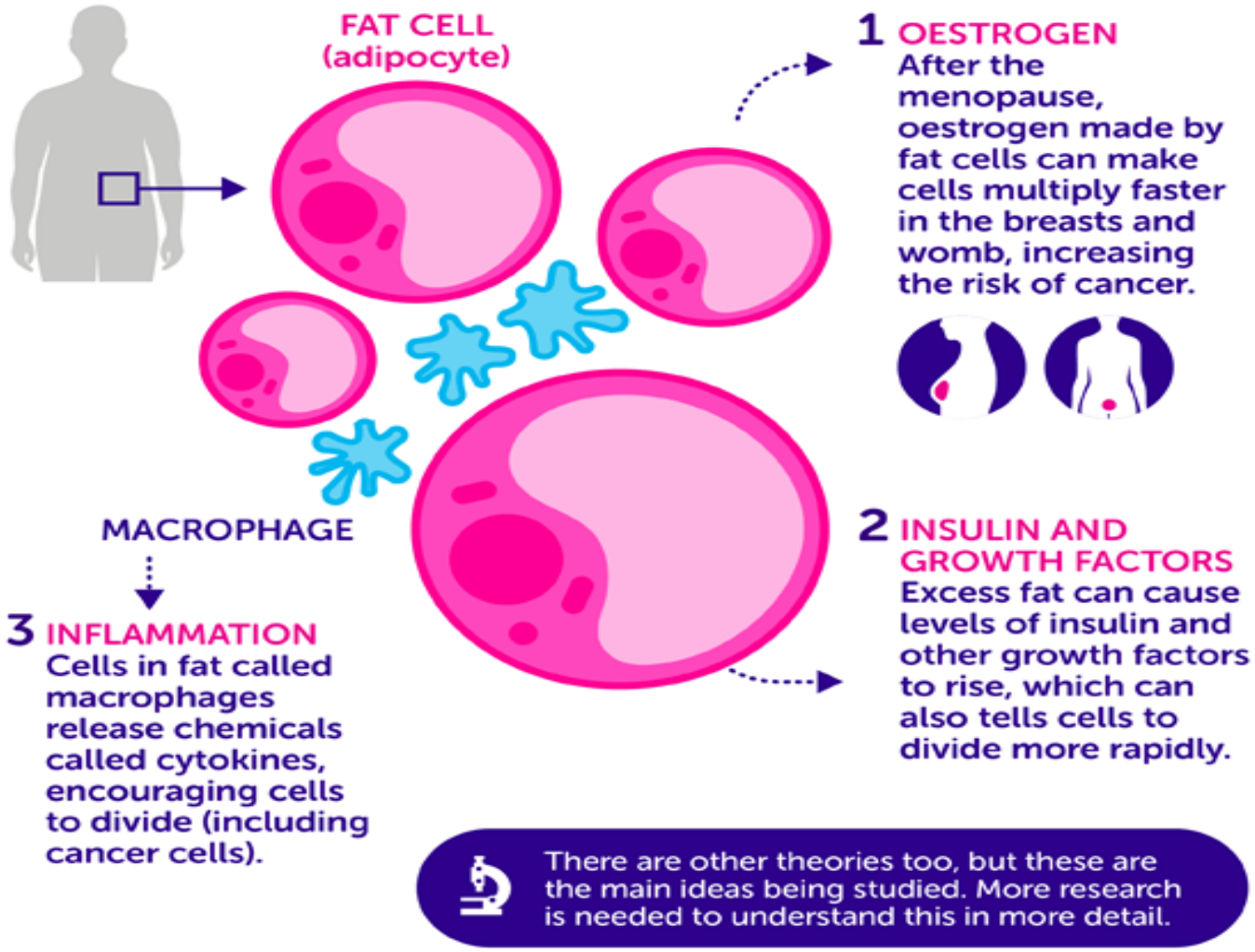
Prevalence of obesity in Scotland 1995-2010

Figure 1.1
Prevalence of overweight and obese in adults 1995-2010 (16-64), 2003-2010 (16+)



Obesity increased from 17% - 27% from 1995-2010 among adults 16-64

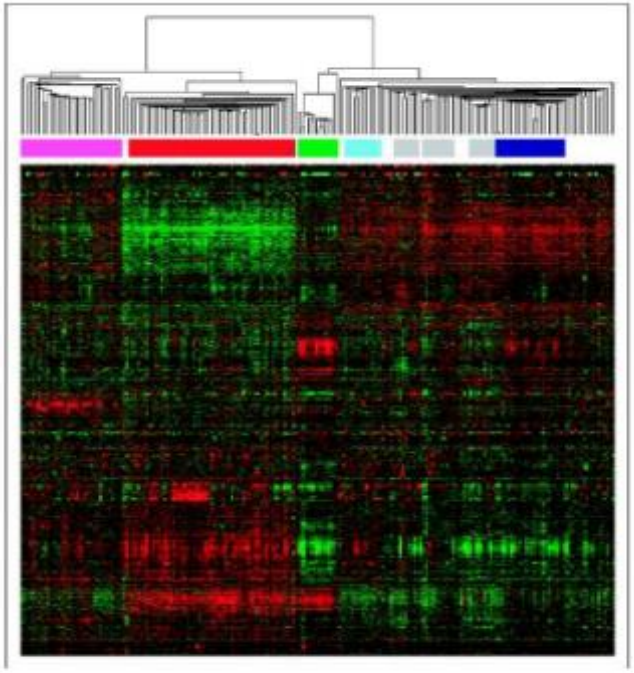
How can obesity influence breast cancer?



