

Prognostic Significance of Selected Lifestyle Factors in Urinary Bladder Cancer

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To examine the prognostic significance of lifestyle factors in urinary bladder cancer, we conducted a follow-up study of 258 incident bladder cancer patients, who were originally recruited in a case-control study in metropolitan Nagoya. Information on individual survivals was obtained from the computer data-file of the tumor registry of the Nagoya Bladder Cancer Research Group. Univariate analyses revealed significant associations of 5-year survivorship with educational attainment, marital status, drinking habits and consumption of green tea in males, and age at first consultation, histological type and grade of tumor, stage and distant metastasis in both sexes. After adjustment for age, stage, histology (histological type and grade) and distant metastasis by means of a proportional hazards model, drinking of alcoholic beverages was significantly associated with the prognosis of bladder cancer in males. Its adjusted hazard ratio was 0.46 (95% confidence interval: 0.26-0.79), favoring patients who had taken alcoholic beverages. In detailed analysis, ex-drinkers and all levels of current drinkers demonstrated hazard ratios smaller than unity, although no clear dose-response relationship was detected. No prognostic significance was found for such lifestyle factors as smoking habit, uses of artificial sweeteners and hairdye, and consumption of coffee, black tea, matcha (powdered green tea) and cola.

Key words: Bladder cancer — Prognosis — Survival — Lifestyle — Hazard ratio

Factors incriminated as prognostic determinants in urinary bladder cancer are stage (T classification),¹⁻³ histological grade,^{2,3} tumor size²⁻⁴ and age at diagnosis.³ Carcinoembryonic antigens (CEA) in urine^{1,5}/cancer tissues⁶ also seem to be of predictive significance. DNA ploidy pattern has recently been investigated as a prognostic factor.^{7,8} By contrast, only a few attempts have been made at exploring the effect of lifestyle on survival in patients with this cancer. Vågerö and Persson⁹ reported that white-collar workers experienced a better survival than blue-collar workers. Goodwin *et al.*¹⁰ found that marital status was not significantly associated with the prognosis in bladder cancer after adjusting for age, gender, stage and treatment. Michalek *et al.*¹¹ suggested that smoking habit had little effect on survival, a finding that was endorsed by Takashi and co-workers.³

For other malignancies, many workers have attempted to explore the relationship between survival and smoking¹²⁻¹⁸ or other lifestyle factors,¹⁷⁻²⁰ and several useful results have emerged. Therefore, to evaluate the prognostic significance of some lifestyle factors in bladder cancer, we undertook a follow-up study and report here its methodology and findings.

SUBJECTS AND METHODS

We previously conducted a case-control study, which included 293 incident cases of urinary tract cancers in

metropolitan Nagoya, Japan, from January 1976 to December 1978. Details of this study have been presented elsewhere.²¹ In the present study, we defined only patients with urinary bladder cancer as eligible for the present study, so we excluded 28 patients with neoplasms of the renal pelvis and ureter among the 293 patients.

Data on lifestyles and demographic variables were collected by direct interview in the case-control study.²¹ Items surveyed in the present study include such demographic data as sex, educational attainment and marital status; smoking and drinking habits; use of artificial sweeteners; use of hairdye; and consumption of such non-alcoholic beverages as coffee, black tea, green tea, matcha (powdered green tea) and cola.

The patients were followed-up by using information obtained from the tumor registry of the Nagoya Bladder Cancer Research Group (Director: K. Obata). Length of survival was measured from the date of first consultation to the date of death or last follow-up contact. Unless otherwise mentioned, no distinctions were made as to cause of death, because the cause of death could not be verified. For seven patients, no follow-up data were available and they did not contribute to the present analysis. Of the remaining 258 patients, 81 had died and 177 were still alive (62) or lost to follow-up (115) at the end of 1983. The median follow-up period was 29.8 months. Table I shows the distribution of study subjects (258 patients) by sex and age.

