Increased Incidence of a Second Lymphoproliferative Malignancy in Patients with Multiple Myeloma – a SEER based Study

SUBHANKAR CHAKRABORTY[1,2], RALPH J. HAUKE[3], NEELIMA BONTHU[3] and STEFANO R. TARANTOLO[4]

Departments of [1]Biochemistry and Molecular Biology and
[2]Internal Medicine, University of Nebraska Medical Center, Omaha, NE, U.S.A.;
[3]Nebraska Cancer Specialists, Omaha, NE, U.S.A.;
[4]Department of Internal Medicine, North Shore Medical Center, Salem, MA, U.S.A.

Abstract. *Background: Improving therapies means longer survival for multiple myeloma (MM) patients. We hypothesized that these patients are at an increased risk for a secondary malignancy. Objectives: (i) To investigate the epidemiology and site-specific risk of second primary cancers (SPCs) in patients with MM (ii) To investigate the factors affecting survival in MM patients with SPCs. Design: This was a retrospective cohort study employing data available in the US Surveillance Epidemiology and End Results (SEER) database. Subjects: Adult patients (>18 years) where MM was the first of two, or more primary cancers, such that the diagnosis of MM and the SPC was separated by at least 1 month. Results: The age-adjusted rate SPCs in MM was 0.22 per 100,000 (95% CI=0.05-2.1). The incidence of SPCs was higher in patients aged ≥70 years, men and blacks. Age, gender and race were significant predictors for the occurrence of SPCs in MM. The risk of solid malignancies was significantly decreased (SIR: 0.94, 95% CI=0.89-0.99), while that of lymphohematopoieitc (LAHM) malignancies increased in MM (SIR: 1.68, 95% CI= 1.46-1.92). 5-year relative survival among MM patients with SPCs was higher in blacks (54.6%, 95% CI=49.5-59.4) than whites (53.8%, 95% CI=51.3-56.3) or other races (49.9%, 95% CI=39.8-59.3). Multivariate analysis revealed that race, site of SPC and year of diagnosis were independent predictors of survival among MM patients with SPCs. Conclusion: MM patients are at a higher risk of a second LAHM.*

Abbreviations: Acute lymphoblastic leukemia (ALL), acute non-lymphocytic leukemia (ANLL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), lymphatic and hematopoeitic malignancies (LAHMS), myeloid and monocytic leukemia (MAML), multiple myeloma (MM), excess absolute risk (EAR), second primary cancer (SPC).

Correspondence to: Subhankar Chakraborty, M.B.B.S., Ph.D., Department of Internal Medicine, 982055 Nebraska Medical Center Omaha. NE 68105, U.S.A. E-mail: schakra@unmc.edu

Key Words: Multiple myeloma, SEER, second primary.

Multiple myeloma (MM) is the second most common hematological malignancy in the United States with an estimated 20,580 new cases diagnosed in 2009 and 10,580 people dying from it in the same year (1). The disease is characterized by proliferation of malignant B-lymphocytes (plasma cells) that produce abnormal immunoglobulin (Ig)-related proteins whose levels are elevated in the serum, and which are excreted in the urine (19). The survival of patients with MM has significantly improved over the years, in large part-due to autologous stem cell transplants and the introduction of novel pharmacological agents (3, 24).

It is estimated that there are currently more than 11 million cancer survivors in the US, nearly 880,300 (*i.e.* about 8%) who have been diagnosed with one or more new second primary malignancies. This has opened a new area of preventive medicine, one that is aimed at an increased active surveillance of patients already diagnosed with one type of cancer, for the early detection of a new primary malignancy. Studies have shown that while the overall lifetime risk of a second primary cancer (SPC) is low among cancer survivors as a whole (about 14%), this risk is significantly higher in certain groups of patients. The factors that have been suggested to influence the risk of a SPC include the site and histological type of the first primary, age at the time of diagnosis of the first primary cancer, environmental influences, genetic factors and type of therapy given for the first primary tumor (1). The prognostic significance of SPCs has also been highlighted by several studies that have shown that SPCs are significant determinants of survival in multiple malignancies including male breast (20), colon (17), gastric (18), esophageal and other head and neck cancers (5, 6).

Although MM has been reported to occur together (*i.e.* synchronously) with other cancers (2, 4, 12, 16), only a few population-based studies have reported the occurrence of metachronous second malignancies in these patients. Dong and Hemminki for instance, reported in a study from Sweden that MM patients are at higher risk of developing non-Hodgkin's lymphoma (7). Storm and Prener on the other hand reported that MM patients in Denmark had a significantly

lower overall risk of developing a second malignancy (23). A study from Australia reported that while patients with MM were not at a significant overall risk of developing a second malignancy, there was an increased risk of a second cancer in the urinary bladder (11). However, no data exist on the incidence of SPCs in patients with MM in the United States and the possible prognostic impact of a second malignancy in these patients. Identification of such an association would be important from both the public health perspective and from the standpoint of understanding the pathogenesis of multiple primary malignancies in the same individual. Knowledge of the risk of SPCs at specific sites is the first key step in planning an active surveillance strategy for MM patients to detect a new primary malignancy. Correlative studies on occurrence of SPCs also provide a clue to investigate the molecular and genetic mechanisms involved in the occurrence of multiple primary malignancies in certain patients.

