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Female breast cancer: who, how and why?

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Assessment of risk factors influencing trends in incidence of female breast carcinoma

- Aims of the study:
  - Identification and assessment of breast cancer risk factors
  - Exploration of mechanism of effect and potential confounding
  - Temporal and geographic patterns of breast cancer
  - Association of trends with risk factors
  - Role of risk factors in breast cancer incidence
  - Gap analysis and uncertainty
  - Recommendations based on findings

- **ALL** risk factors to be considered

Female breast cancer: who, how and why?

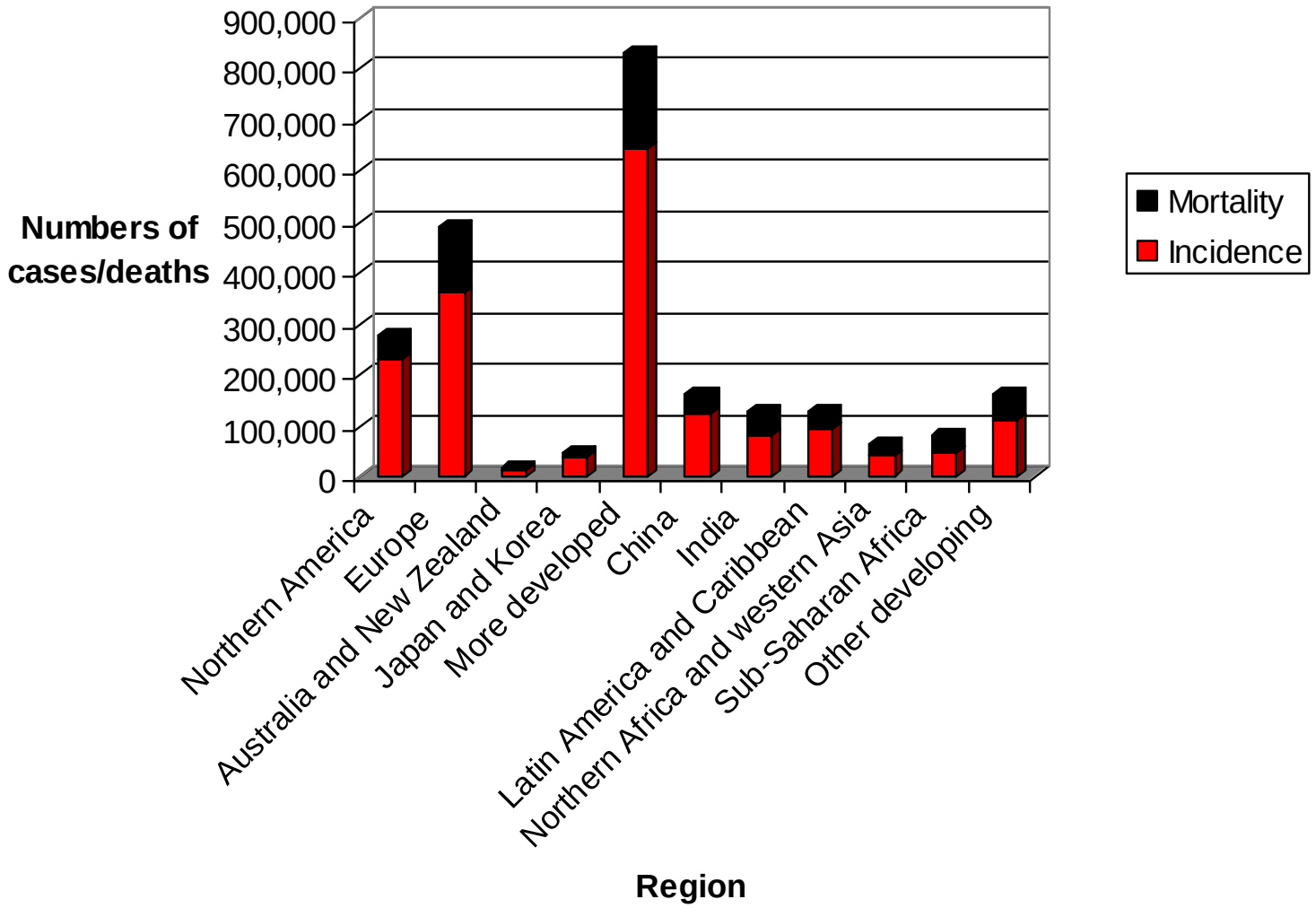
This presentation will include:

- Outline of recent work
  - Who?
  - How?
  - Why?
- Complexities of risk factor interactions
- Measure of burden – example of AF determination
- Next steps and further discussion

