Soz Präventivmed 1993; *38*: 190–195

0303-8408/93/040190-06 $1.50 + 0.20/0

Increased risk of acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) in a county of Hesse, Germany

Gerald Kolb [1], Nikolaus Becker [2], Sigrid Scheller [1], Gerhard Zugmaier [1], Hans Pralle [3], Jürgen Wahrendorf [2], Klaus Havemann [1]

[1] Department of Internal Medicine, Division of Hematology, Oncology, Immunology, Philipps-University Hospitals, Marburg
[2] Department of Epidemiology and Biometry, Division of Epidemiology, German Cancer Research Center, Heidelberg
[3] Department of Internal Medicine, Division of Hematology, Oncology, Justus-Liebig-University Hospitals, Giessen

Besides genetic factors, external noxious agents play a decisive role in the development of neoplastic diseases. The type of agent, its mechanism of action and the duration of exposure determine the induction of a malignant tumor. Benzene is only one example for the tumor-inducing effect of a defined chemical substance [1]. An association between exposure to benzene and a higher incidence of leukemia was already described for shoe workers in the 1930s [2,3]. During World War II the benzene derivative trinitrotoluene (TNT) was used for producing explosives. Some TNT derivatives such as dinitrotoluene can result as byproducts of explosives or as bacterial metabolites of waste in contaminated soil [4]. TNT as well as its derivatives have been shown to induce mutagenic transformations in vitro and in animal experiments [5].
Based on an apparently high number of leukemias occurring in the town of Stadtallendorf, a population-based assessment of the incidence of leukemia in the corresponding county of Marburg-Biedenkopf was conducted and compared to that in the neighbouring county of Giessen. While in Stadtallendorf a heavy contamination of soil with TNT is documented, no such contamination is known in the neighbouring region.

Materials and methods

Patients

All patients were included in the study who were (a) older than 18 years, (b) diagnosed and treated in the Hematologic Departments of the University Medical centers of Marburg and Giessen in the years 1983–1989, and (c) suffered from CML, AML or myelodysplastic syndrome (MDS).
The diagnoses had been confirmed by bone marrow biopsies and were classified according to standardized international criteria in the Pathologic Departments of Göttingen University and Kiel University Medical Centers. Because MDS, especially the RAEB/T forms (stage III and IV in the French-American-British classification), were previously called "preleukemia" or "smoldering leukemia" as an early form of AML, patients with MDS were included in the AML group.

Study design

The incidence rates of leukemias in the population of two adjacent counties in Central Hesse in West Germany: Marburg-Biedenkopf County and Giessen County (Figure 1) were compared. The evaluation was based on case records of leukemias which had been collected in the Hematologic Departments of Marburg University Medical Center from 1979 to 1989, and Giessen University Medical Center from 1983 to 1989. Statistical comparison had to be restricted to a seven-year period (1983–1989) because a complete documentation of diagnosed cases in the Hematologic Department of Giessen has been available only since 1983. The survey completely covered the population of both university towns and the surrounding counties. Rare forms of leukemia and cases of Aplastic Anemia were excluded from the study. The incidence rates of AML and CML were based on the year of diagnosis and related to the counties containing the patients' residences. The neighbouring counties Marburg-Biedenkopf and Giessen, which contain a similar population of about 200 000 inhabitants, were compared. Marburg-Biedenkopf County, containing areas contaminated with TNT, was subdivided into municipal and rural areas. Stadtallendorf City, which belongs to Marburg-Biedenkopf-County, was taken as a separate entity, because the plants for manufacturing explosives had been located in this area during World War II [6]. Giessen County, where there is no contamination with TNT, was used as control. The respective numbers of residents living in the different regions during the period 1983 through 1989 were obtained from the residential

