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ORIGINAL CONTRIBUTIONS

OCCUPATIONAL FACTORS IN THE EPIDEMIOLOGY OF LEUKEMIA IN HIROSHIMA AND NAGASAKI[1]

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Ishimaru, T. (Dept. Statistics, Atomic Bomb Casualty Commission, U.S. Marine Corps Air Station, FPO Seattle, Washington 98764), H. Okada, T. Tomiyasu, T. Tsuchimoto, T. Hoshino and M. Ichimaru. Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Amer J Epidem 93: 157–165, 1971.—This epidemiologic study examined retrospectively occupational and other environmental factors in relation to the incidence of leukemia. A total of 492 cases of leukemia with onset in 1945–1967 in Hiroshima or Nagasaki City, Japan, and controls, were selected from the Atomic Bomb Casualty Commission Leukemia Registry and interviewed during the period 1966–1969. In 303 pairs of adult leukemia cases and controls the risk was approximately 2.5 times higher among those with history of probable occupational exposure to benzene or its derivatives and medical x-ray. The change in relative risk of leukemia due to the coexistence of the two factors (radiation and occupation) was also examined.

benzene; carcinoma; epidemiology; leukemia; occupations; radiation effects

INTRODUCTION

It is well known that exposure to ionizing radiation from the A-bomb has induced leukemia among the heavily exposed survivors of the A-bomb in Hiroshima and Nagasaki (1). Court Brown and Doll (2, 3) have reported a high incidence of leukemia among patients who received x-ray therapy for ankylosing spondylitis. It is clear that radiation can induce leukemia in man. On the other hand, animal experiments have shown that various chemical agents and viruses can also cause leukemia (4).

The Leukemia Registry has been in operation at Atomic Bomb Casualty Commission (ABCC) since 1950 for the study of the leukemogenic effect of A-bomb exposure (5). In this program, all possible cases of leukemia are searched for from a wide

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range of sources. Screening of death certificates and confirmation of diagnosis have been made for almost all leukemia deaths within the cities of Hiroshima and Nagasaki since 1948.

The present study was designed in the hope of obtaining leads to the elucidation of what, if any, environmental factors other than A-bomb exposure, especially occupation, have contributed to the development of leukemia in Hiroshima and Nagasaki since 1945, and how such factors in combination with A-bomb exposure have affected the development of leukemia.

Methods and materials

Subjects

From among the patients included in the ABCC Leukemia Registry as of December 1968, those satisfying the following conditions were selected and designated as index cases:

1) Patients diagnosed by the hematologist to be leukemia and whose certainty of diagnosis was "definite" or "probable".
2) Resident at time of onset in either Hiroshima or Nagasaki City.
3) Onset of disease between 1945 and the end of December 1967.

For each index case, a matched control was selected from one of two ABCC fixed samples (6, 7). Controls for patients born before August 1945 were drawn from the Master Sample (6), while controls for patients born later were selected from the sample (7) for the Mortality Study of Offspring of A-bomb Survivors. The controls were matched with the patients on the following five characteristics: city; sex; date of birth ±30 months; exposure distance (less than 1400 m, 1400–1999 m, 2000–9999 m, not in city at the time of the bombs (ATB), born after bomb); alive and resident in either Hiroshima or Nagasaki City at time of onset of disease in patient.

Methods

In view of the difficulties of retrospective study over a span of 10 or 20 years, it was decided to seek only simple information for which the chance of error due to the forgetfulness of the informant or type of information would be small. Furthermore, inasmuch as most of the leukemia patients were dead at the time of the interview, whereas the controls were often alive, different interviewing approaches were required to obtain an environmental history.

Information was obtained for both patients and controls using the same questionnaire by interview of the subject or a closely related person. The choice of informant in order of preference was as follows: the subject, parent, brother or sister, child, a relative who had been living with the subject, and others.