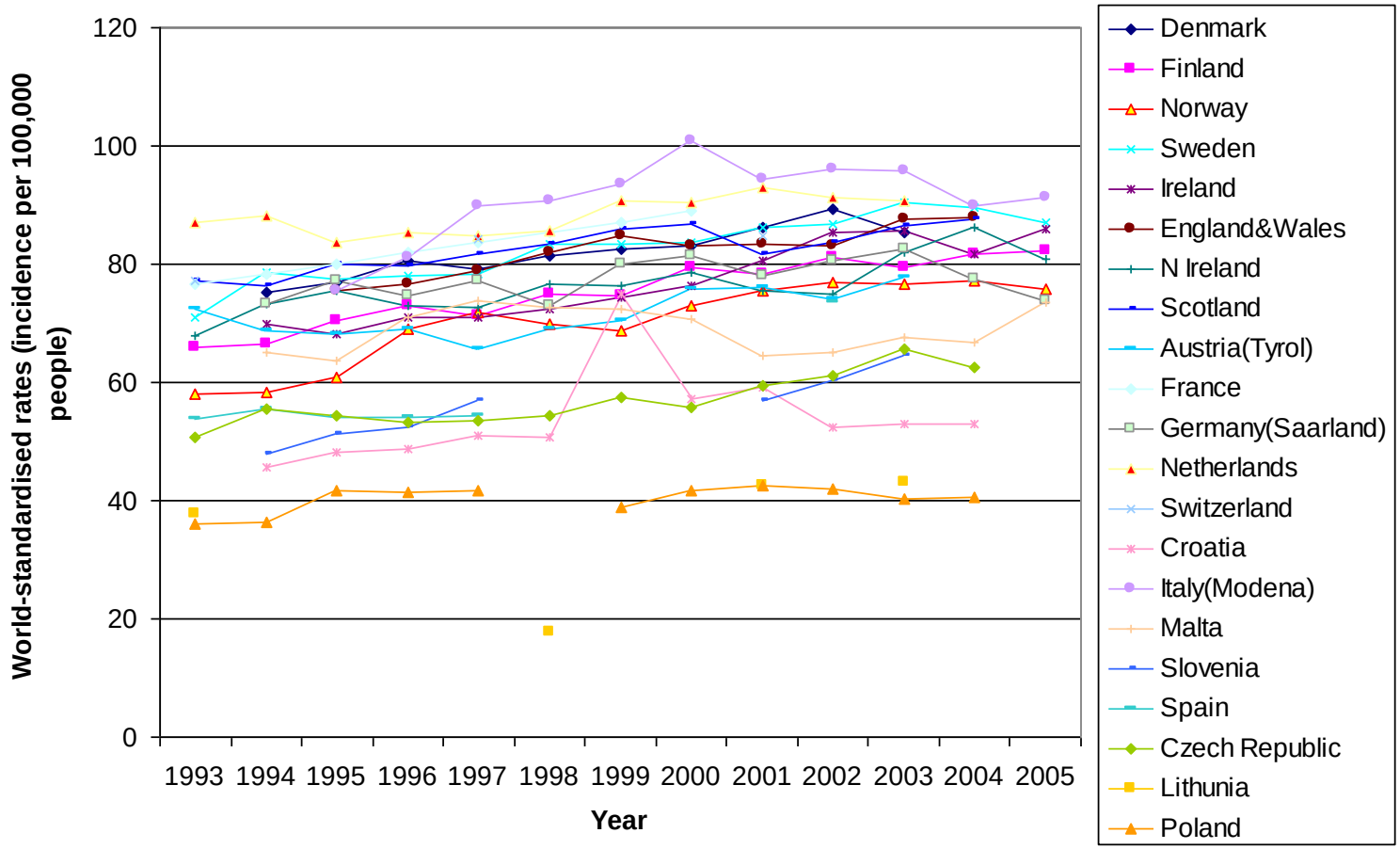
Who?

- Location
- Time trends
- Age

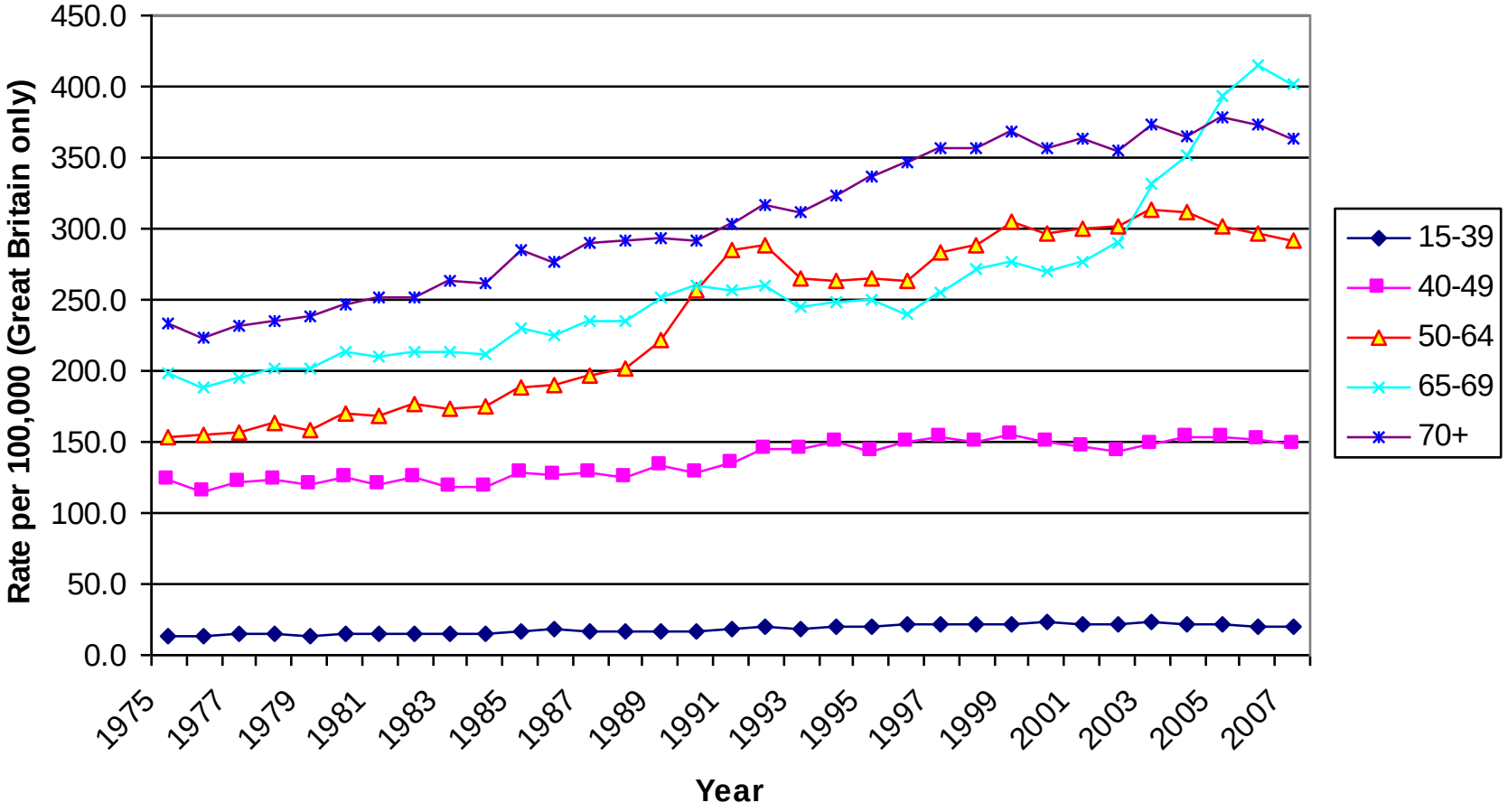
Female breast cancer incidence: Global trends, 2002