In the present study, we investigated the incidence of SPCs in patients with MM using data from the Surveillance, Epidemiology and End Results (SEER) database. Furthermore, we sought to compare the effect of SPCs on the overall survival of MM patients. The study has important implications for streamlining the active surveillance of patients diagnosed with MM and understanding the biology underlying the occurrence of SPCs in this malignancy.

Materials and Methods

Population selection. The United States National Cancer Institute's SEER program collects data on patients with multiple malignancies (15). Seventeen registries participate in the SEER initiative. The information contained in the SEER database includes demographic data (place of birth, place of residence, age, race, gender and marital status at the time of diagnosis), description of the neoplasm (date of diagnosis, primary site, laterality, morphology and extent of disease), first course of cancer direct therapy (surgery, radiation) and follow-up. The database is considered to be a standard-of-quality among cancer databases worldwide. We queried the SEER database for patients with MM (ICD code: 9732/3) and one/more second primary cancers (SPC) who were diagnosed between January 1973 and December 2008. Only cases where MM was the first of two or more primary malignancies were selected. Patients in whom the only mention of a diagnosis of MM was the one made at autopsy or in the death certificate, were excluded. Any SPC diagnosed within 1 month of MM was also excluded.

Statistical analysis. Data from the SEER database were retrieved using the SEER*Stat version 6.5.2 (http://seer.cancer.gov/seerstat/). Statistical analysis was performed using the PASW Statistics 18 software program (Release 18.0, SPSS Inc, IL, USA). Patients were stratified by age, gender, race, site, year of diagnosis of SPC and latency period (time elapsed between the diagnosis of MM and that of the SPC). The standardized incidence ratio (SIR ratio) which is the ratio of the number of observed cases of cancer in the population of cancer survivors divided by the number of cancers expected in the same population was used as an indicator of risk of SPC. The risk of SPCs was examined from 1 month to >20 years after the diagnosis of MM. Two kinds of risk were measured a) risk of second primaries at all sites - termed as the "overall risk" and b) risk of a second malignancy at a specific site (termed as "site-specific risk"). All calculations were made with 95% confidence limits ($p<0.05$).

To determine the survival time in patients with SPCs, we used the variable "survival time in months" which records the survival as measured from the time of diagnosis of the SPC to either death or loss of follow-up. Age at diagnosis of the SPC and interval between the diagnosis of MM and the SPC were considered as continuous variables, while gender, race, year of diagnosis and site of SPC were considered as categorical variables. A two-tailed Student's *t*-test or a two-way analysis of variance (ANOVA) was used to compare the mean values for continuous variables while a chi-square test was applied to categorical variables. Kaplan Meier survival analysis was used to examine the effect of individual factors on the survival of SPC patients. A Cox proportional hazards test, employing forward stepwise logistic regression, was used for multivariate analysis of factors affecting survival of SPC patients. Multinomial regression analysis was used to determine whether specifc factors could predict the occurrence of SPCs in MM. A *p*-value <0.05 was considered significant.

Results

Patients' characteristics. A total of 3,245 cases where MM was the first of one or more SPCs were recorded in the SEER database. The age-adjusted incidence of MM with one/more SPCs was estimated to be 0.22 per 100,000 (or 2.2 per 1 million) with a 95% CI of 0.05-2.1 (adjusted to the 2000 US Standard population). In contrast, the age-adjusted rate of MM as the only primary cancer was 4.31 (±0.03) per 100,000 (95% CI=4.26-4.36). The age adjusted rate of SPCs (±SE) increased with age, being highest in those aged 70 years and older at the time-of-diagnosis (1.29±0.05 per 100,000). The rates were also higher for men than for women (0.3±0.01 and 0.15±0.01 per 100,000 respectively), and for blacks than for whites or other races (0.54±0.03, 0.20±0.01 and 0.11±0.01 per 100,000 respectively, Figure 1A). There was an increase in the number of SPCs from 1974 until 2000, followed by a decline (Figure 1B). In terms of absolute number of cases, the majority of patients (43%) with SPCs were aged between 65-79 years (Figure 1C), whites (78%, Figure 1D) and males (60%, Figure 1E).

Multiple factors affect the risk of second primary cancers in MM patients. Multinomial regression analysis revealed that age (at the time of diagnosis of SPC), gender and race were significantly associated with the risk of developing a SPC. Specifically, blacks, males, and patients ≥71 years at the time of diagnosis were significantly more likely than their comparable groups (*i.e.* whites/other races, females and those <70 years at diagnosis) in developing a SPC (Table I).

As demographic factors can also influence the risk of development of cancers at specific anatomic sites, we next investigated the site-specific risk of SPCs in MM patients stratified by these factors.