For adult leukemia cases and controls, the questioning identified persons who had ever worked as a production process worker or a medical worker. For children with onset of leukemia at less than 15 years of age and their controls, information was obtained on birth order, mother's age at time of birth, any abnormality of mother or subject during pregnancy or at childbirth, and history of medical x-ray exposure of the mother during pregnancy.

Information collected on all subjects included: environment of residence at the time of onset of disease; history of contact with animals; deaths due to cancer among parents, siblings or children; and consanguinity of parents.

Because of the small number of cases, Hiroshima and Nagasaki were combined in the comparison of the index cases and controls. When any factor was found to be associated with the development of leukemia, the data were examined separately by city to determine whether the same association could be seen in each city. Relative risks for index cases and controls for each factor were compared using the matched sample method described by Mantel and Haenszel (8).

Interview Rate

A total of 492 patients in both cities were diagnosed as definite or probable cases with

Controls	
Kind of informant	
Subject	
Parent	
Spouse	
Siblings	
Children	
Others	
Total	
Proportion	

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TABLE 1

Kind of informant between index cases and controls

Controls	Index cases						Total	Proportion
Kind of informant	Kind of informant							
	Subject	Parent	Spouse	Siblings	Children	Others		
Subject	6	21	67	20	14	31	159	38.50
Parent	2	101	9	6	0	12	130	31.48
Spouse	1	6	42	5	5	4	63	15.25
Siblings	0	18	2	0	0	5	25	6.05
Children	0	0	7	1	1	3	12	2.91
Others	0	9	3	5	1	6	24	5.81
Total	9	155	130	37	21	61	413	100.0
Proportion	2.18	37.53	31.48	8.96	5.08	14.77	100.0	

Concordance rate = 156/413 X 100 = 37.8%.

onset of leukemia by the end of December 1967. For 15 of the leukemia patients it was not possible to obtain a control matched on all five factors. For 64 pairs of leukemia cases and controls, interviews could not be completed for one or the other because all possible informants had moved out of the cities. Thus, during the period from September 1966 to March 1969, an interview was completed only for 413 matched pairs of leukemia patients and controls.

Table 1 compares the kind of informants for the index cases and controls in the 413 matched pairs for whom an interview was completed. The type of informant was the same in only 156 pairs, or 38 per cent. There was a large difference in the type of informant between cases and controls mainly because the subject was himself the informant in 39 per cent of the controls, but in only 2 per cent of the index cases. This was because most of the leukemia patients had died by the time of the interview, while most of the controls were still living. Although such obvious biases were to be expected in this interview survey, no restriction was made because it was felt to be impractical to exclude the subjects from the interview. In order to reduce problems arising from such differencesit was decided to seek only simple items of information which, it was thought, the experienced ABCC investigators could obtain without bias as between patients and controls.

RESULTS

The responses to the various questions were compared for the 413 matched pairs of index cases and controls who had been interviewed.

History of possible occupational exposure to benzene or medical x-ray

The risk of leukemia has been reported to be high among workers who handle benzene or are exposed to medical x-ray. Therefore, the following 15 occupations (9) in which benzene or x-ray exposure may be frequent were selected for a comparison of the index cases and controls. In the study of these occupations, 303 adult cases with onset of leukemia at age 15 years or over and their controls were compared. The occupations were: (a) carbon dioxide gas furnace worker; (b) welder, plater, tinsmith or sheet metal worker; (c) battery manufacturing worker; (d) cabinet maker, furniture maker or finishing worker; (e) worker engaged in printing, repairing or cleaning printing machines; (f) platemaker, lithog-

TABLE 2

Comparison of occupational history related to potential exposure to benzene or medical x-ray, frequency of occupational history for 11 occupaliona

Controls	Index cases		Relative risk	x^2 test
	Yes	No		
Yes	2	12	2.5 (30/12)	$x^2 = 6.881$
No	30	259		$df = 1$
				$p < .01$