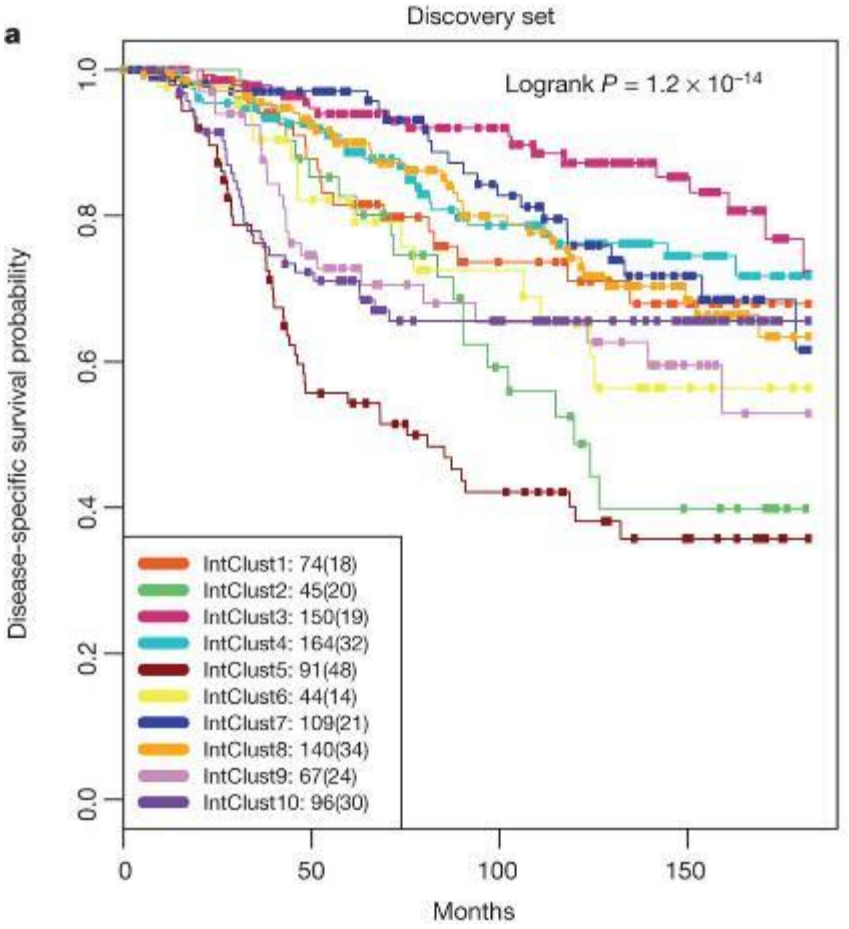
Key T. Steroids 2014

Molecular portraits of breast cancer

mRNA expression defined



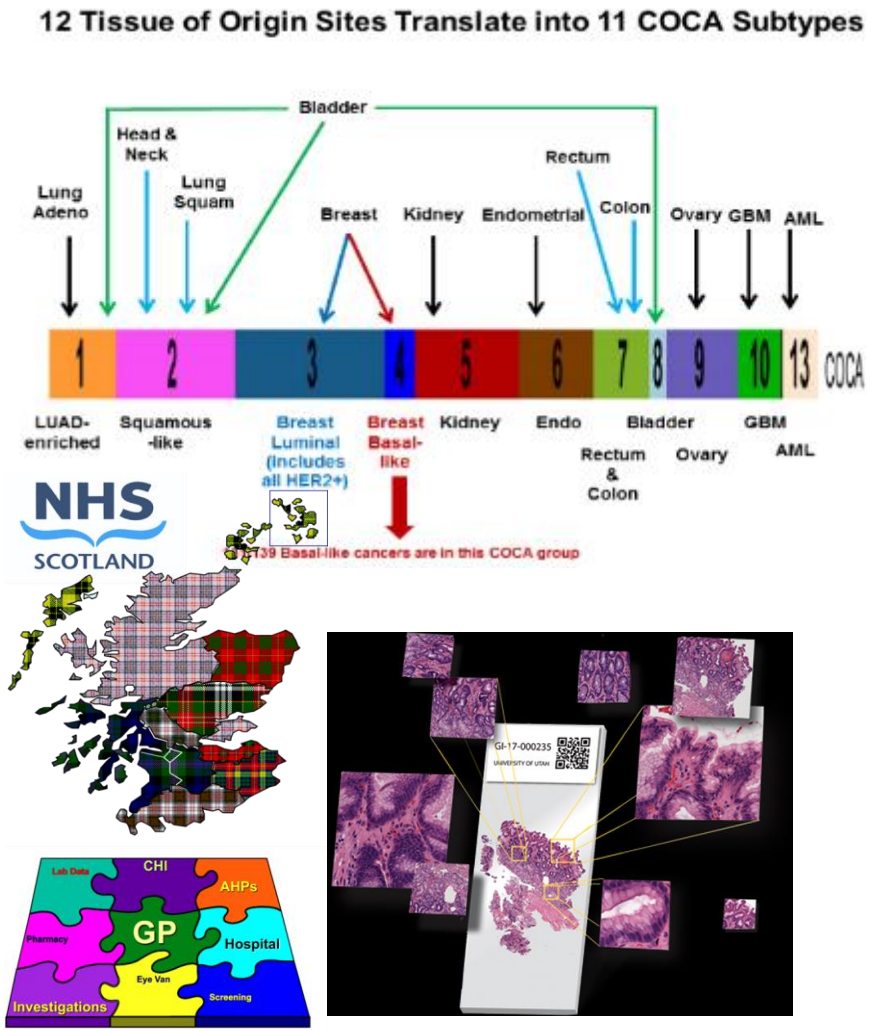
Perou et al. (2000) Nature

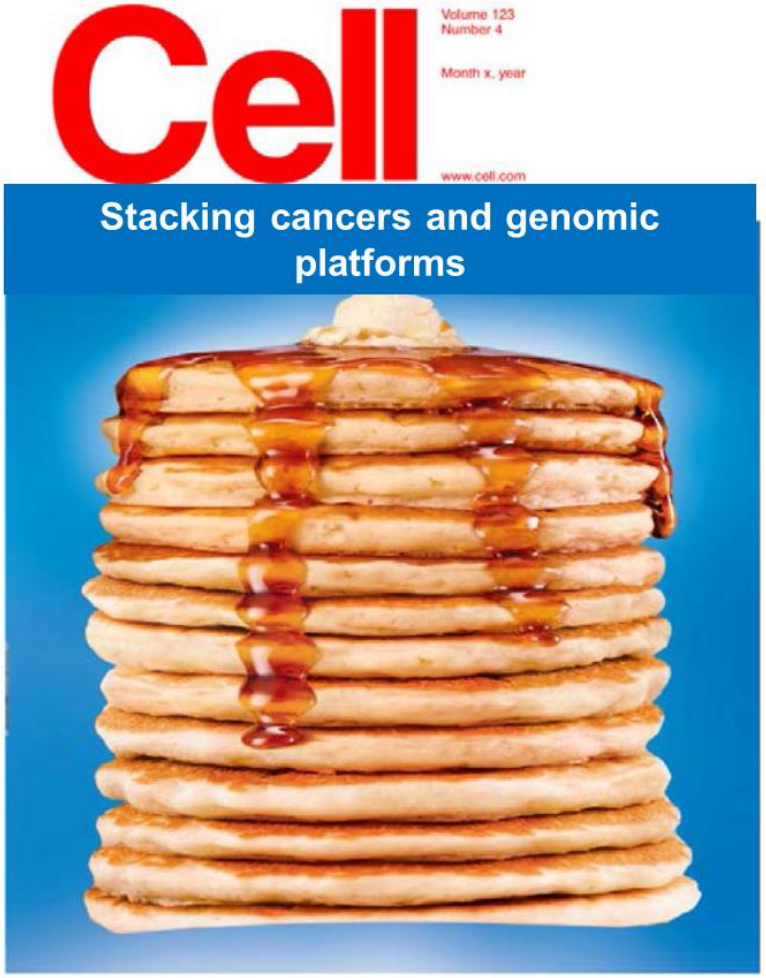


http://cancergenome.nih.gov/

C Curtis *et al*. *Nature* **000**, 1-7 (2012)
doi:10.1038/nature10983

Integrative Omics Analysis with Epidemiologic Data





TCGA Cell 158:929-944 (2014); https://www.synapse.org/#!Synapse:syn2487022

Rates of molecular subtypes of breast cancer over time in Scotland

- Determine possible aetiologic reasons for changes in ER+/- breast cancers over time through linkage with electronic databases including maternity (Ines Mesa-Eguiagaray)
- Determine temporal trends in mortality by ER status (Ines Mesa-Eguiagaray)
- Determine retrospectively the trends of contemporary profiled portraits of breast cancers using archival materials from the tissue repositories of Scotland

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