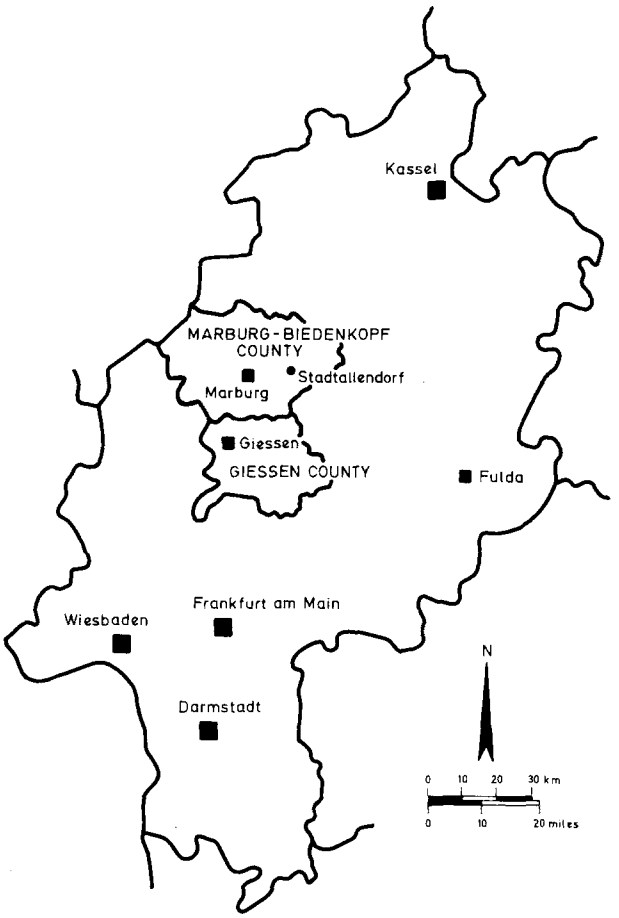

Fig. 1. Map of Hesse with location of the counties Marburg Biedenkopf and Giessen.

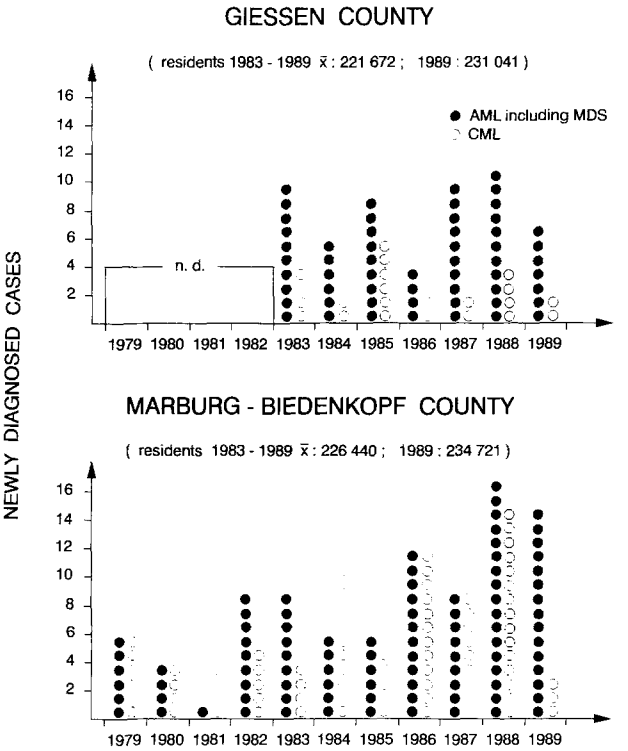

Fig. 2. Newly diagnosed cased of CML and AML including MDS in Marburg County and Giessen County during 1979–1989 and 1983–1989 respectively.

registries, and subdivided into age groups for both sexes.

Statistics

The data have been evaluated in the sense of a follow-up study with person-time denominators. Maximum likelihood (ML) estimates and 95%-confidence limits (CL) of relative risk (RR) were calculated[7], based on the age groups 18–34 years, 35–64 years and ≥ 65 years. Additionally the relative risk was separately determined for the age groups 18–64 years and 65 years and above.

Results

Figures 2 and 3 show the number of Acute and Chronic Myelogenous Leukemias related to the year of diagnosis and to the number of permanent residents in Marburg-Biedenkopf County and Giessen County, and also separately in the cities Marburg, Giessen and Stadtallendorf.