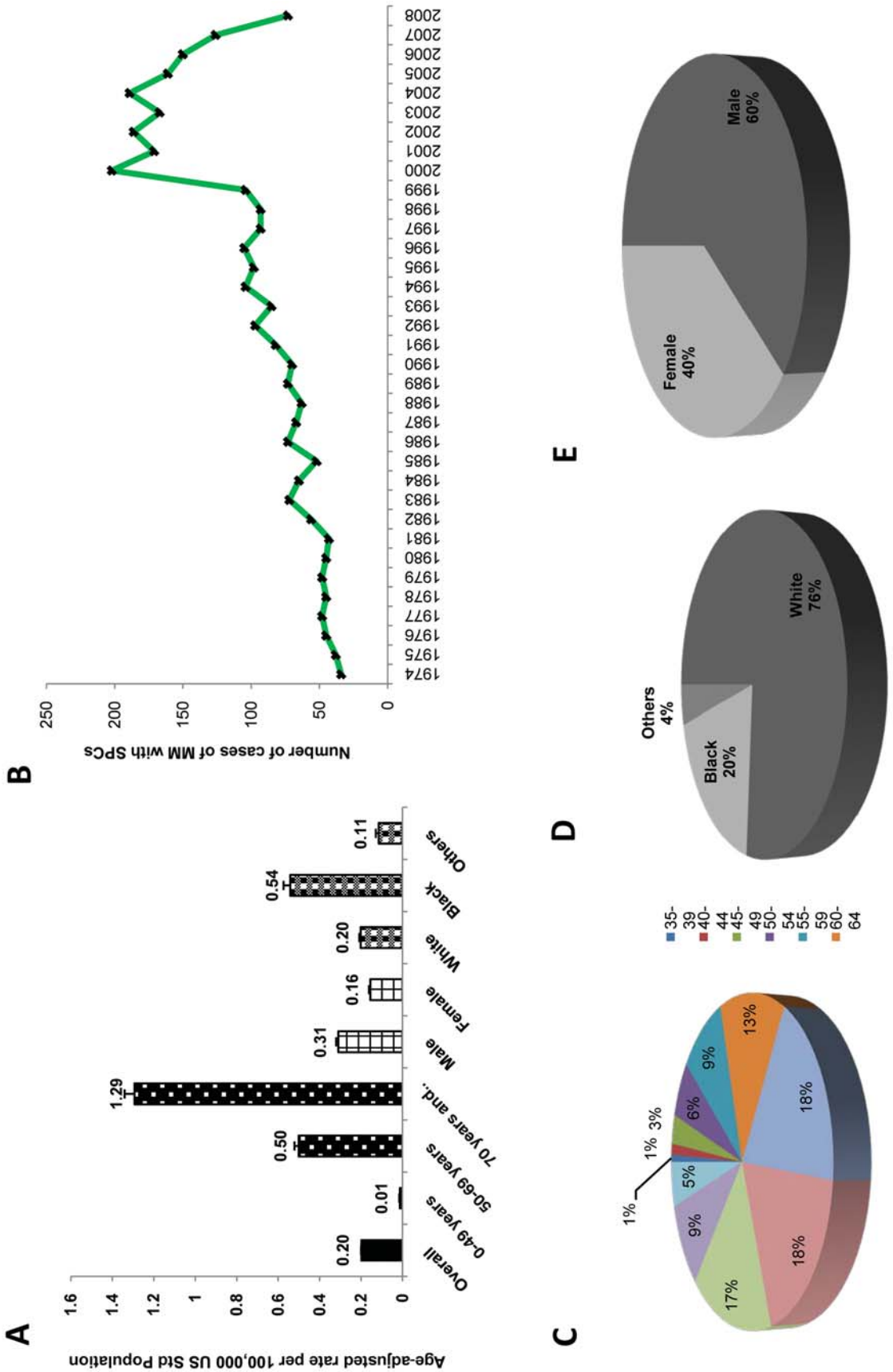

Figure 1. *Incidence of MM with one or more second primary cancers (SPCs). (A) Age-adjusted incidence of MM with one or more SPCs (B) Number of new cases of MM with SPCs identified each calendar year in the SEER database (from 1974-2008) (C-E) Distribution of cases of MM with SPCs by age at the time of diagnosis of SPC (A), race (B) or gender (C).*

Table I. *Multinomial regression analysis of factors associated with risk of SPCs in MM.*

Factor	H.R.	95% CI for H.R.	*p*-Value	*p*-Value (of final model)**
Race				
White	1.18	0.93-1.50	0.16	<0.0001
Black	1.61	1.25-2.08	<0.0001	
Others	1.0 (reference)	-		
Gender				
Male	1.51	1.36-1.66	<0.0001	<0.0001
Female	1.00 (reference)			
Age group at diagnosis				
0-50 years	0.18	0.13-0.24	<0.0001	<0.0001
51-70 years	0.68	0.62-0.75	<0.0001	
≥71 years	1.00 (reference)	-		

**The final model was able to correctly classify the patients into those with only 1 primary *vs*. those with two or more primary cancers, with an accuracy of 100%.

Table II. *Site-specific risk of second primary cancers in MM.*

Site of second malignancy	O (SIR)	95% CI
All sites	1,657 (0.99)	0.95-1.04
All solid tumors	1,394 (0.94)*[a]	0.89-0.99
All lymphatic and hematopoietic diseases	214 (1.68)*	1.46-1.92
Oral cavity and pharynx	31 (0.79)	0.54-1.13
Digestive system	392 (1.05)[b]	0.95-1.16
Liver, GB IHBD, EHBD, other biliary	28 (1.00)	0.67-1.45
Respiratory system	257 (0.91)	0.80-1.02
Bones and joints	1 (0.71)	0.01-4.25
Soft tissue including heart	4 (0.6)	0.16-1.53
Skin excluding BCC and SCC	58 (1.43)*	1.09-1.85
Breast	128 (0.76)*[c]	0.63-0.90
Female genital system	66 (0.92)	0.71-1.17
Male genital System	256 (0.75)*[d]	
Urinary bladder	103 (1.16)	0.95-1.41
Kidney	52 (1.51)*	1.13-1.98
Renal pelvis	2 (0.53)	0.06-1.90
Ureter	3 (1.16)	0.23-3.38
Eye and orbit	2 (0.94)	0.11-3.40
Brain and other nervous system	23 (1.52)	0.96-2.28
Endocrine system	13 (1.25)	0.66-2.13
Lymphoma	75 (1.26)	0.99-1.57
Leukemia	133 (3.07)*[e]	2.57-3.64
Mesothelioma	7 (1.60)	0.64-3.29
Kaposi Sarcoma	5 (3.30)*	1.06-7.69
Miscellaneous	38 (0.82)	0.58-1.13

