TABLE 3 Immunohistochemical staining of hMSH2 and hMLH1 in control patients and atomic bomb survivors

Patient	hMSH2(+) and hMLH1(+)	hMSH2 (−) and/or hMLH1(−)	*p*
Control patients ($n = 82$)	72 (87.8)	10 (12.2)	<0.001
Atomic bomb survivors ($n = 57$)	36 (63.2)	21 (36.8)	

increased incidence rate of cancer in other organs of atomic bomb survivors, including bone marrow, has also been confirmed.[2] In particular, the 1978 study of Beebe et al. reported that the number of deaths from gastric carcinomas in the atomic bomb survivors exposed to more than 200 rad of radiation was 1.38-fold higher than that in survivors exposed to 0 rad between 1959 and 1974 in Hiroshima.[14] Ito et al. reported in 1984 that the prevalence of gastric cancer determined by routine X-ray examinations of the stomach in survivors exposed to more than 100 rad was 4-fold higher than that in survivors exposed to 0 rad.[15] It is possible that a higher quantity of radiation caused cancer formation through chromosomal alterations.[2] We assumed that gastric cancer in atomic bomb survivors and control patients followed different pathways because the characteristic features and survival rates between the two groups varied greatly. A high occurrence of second malignancies has also been reported in survivors.[16] In this study, the occurrence of second primary cancer after early gastric cancer was significantly higher in atomic bomb survivors than in control patients (Table 1, $p = 0.001$). We previously demonstrated that the rate of patients with second primary cancers after early gastric cancer was 10.7 %, and tumors were observed most frequently in the colorectum, lung, pharynx/esophagus, and liver.[5]

Many investigators have demonstrated that the clinicopathological characteristics of patients with colorectal cancer with high-frequency microsatellite instability are younger in age, have a lower incidence of lymph node metastasis, have disease in a proximal location, and have a better survival rate.[17–19] Regarding gastric cancer, studies with a small number of patients have reported conflicting results regarding the association of the microsatellite instability phenotype and better survival.[20,21] Some investigators have demonstrated that the survival of patients with early gastric cancer exhibiting microsatellite instability was not different from that of patients with early gastric cancer exhibiting microsatellite stability, though the survival rate of patients with stage II gastric cancer exhibiting microsatellite instability was higher compared with that of patients with advanced gastric cancer exhibiting microsatellite stability.[20] This study indicated that the survival of patients with early gastric cancer exhibiting microsatellite instability as well as defective hMSH2 and/or hMLH1 expression was not different from that of patients with early gastric cancer exhibiting microsatellite stability.

We have previously demonstrated that the occurrence rate of a second primary cancer occurring after early gastric cancer was related to microsatellite instability, defective hMSH2, and/or defective hMLH1 expression.[8] This study demonstrated that a significant relationship exists between a high occurrence rate of second primary cancer and defective hMSH2 and/or hMLH1 expression in atomic bomb survivors. By means of logistic regression analysis, we found that being an atomic bomb survivor was a factor in being at a greater risk of having defective hMSH2 and/or hMLH1 expression than the occurrence of a second primary cancer.

In conclusion, the survival rate for early gastric cancer in atomic bomb survivors was significantly lower than that

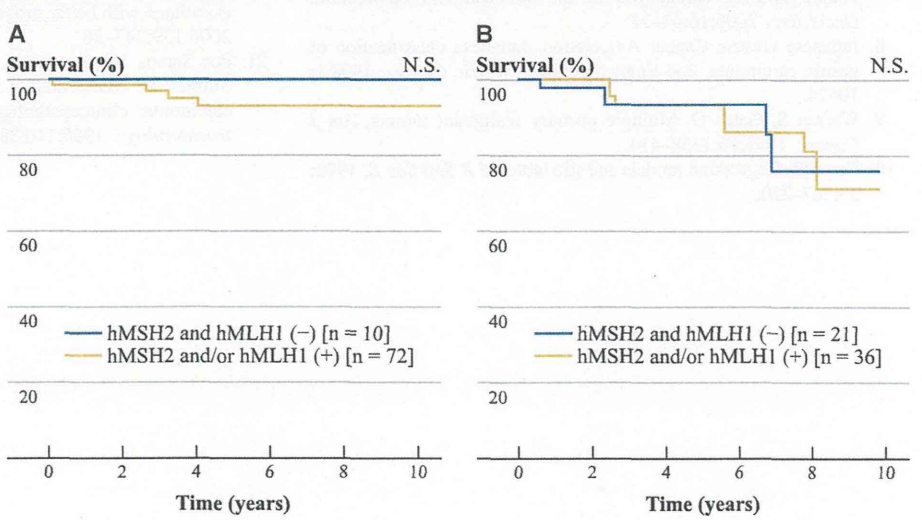

FIG. 3 **a** Ten-year survival rates of 82 control patients in the hMSH2 and hMLH1 (−), and hMSH2 and/or hMLH1 (+) groups. **b** Ten-year survival rates of 57 atomic bomb survivors in the hMSH2 and hMLH1(−), and hMSH2 and/or hMLH1 (+) groups