Table 1 lists the numbers of diagnosed leukemias related to the numbers of inhabitants divided by sex in Marburg-Biedenkopf County and Giessen County during the reference period 1983 through 1989. Marburg-Biedenkopf County was subdivided into the regions Stadtallendorf City, Marburg City and the rural areas of Marburg-Biedenkopf County excluding Stadtallendorf.

The relative risks of AML (Table 2) and of CML (Table 3) were determined for each region as compared to the risks in the other regions investigated. The male population of Stadtallendorf City, an area with a high TNT contamination, had a significantly elevated RR of AML and CML, as compared to the male population of Giessen County, an area lacking contamination with TNT. If Stadtallendorf City was compared to Marburg City, the RR of CML but not that of AML was significantly elevated in the male population of Stadtallendorf City. The female population of Stadtallendorf City showed an increased risk of AML as compared to the female population of Marburg City or Giessen County. The number of women with CML was too low for statistical analysis. The rural areas of Marburg-Biedenkopf County show a significantly higher RR of CML in both sexes than Giessen County.

Tables 4 and 5 show relative risks for persons in the restricted age range of 19–64 years, and Tables 6 and 7 for persons above 65 years of age. The tables show that the relative risk is particularly high among persons above 65 years of age compared to the total relative risks of Tables 2 and 3, and especially to the relative risks combined to the age range 19–64 years.

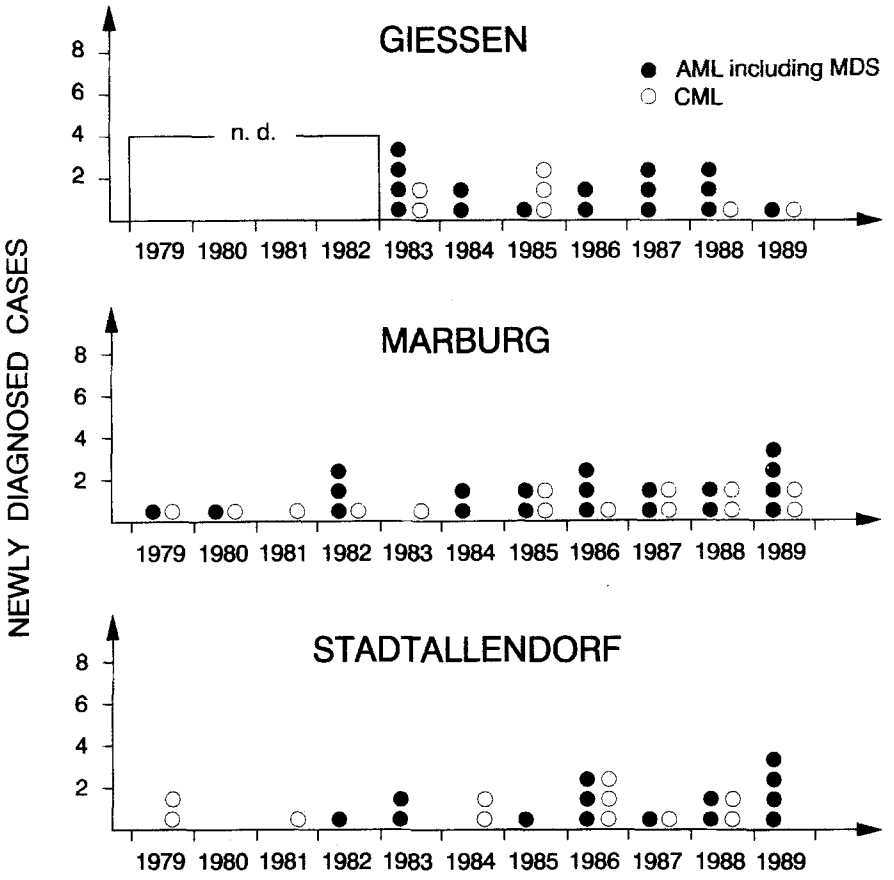

Fig. 3. Newly diagnosed cases CML and AML including MDS in the city regions of Marburg, Giessen and Stadtallendorf during 1979–1989 and 1983–1989 respectively.