*$p<0.05$; O-observed number of cases; SIR-standardized incidence ratio (=ratio of the observed to the number of expected cases); [a]Risk of SPC in the hypopharynx significantly decreased (SIR: 0.0), [b]Risk of SPC in the esophagus was significantly decreased (SIR: 0.35), while that in the small intestine increased (SIR: 2.03), [c]Risk of female breast cancer significantly decreased (SIR: 0.76), [d]Significantly decreased risk of SPC in the prostate (SIR: 0.75), [e]Risk of leukemia (SIR: 3.07), acute lymphocytic leukemia (SIR: 5.48), acute myeloid leukemia (SIR: 7.01), chronic myeloid leukemia (SIR: 2.26), other leukemias (SIR: 6.33) significantly increased.

While the overall number of SPCs in MM patients was not significantly different from that in the general population (SIR: 0.99, 95% CI=0.95-1.04, p=N.S.), the number of solid second primary malignancies was significantly lower than that expected in these patients (SIR: 0.94, 95% CI=0.89-0.99, $p<0.05$). The number of lymphatic and hematological malignancies on the other hand were significantly higher than expected (SIR: 1.68, 95% CI=1.46-1.92). Specific sites where the risk of a second solid primary malignancy was decreased included the hypopharynx, esophagus, female breast and prostate. On the other hand, the risk of an SPC in the skin [excluding basal (BCC) and squamous cell carcinoma (SCC)], urinary bladder and kidneys was significantly increased. The risk of leukemias was increased, particularly that of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) (Table II).

Race, age, time elapsed between the diagnosis of MM and the SPC and the year of diagnosis (of SPC) were significant determinants of the risk of development of a SPC in the lymphohematopoietic system (LAHM). Blacks were at a higher (but non-significant) risk of developing a second LAHM, compared to other races. Compared to those aged ≥71 years, younger patients were at a significantly lower risk of developing another LAHM. The risk of a second LAHM was highest in the first year after the diagnosis of MM (HR 3.26 for the 1st 6 months and 4.37 for the next 6 months, $p<0.001$). This risk decreased but remained significant even after 5 years (HR 1.49 for 1-5 years, p=0.04).

A. Age attained at diagnosis of SPC and site-specific risk of SPCs. Based on their age at the time of diagnosis of the second malignancy, patients were divided into three groups: 0-29 years, 30-59 years and ≥60 years. No patient was <30 years old at the time of diagnosis of the second malignancy (Table III). Patients who were between 30-59 years old had a slightly increased (1.2-fold,) while those older than 60 had no significant change in the risk of SPCs. The risk of LAHMs however was increased in both age groups (2.4 and 1.6 fold respectively).

B. Gender. Males were characterized by a significantly (1.6-fold) increased risk of LAHMs, specifically leukemias (AML and ALL) and lymphomas (non-Hodgkin's lymphoma). While the overall risk of solid SPCs was not increased, the risk of a second primary cancer in the kidney was significantly increased in this group (Table III).

There was no significant increase in the overall risk of SPCs in females (Table III). However, in a window of time between 10 and 20 years after the diagnosis of MM, the risk of SPCs was elevated 1.36-fold (data not shown). Furthermore, the risk of a second hematological malignancy (specifically AML and

Table III. *Effect of age attained, gender and race on the site-specific risk of SPCs in multiple myeloma.*

