



[haematologica reports]  
2006;2(15):42-45

## Environmental risk factors for MDS/AML

LIVIO PAGANO  
MORENA CAIRA  
LUANA FIANCHI  
GIUSEPPE LEONE

*Istituto di Ematologia, Università Cattolica del Sacro Cuore, Roma, Italy*

A B S T R A C T

Little is known about the aetiology of myelodysplastic syndromes/acute myeloid leukemia (MDS/AML). Several factors could play a role in the development of these diseases. Apart from recognized risk factors as alkylating agents, ionizing radiation and benzene, some others have been suggested by few epidemiological published studies (environmental and occupational exposures and lifestyle factors). In this article the currently known risk factors for MDS/AML are reviewed. The better knowledge of their importance in leukemogenesis could lead in the future to improve the prevention of these diseases.

Prof Livio Pagano  
Istituto di Ematologia  
Largo Francesco Vito 1  
00168 Rome, Italy  
Phone +390630154180  
E-mail pagano@rm.unicatt.it

Considerable efforts have been made to identify risk factors for the myelodysplastic syndrome-acute myeloid leukemia (MDS/AML), but only a minority of leukemia cases can currently be attributed to identified or hypothesized factors.

Environmental and occupational exposures to chemicals including pesticides have been widely studied, although the results are not consistent, with the exception of benzene.<sup>1</sup> Smoking seems to be a weak causal risk factor.<sup>2</sup> The risk of ionizing radiation has further been quantified in recent studies, although the effects of low doses have not yet been clarified.<sup>3</sup> The results for non-ionizing radiation continue to be inconsistent, but a large effect of electromagnetic fields on the risk of leukaemia appears to be unlikely.<sup>4</sup>

This article reviews the currently known risk factors for leukemia and their importance for leukemogenesis in the population. It focuses on literature published in the last decades since reviews on leukemia epidemiology including earlier data are available (Figure 1).

### Demonstrated occupational causes

Environmental influences have received widespread attention in the search for causal factors of leukemia. They include a long list of occupational criteria, ionizing and non-ionizing radiations, smoking, diet and other lifestyle

factors. In most cases, the numerous studies that jointly constitute the epidemiological evidence pro or contra the associations with leukemia and other cancers cannot easily be summarized. Apparently inconsistent results in and between studies may be based on different study designs, different populations at risk or uncontrolled biases. Given this heterogeneity, many studies have focused on the following exposures. A causal relation with leukemia, especially AML, has been demonstrated according to the Bradford Hill criteria (strength of association, consistency, specificity, temporality, dose-response relationship, coherence and analogy) for only two agents: benzene and ionizing radiation.<sup>5,6</sup>

### Benzene

Occupational benzene exposure has been demonstrated to cause MDS/AML.<sup>1</sup> There is strong evidence that high daily exposure to benzene is associated with AML, and both dose-response and time-response relations have been demonstrated.<sup>7</sup> For example, a large series of rubber-workers showed an association between benzene exposure and AML incidence and increasing the benzene concentration increased the AML risk.<sup>8,9</sup>

However long periods of low-dose exposure have also been related to leukemia: a Chinese cohort study of almost 74.828 workers exposed to benzene compared to 35.805 not exposed

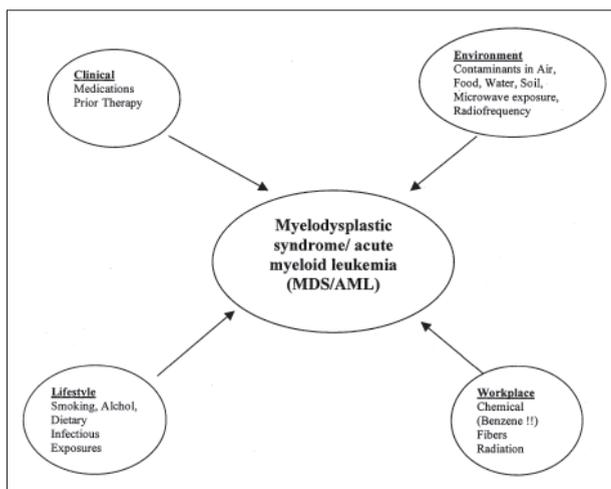


Figure 1. Risk Factors for myelodysplastic syndrome /acute leukemia

workers, demonstrated a higher risk for MDS/AML among benzene workers (RR  $\infty$ , 95% C.I. 1.7- $\infty$ ). Furthermore it has been demonstrated that this risk is also associated to long periods of low-dose exposure (average levels below 10 ppm).<sup>10</sup>

Various workers categories are exposed to benzene and show an increased risk to develop a AML. In particular are considered at higher risk painters, printers, petroleum industry workers and tankers, rubber industry workers, chemical industry workers, tanners, shoemakers.<sup>11</sup>

