Childhood Leukemia – Risk factors and the need for an interdisciplinary research agenda

G Ziegelberger, A Dehos, B Grosche, S Hornhardt, T Jung, W Weiss (wweiss@bfs.de)

„Radiation Protection and Health“
Federal Office for Radiation Protection
Germany
Background

1. KiKK-Study\textsuperscript{1}: elevated leukaemia risk amongst children below the age of 5 in the vicinity of German nuclear power stations
2. Repeated findings on elevated leukaemia risk amongst children exposed to 50Hz electromagnetic fields exceeding 0.3-0.4 µT
3. No plausible explanations
Contents

1. State of knowledge
2. Risk factors
3. The way forward
Incidence rate of childhood cancer in Germany:

0.2% (1800 children per year, age up to 15 yrs)

5 year survival rate: 90%

1 Krebs in Deutschland 2005/2006, Häufigkeiten und Trends, RKI 2010
The time changes of patchiness of the SIRs

SIR leukemias 1984 - 1994

SIR leukemias 1990 - 1999
The key question:

CAUSATION
1. State of knowledge
2. Risk factors
3. The way forward
Risk Factors for Childhood Leukemia
Conclusions of the ICNIRP/WHO/BfS Workshop
Berlin, May 2008

Potential Causes of Childhood Leukemia

- Genetic - yes
- Ionizing Radiation - yes
  - Nuclear power plants?
  - Radon Gas?
  - X-rays?
- Non-ionizing Radiation - hmm
  - ELF-EMF - nice association
  - RF-EMF?
- Chemicals - nothing jumps out
  - Air pollution
  - Smoking
  - Pesticides/herbicides
  - POPs
  - Maternal solvent - maybe
- Socioeconomic factors - ???
- Birth weight - no, it’s growth
  - Maternal diet
    - Topoisomerase inhibitors
  - Nutrition
  - Growth factors
  - Folate
- Immune Status
  - Breastfeeding
  - Childcare
  - Etc.

summarized by C. Portier

Leukemia in twins
M. Greaves et al. 2003

Chromosomal translocations
- genetic
dysregulation

TEL-AML1 (t12;21)
Risk Factors for Childhood Leukemia
Conclusions of the ICNIRP/WHO/BfS Workshop
Berlin, May 2008

Potential Causes of Childhood Leukemia

- Genetic - yes
- Ionizing Radiation - yes
  - Nuclear power plants?
  - Radon Gas?
  - X-rays?
- Non-ionizing Radiation - hmm
  - ELF-EMF - nice association
  - RF-EMF?
- Chemicals - nothing jumps out
  - Air pollution
  - Smoking
  - Pesticides/herbicides
  - POPs
  - Maternal solvent - maybe

- Socioeconomic factors - ???
- Birth weight - no, it's growth
  - Maternal diet
    - Topoisomerase inhibitors
  - Nutrition
  - Folate
- Immune Status
  - Breastfeeding
  - Childcare
  - Etc.

summarized by C. Portier

total attributable fraction < 10%

Japanese A-bomb excess relative risks (ERR) Sv⁻¹

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ERR (Sv⁻¹) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delongchamp et al. (Radiat. Res. 1997 147 385-95) in utero, mortality</td>
<td>-0.40 (-0.10, 0.29)</td>
</tr>
<tr>
<td>Delongchamp et al. (Radiat. Res. 1997 147 385-95) childhood (0-5), mortality</td>
<td>51.28 (19.0, 176.2)</td>
</tr>
<tr>
<td>Preston et al. (Radiat. Res. 2004 162 377-89) childhood (0-14), mortality</td>
<td>9.89 (5.24, 18.53)</td>
</tr>
<tr>
<td>Preston et al. (Radiat. Res. 1994 137 868-97) childhood (0-14), incidence</td>
<td>17.69 (7.95, 41.59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zeitraum der Mortalitätsdaten</th>
<th>Referenz für relatives Risiko</th>
<th>Referenz für Dosimetrie</th>
<th>Risikokoeffizient (Gy)¹</th>
<th>Referenz für Risikokoeffizient</th>
</tr>
</thead>
</table>