Site of second malignancy	Age attained at diagnosis of SPC			Gender		Race		
	0-29 years O (SIR)	30-59 years O (SIR)	≥60 years O (SIR)	Males O(SIR)	Females O (SIR)	White O (SIR)	Black O (SIR)	Others O (SIR)
All sites	0 (0.0)	166 (1.2)*	1,491 (0.98)	1,011 (0.97)	646 (1.0)	1,273 (0.97)	314 (1.1)	70 (1.2)
All solid tumors	0 (0.0)	138 (1.1)	1,256 (0.92)*	866 (0.92)	528 (0.96)	1,057 (0.91)*	278 (1.05)	59 (1.1)
All lymphatic and hematopoietic diseases	0 (0.0)	25 (2.4)*	189 (1.62)*	122 (1.6)*	92 (1.83)	177 (1.7)	29 (1.55)*	8 (1.98)
Oral cavity and pharynx	0 (0.0)	6 (1.1)	25 (0.75)	25 (0.87)	6 (0.6)	21 (0.7)	9 (1.4)	1 (0.75)
Digestive system	0 (0.0)	27 (1.1)	365 (1.05)[b]	218 (0.99)[g]	174 (1.1)	300 (1.05)	75 (1.1)[q]	17 (0.95)*[s]
Liver, GB IHBD, EHBD, other biliary	0 (0.0)	6 (2.5)	22 (0.9)	17 (0.98)	11 (1.0)	17 (0.9)	5 (0.99)	6 (2.1)[t]
Respiratory system	0 (0.0)	23 (0.99)	243 (0.9)	175 (0.9)	8 (0.9)	191 (0.88)	55 (0.98)	11 (1.2)
Bones and joints	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.3)	0 (0)	1 (0.9)	0 (0)	0 (0)
Soft tissue including heart	0 (0.0)	1 (1.3)	3 (1.51)	2 (0.5)	2 (0.77)	3 (0.6)	1 (0.94)	0 (0)
Skin excluding BCC and SCC	0 (0.0)	10 (1.8)	48 (1.4)*[c]	37 (1.33)	21 (1.7)*	54 (1.4)*[m]	3 (3.6)	1 (2.95)
Breast	0 (0.0)	21 (0.92)	107 (0.8)*[d]	1 (0.5)	127 (0.76)*[k]	92 (0.7)*[n]	29 (1.1)	7 (1.2)
Female genital system	0 (0.0)	10 (1.11)	56 (0.9)	-	66 (0.9)	54 (0.9)	11 (0.95)	1 (0.4)
Male genital system	0 (0.0)	13 (0.7)	243 (0.75)*[e]	256 (0.75)*[h]	-	179 (0.7)[o]	64 (0.9)	13 (1.3)
Urinary bladder	0 (0.0)	10 (2.1)	93 (1.1)	81 (1.2)	22 (1.2)	89 (1.14)	11 (1.4)	5 (1.5)
Kidney	0 (0.0)	9 (2.3)*	43 (1.4)*	39 (1.65)*	13 (1.2)	36 (1.34)	14 (2.2)*	2 (1.8)
Renal pelvis	0 (0.0)	0 (0.0)	2 (0.6)	0 (0)	2 (1.5)	1 (0.3)	1 (2.9)	0 (0)
Ureter	0 (0.0)	0 (0.0)	3 (1.2)	1 (0.6)	2 (2.5)	3 (1.3)	0 (0)	0 (0)
Eye and orbit	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.8)	1 (1.2)	2 (0.96)	0 (0)	0 (0)
Brain and other nervous system	0 (0.0)	1 (0.5)	22 (1.7)	14 (1.5)	9 (1.5)	21 (1.6)	1 (0.7)	1 (2.6)
Endocrine system	0 (0.0)	3 (1.3)	10 (1.3)	7 (1.6)	6 (0.99)	10 (1.23)	1 (0.7)	2 (2.6)
Lymphoma	0 (0.0)	8 (1.4)	67 (1.2)	48 (1.4)*[i]	27 (1.10)	62 (1.22)	10 (1.6)	3 (1.3)
Leukemia	0 (0.0)	15 (5.2)*[a]	118 (2.92)*[f]	69 (2.5)*[j]	64 (4.1)*[l]	109 (2.98)*[p]	19 (3.45)*[r]	5 (4.6)*[u]
Mesothelioma	0 (0.0)	0 (0.0)	7 (1.7)	7 (1.9)	0 (0)	5 (1.3)	2 (5.3)	0 (0)
Kaposi Sarcoma	0 (0.0)	3 (5.8)*	2 (2.0)	4 (3.2)	1 (4.0)	4 (3.4)	1 (3.4)	0 (0)
Miscellaneous	0 (0.0)	3 (1.1)	35 (0.8)	18 (0.7)	20 (0.9)	28 (0.8)	7 (0.82)	3 (1.9)

*$p<0.05$; O-observed number of cases; SIR- standardized incidence ratio (ratio of the observed to the number of expected cases); [a]Significantly increased risk of acute non-lymphocytic leukemia (ANLL, SIR: 10.1), myeloid and monocytic leukemias (SIR:8.5), acute myelogenous leukemia (AML, 10.6); [b]Significantly decreased risk of second primary cancer in the esophagus (SIR: 0.44); [c]Risk of non-epithelial skin cancers (excluding melanomas) is significantly increased (SIR: 2.8); [d]Significantly decreased risk of second primary cancer in the female breast (SIR: 0.73); [e]Risk of second primary cancer in prostate significantly decreased (SIR: 0.75); [f]The risk of acute lymphoblastic leukemia (SIR: 5.3), ANLL (SIR: 6.9), AML (SIR: 6.8), chronic myeloid leukemia (SIR: 2.1) and other leukemias (SIR: 6.3) is significantly increased while that of chronic lymphocytic leukemia is significantly decreased (SIR: 0.12); [g]Risk of SPC of the esophagus significantly decreased (SIR: 0.46); [h]Risk of SPC of the prostate significantly decreased (SIR: 0.75); [i]Risk of NHL as a SPC significantly increased (SIR: 1.4); [j]Risk for ALL (SIR: 6.0), ANLL (SIR: 6.0), AML (SIR: 5.6) and other leukemias (SIR: 6.5) was significantly increased while that for CLL was significantly decreased (SIR: 0.08); [k]Risk of SPC in the female breast significantly decreased (SIR: 0.76); [l]Risk of ANLL (SIR: 9.00), AML (SIR: 9.3), Chronic myeloid leukemia (SIR:4.3) and other leukemias (excluding lymphocytic leukemias and MAML, SIR: 6.1) significantly increased; [m]Risk of non-epithelial skin cancers significantly increased (SIR: 2.9); [n]Significantly increased risk of female breast cancer (SIR: 0.7); [o]Significantly decreased risk of second primary cancer (SPC) in the prostate (SIR: 0.7); [p]Significantly increased risk of non-lymphocytic leukemias (SIR: 5.4), chiefly acute non-lymphocytic leukemias (ANLL, SIR: 7.3), acute myelogenous leukemia (AML, SIR: 7.2), chronic myeloid leukemia (CML, SIR: 2.31) and other acute leukemias [excluding lymphocytic leukemias and MAMLs (myeloid and monocytic leukemias), SIR: 9.5]. Also, significantly decreased risk of lymphocytic leukemias (SIR: 0.45), chiefly chronic lymphocytic leukemia (SIR: 0.19); [q]Significant increase in the risk of a small intestine SPC (SIR: 4.1) while the risk of esophageal SPC is significantly decreased (SIR: 0.0); [r]Risk of ALL (SIR: 16.2); ANLL (SIR: 6.7) and MAMLs (SIR:5.2) and other leukemias (excluding lymphocytic leukemias and MAMLs, SIR: 6.2). Among MAMLs, risk of AML is significantly increased (SIR: 6.82); [s]Risk of SPC of the colon, rectum and anus significantly decreased (SIR: 0.34); [t]Significant increase in the risk of liver SPC (SIR: 3.22); [u]significantly increased risk of ANLL (SIR: 5.4).