Tab. 1. Total number of diagnosed cases with AML or CML during the period 1983 through 1989 and average number of residents (res) during the period 1984–1989.

Region	Male			Female		
	AML	CML	res.	AML	CML	res.
Stadtallendorf	6	7	9958	7	1	10083
Marburg City	9	6	35741	6	4	38022
Marburg-Biedenkopf County without Marburg and Stadtallendorf City	21	28	63390	25	20	69246
Giessen County	28	13	105396	29	10	116276

Tab. 2. Relative risks (RR) of AML including confidence limits (CI) in the population of different target regions as compared to the risk in the population of related control regions.

Target-region	Control-region	Male		Female	
		RR	CI	RR	CI
Stadtallendorf	Marburg City	2.3	0.8–6.5	4.3	1.4–12.7
Stadtallendorf	Giessen County	3.5	1.4–8.5	3.2	1.4– 7.2
Marburg-Biedenkopf County	Marburg City	0.6	0.2–1.3	1.7	0.7– 4.2
Marburg-Biedenkopf County	Giessen County	1.0	0.6–1.8	1.3	0.8– 2.2
Marburg City	Giessen County	1.4	0.7–3.1	0.8	0.3– 1.8

Tab. 3. RR of CML as described in Table 2.

Target-region	Control-region	Male		Female	
		RR	CI	RR	CI
Stadtallendorf	Marburg City	4.1	1.4–12.2	1.0	0.1– 8.7
Stadtallendorf	Giessen County	9.1	3.5–23.4	1.3	0.2–10.3
Marburg-Biedenkopf County	Marburg City	1.7	0.7– 4.4	2.1	0.7– 6.0
Marburg-Biedenkopf County	Giessen County	3.0	1.6– 5.9	2.9	1.4– 6.3
Marburg City	Giessen County	2.1	0.8– 5.6	1.5	0.5– 4.7

Tab. 4. RR of AML in residents of 18 to 64 years of age as described in Table 2.

Target-region	Control-region	Male		Female	
		RR	CI	RR	CI
Stadtallendorf	Marburg City	0.0	–	2.0	0.5–8.5
Stadtallendorf	Giessen County	0.0	–	2.7	0.8–9.5
Marburg-Biedenkopf County	Marburg City	0.8	0.2–2.9	0.7	0.2–2.1
Marburg-Biedenkopf County	Giessen County	0.7	0.3–1.7	1.0	0.4–2.4
Marburg City	Giessen County	0.8	0.3–2.4	1.5	0.5–4.1

Tab. 5. RR of CML in residents of 18 to 64 years of age as described in Table 2.

Target-region	Control-region	Male		Female	
		RR	CI	RR	CI
Stadtallendorf	Marburg City	1.2	0.1–11.2	0.0	–
Stadtallendorf	Giessen County	1.3	0.2–10.3	0.0	–
Marburg-Biedenkopf County	Marburg City	3.3	0.9–12.0	2.5	0.3–20.6
Marburg-Biedenkopf County	Giessen County	3.4	1.5– 8.0	1.6	0.5– 4.9
Marburg City	Giessen County	1.2	0.3– 4.6	0.6	0.1– 5.4

Tab. 6. RR of AML in residents above 65 years of age as described in Table 2.

Target-region	Control-region	Male		Female	
		RR	CI	RR	CI
Stadtallendorf	Marburg City	3.5	0.7–17.5	>100	–
Stadtallendorf	Giessen County	7.3	2.0–26.1	2.1	0.5–9.1
Marburg-Biedenkopf County	Marburg City	0.5	0.1– 1.7	>100	–
Marburg-Biedenkopf County	Giessen County	0.9	0.4– 2.3	1.1	0.5–2.5
Marburg City	Giessen County	2.1	0.6– 7.4	0.0	–

Tab. 7. RR of CML in residents above 65 years of age as described in Table 2.

