The KiKK-Study - results put into perspective

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Basic references

- Spix, C., Schmiedel, S., Kaatsch, P., Schulze-Rath, R. & Blettner, M. (2008). Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980-2003. *Eur J Cancer*, **44,** 275-284
- Kaatsch, P., Spix, C., Schulze-Rath, R., Schmiedel, S. & Blettner, M. (2008). Leukaemia in young children living in the vicinity of German nuclear power plants. *Int J Cancer*, **122,** 721-726

Background

- The German Childhood Cancer Register conducted a **case-control study** on childhood cancer near nuclear power plants in Germany
- this study was initiated and funded by BfS

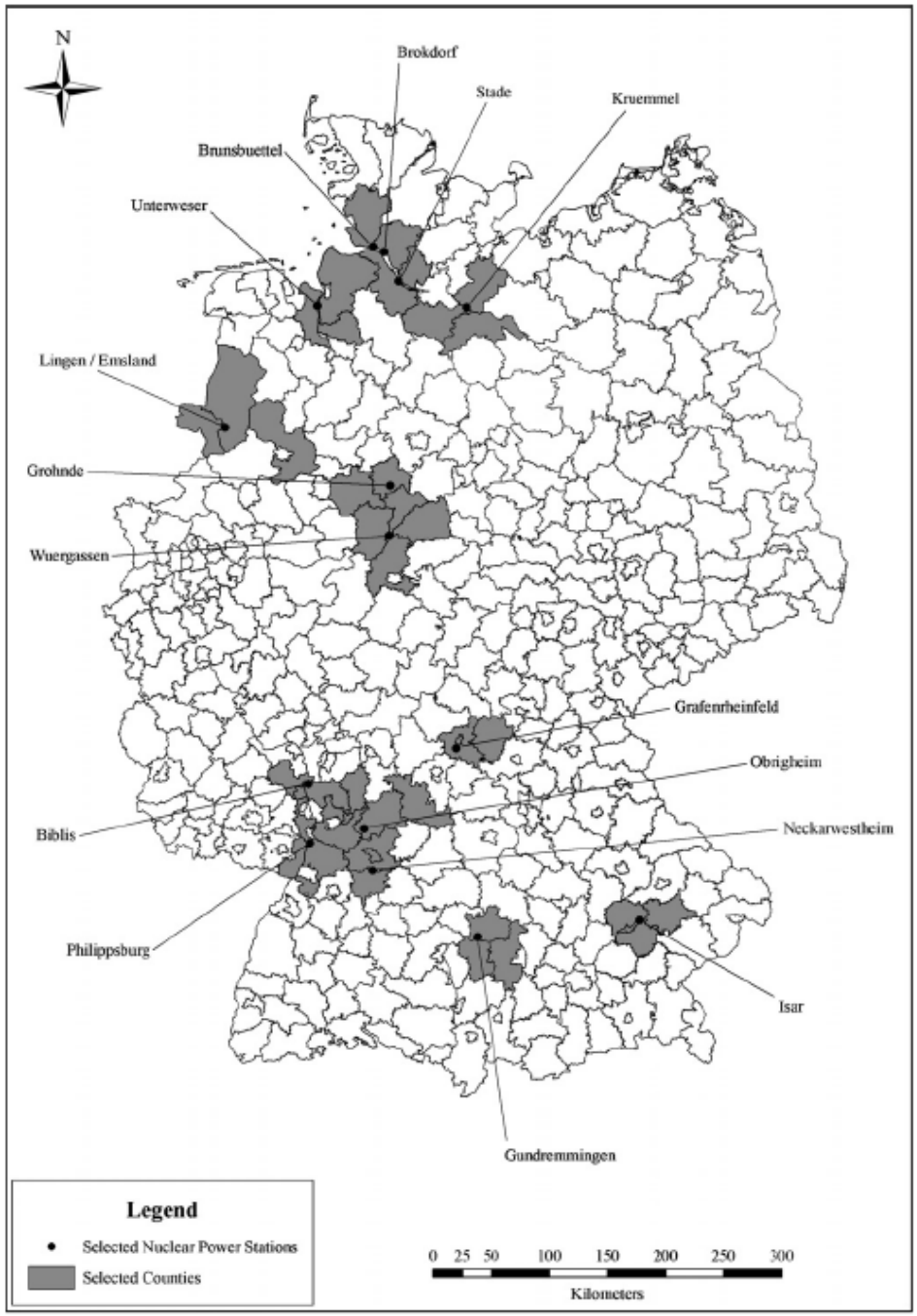
Hypothesis

H_0: There is no correlation between the proximity of the place of residence to a NPP and the cancer risk among children below the age of 5. There is no negative trend of the risk with distance.

