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

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Background

1. KiKK-Study[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

[1] P Kaatsch et al.
Int J Cancer 2008

Contents

1. State of knowledge
2. Risk factors
3. The way forward

Incidence rate of childhood cancer in Germany[1]:

Abbildung 4.1
Krebs bei Kindern (ermittelt aus den Jahren 1999–2008)

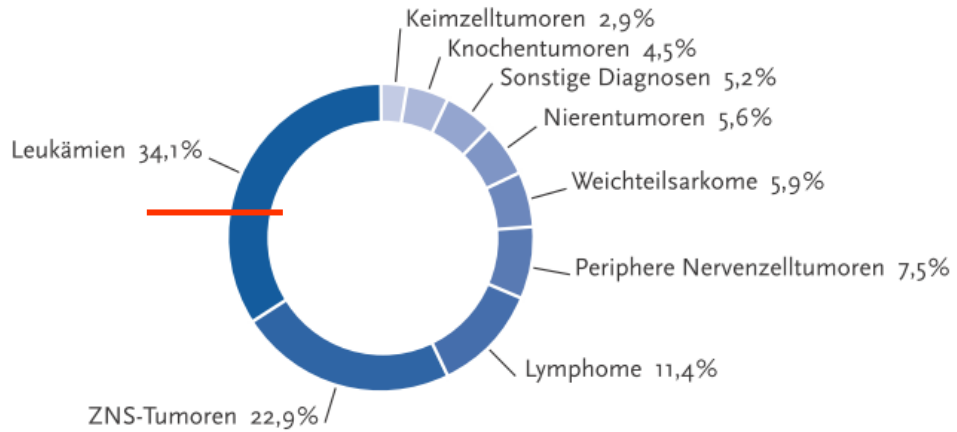
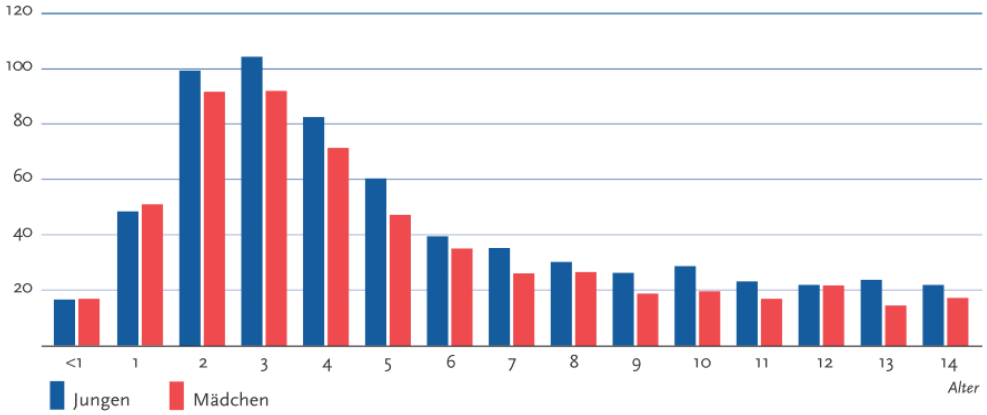
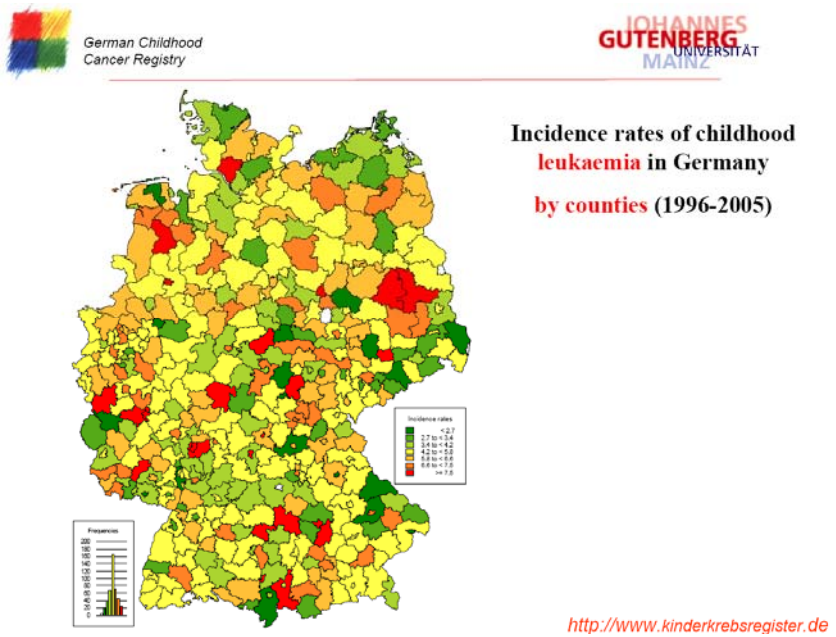