Target-region	Control-region	Male		Female	
		RR	CI	RR	CI
Stadtallendorf	Marburg City	7.1	1.8– 28.3	1.4	0.1–13.2
Stadtallendorf	Giessen County	32.0	9.8–105.0	2.4	0.3–20.0
Marburg-Biedenkopf County	Marburg City	0.6	0.2– 2.0	1.9	0.5–6.6
Marburg-Biedenkopf County	Giessen County	2.5	0.9– 7.3	3.3	1.3–8.7
Marburg City	Giessen County	4.5	1.1– 19.0	1.8	0.4–7.0

Discussion

During the last years an unusually high number of leukemias has been diagnosed in the Hematologic Department of Marburg University Medical Center, mainly due to CML and AML including MDS. The highest occurrence of leukemias seemed to be concentrated in Stadtallendorf, a small town east of Marburg.

Although the population of Stadtallendorf City contains a high proportion of 27% foreigners, especially of Turkish guest workers who moved there in the seventies, all patients with leukemia were Germans. Furthermore, elevated risks of AML and CML were due to the age group > 64 years. Both these observations suggest that exposure for a longer period, possibly for more than 15–20 years, may be required for the clinical manifestation of AML or CML. Such a long latency period has been previously described for leukemia after chronic exposure to benzene [3,8].

In 1938, one year after the German army had given the order to build two plants for manufacturing explosives in Stadtallendorf, the annual production of TNT was 7500 tons. In 1944–1945 the production of TNT reached its peak with about 30000 tons per year [6]. In the past only a few investigations have been done to determine the extent of contamination with TNT and its derivatives, which have oozed away into the soil and been spread out through water waste into large areas outside the manufacturing plant [9].

At the present time the level of contamination is being assessed by geological studies and the results are being plotted on maps [10]. Numerous residences, appartment complexes and businesses have been built since 1945 directly in the area of the former plants or close to huge dumps [6]. Especially during the first years after the end of World War II, the soil and the drinking water in this area were not sufficiently protected from contamination with the TNT waste [11]. Solidified pieces of TNT are still found in wastewater pipes.

Although our data show an increased risk of leukemia in Stadtallendorf and suggest a relation to TNT exposure, a causal relationship can only be established by further epidemiologic evaluation including investigations of the living and working conditions of the local population [12]. Considering the widespread use of TNT during World War II we feel that our data justify such studies, and also studies in other areas where plants for producing TNT were located. Besides, it is generally assumed that chronic exposure to a noxious agent for several years or decades is necessary for leukemias, especially for CML, to become clinically manifest. Therefore the data collected from the seven-years between 1983 and 1989 may represent only the beginning of an increasing number of cases of leukemia in this area.

Summary

The incidence of acute and chronic myelogenous leukemia has been compared for the two neighbouring regions of Marburg and Giessen in Hesse (Germany). The investigation was based on the incident cases of the years 1983–1989 which have been diagnosed in the hematological departments of the universities of the two regions. The epidemiological evaluation of the data has been carried out in terms of a historical follow-up study, and shows an increased relative risk for the region around Marburg with a particular elevation for one community within this region. Potential determinants are discussed and focus on trinitrotoluene (TNT) and decomposition products which are known to contaminate the soil of this community, in some places severely, due to insufficient removal of remnants of the TNT production in large underground plants during World War II.

Résumé

Risque accru de leucémie myéloïde aiguë (LMA) et de leucémie myéloïde chronique (LMC) dans un comté de Hesse, Allemagne

L'incidence des leucémies myeloïdes aiguës et chroniques a été comparée dans les deux régions limitrophes de Marburg et de Giessen dans le Land

de Hesse (Allemagne). L'étude était basée sur les cas incidents des années 1983 à 1989 diagnostiqués dans les départements d'hématologie des hôpitaux universitaires des deux régions. L'analyse des données épidémiologiques a été conduite en termes d'étude de cohorte historique et montre un risque relatif augmenté aux alentours de Marburg avec des valeurs particulièrement élevées pour une localité de la région. Les causes potentielles sont examinées et mettent en évidence le rôle du TNT et de ses produits de dégradation qui sont connus pour polluer, sévèrement par endroit, le sol de cette localité, en raison d'une décontamination insuffisante des déchets déversés par des usines souterraines produisant du TNT lors de la deuxième guerre mondiale.