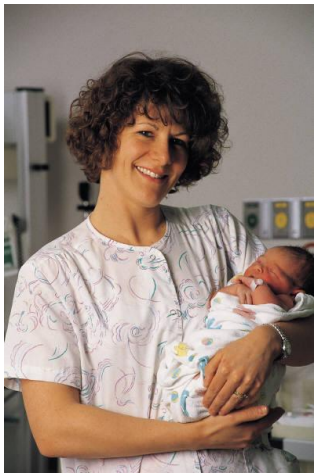
Female breast cancer incidence: European time trends



Female breast cancer incidence: age / time trends



How?



Female breast cancer risk factors: relative risk range 1.1-2.0

Risk Factor	High Risk	Low Risk
Age at menarche	Young age (<12 years)	Older age (>14 years)
Age at 1st birth	Late age (>30 years)	Young age (<20 years)
Parity	No children	Many children
Breast-feeding	None	>12 months
Age at menopause	Older age (>55 years)	Young age (<45 years)
Use of oral contraceptives	Current use	Never use or >10 years ago
Use of hormone replacement therapy	Combined >5 years	None or <5 yrs oestrogen-only
Alcohol drinking	Regular drinker	Non-drinker
Body mass index	Obese (post-menopause)	Normal (post-menopause)
Physical exercise	Low activity	Strenuous, regular
Low penetrance genes (e.g. FGFR2)	Yes	No
Environmental/occupational	Night shiftwork, flight personnel, dioxins/PAHs	Other occupations
Rural vs. urban	Urban	Rural
Socioeconomic status	High	Low
Ethnicity	Caucasian (<40 years) Black (≥40 years)	Asian
Religion	Jewish	Mormon, 7th Day Adventist

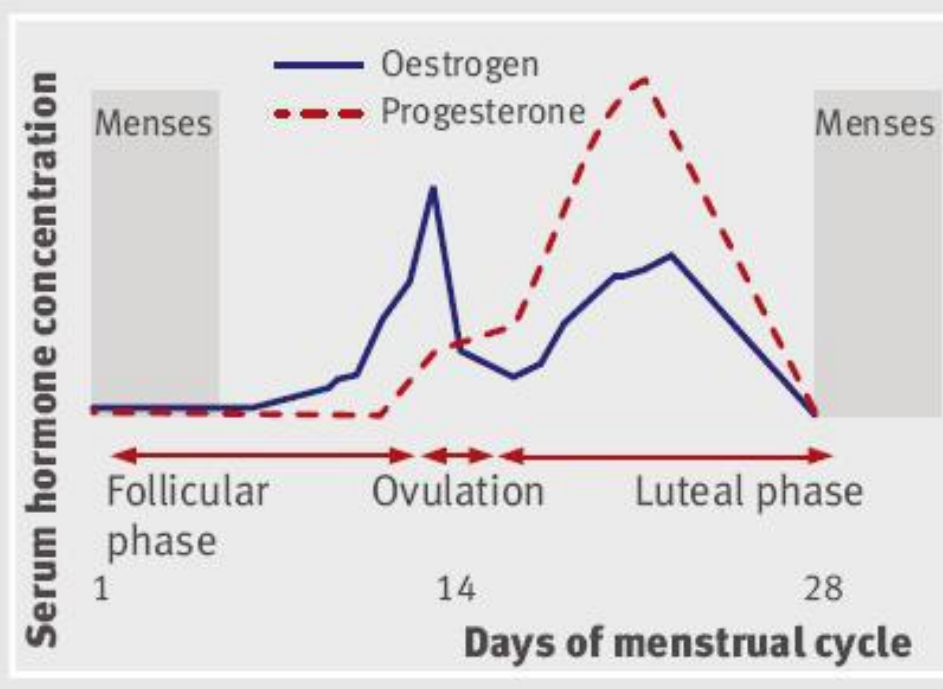
Female breast cancer risk factors: relative risk range 2.1-4.0