TABLE 3

Comparison of occupational history related to potential exposure lo benzene or medical x-ray; and duralion of orcupationnl history for 11 occupations

Controls'	Duration (years]	Index cases'		
		Yes		No
		≧5	<5	0
Yes	≧5	1	1	8
	<5	0	0	4
No	0	24	6	258

Relative risk:
≧5 years 3.0 (24/8) <5 years 1.5 (6/4)
$x^2 = 7.031$, $p < .01$ $p > .05$
$df = 1$

• 1 pair was rejected because of unknown information regarding duration.

rapher; (g) rubber products worker; (h) leather products worker; (i) glass craftsman or pottery painter; (j) painter; (k) chemical worker; (1) soft drink manufacturing worker; (m) barber, beautician or dry cleaning worker; (n) radiologist or x-ray technician; (o) physician, or laboratory technician. In fact, however, no leukemia case or control had a history of the occupations *(c)*, (f), (j), (o), so further discussion is limited to the 11 occupations that were actually reported.

The risk of leukemia is shown in table 2 in relation to a history of any of these occupations, and in table 3 by the duration of such work subdivided into five or more years, less than five years, and never. The risk of leukemia was found to be 2.5 times higher among those with a history of any of these 11 occupations in comparison with those without, and the risk increased with longer duration of occupation. Comparisons were made within each city and the relative risk in each city was about the same, 2.6–2.7. Table 4 shows the frequency of each of the 11 occupations in the index cases and controls. The frequency of each individual occupation is very low. However, the frequency of the following six occupations was found to be higher in the index cascs: 1) welder, plater, tinsmith or sheet metal worker; 2) cabinet maker, furniture maker or finishing worker; 3) rubber products worker; 4) glass craftsman or pottery painter; 5) barber, beautician or dry cleaning worker; 6) radiologist or x-ray technician.

No investigation was made of the specific chemical agents handled by the individuals engaged in these occupations. These are,

TABLE 4

Frequency of history for each of 11 occupations for index cases and controls

Occupation	A Leukemia cases (303 pairs)	B Controls (303 pairs)	Difference (%) A − B
1. Carbon dioxide gas furnace worker	4 (1.3)*	5 (1.7)	(−0.4)
2. Welder, plater, tinsmith or sheet metal worker	6 (2.0)	0 (0.0)	(2.0)
3. Cabinet maker, furniture make or finishing worker	7 (2.3)	3 (1.0)	(1.3)
4. Worker engaged in printing, repairing or cleaning printing machines	1 (0.3)	1 (0.3)	(0.0)
6. Rubber products worker	2 (0.7)	0 (0.0)	(0.7)
6. Leather products worker	1 (0.3)	1 (0.3)	(0.0)
7. Glass craftsman or pottery	2 (0.7)	0 (0.0)	(0.7)
8. Chemical worker	1 (0.3)	1 (0.3)	(0.0)
9. Soft drink manufacturing worker	1 (0.3)	2 (0.7)	(−0.4)
10. Barber, beautician or dry cleaning worker	6 (2.0)	2 (0.7)	(1.3)
11. Radiologist or x-ray technician	2 (0.7)	0 (0.0)	(0.7)

• Parentheses show percentages.

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however, occupations in which organic solvents or x-rays are gcncrally used. Thus, this suggests that these occupations and in particular the occupntional use of benzene for a long duration increases the risk of leukemia. The leukemia risk was examined in relation to a history of any of the 11 occupations and chronicity of leukemia. The relative risk mas 2.9 for acute and 1.8 for chronic leukemia.

No relationship was evident between a history of one of the 11 listed occupations and year of onset of leukemia: For cases with onset between 1945 and 1957 the relative risk was 2.6, and for the years 1958 to 1967 the risk was 2.4.

To guard against the possibility that the data might be affected by the fact that the kind of informant was not always the same for the leukemia cases and the controls, the pairs were subclassified into those in which the kinds of informant were identical, and those in which they mere different. The relative risk was 11.0 (11/1) for the pairs that had similar informants, but only 1.7 (19/11) for the pairs where they were different. Clearly, the effect of differences in kind of informant was to reduce markedly the apparent relative risk.