Information on age at first consultation, stage, histological type, grade of tumor, and distant metastasis at diagnosis was also obtained from the registry. Tumors

were staged using the TNM classification²²⁾ and graded according to the criteria of the World Health Organization.²³⁾

Table I. Distribution of Study Subjects (258 Patients) by Sex and Age (at First Consultation)

Age	Male		Female	
	No.	%	No.	%
20-29	3	1.5	0	0.0
30-39	7	3.4	0	0.0
40-49	22	10.8	2	3.6
50-59	36	17.7	13	23.6
60-69	68	33.5	18	32.7
70-79	60	29.6	18	32.7
80-89	7	3.4	4	7.3
Total	203	100.0	55	100.0

Statistical analysis Product-limit estimates according to Kaplan and Meier²⁴⁾ were used for survival rates. The log-rank test²⁵⁾ was employed to compare survival curves. Multivariate analyses by Cox's proportional hazards model²⁶⁾ were performed to assess the relationship between survival and the selected factors, adjusting for age at first consultation, stage, histology and distant metastasis.

The patients were dichotomized by factor in the analysis, unless otherwise mentioned. In the multivariate analyses, patients with missing information for stage, histology and distant metastasis were included as an additional category, because lack of these data itself may be linked to a poorer prognosis, and findings obtained by excluding such patients might be biased.

Table II. Five-year Survival Rates for the Selected Factors by Sex

Factor	Category	Male			Female		
		No.	5-year survival rate	Difference in survival curves <i>P</i> ^{a)}	No.	5-year survival rate	Difference in survival curves <i>P</i>
Age (at first consultation)	< 65	99	0.814		24	0.947	
	≥ 65	104	0.462	0.000	31	0.460	0.002
Age at the highest educational attainment	< 15	102	0.559		38	0.603	
	≥ 15	100	0.727	0.027	17	0.831	0.165
Marital status	Married	174	0.693		29	0.769	
	Never married, divorced, widowed	28	0.314	0.000	25	0.432	0.134
Smoking	Never	28	0.502		36	0.757	
	Ever	175	0.662	0.072	18	0.491	0.135
Drinking	Never	65	0.491		41	0.642	
	Ever	138	0.714	0.000	14	0.750	0.360
Artificial sweetener	Never used	111	0.645		31	0.673	
	Ever used	89	0.623	0.958	23	0.698	0.723
Hairdye	Never used	178	0.641		18	0.706	
	Ever used	25	0.631	0.815	37	0.637	0.461
Coffee	Never drunk	67	0.578		34	0.590	
	Ever drunk	136	0.671	0.173	21	0.799	0.158
Black tea	Never drunk	122	0.654		38	0.622	
	Ever drunk	81	0.625	0.835	17	0.766	0.353
Green tea	Never drunk	10	0.320		0		
	Ever drunk	193	0.658	0.034	55	0.667	
Matcha	Never drunk	154	0.674		48	0.648	
	Ever drunk	48	0.542	0.229	7	0.800	0.329
Cola	Never drunk	150	0.637		46	0.603	
	Ever drunk	53	0.648	0.862	9	1.000	0.066
Histological type and grade	TCC ^{b)} Grade 0-2	118	0.776		20	1.000	
	TCC Grade 3, non-TCC	53	0.434	0.000	19	0.450	0.001
Stage	pTa, pT1, pT2	113	0.743		22	0.929	
	pT3, pT4	39	0.360	0.000	10	0.500	0.003
Distant metastasis	No	173	0.728		43	0.813	
	Yes	6	0.000	0.000	2	0.000	0.000

a) *P* value by log-rank test.

b) TCC: Transitional cell carcinoma.

Survival analyses were limited to five-year follow-up, because diseases other than bladder cancer might substantially distort the survival state if the end-point is too distant. Patients followed-up for more than five years were, therefore, assumed to be censored at the end of the five-year observation period.

RESULTS

The 5-year survival probability of the 258 patients was 64% (95% confidence interval (CI) 56–72%) for males and 67% (95% CI 52–81%) for females.

Table II shows the 5-year survival rates and *P*-values by log-rank test for the selected factors by sex. Older age, non-transitional cell carcinoma (TCC) or higher grade TCC, higher stage and distant metastasis were all significantly associated with a poorer survival in both sexes. Among lifestyle factors, higher educational attainment, being married, a history of drinking, and a history of consuming green tea were all significantly linked with a better survival in male patients. No significant association of the survival with smoking habit, use of artificial sweeteners, use of hairdye, or consumption of coffee, black tea, matcha or cola was found.

To examine the prognostic significance by allowing for age and other clinico-pathological factors (histology, stage and distant metastasis), multivariate analyses were conducted. These analyses were made only for male patients, because too few female patients were available. Table III presents the hazard ratios for males by age and tumor-related factors adjusted for the other variables. Older age, higher stage and distant metastasis were significantly associated with a poorer prognosis, independently of the other variables. Lack of information con-

cerning distant metastasis was also related to a poorer prognosis.