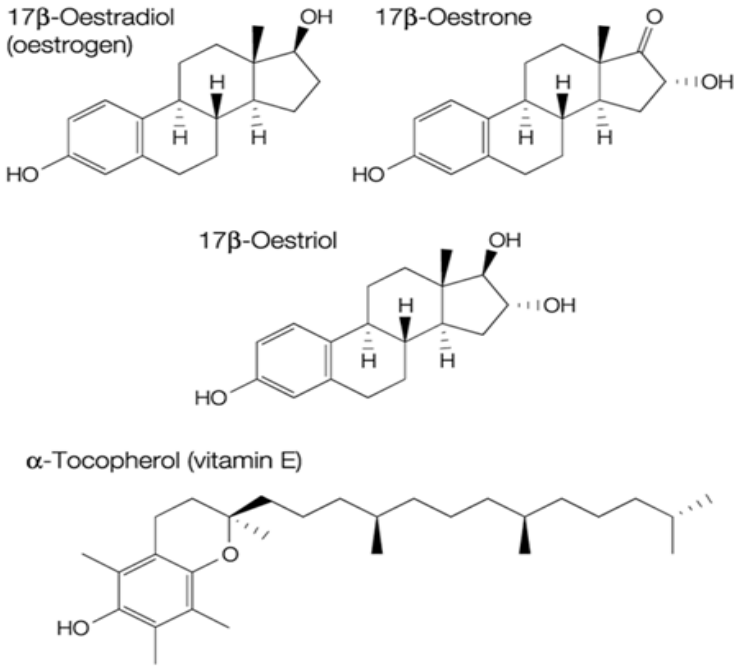
Risk Factor	High Risk	Low Risk
Mammographic density	>75% density	<25% density
Moderate penetrance genes (ATM, CHEK2, BRIP1, PALB2)	Yes	No
One 1st degree relative diagnosed (<50 years)	Yes	No
Biopsy-confirmed atypical hyperplasia	Yes	No
High dose radiation to chest	Yes	No
Ovariectomy (< 35 years)	No	Yes

Female breast cancer risk factors: relative risk range >4.0

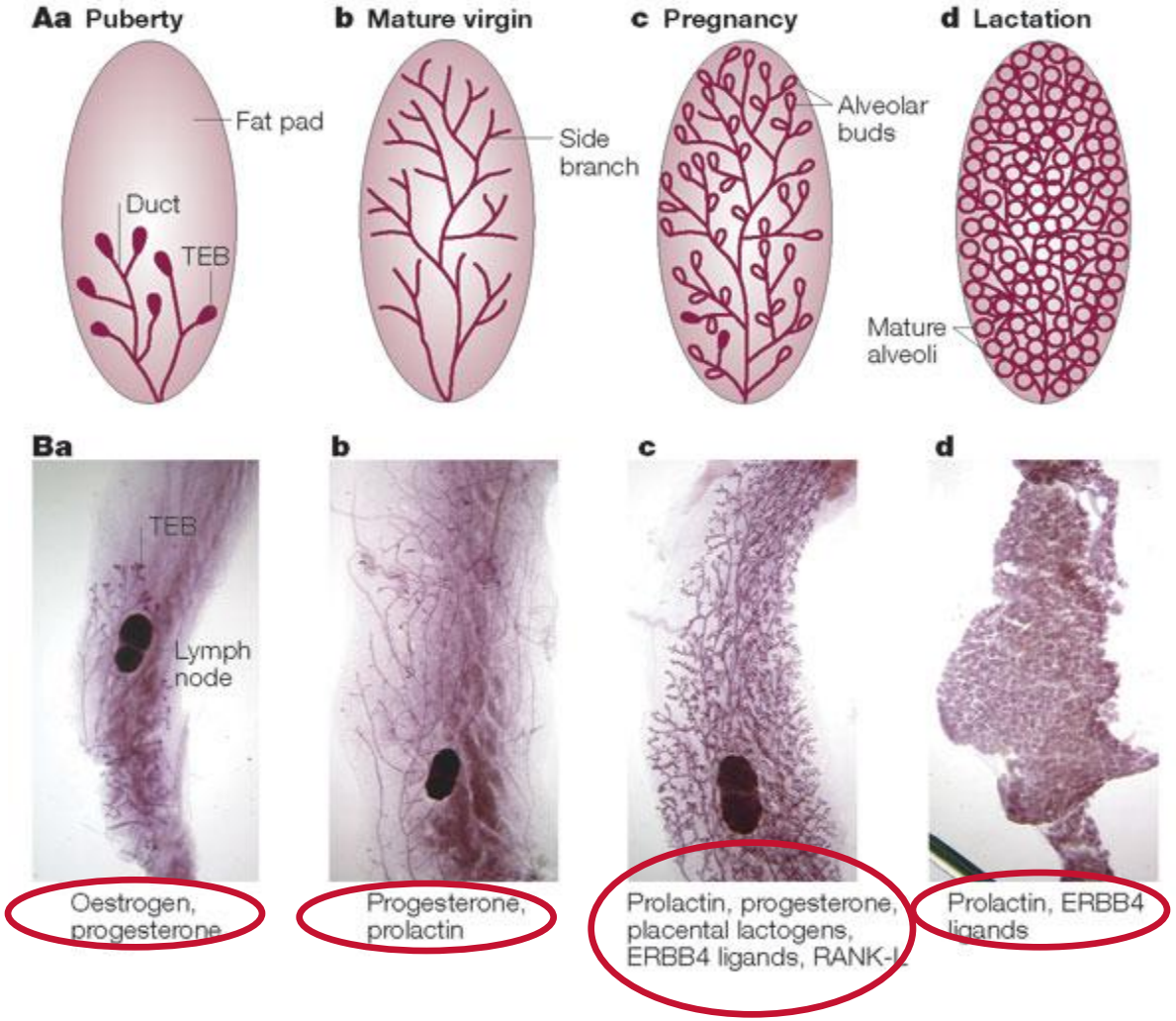
Risk Factor	High Risk	Low Risk
Age	≥50 years	<45 years
Country of birth	Europe & North America	Asia
BRCA mutation carrier / high penetrance genes	Yes	No
Two 1st degree relatives diagnosed (<50 years)	Yes	No
History of cancer in one breast	Yes	No

Why?