Tobacco smoking is the major source of non occupational benzene. It is well stated that cigarette smoke contains a number of well-known or potential leukemia-causing agents of which benzene is the most relevant. Evidence is accumulating that cigarette smoking increases the risk of AML, and the *International Agency for Research on Cancer* (IARC) has reported recently that there is sufficient evidence for the causality between active smoking and adult AML.<sup>12</sup> Cohort studies demonstrated that a higher risk is strictly correlated to the number of pack/year smoked cigarettes, and the increased risk associated with smoking started to decline 5 years after smoking cessation.<sup>2</sup>

### Electromagnetic fields

Electromagnetic fields (EMF) in occupational settings or as residential exposure have been suspected to be leukemia risk factors since 1979 when an association between household wiring codes and childhood leukemia was reported.<sup>4</sup> An interesting study, analyzing data from New Zealand can-

cer registry, demonstrated an overall leukemia elevated risk in electrical workers (OR 1.62, 95% CI 1.04-2.52), in particular for radio and television repairers (OR 7.86, 2.20-28.09), electricians (OR 1.68, 0.75-3.79), linemen (OR 2.35, 0.97-5.70) and power station operators (OR 3.89, 1.00-15.22).<sup>13</sup> In a subsequent case-control study nested in a cohort study among electric utility employees in Canada, electric and magnetic field exposures were evaluated separately.<sup>14</sup> An increased risk for leukemia with increasing cumulative electric field exposure was noted (adjusted OR 4.45; 95% CI 1.01-19.7), while the effect for cumulative magnetic field exposure was insignificantly elevated (OR 1.56; 95% CI 0.47-5.14).

With regard to residential exposure to high-voltage power lines, some available studies evidence not strong enough to support a hypothesized link between adult leukemia and residential exposure to EMF. Considering the association between childhood leukemia and EMFs, this correlation has been supported in various studies showing moderately elevated risks, while other large case-control studies found no overall risk elevation for leukemia in children exposed to residential magnetic fields.

Due to rather inconsistent results, currently the possible evaluation of EMFs role in leukemia development is still preliminary.

### Ionizing radiation

The causal relation between ionizing radiation and hematological malignancies was first demonstrated during the follow-up of the Nagasaki and Hiroshima atomic-bomb survivors by their high incidence of AML.<sup>6</sup> The United Nations Scientific Committee on Effects of Atomic Radiations (UNSCEAR) reported in 2000 that levels of occupational radiation exposure today are approximately half of what they were in earlier decades. Some studies of nuclear and medical workers have examined in more detail the relation between exposure to low doses of ionizing radiation (<5 mSv/year) and leukemia.<sup>8-13</sup> Pooling mortality data from seven cohort studies covering 96,673 nuclear workers, the IARC study group found a significant excess relative risk of leukemia associated with exposure to ionizing radiation.<sup>15</sup> A cohort study demonstrated a significantly increased relative risk of MDS/AML in workers participating in the United Kingdom's atmospheric weapons tests and experimental program.<sup>16</sup>

Considering working medical exposure to ionizing radiation a recent review evaluated the cancer risk among more than 270.000 radiologist and radiologic technologists compared to controls not

exposed collected in 8 major cohort from United Kingdom, Denmark, China, Japan, USA and Canada. The results of these wide cohort series of workers presented conflicting results about the leukemia risk. In some series an increased risk of AML among these workers was observed while in others no difference with the control population was detected. Of interest the risk seems correlated with the number of years worked (higher in those that worked more than 5 years) principally before of 1950.<sup>17</sup>

### Lifestyle factors

More than tobacco smoking others lifestyle factors are considered favoring AML/SMD. Epidemiological evidence suggesting the role of some dietary factors in MDS/AML etiology and prevention is accumulating. Of these dietary factors, fruits and vegetables contain numerous bioactive and potentially anti-carcinogenic substances that might inhibit the process of carcinogenesis. Some recent studies demonstrated that increased vegetable and fruit consumption may decrease the risk of AML.<sup>2</sup> On the other hand diets rich in meat and protein, lack of breastfeeding, and ingestion of arbutin-containing foods is associated with a high risk of MDS/AML.<sup>18</sup>

Of note case-control studies suggest that AML may be related to exposure to infectious agents among occupational groups as butchers but it did not take into account confounding factors, such as exposure to chemicals in the meat industry.<sup>19</sup>

Discordances on the role of obesity are reported. There is growing evidence that overweight and obesity are associated with MDS/AML.

The role of overall alcohol consumption on risk of MDS/AML has been explored in a few studies with conflicting results.<sup>20,21</sup> Resveratrol, an antioxidant found in the skin of grapes, has been shown, in *in vitro* and *in vivo* studies, to affect initiation, promotion, and progression of different cancers, including leukemia. Different mechanistic pathways have been proposed for its antileukemic effect including induction of leukemia cell differentiation, apoptosis, cell cycle arrest, and inhibition of DNA synthesis.