Table IV summarizes hazard ratios for male patients by the selected lifestyle factors. After adjusting for age and the three tumor-related variables, only drinking of alcoholic beverages revealed a significant association with prognosis of bladder cancer. The adjusted hazard ratio for drinking (“ever drunk”) was 0.46 (95% CI 0.26–0.79). Other lifestyle factors were not associated with statistically significant hazard ratios.

Further, for male patients, we used the proportional hazards model to examine the relationship between details of drinking habits and survival after diagnosis of bladder cancer (Table V). In model I, male patients were divided into “never drunk,” ex-drinkers and current drinkers. In model II, current drinkers were divided into three groups by level of alcohol consumption. Ex-drinkers and all levels of current drinkers clearly demonstrated hazard ratios smaller than unity, although no clear dose-response relationship was detected.

DISCUSSION

The 5-year survival rate of the present series was 65% (95% CI 58–71%), which is compatible with the rate in Japan reported by Takashi *et al.*³⁾ (67%) or Tachibana *et al.*⁷⁾ (65%). Older age at first consultation, non-TCC or higher grade TCC, higher stage and distant metastasis were significantly associated with a poorer survival of patients with bladder cancer, in good agreement with previous findings.^{1–3)}

We also attempted to examine whether some lifestyle factors affect the prognosis of bladder cancer, independently of age and tumor-related factors. A previous

Table III. Hazard Ratios for Male Patients by Age and Other Clinical Factors^{a)}

Factor	Category	HR ^{b)}	95% CI ^{c)}
Age (at first consultation)	< 65	1.00 ^{e)}	
	≥ 65	3.04	1.66–5.55
Histological type and grade	TCC ^{d)} Grade 0–2	1.00 ^{e)}	
	TCC Grade 3, non-TCC	1.85	0.97–3.53
	Unknown	1.76	0.68–4.54
Stage	pTa, pT1, pT2	1.00 ^{e)}	
	pT3, pT4	2.43	1.22–4.85
	Unknown	1.04	0.43–2.56
Distant metastasis	No	1.00 ^{e)}	
	Yes	6.19	2.12–18.0
	Unknown	4.70	2.41–9.17

a) Adjusted for the other factors listed.

b) HR: Hazard ratio.

c) CI: Confidence interval.

d) TCC: Transitional cell carcinoma.

e) Reference category.

Table IV. Hazard Ratios for Male Patients by Selected Lifestyle Factors^{a)}

Factor	Category	HR ^{b)}	95% CI ^{c)}
Age at the highest educational attainment	< 15	1.00 ^{d)}	
	≥ 15	0.79	0.44–1.41
Marital status	Married	1.00 ^{d)}	
	Never married, divorced, widowed	1.68	0.90–3.14
Smoking	Never	1.00 ^{d)}	
	Ever	0.88	0.45–1.72
Drinking	Never	1.00 ^{d)}	
	Ever	0.46	0.26–0.79
Artificial sweetener	Never used	1.00 ^{d)}	
	Ever used	1.05	0.62–1.79
Hairdye	Never used	1.00 ^{d)}	
	Ever used	0.65	0.28–1.47
Coffee	Never drunk	1.00 ^{d)}	
	Ever drunk	0.88	0.49–1.59
Black tea	Never drunk	1.00 ^{d)}	
	Ever drunk	0.77	0.44–1.33
Green tea	Never drunk	1.00 ^{d)}	
	Ever drunk	0.62	0.22–1.74
Matcha	Never drunk	1.00 ^{d)}	
	Ever drunk	1.36	0.75–2.44
Cola	Never drunk	1.00 ^{d)}	
	Ever drunk	1.11	0.61–2.01

a) Adjusted for age (at first consultation), histological type and grade, stage and distant metastasis.

b) HR: Hazard ratio.

c) CI: Confidence interval.

d) Reference category.