Oestrogen
Progesterone
Menses
Menses
Serum hormone concentration
Follicular phase
Ovulation
Luteal phase
1
14
28
Days of menstrual cycle


17β-Oestradiol (oestrogen)
17β-Oestrone
17β-Oestriol
α-Tocopherol (vitamin E)
OH
HO
O
H

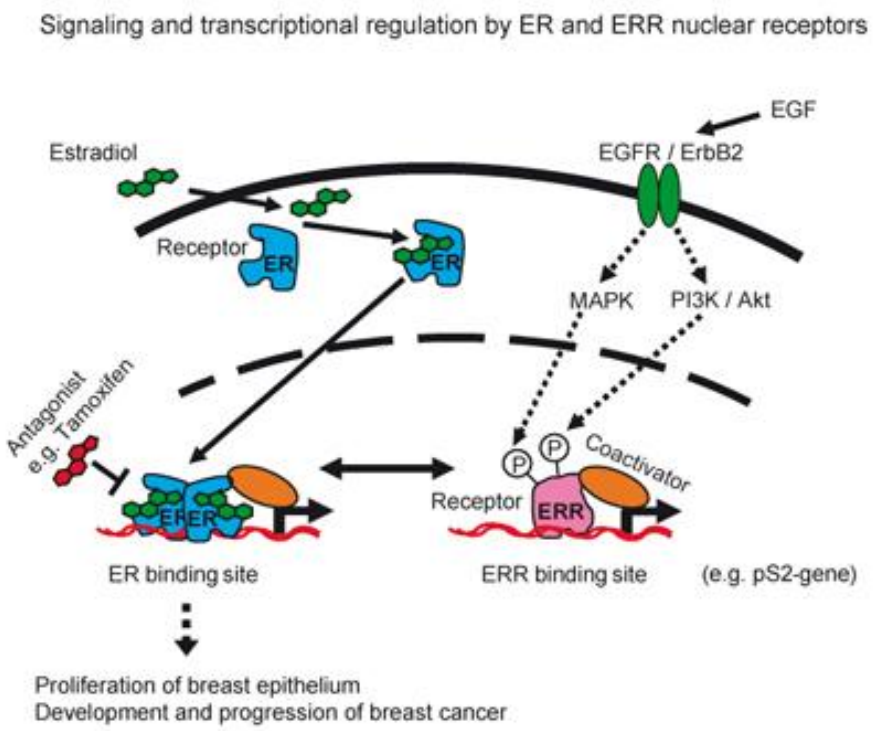
Hormonally-mediated development of mammary tissue



Breast cancer and endogenous hormones

Mechanisms:

- approximately 75% breast cancers are ER+ (oestrogen receptor positive)
- ER+ are generally postmenopausal – lifetime exposure to oestrogen
- ER- = premenopausal, familial, aggressive
- lifetime exposure to oestrogen – risk factors generally associated with increased oestrogen levels