Secondary question: Can an elevated risk be observed within 5 km distance from the sites?

Study area

- vicinity of 16 nuclear sites in Germany with 21 NPPs
- study area of 42 districts
  - two next to the sites plus the next neighbour to the east
  - some overlap



(Spix et al., Eur J Cancer, 2008)

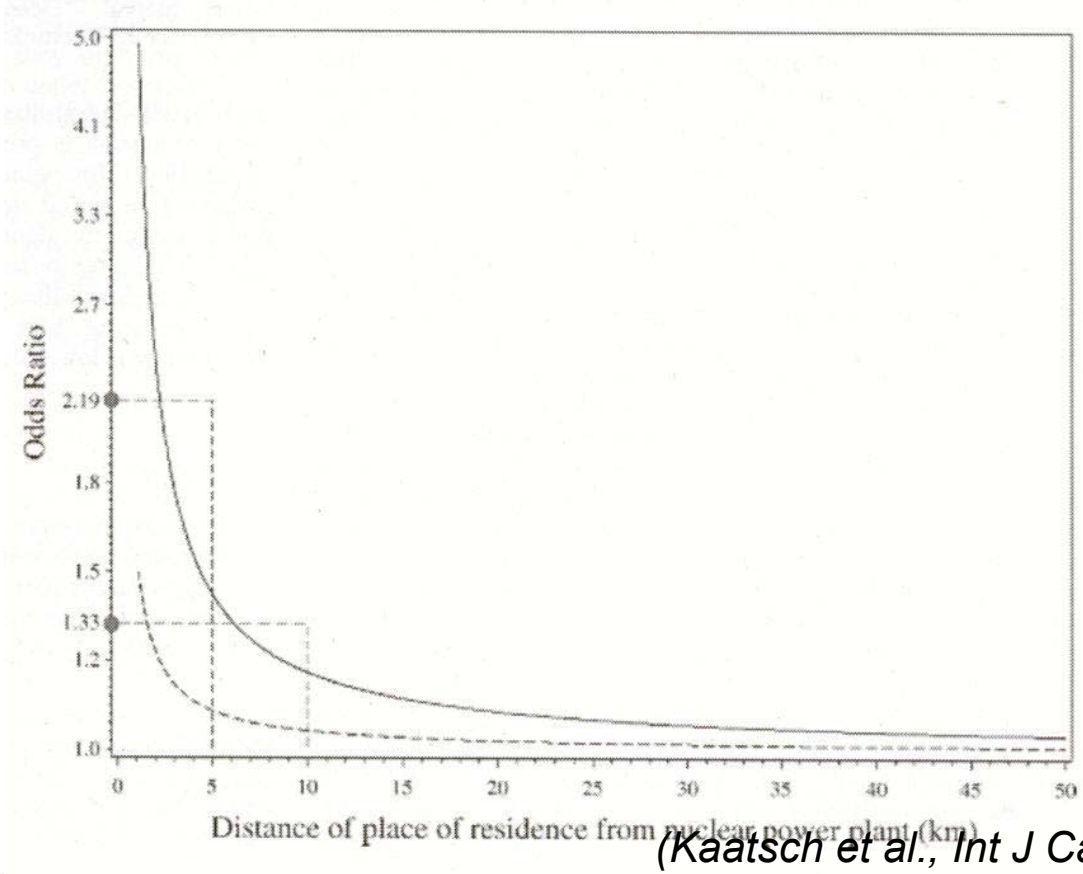
Cases and Controls

- all cases registered
  - with diagnosis 1980 – 2003 (GCCR started operation in 1980)
  - below 5 years of age at time of diagnosis
- population based controls, randomly selected from the registration offices
  - individually matched by age and gender
  - had to live in the same NPP area as the reference case at time of diagnosis
  - 1:3 matching

Diagnostic groups

- all cancers
- leukaemias
  - ALL
  - AML
- CNS cancers
- all embryonic cancers but medulloblastoma

Results – regression analysis leukaemia



(Kaatsch et al., Int J Cancer, 2008)

Results – regression analysis

Diagnostic group	ß	lower 95%-Ci	cases	controls
all leukaemias	1.75	0.65	593	1,766
ALL	1.63	0.39	512	1,523
ANLL	1.99	-0.41	75	255

