Childhood Leukaemia, Intrauterine Growth and Diet

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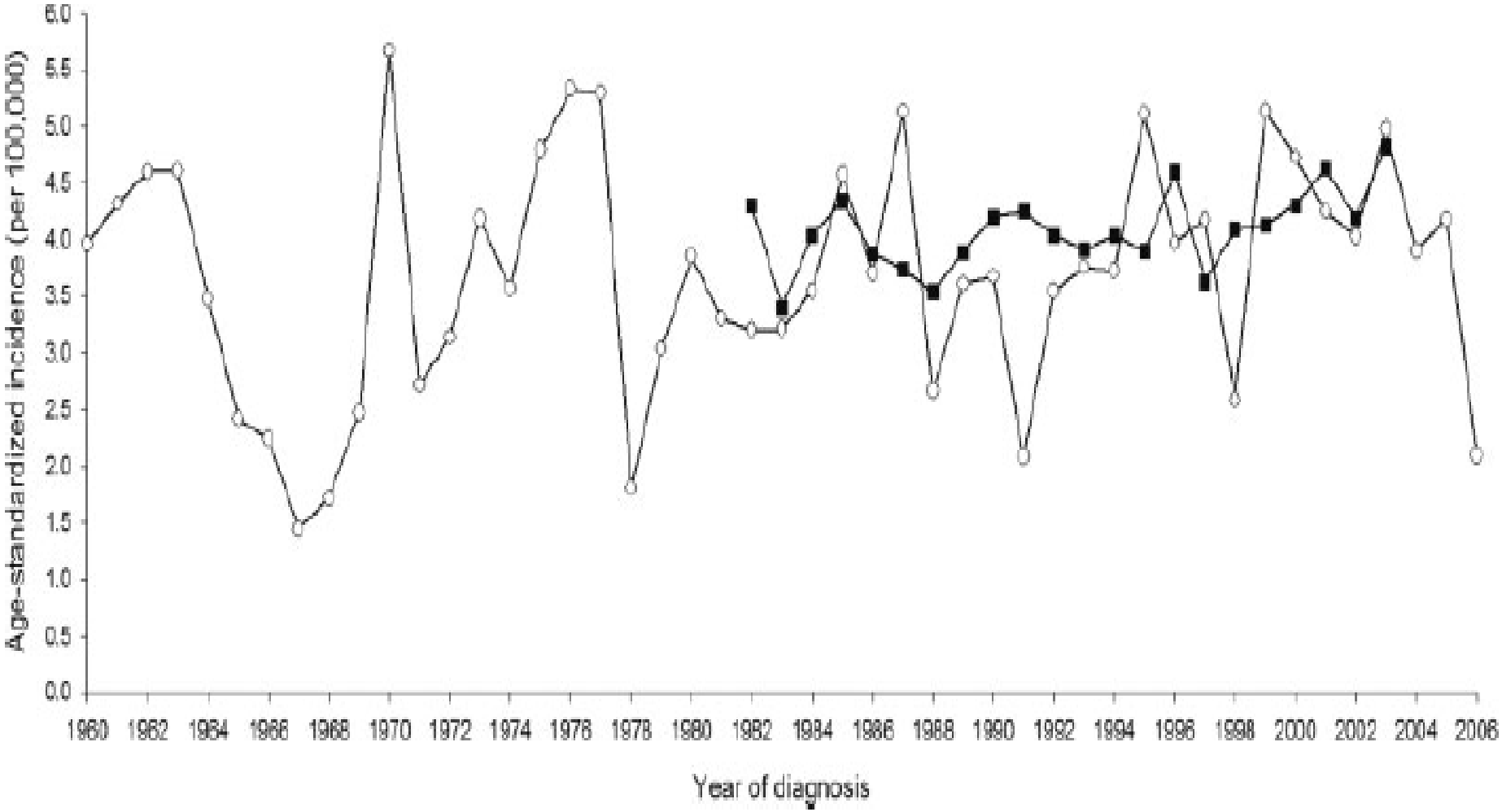
Age-standardized incidence of ALL in Western Australia and Australia. (0-14)