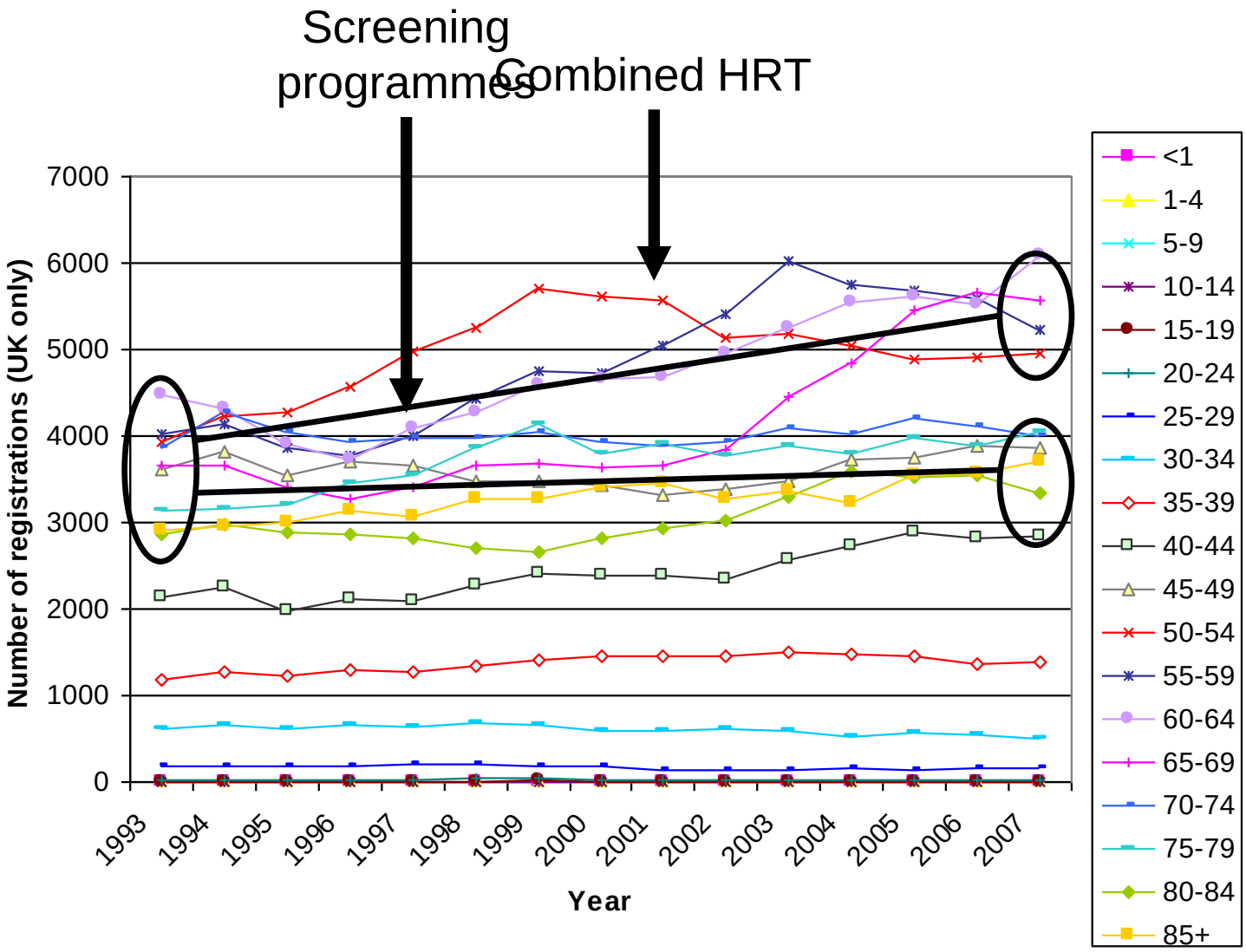


Who, How & Why?

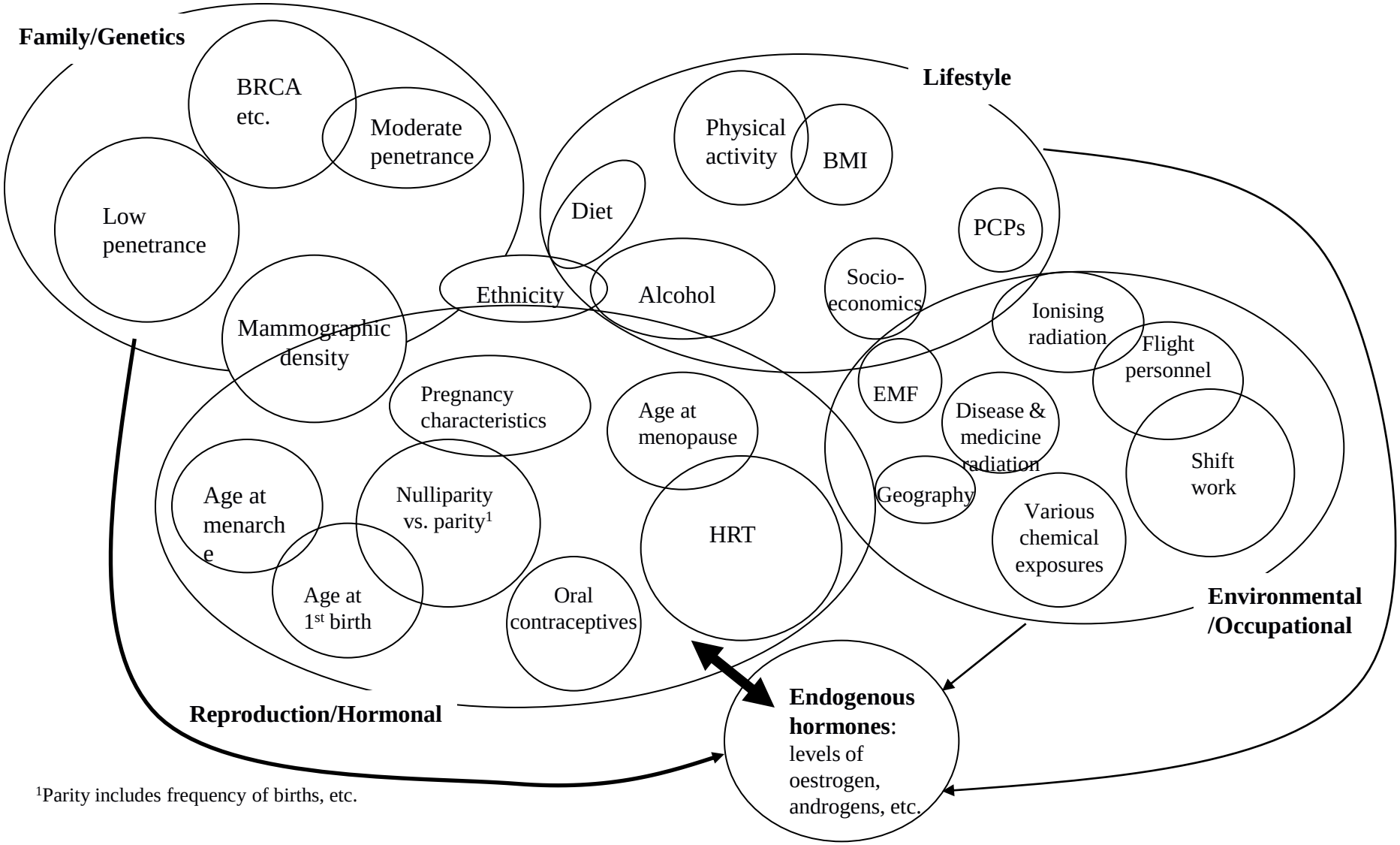
Incidence trends and risk factors

- Within trend: age and location-specific over time:
  - screening programmes
  - exogenous hormone use
  - changing reproductive patterns
- Between trends: different ages/locations over time
  - lifestyle factors (diet, exercise, alcohol)
  - genetics
  - reproductive patterns
  - environmental exposures (ionising radiation, dioxins)