Effect of A-bomb exposure and history of occupational exposure to benzene or medical x-ray upon the development of leukemia

Recent estimates of the radiation dose received by A-bomb survivors (tentative 1965 dose—T65D) (10) indicate that doses of 100 rad or more had been received within 1200 m in Hiroshima and within 1500 m in Nagasaki. The dose was lower, generally in the range of 1 to 99 rad between 1200–1999 m in Hiroshima and between 1500–2499 m in Nagasaki, and was negligible beyond 2000 m in Hiroshima and 2500 m in Nagasaki. Exposure to doses of 100 rad or more has been found to result in a marked increase in leukemia in both Hiroshima and Nagasaki, while exposure to lower doses, less than 100 rad, has resulted in increased risk of leukemia, particularly chronic leukemia, only among survivors in Hiroshima (2).

TABLE 5

Relationship between occupational exposure to benzene or medical x-ray and atomic bomb exposure status; and frequency of occupational history for 11 selected occupations by three groups of exposure status

Exposure status† (T65 dose)	Controls*	Index cases. Yes	Index cases. No	Relative risk
1) Inner proximal exposed (100 rad or more)	Yes	0	2	1.6 (3/2)
	NO	3	41	
2) Outer proximal exnosed (1-99 rad)	Yes	1	1	4.0 (4/1)
	No	4	36	
3) Distal exposed and others (negligible or none)	Yes	1	9	2.4 (22/9)
	NO	22	176	$\chi^2 = 4.645$, $p < .05$ df = 1

* One pair in which the index case developed leukemia before the bombing is excluded.

† Exposure classification:

Distance from the hypocenter: Hiroshima	Distance from the hypocenter: Nagasaki	T65 Dose (rad)
1) <1200 m	<1500 m	≧100
2) 1200-1999 m	1500-2499 rn	1-99
3) 2000 m & over	2500 rn & over	Negligible
Non-exposed	Non-exposed	None

The cases were therefore classified into the three groups described below, and in table 5 the relative risk of leukemia in these three exposure groups is compared with respcct to a history of any of the selected occupations. The heavily exposed group, in which the dose is estimated to have been 100 rad or more, had a relative risk from the selected occupations of 1.5, whereas the low dose group, consisting of outer proximally exposed individuals, had a risk of 4.0, and the unirradiated other group had a relative risk of 2.4. Of course, among the proximally exposed persons, a history of any of the selected occupations was noted in only eight of the leukemia patients and four of the controls. These 12 individuals are shown by T65D, disease type, occupation, etc. in table 6. Examination of the relative risk

TABLE 6

Relationship between occupational exposure to benzene or medical x-ray and atomic bomb exposure status; eight proximal exposed cases and four controls with a history of any of 11 selected occupations

Controls: history of selected occupation	Index cases: history of selected occupation								
	Yes*					No*			
	MF No.	Age at	Type†	T65D rad	Occupation‡	MF No.	Type	T65D rad	Occupation‡
Yes*	249-266	32	CGL	31	2	121-894	Control	361	I
	295-993	—	Control	Not estimated	1	441-238	Control	226	1 & 8
						207-042	Control	32	3
No*	400-538	31	AL	573	11				
	295-870	51	AL	212	10				
	220-344	51	CGL	44	8				
	437-743	70	AL	38	2				
	400-257	23	AL	19	3				
	233-136	64	AL	17	3				
	138-148	50	AL	6	2				

* **Answers to** history of **11 selected occupations.**
† **AL = Acute leukemia;** CGL = **Chronic ernnulocytic leukemia.**
‡ **Number corresponds to occupation in table 4.**

TABLE 7

*Relationship between occupational exposure to benzene or medical x-ray occupations and atomic bomb exposure status; frequency of history of 6 selected occupations**