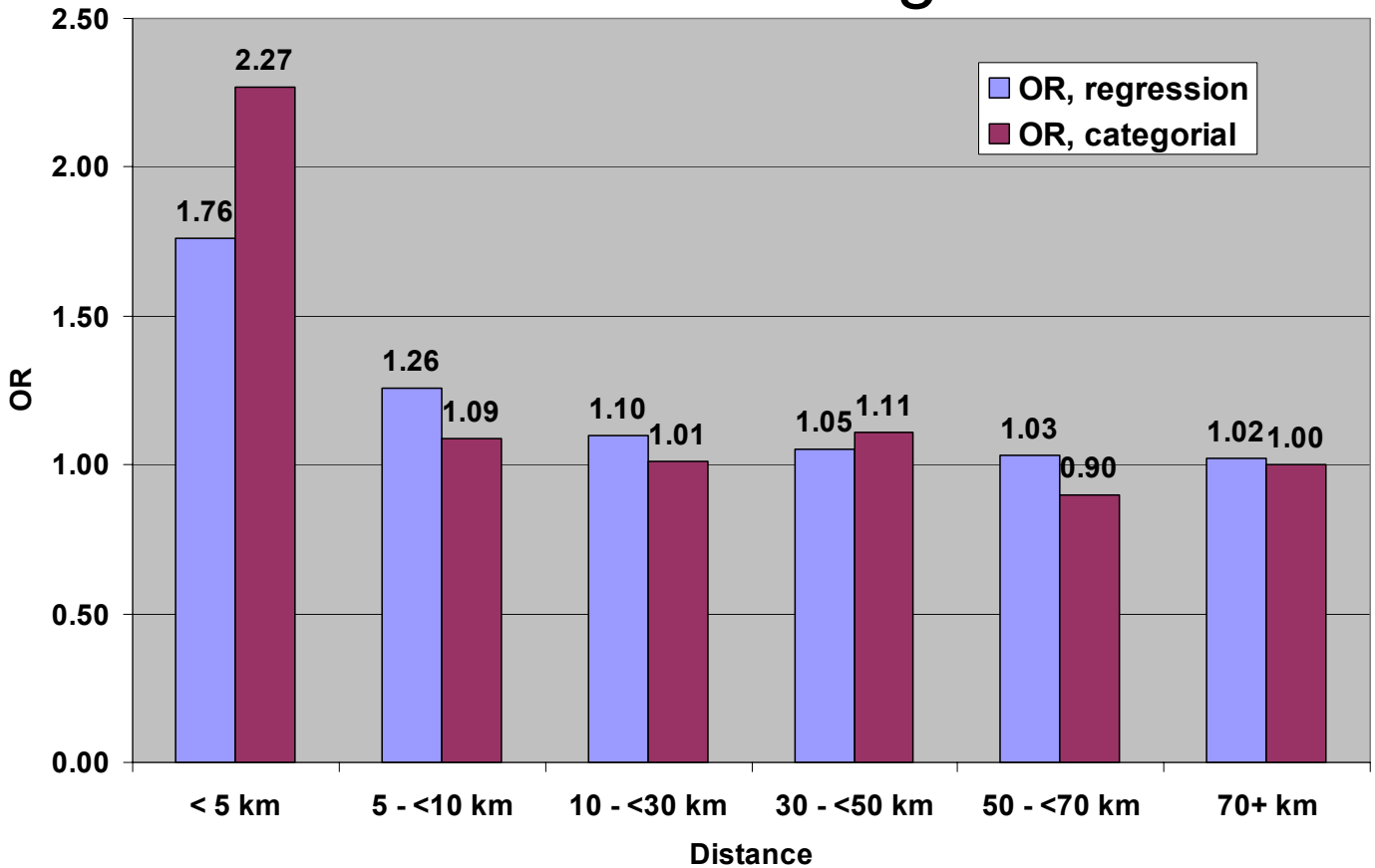
(Kaatsch et al., Int J Cancer, 2008)

Results – categorial analysis

Diagnostic group	distance	OR	lower 95%-CI	cases
all leukaemias	≤5km vs. >5km	2.19	1.51	37
	≤10km vs. >10km	1.33	1.06	95
ALL	≤5km vs. >5km	1.98	1.33	30
	≤10km vs. >10km	1.34	1.05	84
ANLL	≤5km vs. >5km	3.88	1.47	7
	≤10km vs. >10km	1.30	0.66	10

(Kaatsch et al., Int J Cancer, 2008)

all leukaemias: Results from regression and categorial analyses by circles / rings



(data taken from Kaatsch et al., Int J Cancer, 2008)

Odds Ratios, Germany, 5 km circles, by time period

Study period	case-control study OR and 1-tailed lower 95% CL
1980-1990	3.00 (1.54)
1991-1995	2.10 (1.04)
1996-2003	1.78 (0.99)

(acc. to: Kaatsch et al., Int J Cancer, 2008)

Discussion

- Effect of confounders in Part 2 of the study
- Comparison with Gardner study
- Decreasing ORs over time
- Power lines as confounders?
- Comparison with previous ecological studies

Part 2 of the study

(Kaatsch et al., Report, 2007)