Birth weight and risk of CL

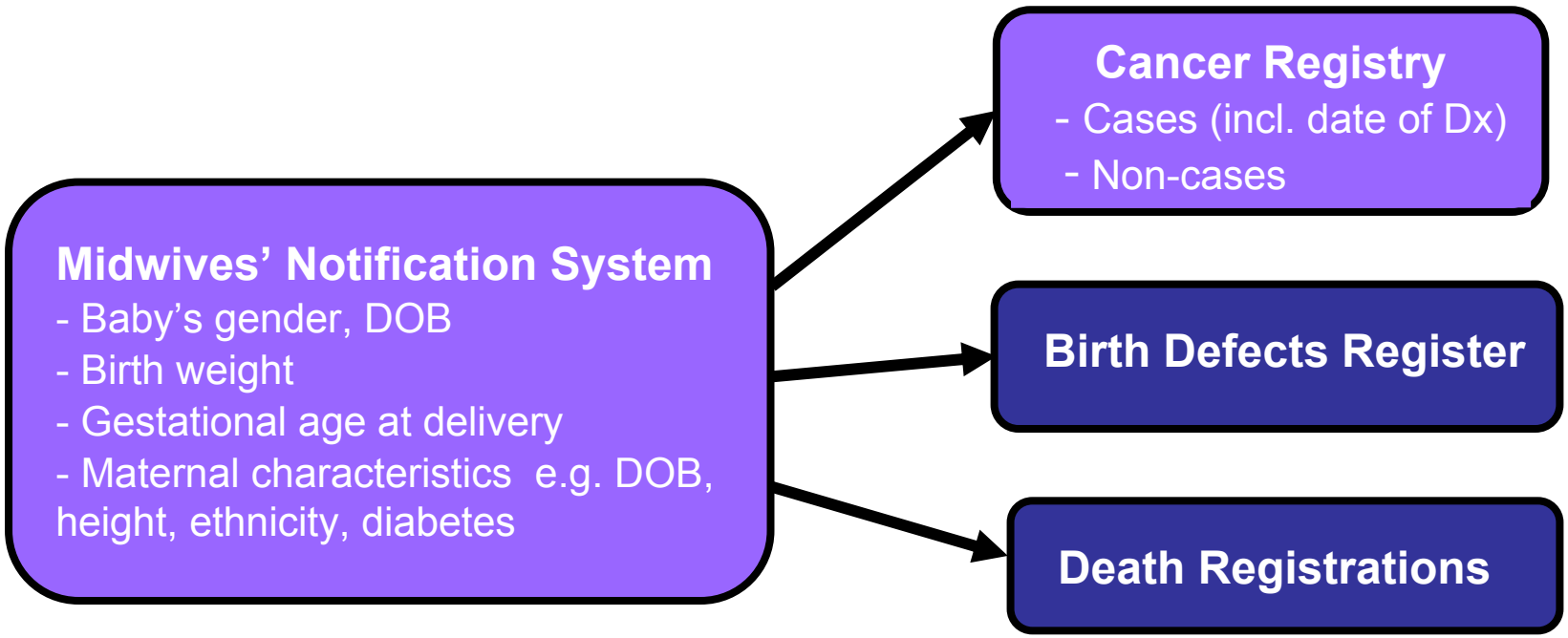
- Results of studies of birth weight
  - ALL mostly positive associations
  - AML less consistent
- Differences in study design, case definition, age at diagnosis, source of data etc.
- Different cut-offs for ‘high birth weight’ (eg 3500g, 3800g, 4000g)
- Not all studies have taken account of gestational age

Appropriate birthweight

- OBW = expected birth weight estimated from gestational age, gender, birth order, and maternal height
- Caucasian, singletons, no SB, NND, BD
- No maternal smoking, vascular disease, diabetes, TORCH infections
- POBW measure of appropriateness of IU growth =Observed BWT / Optimal BWT (OBW)

Blair et al. 'Optimal fetal growth for the Caucasian singleton & assessment of appropriateness of fetal growth: an analysis of a total population perinatal database'. *BMC Pediatrics* 2005;5:13

Data - WA Data Linkage System



POBW & risk of CL

	n cases	HR*	95% CI
AML	36	0.94	0.67, 1.31
ALL	243	1.21	1.07, 1.36
ALL: 0-4yrs	144	1.25	1.07, 1.47
ALL: 5-14 yrs	99	1.14	0.94, 1.38

*per 1SD increase in POBW

Milne, E et al. (2007). Fetal Growth and Acute Childhood Leukemia: Looking Beyond Birth Weight. *American Journal of Epidemiology*, 166, 151-159.

POBW and risk of ALL by birthweight

	n cases	HR*	95% CI
ALL (0-4yrs)	144	1.25	1.07, 1.47
BWT <4000g	127	1.38	1.13, 1.68
BWT <3800g	110	1.40	1.12, 1.74
BWT <3500g	72	1.43	1.09, 1.88

*per 1SD increase in POBW

Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children

1. Folate effects
    1. Maternal folate supplementation (including dose) during pregnancy
    2. Maternal dietary folate, B6, B12, fruit & veg, protein in pregnancy
    3. MTHFR polymorphisms in mother and child
    4. Interactions and within sub-types
2. Environmental, occupational, other diet.
    1. Multiple risk factor analyses.
    2. Candidate genes (c-c and trios).
    3. GXE interactions.
    4. GWAS.
    5. No EMF measurements