TABLE 4 Univariate and multivariate analysis of defective hMSH2 and/or hMLH1 expression in 139 patients

Variable	Univariate analysis			Multivariate analysis		
	p	Odds ratio	95 % CI	*p*	Odds ratio	95 % CI
Age	0.0970	1.9720	0.8833–4.4222	0.3286	1.5550	0.6379–3.7727
Second primary cancer	0.1697	1.9347	0.2083–1.3411	0.5276	1.3831	0.5384–3.8232
Atomic bomb survivor	0.0013	3.7652	1.6671–8.9161	0.0079	3.3774	1.3711–3.8232
Histology	0.8458	1.0904	0.4654–2.7221	0.4565	1.4836	0.4939–3.6880

CI confidence interval

in control patients. The prognosis for this disease in atomic bomb survivors is related to older age and to sex, rather than to being an atomic bomb survivor.

REFERENCES

1. Maloney WE, Kastenbaum MA. Leukemogenic effects of radiation in atomic bomb survivors in Hiroshima city. *Science.* 1995;121:308–9.
2. Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. *Radiat Res.* 1982;90:32–395.
3. Nowell PC, Cole LJ, Ellis ME. Neoplasms of the glandular stomach in mice irradiated with X-rays or fast neutrons. *Cancer Res.* 1958;18:257–60.
4. Suehiro S, Nagasue N, Abe S, Ogawa Y, Sasaki Y. Carcinoma of the stomach in atomic bomb survivors; a comparison of clinicopathological features to the general population. *Cancer.* 1986;57:1894–8.
5. Yoshino K, Asanuma F, Hanatani Y, Otani Y, Kumai K, Ishibiki K. Multiple primary cancers in the stomach and another organ: frequency and the effects on prognosis. *Jpn J Clin Oncol.* 1985;15:183–90.
6. Yamamoto M, Yamanaka T, Baba H, Kakeji Y, Maehara Y. The postoperative recurrence and the occurrence of second primary carcinomas in patients with early gastric carcinoma. *J Surg Oncol.* 2008;97:231–5.
7. Yamamoto M, Taguchi K, Baba H, Endo K, Kohnoe S, Okamura T, et al. Loss of protein expression of hMLH1 and hMSH2 with double primary carcinomas of the stomach and colorectum. *Oncol Rep.* 2006;16:41–74.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 2nd English edition. *Gastric Cancer.* 1998;1: 10–24.
9. Warren S, Gates O. Multiple primary malignant tumors. *Am J Cancer.* 1932;16:1358–414.
10. Cox DR. Regression models and life tables. *J R Stat Soc B.* 1972; 35:187–220.
11. Yamamoto M, Matsuyama A, Kameyama T, Okamoto M, Okazaki J, Utsunomiya T, et al. The long-term outcome of atomic bomb survivors with gastric carcinoma. *J Surg Oncol.* 2009;100: 594–7.
12. Maruta K, Shida H. Some factors which influence prognosis after surgery for advanced gastric cancer. *Ann Surg.* 1968;167:313–8.
13. Kamada N, Uchino H. Preleukemic status in atomic bomb survivors in Japan. *Blood Cell.* 1976;345–7.
14. Beebe GW, Kato H, Land CC. Studies of mortality of A-bomb survivors. *Radiat Res.* 1978;75:138–201.
15. Ito C, Hasegawa K, Kumazawa T. Incidence of gastric cancer in atomic bomb survivors residing in the Hiroshima area. *Hiroshima J Med Sci.* 1984;33:47–52.
16. Nakashima M, Kondo H, Miura S, Soda M, Hayashi T, Matsuo T, et al. Incidence of multiple primary cancers in Nagasaki atomic bomb survivors: association with radiation exposure. *Cancer Sci.* 2008;99:87–92.
17. Gryfe R, Kim H, Hsieh ET, Aronson MD, Holowaty EJ, Bull SB, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *N Engl J Med.* 2000;342: 69–77.
18. Liang JT, Huang KC, Cheng AL, Jung YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. *Br J Surg.* 2003;90:205–14.
19. Jass JR, Walsh MD, Barker M, Simms LA, Young J, Leggett BA. Distinction between familial and sponradic forms of colorectal cancer showing DNA microsatellite instability. *Eur J Cancer.* 2002;139:347–56.
20. Beghehi S, de Manzoni G, Barbi S, Tomezzoli A, Roviello F, Di Gregorio C, et al. Microsatellite instability in gastric cancer is associated with better prognosis in only stage II cancers. *Surgery.* 2006;139:347–56.
21. dos Santos NR, Seruca R, Constância M, Seixas M, Sobrinho-Simões M. Microsatellite instability at multiple loci in gastric carcinoma: clinicopathologic implications and prognosis. *Gastroenterology.* 1996;110:38–44.