Ik6 could be detected even with nested RT-PCR (M.T. et al, unpublished observation, 2000), indicating that there are yet-to-be-clarified differences aside from PCR technical issues that Dr Ishimaru is most concerned with. In accord with other studies in Japan,[4,5] we demonstrated that among childhood lymphoid leukemia, Ik 6 was detectable in 26.3% of B-precursor acute lymphoblastic leukemia (ALL) with first-round RT-PCR and Western blot.[6] Finally, in our article,[1] we clearly showed that the pathogenesis of myelomonocytic/monocytic AML may involve aberrant regulation of apoptosis due to unscheduled expression of the Ik6 isoform.

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To the editor:

Frequency of *BCL-2/J$_H$* translocation in healthy males exposed to low-level radiation in comparison to age-matched healthy controls

The t(14;18) translocation has been detected by cytogenetic and molecular techniques in about 90% of follicular lymphomas, 50% of adult undifferentiated lymphomas, and 20% of diffuse large-cell lymphomas. Based on Southern blot and polymerase chain reaction (PCR) analysis, 50% to 60% of follicular lymphomas carry t(14;18)-MBR-translocations.[1] The occurrence of t(14;18) is not restricted to malignant lymphoma: 50% to 60% of healthy individuals were found to carry t(14;18)-MBR–positive cells detectable by sensitive PCR techniques.[2-4] Therefore, the number of circulating t(14;18)-positive cells might serve as an indicator for environmental exposure to carcinogens and possibly correlate with the cumulative risk of developing t(14;18)-positive non-Hodgkin lymphoma (NHL).[5] Since ionizing radiation can induce chromosomal translocations in human cells in vitro, for example, t(9;22) and t(8;21),[6] we initiated this study to investigate whether exposure to low-level radiation has an influence on the frequency as well as the total number of circulating t(14;18)-positive cells in healthy individuals, that is, the generation of the translocation as well as clonal expansion or progression.[7]

At the occasion of routine health checks, peripheral blood samples were obtained with informed consent from 131 healthy male employees working at the local nuclear power plant (NPP) in

Table 1. Frequency of *BCL-2/J$_H$* translocation in peripheral blood lymphocytes from males working at a nuclear power plant and from age-matched healthy male volunteers

Group	n	t(14;18)-positive/total number tested (%)	Multiple translocations/positive individuals (%)
NPP (all)	131	79/131* (60.3)	27/79‡ (34.2)
NPP—A (less than 50 mSv)	61	36/61† (59.0)	16/36 (44.4)
NPP—B (50-100 mSV)	34	21/34† (61.8)	6/21 (28.6)
NPP—C (100-200 mSv)	24	14/24† (58.3)	1/14 (7.1)
NPP—D (200-400 mSv)	12	8/12† (66.6)	4/8 (50.0)
HV (all)	131	72/131* (55.0)	27/72‡ (37.5)
HV—A	61	32/61† (52.5)	15/32 (46.8)
HV—B	34	16/34† (47.1)	3/16 (18.8)
HV—C	24	14/24† (58.3)	5/14 (35.7)
HV—D	12	10/12† (83.3)	4/12 (33.3)
All	262	151/262 (57.6)	54/151 (35.8)

NPP workers were separated into 4 groups based on their cumulative radiation exposure (50 to 400 mSv). The statistical analyses between the different groups were performed using the χ^2-test.

NPP indicates male nuclear power plant workers; HV, age-matched healthy male volunteers.

*These values represent the number of samples giving positive PCR results/the total number of samples in the group of NPP workers and healthy controls (χ^2-test: $P = .38$).

†These values represent the number of samples showing positive PCR results/the numbers of samples in subgroups A-D of NPP workers and healthy controls (χ^2-test: A, $P = .46$; B, $P = .22$; C, $P = 1.0$; D, $P = .35$).

‡These values represent the number of samples with multiple translocations/the numbers of positive individuals in the group of NPP workers and healthy controls (χ^2-test: all individuals in each group: $P = 0.67$; in subgroups: A, $P = .84$; B, $P = .49$; C, $P = .065$; D, $P = .67$).

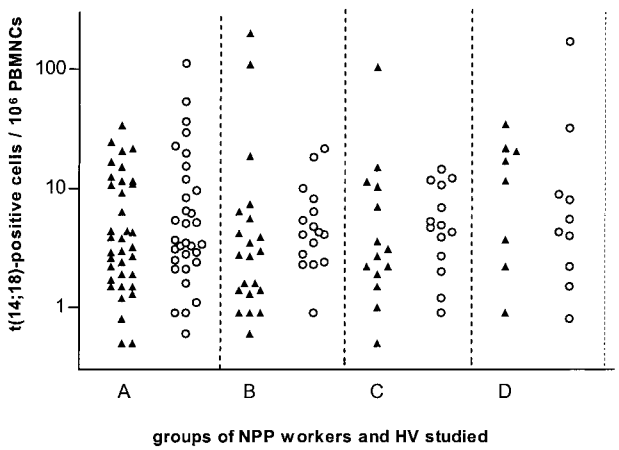

Figure 1. *BCL-2-MBR/J$_H$* translocation–carrying cells in NPP workers and in healthy controls. Total number of circulating *BCL-2-MBR/J$_H$* translocation–carrying cells in t(14;18)-positive healthy males working at a nuclear power plant (▲) grouped according to their cumulative radiation exposure (see Table 1) and age-matched healthy controls (○). There were no significant differences between NPP workers and healthy controls as well as their subgroups, A to D (Mann Whitney test; all positive individuals: $P = .19$; subgroup A, $P = .45$; B, $P = .15$; C, $P = .46$; D, $P = .51$).