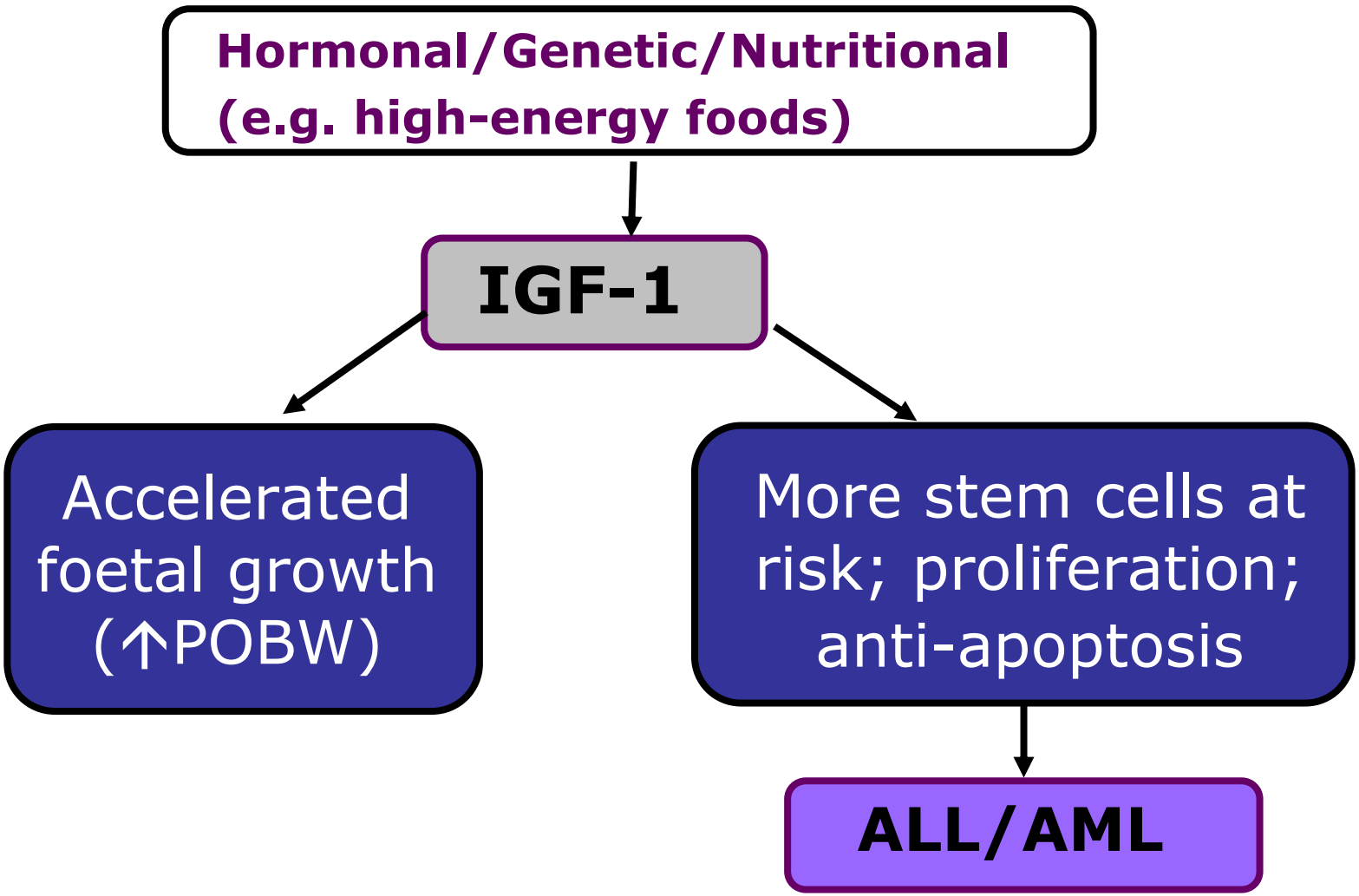
AUS-ALL: analysis of fetal growth

- 338 ALL cases and 803 controls born 1988-2006
- Multiples or children with congenital anomalies excluded
- Mother report: infant birth weight, GA, sex, birth order, maternal height
- Logistic regression: POBW z-scores, all ORs adjusted for gender, age, State, family income

Suggested growth factor pathway

- IGF-1 in cord blood associated with foetal growth: BWT, birth length, lean mass, fat mass, bone mass, & placental weight
- IGF-1 plays a role in normal haematopoiesis
- IGF-1 implicated in childhood ALL…
  - Receptors present on leukaemic lymphoblasts
  - Proliferative stress on pre-leukaemic cells in marrow and protects against apoptosis
  - Stimulates growth of leukaemic cells in vitro

Potential pathway



Diet and risk of cancer

- Long history of study of diet in relation to cancer risk
- WCRF and AICR report (2007): Food, Nutrition, Physical Activity, and the Prevention of Cancer
- Studies of diet and risk of CL have generally been inconclusive
- Need to specify who and when

