Preconception exposures to potential germ-cell mutagens

Gerald Draper

Childhood Cancer Research Group
57 Woodstock Road,
Oxford OX2 6HJ

Numbers of Seascale leukaemia cases and their controls by paternal employment and total dose of external ionising radiation

	Cases	Controls	
		Local (Seascale)	Area
Not employed at Sellafield	0	4	17
No dose record	0	0	1
1-49 mSv	0	8	6
50-99 mSv	1	7	3
≥100 mSv	3	1	0
Total	4	20	27

Summary of Gardner's Seascale results

- 3 Seascale cases had total preconception doses of 102, 162, 188 mSv; 1 had 97 mSv. For each of these 4 cases, the dose was higher than for any of the multiple matched controls
- "The association can explain statistically the observed geographical excess"

Cancer in the offspring of radiation workers

Draper et al (1997) in BMJ **315**:1181-1188

- ~36,000 case children and ~38,000 matched controls
- Parental information obtained from birth registers
- Probabilistic record linkage used to match parents to NRRW workers (~117,000 men and ~11,600 women)
- 161 fathers and 18 mothers matched

Results for offspring of male workers

- Increased risk of Leukaemia and non-Hodgkin Lymphoma (LNHL):
  RR 1.77 (95%CI 1.05-3.03)
- No dose-response relation for any of the time periods studied
- Results did not support Gardner hypothesis
- Paternal preconception irradiation not associated with other childhood cancers
- Excess LNHL either due to chance or to some characteristic other than exposure to radiation

Results from the Record Linkage Study

Numbers of LNHL cases and controls by paternal preconception radiation exposure, excluding 'Gardner cases'

Variable	Dose group (mSv)	Cases (13,621)	Controls (15,995)
Total preconception dose	< 0.1	5	0
	0.1 –	30	32
	50 –	3	2
	≥ 100	2	4
Six month preconception dose	< 0.1	19	17
	0.1 –	18	16
	5 –	0	1
	≥ 10	3	4

Results for the Record Linkage Study (Sorahan et al., 2003)

	Cases	Controls	Relative risk
Left employment before conception:			
No	13,637	16,008	1.00
Yes	12	15	1.04
Employment on date of conception:			
No	13,612	15,994	1.00
Yes	37	29	2.34

Nuclear Industry Family Study: LNHL under 25 years in children of male nuclear workers (Roman et al., 1999)

	LNHL (all cases)		Excluding Cumbria before 1986	
	No. of cases	RR	No. of cases	RR
Cumulative dose (mSv)				
<50	10	1.7	9	2.3
50-	1	1.2	0	0.0
≥100	3	3.9	1	4.3
Estimated cumulative dose in six months before conception				
<5	11	1.7	9	2.2
5-	0	0.0	0	0.0
≥10	3	5.4	1	7.4

Case-control study in Germany: (Meinert et al., 1999)

Paternal occupation exposure	Leukaemia (1184)		Controls (2588)		Odds ratio
	n	%	n	%	
In year before pregnancy	50	4.4	99	3.9	1.20
Involving exposure	16	1.4	22	0.9	1.80

Congenital malformations in 82 offspring of 1345 Danish cancer survivors (Boice et al., 2003)

Radiation exposure potential	Observed	Expected	O/E
None	59	50.3	1.17
Low	12	7.2	1.67
Low – medium	5	2.2	2.31
Medium	3	3.1	0.96
Medium – high	10	9.5	1.06
High	5	4.8	1.05

Workshop on assessing human germ cell mutagenesis (Wyrobek et al., 2007)

- Eight decades of research in animal systems have identified numerous germ cell mutagens. No human germ cell mutagen has been identified to date.
- "… the inability to identify human germ cell mutagens is due to technological limitations … rather than biological differences between animal and human susceptibility."

Summary

- Germ cell mutation as a possible cause of the Sellafield/Seascale excess of childhood leukaemia pre-dated, but was given credibility by, Gardner's results
- Good epidemiology – but now not believed
- Other explanations:
  - Chance
  - Bias
  - Confounding
  - Population mixing – infectious agent(s)