Exposure status	Controls	Index case		Relative risk	x^2 test
		Yes	No		
Proximal† exposed	Yes	0	1	6.0 (6/1)	$p > .05$
	No	6	87		
Distal‡ and others	Yes	0	4	4.5 (18/4)	$x^2 = 7.682$ $df = 1$ $P < .01$
	No	18	186		
Total	Yes	0	5	4.8 (24/5)	$x^2 = 11.172$ $df = 1$ $p < .01$
	No	24	273		

* Welder, plater, tinsmith or sheet metal worker. Cabinet maker, furniture making and finishing worker. Rubber products worker. Glass craftsman or pottery painter. Barber, beautician or dry cleaning. Radiologist or x-ray technician.
† Exposed under 2000 m in Hiroshima and under 2500 m in Nagasaki.
‡ Exposed ≧2000 m in Hiroshima and ≧2500 m in Nagasaki, and not in city or born after August 1945.

after classifying the cases grossly into high and low dose groups revealed an occupational risk of 1.0 in the high dose group. The relative **risk** in the **low** dose group, however, was 5.0, approximately twice as high as the **risk** of **2.4** in the distal exposed and non-exposed groups, but the number **of** cases is small.

The *six* occupations noted at a higher frequency among the index cases than in the controls in table **4** were selected for an *examination* in more detail of the relation of occupational exposure and A-bomb exposure (table **7**). In general, the **risk** was approximately **5** times higher among those with a history of any of these **six** occupations in comparison with those without. The relative risks in the proximal group and in the distal and non-exposed group were 6.0 and **4.5,** respectively.

Age of mother, birth order and abnormality during pregnancy or at childbirth

The 106 matched pairs of children with onset of leukemia at less than **15** years of age and their controls are compared with respect to mother's age at time of birth of subject, and birth order. However, no statistically significant relation could be found between mother's age or birth order and the

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risk of leukemia. Information was also obtained as to whether the mother had any abnormality during pregnancy or at birth of the subject. Abnormalities were reported in 11 of the 106 index cases but in only two of the 106 controls. In the leukemin group, nine reported severe "morning sickness" or other complications during pregnancy, but since it is possible that the mother of index cases had greater concern over such abnormalities during pregnancy as compared with the controls, it cannot be concluded that abnormalities during pregnancy increase the risk of leukemia. Information on exposure to medical x-ray was sought, but the number of cases was small and no relation could be found.

Consanguinity of parents and environmental factors

Consanguinity of parents and such factors as socioeconomic status and history of contact with animals, including pets were examined, but none appeared to be factors related to the incidence of leukemia.

Discussion

Numerous epidemiologic studies have been made on the etiology of leukemia. Of the various causes of leukemia in man, most evident is the effect of radiation. It is well known that radiation can induce leukemia, and that there is a marked increase of leukemia among A-bomb survivors and among patients receiving radiation therapy for ankylosing spondylitis (1–3).

On the other hand, the results of animal experiments suggest that viruses may be one of the causes of leukemia (4), but there are few reports of human experience which provide epidemiologic evidence of a transmission theory beyond the report (11) of the development of eight cases of leukemia between 1957 to 1960 among children at the primary school in Niles, Illinois.

Other causes of leukemia reported from experimental studies include various chemical agents which disturb the hematopoietic function of the bone marrow. A typical example is the induction of leukemia by benzene or its derivatives. For this reason, 11 classification of occupations in which benzene or its derivatives, or x-ray is frequently handled were selected for a study of the risk of leukemia by whether there had been a history of such occupations. The risk of leukemia was found to be significantly higher (about 2.5 times higher) among those with a history of such occupations as compared with those without, especially among those who had engaged in these occupations for at least five years. The risk of leukemia was also examined by whether there had been a history of having worked as a production process worker in any occupation other than the above 11, but no significant relationship could be found. The increase of risk was noted specifically only in those occupations in which there is frequent contact with benzene or x-rays. Examination in more detail revealed that the risk was higher in those occupations in which various volatile organic solvents are used.

