Risk factors of childhood leukemia: the French research program

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Childhood leukemia: main hypotheses

- Environment
  - Ionising radiation
  - Extremely low-frequency - electromagnetic fields (ELF-EMF)
  - Air pollution
  - Pesticides
  - Passive smoking
- Infections and immune system
  - Specific infections
  - Hygiene hypothesis
- Genetic factors
  - Family history of leukemia
  - Genetic factors (GWAS)
  - Genetic susceptibility to environment
Domestic radon exposure and childhood leukemia

- Lucie et al., 1990, UK, ALL
- Henshaw et al., 1990, 13 countries, Leukemia
- Butland et al., 1990, 7 countries, Leukemia
- Alexander et al., 1990, UK, ALL
- Muirhead et al., 1991, UK, Leukemia
- Collman et al., 1991, USA, Leukemia
- Foreman et al., 1994, UK, Leukemia
- Richardson et al., 1995, UK, Leukemia
- Thorne et al., 1996, UK, AML
- Kohli et al., 2000, Sweden, ALL
- Evrard et al., 2005, France, ALL/AML

Ecological association AML x radon

- Evrard et al., Eur J Cancer Prev, 2005
- Evrard et al., Health Physics, 2006
Vicinity of nuclear sites and childhood leukemia
multisite studies

→ Distance from sites (SIR ≈ 1)
  White-Koning et al, Br J Cancer 2004

→ Modelled exposure of the commune (SIR ≈ 1)
  Evrard et al, Br J Cancer 2006

Specific infection and childhood leukemia

Population mixing

⇒ Incidence increased with population mixing in rural isolated municipalities
  • At the place of birth
    Rudant et al, Eur J Cancer 2006
  • At the residence at diagnosis
    Bellec et al, Br J Cancer 2007
The GEOCAP study
Domestic radon exposure

Geolocation (GIS)
- Registry cases (9,000 leukemia cases)
- Population controls (30,000 children)

Case-control study

Modeling the discharges

Geolocation (GIS)
- Registry cases (9,000 leukemia cases)
- Population controls (30,000 children)

Case-control study
The GEOCAP study:
Living next to powerlines

- Mapping the lines
- Quantifying EMF-ELF

- Geolocation (GIS)
  - Registry cases (9,000 leukemia cases)
  - Population controls (30,000 children)

Case-control study

The GEOCAP study:
Traffic and air pollution

- Exposure to NO2 and benzene
- Proximity to main roads

- Geolocation (GIS)
  - Registry cases (9,000 leukemia cases)
  - Population controls (30,000 children)

Case-control study
The GEOCAP study:
- Nuclear
- Rn
- ELF-EMF
- NO₂/Bz
- Traffic

Permanent survey
Objective assessment of exposure based on GIS

In-depth case-control studies:

Interviews
- Residential history
- Confounders

DNA
- GWAS
- Gene-environment interactions

2010 ESTELLE study
2003 ESCALE study
1995 ADELE and ELECTRE studies

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In-depth case-control studies
Environment

Association with maternal use of insecticides
- Menegaux et al, Occup Env Med, 2006
- Rudant et al, Env Health Persp, 2007

Maternal use of insecticides during pregnancy
Association with neighbouring gas stations (benzene?)
- Steffen et al, Occup Env Med, 2004

Relative risk

Adele – hosp 1995-99
300 AL / 300 Co

Escale – national 2003-04
1500 K / 1700 Co
In-depth case-control studies
Infections, hygiene hypothesis

Incidence peak of ALL higher and earlier with growing socio-demographic conditions
⇒ Hygiene improvement?
- Delayed common infections
- Decrease in breastfeeding

Deregulated response
Early common infections
(Guthrie spots)

Regulated response

Preleukemic clone
((12;21) TEL-AML1
MLL, hyperdiploidy

Repeted early infections
- Perrillat et al, Br J Cancer 2002
- Jourdan da Silva et al, Br J Cancer 2004
- Rudant et al, 2009 (in revision)

Day-care attendance
- Perrillat et al, Br J Cancer 2002
- Jourdan da Silva et al, Br J Cancer 2004
- Rudant et al, 2009 (in revision)

Breast-feeding
- Perrillat et al, Eur J Pediatr 2002
- Rudant et al, 2009 (in revision)
Early common infections

Genes and gene-environment interactions

Radiation
- Ionising radiation
- Electromagnetic fields
- Chemicals
  - Air pollution
  - Passive smoking
  - Pesticides

Infection and immunity
- Specific infections
- Hygiene hypothesis
- Candidate polymorphisms
  - DNA repair and cell cycle control
  - Metabolism of xenobiotics
- Interleukins, TNF, TLR...
- HLA class II
- Male gender
- Embryonal development
- Genome-wide association study

In-depth case-control studies

Candidate polymorphisms
- DNA repair and cell cycle control
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Infante-Rivard et al. 2000
- Interleukins, TNF, TLR...
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Clavel et al. 2005
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