Telephone interviews for a subset of cases and controls (1993 – 2003)
for leukaemias:
ß = 0.44, lower 95% CI = -1.86 (237 cases, 463 controls)
but:
self selection – among cases the response within 5 km circle is lower than outside; same effect for controls, but less pronounced
as defined in advance, confounders found in Part 2 must not be used as an explanation for the results of Part 1 (estimate for Part 2 outside 90% CI for that derived one from Part 1)

Part 2 – Change in estimate

Confounders:

- SES,
- radiation exposure,
- further risk factors mentioned in the literature,
- child's immunological situation,
- others

based on 251 leukaemia cases and 487 controls

→ no change in estimate

(Kaatsch et al., Report, 2007)

A result from the Gardner study

(Gardner et al., BMJ; 1990)

Distance from the site	OR	(*OR* *with ref.: 30+km)*	95% CI
≤ 5 km	1	(*5.88*)	
5 - ≤ 10 km	0.35	(*1.35*)	[0.08;1.62]
10 - ≤ 15 km	0.21	(*1.24*)	[0.05;0.92]
15 - ≤ 20km	0.22	(*1.29*)	[0.04;1.22]
20 - ≤ 25km	0.22	(*1.29*)	[0.03;1.59]
25 - ≤ 30 km	0.14	(*0.82*)	[0.02;0.19]
30+ km	0.17	(*1*)	[0.02;1.18]

Decreasing odds ratios over time

Study period	case-control study OR and 1-tailed lower 95% CL
1980-1990	3.00 (1.54)
1991-1995	2.10 (1.04)
1996-2003	1.78 (0.99)

(acc. to: Kaatsch et al., Int J Cancer, 2008)

Decreasing odds ratios over time

- Is there an agent active of which the prevalence decreases over time?

- But: No change in leukaemia mortality in small areas near nuclear installations in England and Wales before and after start up

(Baron, Br J Cancer, 1984)

Power lines as confounder ?

- A large number of studies reported on a correlation between exposure to EMF and childhood leukaemia, namely in young children
- But: the power lines do not cover the entire study area, but only corridors in less populated parts of it

Ecological studies, Germany, 5 km circles

Study period	ecological study RR and 95% CI	case-control study OR and 1-tailed lower 95% CL
1980-1990	3.01 [1.25;10.3]	3.00 (1.54)
1991-1995	1.39 [0.69;2.57]	2.10 (1.04)
1996-2003		1.78 (0.99)
1980-1995	1.49 [0.98;2.20]	2.53 (1.57)
1980-2003		2.19 (1.51)

(acc. to: Kaatsch et al., Int J Cancer, 2008)

Ecological studies

- Assume there is no ecological fallacy
  - studies showed elevated risks amongst youngest age group and closest vicinity
  - no effect for all children (0-14)
    - review by Laurier
    - COMARE results
- Elevated risk amongst 0-4 years old would mean a lower risk amongst the 5-14 years old

Lower risk amongst 5-14 years old

- Does that mean, that a – yet undefined – agent causes an earlier onset of the disease close to the sites?
- If so, this would explain the absence of additional cases for all children.

1980-1995
RR = 1.31
(Kaletsch, Report, 1997)

age	0-4	5-9	10-14
RR	2.87*	1.15	0.52

Ecological studies II

- Potential sites
  - limited evidence due to limited number of studies, actually only one looked at 0-4 years old
  - but
    - highest risk amongst the youngest age group and closest vicinity
- Is there something special about the locations?

Observations near potential sites, youngest age group, 5 km vicinity

Reference	study area	age group	study period	relative risk
Keller, 1992	West Germany	incidence, age ≤ 4	1980-1991	4.16*
Kaletsch, 1997	West Germany	incidence, age ≤ 4	1991-1995 1980-1995	1.52 3.82

(Laurier et al., 2002, Acta Oncol.)

Knowledge on radiation effects

- current risk estimates indicate that the radiation exposure from NPPs is too low by at least a factor of 1,000 to explain the findings
- but little is known about the risk
  - at exposure during pregnancy and early childhood

  and

  - disease onset in early childhood

Possible explanations

- Radiation at low exposures with a high risk for young ages ?
- Combined effects with radiation:
  - Which factors are involved ?
  - What is the total risk ?
  - What is the contribution of radiation ?
- Which potential risk factors are characterized by the observed distance dependence from a site ?

Conclusion (1)

"It is, therefore, necessary to consider carefully whether each of the positive results may be due to chance, or to socio-economic / environmental differences, or to the direct presence of the installations."

(Forman et al., Nature, 1987)

Conclusion (2)

- KiKK study points into direction of "Presence of the installations"
- Effect only seen for leukaemias
- But no explanation for a causal relation between a risk factor and the observed risk is possible