### Discussion and conclusions

Causal relations are now well-documented between MDS/AML and high levels of exposure to benzene and ionizing radiation; various studies demonstrated also associations between MDS/AML and exposure to low levels of benzene or ionizing radiation. Despite many studies of occupational risk

factors, MDS/AML due to occupational exposure have not been adequately studied in epidemiologic situations and discordances are present in literature. The relative rarity, long latency periods, and confounding factors help to explain the scarcity of epidemiological studies concerning this matter.

Information about the types of pesticides, solvents and infectious agents, or the role of EMF or pollution in the development of MDS/AML is scanty and some confounding bias could be added by lifestyle factors. Better identification by clinicians of those occupational jobs characterized by an higher MDS/AML incidence, might improve in the future their prevention.

### References

1. Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia. An epidemiologic risk assessment. *N Engl J Med*. 1987 ;316:1044-50.
2. Kasim K, Levallois P, Abdous B, Auger P, Johnson KC. Lifestyle factors and the risk of adult leukemia in Canada. *Cancer Causes Control*. 2005 ;16:489-500.
3. Tondel M, Lindgren P, Hjalmarsson P, Hardell L, Persson B. Increased incidence of malignancies in Sweden after the Chernobyl accident—a promoting effect? *Am J Ind Med* 2006; 49 :159-68.
4. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. *Am J Epidemiol*. 1979 ;109:273-84.
5. Descatha A, Jenabian A, Conso F, Ameille J (2003) Affections hématologiques malignes et activité professionnelle. *Encycl Me d Chir Paris (Editions médicales et scientifiques Elsevier SAS. Tous droits réservés)*, Toxicologie-Pathologie professionnelle, 16530. A10: 1-12.
6. United Nations Scientific Committee on the Effects on Atomic Radiation (UNSCEAR) (2000) Sources and effects of ionizing radiation. United Nations.
7. Hayes RB, Songnian Y, Dosemeci M, Linet M Benzene and lymphohematopoietic malignancies in humans. *Am J Ind Med* 2001; 40: 117-26.
8. Wong O. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med* 1995; 52: 380-4.
9. Hayes RB, Yin SN, Dosemeci M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine-National Cancer Institute Benzene Study Group. *J Natl Cancer Inst* 1997; 89: 1065-71.
10. Yin SN, Hayes RB, Linet MS, Li GL, Dosemeci M, Travis LB, Zhang ZN, Li DG, Chow WH, Wacholder S, Blot WJ. An expanded cohort study of cancer among benzene-exposed workers in China. Benzene Study Group. *Environ Health Perspect*. 1996 ;104 Suppl 6:1339-41.
11. Terry PD, Shore DL, Rauscher GH, Sandler DP. Occupation, hobbies, and acute leukemia in adults. *Leuk Res*. 2005; 29:1117-30.
12. IARC. IARC monographs on the evaluation of carcinogenic risks to human. Tobacco smoke and involuntary smoking. Volume 83. International Agency for research on Cancer, Lyon.
13. Pearce N, Reif J, Fraser J. Case-control studies of cancer in New Zealand electrical workers. *Int J Epidemiol*. 1989 ;18:55-9.
14. Miller AB, To T, Agnew DA, Wall C, Green LM. Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers. *Am J Epidemiol*. 1996 15;144:150-60.
15. Direct estimates of cancer mortality due to low doses of ionizing radiation: an international study. IARC Study Group on Cancer Risk among Nuclear Industry Workers. *Lancet*. 1994 15; 344:1039-43
16. Muirhead CR, Bingham D, Haylock RG, O'Hagan JA, Good-

- ill AA, Berridge GL, English MA, Hunter N, Kendall GM. Follow up of mortality and incidence of cancer 1952-98 in men from the UK who participated in the UK's atmospheric nuclear weapon tests and experimental programmes. *Occup Environ Med.* 2003 ;60:165-72.
17. Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM, Ron E. Cancer risks among radiologists and radiologic technologists: review of epidemiologic studies. *Radiology.* 2004;233:313-21.
  18. McDonald TA, Holland NT, Skibola C, Duramad P, Smith MT. Hypothesis: phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia. *Leukemia* 2001; 15:10-20.
  19. Bethwaite P, McLean D, Kennedy J, Pearce N. Adult-onset acute leukemia and employment in the meat industry: a New Zealand case-control study. *Cancer Causes Control.* 2001;12:635-43.
  20. Dalamaga M, Petridou E, Cook FE, Trichopoulos D. Risk factors for myelodysplastic syndromes: a case-control study in Greece. *Cancer Causes Control.* 2002 ;13:603-8.
  21. Strom SS, Gu Y, Gruschkus, Pierce SA, Estey EH. Risk factors of myelodysplastic syndromes: a case-control study. *Leukemia.* 2005 ;19:1912-8.