Abbildung 4.3
Neuerkrankungen nach Alter und Geschlecht, akute lymphatische Leukämie im Kindesalter (ALL)
Erkrankungen pro 1.000.000 in Altersgruppen, ermittelt aus den Jahren 1999–2008



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

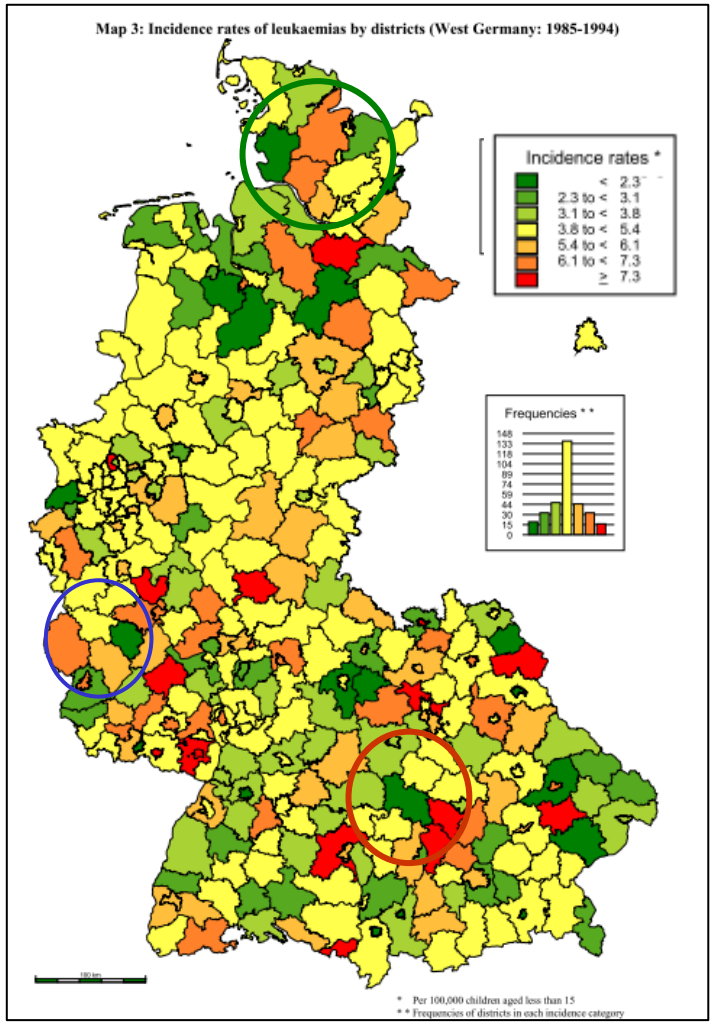
5 year survival rate: 90%



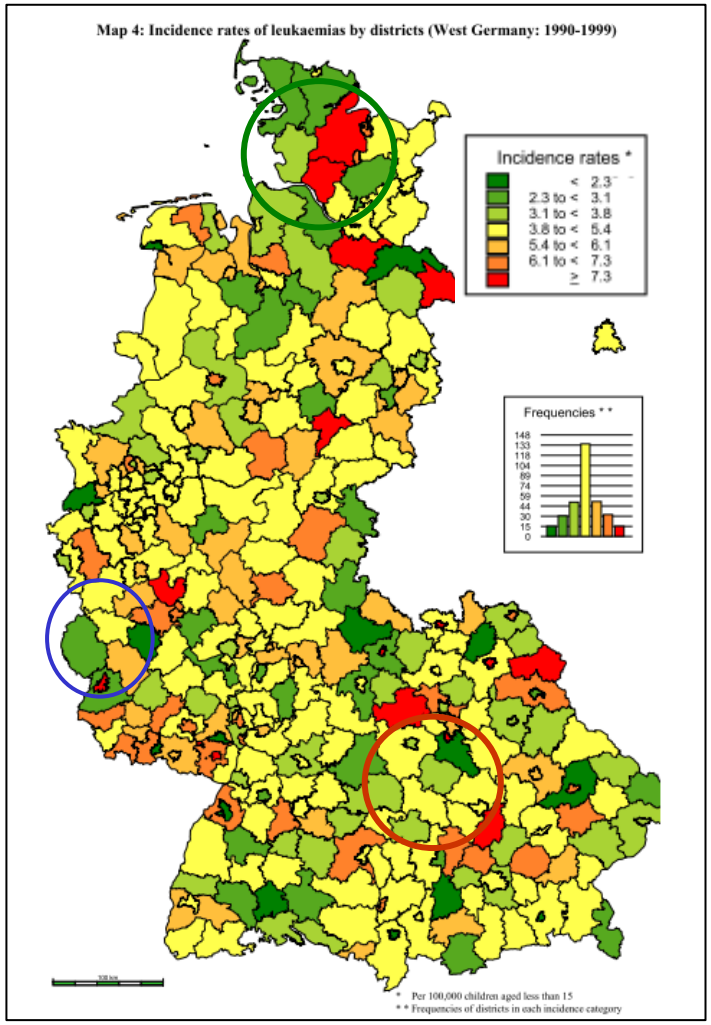
[1] Krebs in Deutschland 2005/2006, Häufigkeiten und Trends, RKI 2010

Bundesamt für Strahlenschutz

SIR leukemias 1984 - 1994



SIR leukemias 1990 - 1999



The time changes of patchiness of the SIRs