Approximately one-third of all cases of leukemia in Hiroshima and Nagasaki are among the proximally exposed persons and presumably are due to exposure to significant amounts of radiation from the A-bomb. As shown in tables 5 and 6, the distal and non-exposed group had a risk of leukemia about 2.5 times higher among those with a history of occupational exposure to benzene or medical x-rays as compared to those without. In the so-called heavily exposed group, however, the effect of A-bomb radiation is so large that there seemed no change in the risk by whether or not there was a history of any of the selected occupations. In the low dose group, the risk was approximately 5 times higher among those with a history of any of the selected occupations but the numbers are so small that the relative risk is not measured very accurately. However, of the five leukemia patients in the low dose group with a history of such occupations, four were acute leukemia so that this does not explain the high

risk of chronic leukemia that has been noted in the so-called lightly exposed group of Hiroshima (1).

Manning (12), Stewart (13), MacMahon (14), and others have reported that the risk of leukemia is high in children of older mothers and in the first child. Therefore, the risk of leukemia was esamined in relation to age of mother and birth order, but no statistically significant evidence was found that these factors affect the risk of leukemia.

Awa, Bloom et al. have reported that the incidence of stable chromosome aberrations increase with age (15, 16). When considered in association with the report of the possible relation between congenital or acquired chromosome breakage and the development of leukemia **(17)**' and the report of the higher frequency of Down's syndrome among children of older mothers (18), the suggestion that there is a tendency for the risk of leukemia to increase with the age of mother may be epidemiologically significant. However, the mother's age was 40 or over in only six eases of leukemia so that it cannot be concluded from the present investigation that the incidence of leukemia increased significantly with age of mother.

A number of reports have been published on the relation between Down's syndrome and leukemia in children (19–21), but we did not attempt to study this condition since accurate information concerning such medical matters could not be ohtnined from interview of persons closely related to the patients. Questions mere asked about congenital abnormalities, but none were reported so that retrospective study of such conditions by interview does not appear to be practical.

With regard to the relation between leukemia and socioeconomic factors, it has been reported in the United States that the risk of leukemia is increased among persons of higher socioeconomic status and among Jews (22). Therefore, in an attempt to study the effect of social factors in the development of leukemia, the social environment of the residence at time of onset and the history of contact with animals were reviewed for possible differences between the leukemia patients and the controls. If it is assumed that leukemia is transmissible and that animals carry the leukemia virus, the proportion of households in which there is greater contact with animals should be higher in the leukemia group as compared with the controls, although Miller states that even if viruses contribute to the development of leukemia, it would be extremely difficult to demonstrate horizontal transmission of leukemia epidemiologically **(23).** Moreover, we also wanted to examine any difference in socioeconomic factors between leukemia cases and controls. The present study, however, did not show any significant difference by occupation of head of household, environment of residence, consanguinity of parents, whether ever bitten by a dog or whether any animal had been kept during the five years prior to onset, so that there was no finding suggesting transmission via man or animal or the importance of socioeconomic factors.

The present study was done using the ABCC Leukemia Registry and the data that have been accumulated over the approximately 20 years since 1950, in order to determine whether any factors other than A-bomb exposure are related to leukemia. It was thought that a case history study would be the only possible approach to the investigation of factors involved in **a** disease with so low an incidence as leukemia. Even for such a study, however, no effective method of investigating patients who had developed leukemia over the past 10 or more years could be found other than to interview closely related individuals. On the other hand, most of the members of the ABCC fixed sample who were chosen for use as controls were alive, whereas the index cases were dead so that there was some doubt concerning the homogeneity of the two groups as to the accuracy of data collection because of the difference in the type of informant for each. Nevertheless, it

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is hoped that the present results will be suggestive for future studies.

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