Studies of diet and risk of ALL

Author	Who	Food	OR (95% CI)
Shu 1988	Mother	Cod liver oil (vits A and D), use for >1 yr	0.4 (0.2-0.9)
Sarasua & Savitz, 1994	Mother	Ham, bacon, sausage (HBS)	1.5 (0.7-3.0)
		H, B, S (no vit supps)	2.9 (1.1-7.9)
	Child	Hamburgers (1+/week)	2.0 (0.9-4.6)
		Lunch meats (no vit supps)	2.3 (0.7-7.5)
		H, B, S (no vit supps)	2.9 (0.9-8.9)
Ross 1996	Mother	Foods containing DNA-t-2 inhibitors	No association (infants)

Studies of diet and risk of ALL

Author	Who	Food	OR (95% CI)
Jensen 2004	Mother	Fruits (esp. cantaloupe)	0.7 (0.5-1.0)
		Vegetables	0.5 (0.3-0.8)
		Protein sources	0.4 (0.2-0.9)
		Cured meats	0.7 (0.4-1.1)
		Fats, sweets, snacks	1.2 (0.7-2.1)
Petridou 2005	Mother	Fruits	0.7 (0.6-0.9)
		Vegetables	0.8 (0.6-0.9)
		Fish & seafood	0.7 (0.6-0.9)
		Meat & meat products	1.2 (1.0-1.6)
		Sugars & syrups	1.3 (1.0-1.7)
		Total energy intake/day	1.3 (1.0-1.7)

Studies of diet and risk of AML

Author	Who	Food	OR (95% CI)
Shu 1988	Mother	Cod liver oil (vits A and D), use for >1 yr	0.3 (0.1-1.0)
Ross 1996	Mother	Foods containing DNA-t-2 inhibitors - Medium intake - High intake	(Infants) 9.8 (1.1-84.8) 10.2 (1.1-96.4)
Spector 2005	Mother	Foods containing DNA-t-2 inhibitors	(Infants) Weak +ve assoc in MLL+

Studies of diet and risk of ALL/AML

Author	Who	Food	OR (95% CI)
Peters 1994	Child	Hot dogs (12+/month)	9.5 (1.6-57.6)
Kwan 2004	Child <2yrs	Oranges/bananas Orange juice Vegetables Vitamins Hot dogs/lunch meat Beef/hamburger	0.5 (0.3-0.9) 0.5 (0.3-0.9) 0.6 (0.3-1.0) 0.9 (0.6-1.3) 1.6 (0.7-3.6) 1.6 (0.8-3.1)
Spector 2005	Mother	Fruit and vegetables	Modest inverse assoc with infant ALL/AML

Diet and CL: summary

Limited evidence

Foods that *may* increase risk:

- Processed/cured meats
- Those containing DNA t2 inhibitors
- High energy foods

- Foods that *may* reduce risk:
  - Fruit and vegetables (flavonoids, carotenoids, folate…)

Folate supplements

Study	Where	n cases	OR
Thompson 2001	W. Aust	83	0.4 (0.2-0.7)
Dockerty 2007	NZ	97	1.1 (0.5-2.7)

Multi-vitamins

Study	Where	n cases	OR
Wen, 2002	US	1842	0.7 (0.5-1.0)
Shaw, 2004	Quebec	789	1.0 (0.8-1.2)
Ross, 2005*[DS]	US	97	0.5 (0.3-1.9)
Schüz, 2007	Germany	650	0.8 (0.7-1.0)
Dockerty, 2007	NZ	97	0.8 (0.2-3.1)
Ross, 2005*[DS]	US	61[AML]	0.9 (0.5-1.8)
Schüz, 2007	Germany	105[AML]	1.1 (0.7-1.7)

Fits with 2-hit model

- Inadequate folate may cause 1st hit *in utero* through aberrant methylation or synthesis of DNA
- Inadequate folate may reduce foetus' ability to repair 1st hit caused by something else
- Other possibilities
- Some support for role of folate from genetic studies

Studies of *MTHFR* SNPs (ALL)

- 12 original studies (2001-2008)
  - 6/12 studies suggested a protective effect of *C677T*
  - 3/10 studies suggested a protective effect of *A1298C*
- 2 meta-analyses in 2006
  - contradictory findings, probably due to differences in inclusion criteria
  - Pereira et al (2006) (more inclusive):
    - 0.87 (0.72-1.06) for *C677T* variant
    - 0.80 (0.56-1.16) for *A1298C* variant
- SNP x Folate interactions: mixed results

Summary and conclusions

- Accelerated foetal growth seems important
- Roles of folate + folate-related genes, and diet overall, not clear, but promising
- Suggested pathways involving IGF-1 (and/or other growth factors) could include other dietary factors