Lubmin, Germany. They were grouped according to their total cumulative radiation dose exposure: group A, < 50 mSv (n = 61); B, 50-100 mSv (n = 34); C, 100-200 mSv (n = 24); and D, 200-400 mSv (n = 12). Serving as controls were 131 age-matched male healthy volunteers with no previous radiation exposure. DNA was extracted from peripheral blood mononuclear cells (PBMNCs) by standard procedures, quantitated spectrophotometrically, and stored at −80°C.

The real-time quantitative PCR technique used for the detection of *BCL-2-MBR/IgH* -rearrangements has been described in detail.[8] At least 5 1.0 μg aliquots of cellular DNA (~5 × 140 000 cells) isolated from each blood sample were tested for the presence of the t(14;18) translocation. To determine the total number of cells tested, 3 0.1 μg DNA aliquots were quantitatively analyzed for K-ras. All amplification products were analyzed by agarose gel electrophoresis for the presence of several t(14;18) DNA fragments; 28 amplification products were selected for nucleotide sequence analysis because they revealed t(14;18)-DNA fragments of a quite similar size. In no case were identical sequences found.

The frequency of *BCL-2-MBR/J_H* translocation in peripheral blood lymphocytes from healthy males working at a nuclear power plant was 60.3% (79/131), which is statistically not different from the frequency of 55% (72/131) in age-matched healthy controls (Table 1). At least 700 000 cells (~5 μg cellular DNA) were tested per individual based on the quantitative determination of the K-ras gene. There were no statistical differences between the frequency of *BCL-2/J_H* translocation observed in the 4 groups of NPP workers defined by increasing cumulative radiation exposure as well as between the frequency in these 4 groups and age-matched healthy controls (Table 1). Furthermore, the incidence of more than one t(14;18)-positive cell clone was about the same in both study populations. The quantitative determination of circulating t(14;18)-positive cells (Figure 1) revealed no significant differences between NPP workers and age-matched healthy controls.

Based on these results it may be concluded that low-level radiation exposure up to 400 mSv has no significant effect on the frequency of the t(14;18) translocation as well as the total number of circulating t(14;18)-positive cells in the individuals studied. At present, possible effects of higher cumulative doses cannot be excluded.

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To the editor:

Second malignancy after treatment of acute promyelocytic leukemia: experience of GIMEMA trials

In a recent issue Latagliata et al reported 5 cases of therapy-related myelodysplastic syndrome-acute myelogenous leukemia (tMDS-AML) following acute promyelocytic leukemia (APL) in a cohort of 77 patients who achieved a complete remission (CR) after chemotherapy according to GIMEMA 0389 and AIDA trials.[1] The authors, on the basis of these data, concluded that the observation of tMDS-AML is an emerging problem that could increase in the future. The responsibility of this phenomenon was attributed to chemotherapy, which in some cases included topoisomerase II inhibitors or alkylating agents; furthermore, APL patients presented a high percentage of curability with a consequently large number of long-term survivors.

Between 1982 and 1997 in the GIMEMA APL trials (LAP 0383, 0389, and 0493), 1145 patients were recruited (261 patients in the 0389 trial, 113 patients in the 8303 trial, and 771 patients in the 0493 trial). Details on treatment schedule were previously reported.[2-4] All trials included anthracycline administration (daunorubicin or idarubicin) during the induction and consolidation phases. Maintenance therapy was randomly administered only in the 8303 trial (no therapy vs methotrexate plus 6-mercaptopurine for 2 years) and in the 0493 trial (no therapy vs ATRA vs methotrexate plus 6-mercaptopurine vs 2 + 3 for 2 years). Among these patients, only 4 males (0.3%) aged 36, 38, 61, and 76 years, respectively, developed a second primary malignancy (SPM) (kidney, bowel, melanoma, and thyroid, respectively). All these patients were treated according to the 0493 trial. The median latency between APL diagnosis and SPM was 6.6 months (range, 3.8-7.6 months). The median follow-up was 2.2 years (range, 0-13.8 years). None of them received methotrexate plus 6-mercaptopurine as maintenance therapy. Two patients died from progression of secondary malignancy (bowel and melanoma), without signs of APL relapse, after 3 and 12 months, respectively. The other 2 patients are still alive without signs of relapse of either of the malignancies after 46 months (kidney) and 97 months (thyroid).

Based on the incidence rate data produced by the combined Italian Cancer Registries in the general population,[5] among the APL population the expected number of patients with a second cancer was estimated in 11.98 cases; conversely, in our series only 4 cases were observed (standardized incidence ratio 0.33; 95% CI 0.09-0.86). The estimated cumulative incidence of a second