Table V. Hazard Ratios for Male Patients by Alcohol Consumption^{a)}

Model I^{b)}

Category	No.	HR ^{c)}	95% CI ^{d)}
Never drunk	65	1.00 ^{e)}	
Ex-drinker	17	0.61	0.23–1.61
Current drinker	121	0.43	0.24–0.77

Model II^{b)}

Category	No.	HR	95% CI
Never drunk	65	1.00 ^{e)}	
Ex-drinker	17	0.60	0.23–1.59
Current drinker			
< 2 gou/day ^{f)}	75	0.41	0.22–0.77
2–4 gou/day	35	0.43	0.16–1.14
≥ 4 gou/day	11	0.82	0.22–3.13

a) Adjusted for age (at first consultation), histological type and grade, stage and distant metastasis.

b) See text.

c) HR: Hazard ratio.

d) CI: Confidence interval.

e) Reference category.

f) 1 "gou" is the alcohol equivalent to 180 ml of Japanese sake which contains 29 g of alcohol.

report⁹⁾ suggested that bladder cancer patients in higher social class were at an advantage with regard to survival. In the present study also, higher education was significantly associated with a better survival in males. But when age and the tumor-related variables were adjusted in multivariate analysis, it turned out to be an insignificant association, though the adjusted hazard ratio was apparently in favor of those with higher educational attainment. Therefore, whether social class is an independent prognostic factor in bladder cancer still remains to be explored further.

After adjustment for the covariates, the prognostic difference by marital status was not significant in males. This finding is consistent with the previous study.¹⁰⁾ However, further studies may possibly detect moderate and favorable effects of being married on survival, because the adjusted ratio for never married, divorced or widowed was found to be greater than unity in the previous study¹⁰⁾ and the present study (Table IV) as well.

Male patients who had never drunk green tea demonstrated a poorer survival when compared to those who had drunk it, but the adjusted hazard ratio was not statistically significant.

There is evidence that smokers have a poorer prognosis than nonsmokers in other sites of cancer,^{12, 14–16)} and

smoking is one of the best established risk factors for bladder cancer.^{21, 27-29)} It is, therefore, quite rational to hypothesize that smoking might contribute to a poorer survival in patients with this tumor. Nevertheless, previous reports^{3, 11)} did not endorse this hypothesis. In our study also, smoking habit made no significant contribution to the prognosis. These findings imply that smoking is not an important prognostic determinant in bladder cancer. However, some patients might have changed their smoking habits during the follow-up period. The present study, like previous ones^{3, 11)} did not take possible chronological changes of smoking habit into consideration. Thus, further investigations monitoring the smoking habits of patients will be required to assess properly its prognostic significance. More detailed study on smoking habits in females would also be necessary, since the 5-year survival rate of female smokers appeared to be lower than that of nonsmokers.

Drinking of alcoholic beverages was significantly linked with a better survival of male patients in our study. It is quite probable in general that individuals with declining health owing to bladder tumor or other disease are more likely to stop drinking. In our analysis, however, ex-drinkers did not demonstrate a hazard ratio larger than unity. Therefore, an association between drinking habit and the 5-year prognosis could not be entirely explained by the health status of the patients at interview. One may argue that alcohol consumption might have affected the mortality from diseases other than bladder cancer, since light drinkers are at lower risk for death, especially for death from cardiovascular diseases.³⁰⁻³²⁾ However, when patients who died of causes not linked to bladder cancer were assumed to be censored at the time of death, drinking habit still remained as an independent prognostic factor. The hazard ratio, adjusted for age and tumor-related factors, was 0.46 (95% CI 0.23-0.91), favoring the patients who had taken alcoholic beverages. Though the causes of death available in the registry may not necessarily be accurate, it is quite unlikely that the diagnosis of cause of death in bladder cancer patients was distorted by the patient's drinking habits. The potential bias in the diagnosis suggests, therefore, that this estimate of hazard ratio is likely to be conservative.

In the present study, we could not find a clear dose-response relationship. However, our finding that all levels of alcohol consumption gave a hazard ratio smaller than unity certainly indicates probable relevance of drinking habit to prognosis of bladder cancer itself. The lack of a clear dose-response relationship might be due to our

small sample size for each category of drinking practice. Another possibility is that light to moderate drinking might be associated more strongly with a better survival than heavy drinking.