¹ Eingangsdaten mit der Geburtsstätte 1940-1976
² Eingangsdaten mit der Geburtsstätte 1940-1976
³ Keine Angabe des Konditionalisrisikos
Model for leukemogenesis in children

In utero

1st hit

Molecular event

Hematopoietic stem cell
Preleukemic clone

~1 in 100

Postnatal

2nd hit

Molecular event(s)

Leukemia cell

4-5 in 100,000

Prenatal Origin of ALL, Mori et al. 2002
provided by C Rossig, Berlin 2008
Risk Factors for Childhood Leukemia
What do we know now?¹

• CL is a heterogeneous, multicausal disease, with acute lymphatic leukemia (ALL) being the most common subtype.

• CL derives from a multistage process where the initial event is either inherited or the result of a DNA damaging event during gestation; one or more postnatal hits are needed to transform the preleukemic clones into leukemia cells.

• the increasing incidence rates of B-cell ALL (but not for T-ALL and AML) in industrialized countries point toward a role for modern lifestyle.

• no risk factor, known so far, has major explanatory power.

• the limited understanding of the genetic and environmental causes is urging for new ways in research.

¹ Radiation Protection Dosimetry, Vol. 132, No 2, 2008
1. State of knowledge
2. Risk factors
3. The way forward
Towards a strategic research agenda
…..for a better understanding of the causes of CL

BfS has established a research agenda based on a broadened, interdisciplinary approach.

The starting point was a small meeting in July 2010 with experts from various disciplines, e.g. epidemiology, gene-environment interactions, immunology, molecular biology, experimental and theoretical modelling and radiation biology.
Key elements of the proposed research agenda

Human studies
(A) **Prevalence of ‘first-hit’ events**, i.e. chromosomal translocations (TEL-AML1, AML1-ETO, MLL-AF4, MLL-ENL, MLL-AF9, E2A-PBX)
   (A1) in a German birth cohort
   (A2) in countries with different incidence rates of ALL
(B) **Deep sequencing**
   (B1) of children with ALL
   (B2) of the preleukemic clone from predisposed children
      (from Project A1)
(C) Study the **role of the hematopoietic stem cells niche** (for example, mesenchymal cells) for the origin and maintenance of ALL
   (C1) Verification of the correlation between leukemia-specific aberrations in MSCs and prognosis/relapse

1 G Ziegelberger et al. Blood Cancer Journal 2010
Key elements of the proposed research agenda

Animal models

(D) Generation of appropriate mouse models
   (D1) Check availability of existing animal models and the need for further refinement
   (D2) Generation of several new mouse strains
   (D3) Expose animal model to possible risk factors; generate a B-cell leukemia model of genetic variability by backcrossing; expose a cohort to possible risk factors

(E) Verification of the contribution of gene variants identified in human studies to the development of B-cell leukemias in mice

(F) Verification that the mechanisms outlined in A-E can quantitatively account for the totality of human data (via novel quasi-mechanistic models)
Pilot studies will start this year (2011)

- **Feasibility of building-up (or joining) a German birth cohort (A1)**
  availability of cordblood samples?
  synergism with ongoing or planned studies?

- **Development of PCR-primers** as a tool to detect the most frequent chromosomal translocations (ad A)

- pilot study for **comparing regional ALL differences** (A2)

- pilot study on **deep sequencing of 10 ALL individuals** (whole-genome or transcriptome sequences, exome capture and sequencing) already analyzed by GWAS (B1)

- literature study and **evaluation of existing animal models** (D)
International collaboration is crucial

• The **low incidence** of CL and the expected **small relative risk** of any related risk factor require **large sample sizes** and a broad worldwide consortium.

• Initiatives have already started among epidemiologists (see CLIC and I4C), but epidemiology alone might not be able to come to final conclusions.

• The results of the German KiKK-study and the consistent finding of a statistical association between low-level magnetic fields and CL have renewed the efforts of radiation experts to **pursue the causes of CL** - see recent activities and recommendations by COMARE in UK and ISRN in France.

  It’s time for combined efforts!