CML) was significantly increased between 5 and 20 years after the diagnosis of MM, but not before or after that.

C. Race. Although none of the three racial groups (whites, blacks and other races) had a significant change in the overall risk of SPCs compared to the general population (Table III), the risk of a second malignancy in solid organs was decreased by about 9% in whites, but not in other races. Furthermore, a comparison of the site-specific risk of SPCs in the three groups revealed certain interesting differences. While whites had an increased risk of skin cancer and a decreased risk of prostate and female breast cancer, blacks experienced an increased risk of a second malignancy in the small intestine and kidneys. Patients belonging to the other

Table IV. *Relative survival and age of onset of SPCs in MM patients with one or more SPCs.*

	Relative survival				Age of onset of SPC			
	1 year	95% CI	5 year	95% CI	Mean (±SE)	Median	Range	*p*-Value (ANOVA)
All cases	88.5%	87.2-89.7	53.8%	51.6-55.9				
Race								
White	89.3%	87.8-90.7	53.8%	51.3-56.3	72.4±0.3	73.0	39-101	<0.0001
Black	86.1%	82.7-88.9	54.6%	49.5-59.4	69.2±0.5	69.5	34-96	
Others	84.4%	76.6-89.8	49.9%	39.8-59.3	69.17±0.5	72.5	57-89	
AI/AN*	88.9%	56.7-97.6	52.3%	22.9-75.2	71.2±2.6	74.0	53-83	
Chinese	88.4%	62.8-96.8	46.5%	22.1-67.8	74.2±2.2	72.5	62-84	
Japanese	86.2%	57.7-96.1	33.2%	34.6-81.4	73.2±2.6	74.0	57-84	
Filipino	82.0%	64.0-91.5	44.8%	25.7-62.2	77.1±1.8	78.0	65-89	
Hawaiian	74.4%	43.6-90.0	39.9%	14.7-64.5	69.9±2.2	68.5	57-86	
Korean	61.0%	12.2-89.0	N/C		67.5±6.5	67.5	61-74	
Vietnamese	85.0%	23-98.2	38.7%	4.4-74.9	76.5±1.5	76.5	75-78	
Asian India/Pakistani	100%	N/C	65.4%	10.0-92.4	76±14.4	76.0	66-86	
Samoan	100%	N/C	50.8%	0.5-91.6	59.5±2.5	59.5	57-62	
Gender								
Male	88.4%	86.6-90.0	53.9%	51-56.7	71.5±0.3	72.0	34-101	0.068
Female	88.6%	86.5-90.4	53.7%	50.4-57.0	72.3±0.4	73.0	39-97	
Age								
35-39 years	88%	66.7-96	75.1%	51.1-88.5				
40-44 years	90%	74.9-96.0	72.3%	54.8-83.9				
45-49 years	95.4%	88.3-98.2	70.8%	59.6-79.5				
50-54 years	92.3%	87.3-95.4	73.2%	65.5-79.5				
55-59 years	94.7%	91.1-96.8	65.1%	58.4-71.0				
60-64 years	92.9%	89.6-95.2	60.7%	54.9-66.0				
65-69 years	90.2%	87.1-92.6	54.9%	49.9-59.6				
70-74 years	87.8%	84.4-90.5	49.1%	43.9-54.2				
75-79 years	86.1%	82.2-89.1	42.8%	37.2-48.3				
80-84 years	81.3%	75.2-86.0	41.5%	32.7-49.9				
85+ years	72.7%	62.8-80.4	29.9%	17.8-42.8				

N/C: Could not be calculated, *AI/AN: American Indian/Alaskan Native.

races had a significant reduction in the risk of a colon, rectal and anal SPC. Notably, the risk of leukemias was increased in MM patients of all races (Table III).

Prognostic impact of SPCs in MM patients. Having determined the incidence and site-specific risk of SPCs, we next sought to investigate their effect on prognosis in MM patients. The overall 1- and 5-year relative survival of MM patients with SPCs was 88.5% (95% CI 87.2%-89.7%) and 53.8% (95% CI=51.6%-55.9% respectively). Both 1- and 5-year survival declined with advancing age. Blacks had a slightly higher (not statistically significant) 5-year relative survival compared to whites. There was, however, no significant difference in either the 1- or 5-year relative survival between males and females (Table IV).

Univariate analysis also revealed that advanced age, race, site of SPC and year of diagnosis but not gender or time elapsed between the diagnosis of MM and the SPC were predictors of survival in patients with SPCs (Table V). A multivariate analysis revealed that the site of the SPC, race and the year of diagnosis were independent predictors of survival in SPC patients (Table VI).