In assessment of these results in our study, some methodological limitations should also be kept in mind. First, the present study did not assess the chronological changes of drinking habits during follow-up. Second, alcohol consumption might be correlated with prognostic factors which were not examined in the present study, so that drinking itself might not have been directly related to the prognosis. Despite these limitations, further investigations on drinking habits and survival from bladder cancer seem warranted, since several biological mechanisms may contribute to the association between alcohol intake and the prognosis. Drinkers might have higher levels of natural-killer-cell activity in peripheral blood than nondrinkers.^{33, 34)} Alcohol diuresis could affect the survival of bladder cancer patients treated without cystectomy, because urine stasis is a possible risk factor for bladder cancer.³⁵⁾

In short, our study found that alcohol consumption was significantly related with a better survival of male patients with urinary bladder cancer. Other lifestyle factors, such as educational attainment, marital status, smoking habit, use of artificial sweeteners, use of hairdye, and consumption of various non-alcoholic beverages, were not found to be independently associated with the prognosis of urinary bladder cancer.

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REFERENCES

- 1) Nilsson, B., Wahren, B., Esposti, P. L. and Edsmyr, F. Prediction of survival and recurrence in bladder carcinoma. *Urol. Res.*, **10**, 109-113 (1982).
- 2) Narayana, A. S., Loening, S. A., Slymen, D. J. and Culp, D. A. Bladder cancer: factors affecting survival. *J. Urol.*, **130**, 56-60 (1983).
- 3) Takashi, M., Murase, T., Mizuno, S., Hamajima, N. and Ohno, Y. Multivariate evaluation of prognostic determinants in bladder cancer patients. *Urol. Int.*, **42**, 368-374 (1987).
- 4) Co-operative Urological Cancer Group. Prognostic factors in a T3 bladder cancer trial. *Br. J. Cancer*, **59**, 441-444 (1989).
- 5) Wahren, B., Nilsson, B. O. and Zimmerman, R. Urinary CEA for prediction of survival time and recurrence in bladder cancer. *Cancer*, **50**, 139-145 (1982).
- 6) Nakatsu, H., Kobayashi, I., Onishi, Y., Igawa, M., Ito, H., Tahara, E. and Nihira, H. ABO (H) blood group antigens and carcinoembryonic antigens as indicators of malignant potential in patients with transitional cell carcinoma of the bladder. *J. Urol.*, **131**, 252-257 (1984).
- 7) Tachibana, M., Deguchi, N., Baba, S., Jitsukawa, S., Hata, M. and Tazaki, H. Multivariate analysis of flow cytometric deoxyribonucleic acid parameters and histological features for prognosis of bladder cancer patients. *J. Urol.*, **146**, 1530-1534 (1991).
- 8) Hug, E. B., Donnelly, S. M., Shipley, W. U., Heney, N. M., Kaufman, D. S., Preffer, F. I., Schwartz, S. M., Colvin, R. B. and Althausen, A. F. Deoxyribonucleic acid flow cytometry in invasive bladder carcinoma: a possible predictor for successful bladder preservation following transurethral surgery and chemotherapy-radiotherapy. *J. Urol.*, **148**, 47-51 (1992).
- 9) Vägerö, D. and Persson, G. Cancer survival and social class in Sweden. *J. Epidemiol. Community Health*, **41**, 204-209 (1987).
- 10) Goodwin, J. S., Hunt, W. C., Key, C. R. and Samet, J. M. The effect of marital status on stage, treatment, and survival of cancer patients. *J. Am. Med. Assoc.*, **258**, 3125-3130 (1987).
- 11) Michalek, A. M., Cummings, K. M. and Pontes, J. E. Cigarette smoking, tumor recurrence and survival from bladder cancer. *Prev. Med.*, **14**, 92-98 (1985).
- 12) Johnston-Early, A., Cohen, M. H., Minna, J. D., Paxton, L. M., Fossieck, B. E., Ihde, D. C., Bunn, P. A., Matthews, M. J. and Makuch, R. Smoking abstinence and small cell lung cancer survival: an association. *J. Am. Med. Assoc.*, **244**, 2175-2179 (1980).
- 13) Koh, H. K., Sober, A. J., Day, C. L., Lew, R. A. and Fitzpatrick, T. B. Cigarette smoking and malignant melanoma: prognostic implications. *Cancer*, **53**, 2570-2573 (1984).
- 14) Kucera, H., Enzelsberger, H., Eppel, W. and Weghaupt, K. The influence of nicotine abuse and diabetes mellitus on the results of primary irradiation in the treatment of carcinoma of the cervix. *Cancer*, **60**, 1-4 (1987).
- 15) Archimbaud, E., Maupas, J., Lecluze-Palazzolo, C., Fiere, D. and Viala, J.-J. Influence of cigarette smoking on the presentation and course of chronic myelogenous leukemia. *Cancer*, **63**, 2060-2065 (1989).
- 16) Browman, G. P., Wong, G., Hodson, I., Sathya, J., Russell, R., McAlpine, L., Skingley, P. and Levine, M. N. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. *N. Engl. J. Med.*, **328**, 159-163 (1993).
- 17) Kato, I., Tominaga, S. and Ikari, A. Lung cancer prognostic factors from the Aichi Cancer Registry. *Jpn. J. Clin. Oncol.*, **20**, 238-245 (1990).
- 18) Ewertz, M., Gillanders, S., Meyer, L. and Zedeler, K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. *Int. J. Cancer*, **49**, 526-530 (1991).
- 19) Gregorio, D. I., Emrich, L. J., Graham, S., Marshall, J. R. and Nemoto, T. Dietary fat consumption and survival among women with breast cancer. *J. Natl. Cancer Inst.*, **75**, 37-41 (1985).
- 20) Attali, P., Prod'homme, S., Pelletier, G., Papoz, L., Ink, O., Buffet, C. and Etienne, J.-P. Prognostic factors in patients with hepatocellular carcinoma: attempts for the selection of patients with prolonged survival. *Cancer*, **59**, 2108-2111 (1987).
- 21) Ohno, Y., Aoki, K., Obata, K. and Morrison, A. S. Case-control study of urinary bladder cancer in metropolitan Nagoya. *Natl. Cancer Inst. Monogr.*, **69**, 229-234 (1985).
- 22) Union International Contre le Cancer. "TNM Classification of Malignant Tumors" (1974). Union International Contre le Cancer, Geneva.
- 23) Mostofi, F. K., Sobin, L. H. and Torloni, H. Histological typing of urinary bladder tumours. In "International Histological Classification of Tumors, No. 10," pp. 9-34 (1973). World Health Organization, Geneva.
- 24) Kaplan, E. L. and Meier, P. Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.*, **53**, 457-481 (1958).
- 25) Peto, R. and Peto, J. Asymptotically efficient rank invariant test procedures. *J. R. Stat. Soc. A*, **135**, 185-207 (1972).
- 26) Cox, D. R. Regression models and life tables. *J. R. Stat. Soc. B*, **34**, 187-220 (1972).
- 27) Morrison, A. S., Buring, J. E., Verhoek, W. G., Aoki, K., Leck, I., Ohno, Y. and Obata, K. An international study of smoking and bladder cancer. *J. Urol.*, **131**, 650-654 (1984).
- 28) López-Abente, G., González, C. A., Errezola, M., Escolar, A., Izarzugaza, I., Nebot, M. and Riboli, E. Tobacco smoke inhalation pattern, tobacco type, and bladder cancer in Spain. *Am. J. Epidemiol.*, **134**, 830-839 (1991).
- 29) Chyou, P.-H., Nomura, A. M. Y. and Stemmermann,