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

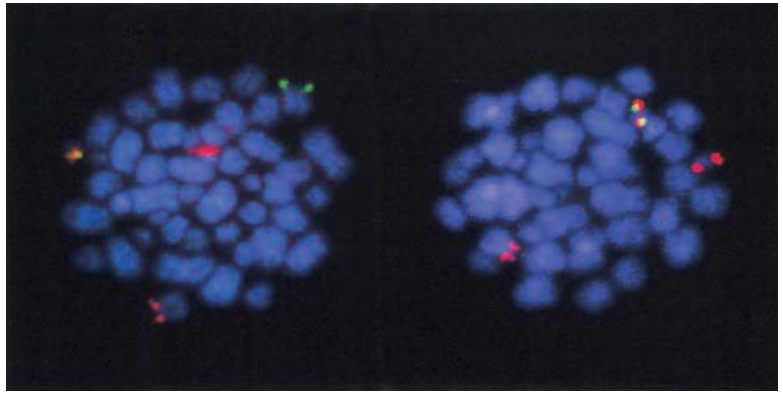
- Genetic - yes
- Ionizing Radiation - yes
  - Nuclear power plants ?
  - Radon Gas ?
  - X-rays ?
- Non-ionizing Radiation - hmm
  - ELF-EMF - nice association
  - RF-EMF ?
- Chemicals - nothing jumps out
  - Air pollution
  - Smoking
  - Pesticides/herbicides
  - POPs
  - Maternal solvent - maybe
-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



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total attributable fraction < 10%