Discussion

Second primary cancers have emerged in recent years as important determinants of morbidity and mortality among cancer survivors. In the present study, we sought to investigate the incidence of SPCs in MM, the risk factors that predict their occurrence and to determine their effect on survival. The results of our analysis suggest that the risk of LAHMs is significantly increased while that of a solid tumors is significantly decreased in these patients.

Table V. *Kaplan Meier analysis of factors affecting survival in MM with SPCs.*

Patient group	Total N	Censored (N, %)	Median (±SE) survival	Mean (±SE) survival	Log-Rank test (Mantel-Cox)
Age at diagnosis					
0-50 yrs	39 (2.3%)	11 (28.2%)	20±7.2	25.3±4.3	0.010
51-70 yrs	695 (40.2%)	127 (18.3%)	15.0±1.15	32.2±1.8	
≥71 yrs	996 (57.6%)	102 (10.2%)	11.0±1.05	25.9±1.2	
Gender					
Male	1,048 (60.6%)	136 (13%)	12±0.96	28.3±1.3	0.76
Female	681 (39.4%)	104 (15.2%)	15±1.27	28.3±1.7	
Race					
White	1,308 (75.7%)	172 (13.1%)	12±0.9	26.8±1.1	0.004
Black	346 (20%)	57 (16.5%)	16±1.9	35.3±2.5	
Others *	75 (4.3%)	11 (14.7%)	11±3.3	25.7±4.3	
Organ system**					
GU	488	93 (19%)	17±1.6	32.4±2.0	0.004
LH	227	33 (14.5%)	11±1.4	26.1±3.1	
GI	433	39 (9%)	9±0.96	24.5±1.9	
Bone, soft tissue, CNS and orbit	37	3 (8.1%)	18±4.5	21.8±3.4	
Respiratory	264	15 (5.7%)	13±1.8	26.9±2.1	
Skin	63	13 (20.6%)	22±4.8	42.9±8.1	
Endocrine	175	36 (20.6%)	15±2.2	30.2±3.1	
Year of diagnosis					
1974-1978	75	0 (0%)	6±1.4	24.4±4.8	<0.0001
1979-1983	159	0 (0%)	6±0.95	20.4±3.2	
1984-1988	220	0 (0%)	8±1.7	21.8±2.1	
1989-1993	299	3 (1%)	11±1.6	24.3±1.9	
1994-1998	295	17 (5.8%)	15±1.8	31.5±2.5	
1999-2003	303	43 (14.2%)	15±1.9	28.6±2.2	
2004-2008	377	177 (46.9%)	24±2.7	38.9±3.1	
Months elapsed***					
0-6	291	34 (11%)	12±2.3	25.6±2.1	0.40
7-12	166	17 (10%)	15±2.2	25.1±2.7	
13-60	798	104 (13%)	14±1.1	28.1±1.4	
≥61	453	81 (18%)	12±1.4	31.7±2.4	

N: Number of patients, Multiple myeloma (MM), second primary cancer (SPC), *American Indian/AK Native, Asian/Pacific Islander; **sites of occurrence of SPCs,***between diagnosis of MM and the SPC, genitourinary (GU), lymphohematopoietic (LH), gastrointestinal (GI).

While there are no specific studies investigating the occurrence of SPCs in MM, several population-based studies have investigated the occurrence of SPCs in hematological malignancies. The report of a 20-year-long study on the risk of SPCs among patients with various known primary malignancies from Victoria noted that the overall risk of SPCs was not increased in MM patients. However, there was a significant increase in the risk of bladder cancer in these patients . The converse however was not true (*i.e.* patients with bladder cancer were not at a higher risk of developing MM) (11). Storm and co-workers, in an study among Danish patients with LAHMs, reported that the risk of both solid and hematological SPCs was significantly decreased in MM (relative risk 0.8, relative to the general population) (23). We, however, observed that while the overall the risk of SPCs was not significantly affected, risk of solid malignancies decreased and that of hematological malignancies increased in MM patients. One possible explanation is that similar molecular mechanisms may drive the development of different hematological malignancies. These factors may be influenced by local and environmental factors including hormones, environmental factors, dietary habits and genetics. Unraveling the underlying mechanisms would help design better surveillance strategies in MM patients.

We observed that black race, age <70 years at the time of diagnosis of the SPC, and the location of an SPC in the skin were factors that predicted a longer survival in MM patients with SPCs. Waxman and colleagues recently reported that while the age at onset of SPCs was lower for blacks than whites (65.7 years *vs*. 70.0 years, $p<0.0001$), and the incidence two-fold higher, MM-specific survival was better in blacks than in whites (25). This is similar to our observation that MM was diagnosed about 2.8 years earlier in blacks than in whites. Their mean survival was also about 8.5 months

Table VI. *Multivariate analysis of factors that influence overall survival in patients with MM and SPCs.*

Variable*	H.R. (95% CI)	*p*-Value
Organ system		0.014
GU system	1.0 (reference)	
LH system	1.14 (0.96-1.36)	0.13
GI system	1.25 (1.08-1.43)	0.002
Bones, soft tissue, CNS and orbits	1.17 (0.82-1.67)	0.38
Respiratory system	1.14 (0.97-1.33)	0.11
Skin	0.79 (0.59-1.07)	0.14
Endocrine	1.09 (0.89-1.33)	0.37
Race		0.003
Black	1 (reference)	
White	1.23 (1.08-1.41)	0.002
Others	1.39 (1.05-1.84)	0.021
Year of diagnosis		<0.0001
1974-1978	1 (reference)	
1979-1983	1.08 (0.81-1.43)	0.60
1984-1988	0.99 (0.76-1.30)	0.98
1989-1993	0.93 (0.72-1.20)	0.58
1994-1998	0.77 (0.60-1.00)	0.05
1999-2003	0.81 (0.63-1.06)	0.12
2004-2008	0.59 (0.45-0.77)	<0.0001