- G. N. A prospective study of the attributable risk of cancer due to cigarette smoking. *Am. J. Public Health*, **82**, 37-40 (1992).
- 30) Klatsky, A. L., Armstrong, M. A. and Friedman, G. D. Alcohol and mortality. *Ann. Intern. Med.*, **117**, 646-654 (1992).
- 31) Farchi, G., Fidanza, F., Mariotti, S. and Menotti, A. Alcohol and mortality in the Italian rural cohorts of the seven countries study. *Int. J. Epidemiol.*, **21**, 74-82 (1992).
- 32) Scherr, P. A., LaCroix, A. Z., Wallace, R. B., Berkman, L., Curb, J. D., Cornoni-Huntley, J., Evans, D. A. and Hennekens, C. H. Light to moderate alcohol consumption and mortality in the elderly. *J. Am. Geriatr. Soc.*, **40**, 651-657 (1992).
- 33) Saxena, Q. B., Mezey, E. and Adler, W. H. Regulation of natural killer activity *in vivo*. II. The effect of alcohol consumption on human peripheral blood natural killer activity. *Int. J. Cancer*, **26**, 413-417 (1980).
- 34) Nakachi, K. and Imai, K. Environmental and physiological influences on human natural killer cell activity in relation to good health practices. *Jpn. J. Cancer Res.*, **83**, 798-805 (1992).
- 35) Matanoski, G. M. and Elliott, E. A. Bladder cancer epidemiology. *Epidemiol. Rev.*, **3**, 203-229 (1981).