Varying impact of causal agents over time



Interaction of risk factors: complexities of exposure



[1]Parity includes frequency of births, etc.

Approaches for combining estimates of burden

- **Define a '*sufficient cause*' as:**
  - A set of minimal conditions that produce disease
  - Consisting of a number of *component* risk factors in a causal pathway
  - Each component factor is necessary for the causal mechanism to operate.
  - Includes cancer *initiators* and *promoters* acting early and late
- **For each set:**
  - Choose a dominant exposure
  - Partition exposed numbers between overlapping exposures
  - Assume overlapping exposures are independent and joint effects are multiplicative:

$$AF_{set} = 1 - \Pi_k(1-AF_k) \text{ for the k exposures in the set}$$

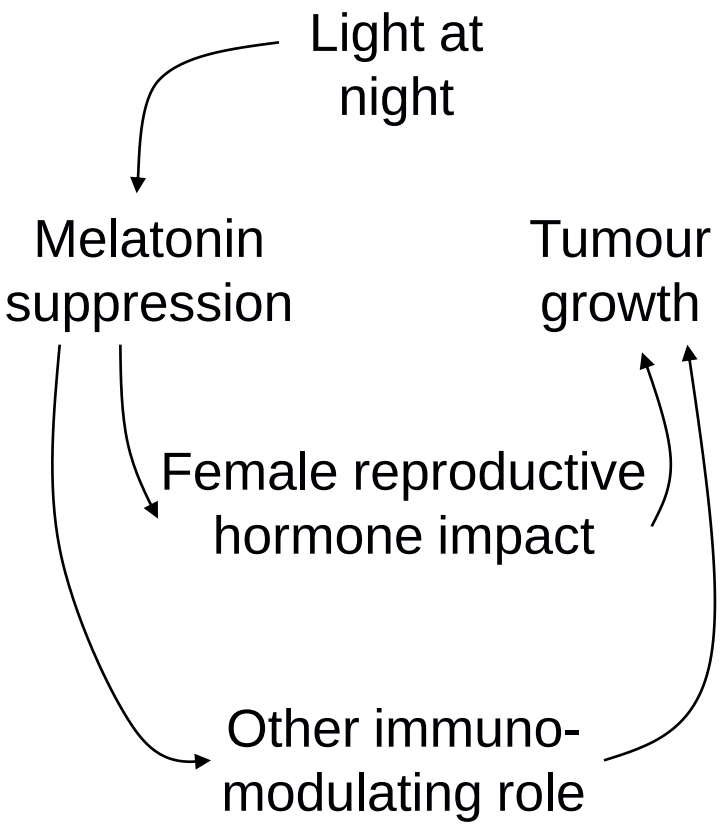
One methodological example: measure of occupational burden

- Measure of burden used is the AF - proportion of cases attributable to exposure; needs
  - risk of disease associated with the exposure of concern (e.g. relative risk (RR))
  - proportion exposed in the population
- RR from published literature: meta-analyses, pooled studies, narrative reviews where available
- Risk estimates obtained for overall 'higher' level of exposure and lower/background exposure
- To take into account latency (length of time before disease risk increases) we defined the risk exposure period (REP) for solid tumours: 10-50 years; 1956-95
- Proportion exposed over the REP is:

  number ever exposed/number ever worked
- Estimated using national data sources (CAREX, LFS, CoE)
- Adjusted for turnover, change in numbers employed over REP

Example of burden measurement:

Shift-work



Reference	Results (95% CI; nos.)
Megdal *et al*, (2005)	**Meta-RR=1.51 (1.36-1.68)**
Erren *et al*, (2008)	FES RR=1.4 (1.3-1.6)
Tynes *et al*, (1996)	SIR=1.50 (1.1-2.0; 50)
Schernhammer *et al*, (2001)	RR=1.36 (1.04-1.78; 58)
Kliukiene *et al*, (2003)	SIR=1.30 (1.05-1.58; 99)
Schernhammer *et al*, (2006)	RR=1.79 (1.06-3.01; 15)
Schwartzbaum *et al*, (2007)	RR=0.94 (0.74-1.18; 70)
Tynes *et al*, (1996)	OR=4.3 (0.7-26.0; 12)
Lie *et al*, (2006)	OR=2.21 (1.10-4.45; 24)
Davis *et al*, (2001)	OR=1.6 (1.0-2.5; 54)
Hansen (2001)	OR=1.5 (1.3-1.7; 434)
O'Leary *et al*, (2006)	OR=1.04 (0.79-1.38; 174)