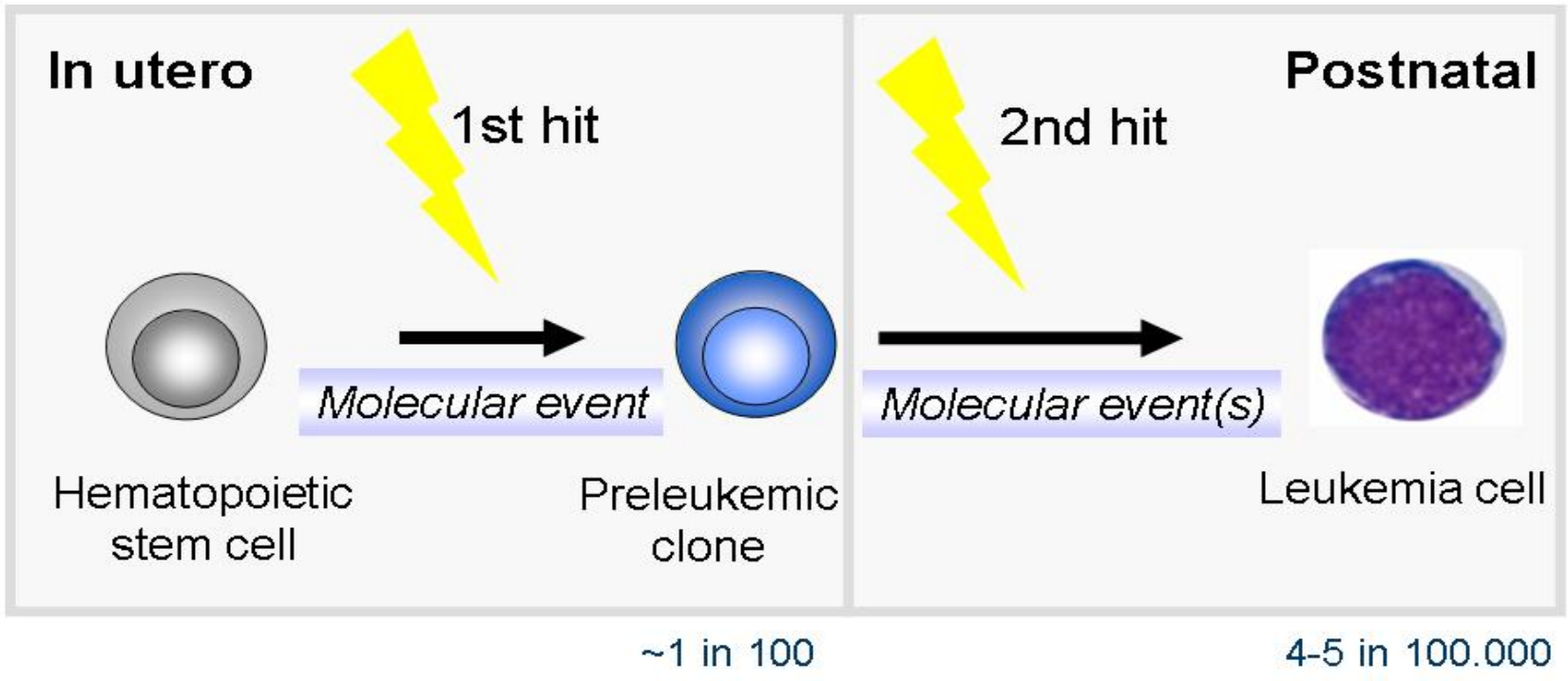
Japanese A-bomb excess relative risks (ERR) Sv^{-1}

Cohort	ERR (Sv^{-1}) (+95% CI)
Delongchamp *et al* (*Radiat. Res.* 1997 **147** 385-95) *in utero*, mortality	-0.40 (<-0.40, 29.2)
Delongchamp *et al* (*Radiat. Res.* 1997 **147** 385-95) childhood (0-5), mortality	51.28 (19.0, 176.2)
Preston *et al.* (*Radiat. Res.* 2004 **162** 377-89) childhood (0-14), mortality	9.89 (5.24, 18.53)
Preston *et al.* (*Radiat. Res.* 1994 **137** S68-S97) childhood (0-14), incidence	17.69 (7.95, 41.59)

Zeitraum der Mortalitätsdaten	Referenz für relatives Risiko	Referenz für Dosimetrie	Risikokoeffizient $(Gy)^{-1}$	Referenz für Risikokoeffizient
1953-1972[a]	Bithell und Stiller (1988) [Bit 88]	UNSCEAR (1972) [UNSC 72]	29 (17 - 44)	Bithell und Stiller (1988) [Bit 88]
1953-1978[b]	Bithell (1993) [Bit 93]	Mole (1990b) [Mol 90b]	51 (28 - 76)	Doll und Wakeford (1997) [Dol 97]
1958-1961	Mole (1990b) [Mol 90b]	Mole (1990b) [Mol 90 b]	38 (7 - 79)	Wakeford and Little (2003) [Wak 03]
1953-1972[a]	Bithell und Stiller (1988) [Bit 88]	Mole (1990a) [Mol 90a]	13[c]	Wakeford and Little (2003) [Wak 03]

[a]: Eingeschränkt auf die Geburtskohorte 1943-1972
[b]: Eingeschränkt auf die Geburtskohorte 1940-1976
[c]: Keine Angabe des Konfidenzintervalls

Model for leukemogenesis in children



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 urgeing 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[1]

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[1]

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)

[1] G Ziegelberger et al. Blood Cancer Journal 2010

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!