Zusammenfassung

Erhöhtes Risiko für akute myeloische Leukämie (AML) und chronisch myeloische Leukämie (CML) in einem Landkreis des Bundeslandes Hessen, Deutschland

Es wurden die Inzidenzen für akute und chronisch myeloische Leukämien in den zwei benachbarten mittelhessischen Landkreisen, Marburg-Biedenkopf und Giessen, verglichen. Grundlage der Untersuchung waren alle Erkrankungsfälle, die im Zeitraum 1983–1989 in den Abteilungen für Hämatologie der Universitäten Marburg und Giessen diagnostiziert wurden. Die epidemiologische Auswertung erfolgte in der Art einer historischen Follow-up Studie und wies ein erhöhtes relatives Risiko im Landkreis Marburg mit einer besonderen Risikoerhöhung im Gebiet einer Kleinstadt dieser Region auf. Mögliche Ursachen hierfür werden diskutiert, wobei einer bereits bekannten Belastung mit Trinitrotoluol (TNT) eine besondere Rolle zukommt. Die teilweise im Ausmaß erhebliche lokale Bodenkontamination mit TNT und TNT-Abkömmlingen im Gebiet dieser Stadt stammt noch aus der Rüstungsproduktion während des Zweiten Weltkrieges.

References

1 *Tough IM, Court Brown WM.* Chromosome aberrations and exposure to ambient benzene. Lancet 1965; *i*:684.
2 *Vigliani EC, Saita G.* Benzene and leukemia. N Engl J Med 1964; *271*:872–876.
3 *Aksay M, Erdem S, DinCol G.* Leukemia in shoe-workers exposed chronically to benzene. Blood 1974; *44*:837–841.
4 *Channon HJ, Mills GT, Williams RT.* The metabolism of 2:4:6 trinitrotoluene (alpha-T.N.T.) Biochem J 1944; *38*:70–85.
5 *Koss G, Lommel A, Ollroge I, Tesseraux I, Haas R, Kappos AD.* Zur Toxikologie der Nitrotoluole und weiterer Nitroaromaten aus rüstungsbedingten Altlasten. Bundesgesundhbl 12/1989; 527–536.
6 *Wolff HJ.* Die Allendorfer Sprengstoffwerke DAG und WASAG. Magistrat der Stadt Stadtallendorf (Ed.), Marburg, Verlag J. A. Koch 1989.
7 *Rothman KJ.* Modern epidemiology. Boston, Little, Brown and Company, 1986; pp 192.
8 *Infante PF, Rinsky RA, Wagoner JK, Young RJ.* Leukemia in benzene workers. Lancet 1977; *ii*:76–78.
9 *Preuss J, Haas R, Koss G.* Altstandorte, Altablagerungen, Altlasten. Geogr Rdsch 1988; *6*:31–38.
10 *Preuss J.* Geographic institute Philipps-University of Marburg, personal communication 1991 of an expert study in preparation.
11 *Haas R, v. Löw E.* Grundwasserbelastung durch eine Altlast. Die Folgen einer ehemaligen Sprengstoffproduktion für die heutige Trinkwassergewinnung. Forum Städte-Hygiene 1986; *37*:33–43.
12 *Becker N, Wahrendorf J.* Regionale Häufung von Krebsfällen. Eine Bewertung aus epidemiologischer Sicht. Dt Ärzteblatt 1991; *88*:2411–2415.

Address for correspondence:
Priv.-Doz. Dr. Dr. Gerald Kolb
Klinikum der Philipps-Universität
Zentrum für Innere Medizin
Abteilung für Hämatologie,
Onkologie, Immunologie
Baldingerstrasse
D-35043 Marburg/Germany