Numbers exposed: Great Britain, 2002

Type of shift pattern	Numbers employed	95% CI (+/- change)
All women usually/sometimes doing shift work	1,803,947	1589
Three-shift working (‘slow’ rotation through 3-shift system morning-afternoon-night)*	221,603	557
Continental shifts (rapid rotation through 3-shift system morning-afternoon-night)*	18,209	160
Two-shift system early/late-double day (2-shift system – day only)	562,849	888
Sometimes nights, sometimes day (2-shift system rotating between day and night)*	169,483	487
Split shifts (one shift split across day: night-work possible)	90,381	356
Morning shifts (day only)	47,543	258
Evening/twilight shifts (until midnight)	121,168	412
Night shifts (6 pm - 6 am, includes after midnight)*	154,400	465
Weekend shifts (6am – 6 pm only – day)	24,639	186
Other types of shift work (if different from above)	390,872	740

Numbers exposed: Great Britain, 2002

Approximately 31% of shift-work involves working at night

Female night-workers

= 31% of ~2 million

= ~400,000

Attributable fraction: breast cancer and shift work, GB, 2002

Attributable Fraction (%)		Attributable Deaths		Attributable Registrations	
AF	95% CI	AN	95% CI	AR	95% CI
4.53	3.23, 5.94	552	393, 724	1957	1395, 2568

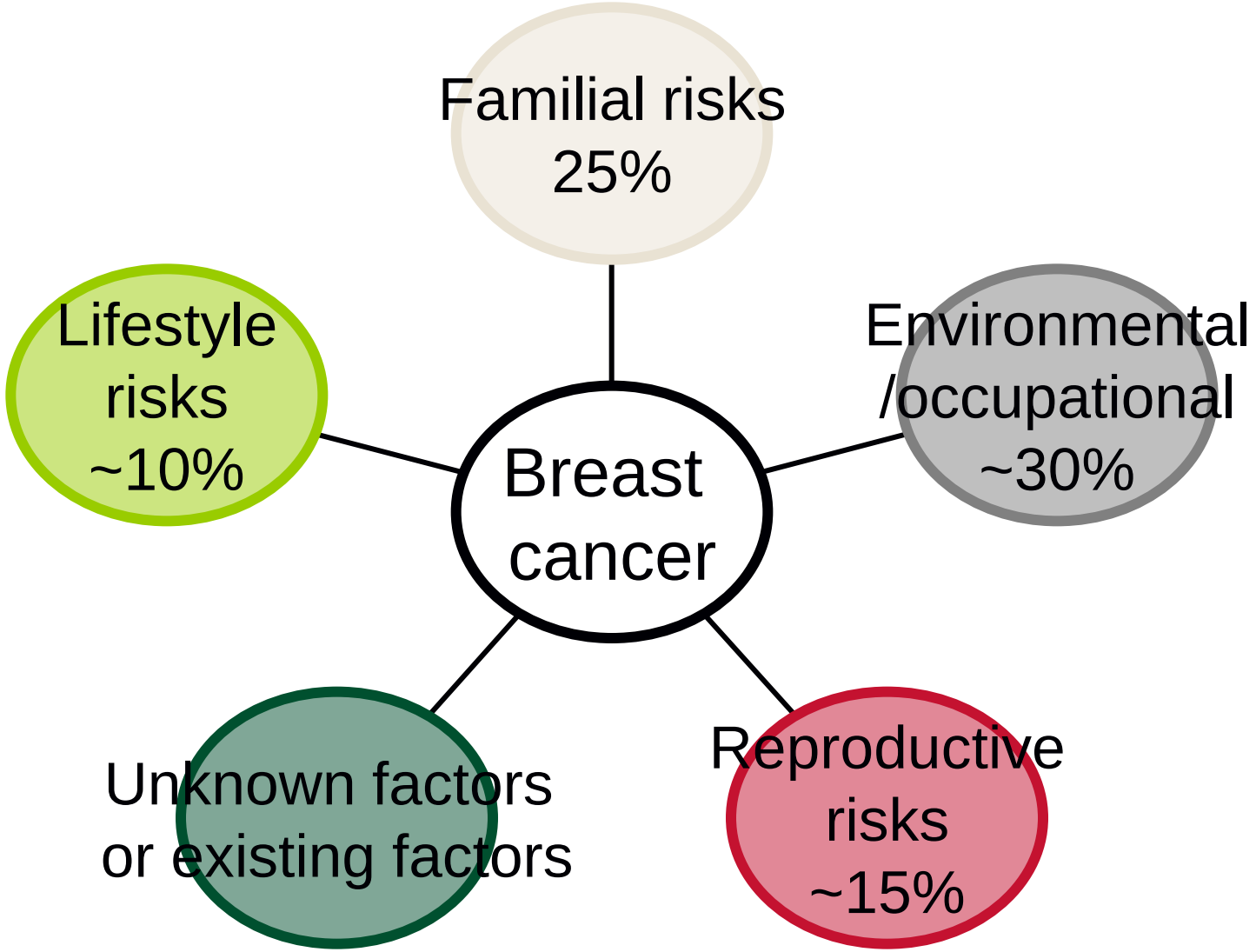
All cancers for women from all IARC 1 and 2a carcinogens

AF = 2.3% (95%CI 1.7, 3.2)

1657 attributable deaths (33% breast cancer)

3616 attributable registrations (54% breast cancer)

Estimated attributable fraction across risk factors



Future research needs

- Development of robust methodologies to consider joint exposures/confounding
- Where data allow, estimate attributable risk for different exposed populations in different locations
- Assess the affect of uncertainty and bias on the estimates of burden
- Expand to other cancer sites