Hazards ratio (H.R.), confidence interval (CI), second primary cancer (SPC), genitourinary (GU), Lymphohematopoietic (LH), gastrointestinal (GI), central nervous system (CNS). *Age at diagnosis of SPC was not retained in the final model.

longer in blacks than in whites. An earlier age of onset could be one of the factors underlying the longer survival observed in blacks, possibly owing to greater number of patients being able to tolerate stem cell transplant and chemotherapy.

Although the female gender has been reported to be associated with shorter overall survival in MM (10), we did not observe such a trend among patients with SPCs. Overall survival was, however, higher in patients diagnosed with SPCs in and after 1994 compared to those diagnosed earlier, possibly due to advancements in diagnostic and therapeutic modalities.

We also observed that the organ system where an SPC arose had a significant impact on survival of MM patients. Specifically, survival was lower if the SPC arose in the bone, soft tissues, CNS or orbits and highest if it arose in the skin. Furthermore, patients with genitourinary or endocrine tumors had a longer survival than those with gastrointestinal and lymphohematopoeitic malignances. Studies in other tumors (*e.g.* retinoblastoma (8)) have also shown that deaths in patients with secondary malignancies depend, among other things, on the site of the second primary and the treatment given for the first primary tumor. The differences observed in specific patient groups could be a useful aid to help clinicians maintain a high index of suspicion in a particular patient for SPCs at a specific site. Whether the aggressiveness of the SPC is more or less compared to the same tumor occurring as a primary malignancy, however, is unknown and will need to be explored.

An interesting observation in our study was that patients of Asian origin (Indian, Pakistani, Chinese, Filipinos, Vietnamese and Japanese) had a higher mean age of development of the SPC compared to whites, blacks or others. Furthermore, they had a similar 1-year but shorter 5-year survival than the other three ethnic groups (Table IV). While their numbers are too few to permit an in-depth analysis, genetic, dietary, environmental, cultural and lifestyle factors are likely to influence their later diagnosis and hence shorter survival. Studies involving cancer registries from the Asian countries will help answer this question in the future.

It is notable that patients who developed MM were at a significantly higher risk of developing another lymphatic or hematopoietic malignancy (Table II). Particularly, there was an increased risk of leukemias but not of lymphomas. Among leukemias, the risk of ALL, AML and CML was significantly increased (Table II). Regression analysis revealed that the factors that increased the risk of a second LAHM were male gender, black race and age ≥71 years at the time of diagnosis (Table I). A key question is how is the occurrence of MM and leukemias connected? A report by Garipidou and colleagues described a complex Philadelphia chromosome that contained translocations between chromosomes 9, 14 and 22 and involved the locus coding for the lambda light chain on 22q11. The patient in this case developed MM after being initially diagnosed with CML 7 months back. It was also suggested that imatinib (used in treating CML), which has a small stimulatory effect on MM cells *in vitro* could have triggered the development of MM (9). It is unclear however if the reverse is possible, *i.e.* patients with a similar genetic pattern developing MM prior to a CML. Familial clustering of MM (in child) with CML (in mother) has been reported although the mechanism is unclear (26). AML has been described to occur following long term alkylating therapy for MM (21), and in certain case reports to occur concurrently with MM (14, 22). A study from Sweden found that first-degree relatives of MM patients had a significantly higher risk of developing MM, ALL and bladder cancer (13). These studies suggest a link between MM and leukemias, but further dissection of the underlying genetics is awaited.

In conclusion we have observed that MM patients are at a significantly higher risk of a second LAHM and at a lower risk for a solid organ SPC. Black race, male gender and advanced age are risk factors that predict the occurrence of SPCs in MM patients. Race, site of the SPC and year of diagnosis of SPC but not age, gender or time elapsed between MM and the SPC were independent predictors of survival in these patients. The results of our study suggest the need for closer surveillance of at-risk MM patients for the development of SPCs and for further research into the molecular pathways underlying the occurrence of SPCs.

Conflicts of Interest

The Authors declare no conflicts of interest.

References

1 American Cancer Society. Cancer Facts & Figures 2009. 2009. Atlanta, American Cancer Society.

2 Bhandari MS, Mazumder A, Jagannath S and Vesole DH: Association between renal cell carcinoma and plasma cell dyscrasias: a case series of six patients. Clin Lymphoma Myeloma *8*: 188-190, 2008.

3 Blade J, Dimopoulos M, Rosinol L, Rajkumar SV and Kyle RA: Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome, and follow-up recommendations. J Clin Oncol *28*: 690-697, 2010.

4 Ceres F, Rivera F, Yague JL, Blanco J, Garcia-Rojo M, Sanchez de la Nieta MD, Alcazar R and de la TM: Non-Hodgkin lymphoma, IgA nephropathy and renal cell carcinoma. Nefrologia *23*: 554-557, 2003.

5 Chuang SC, Hashibe M, Scelo G, Brewster DH, Pukkala E, Friis S, Tracey E, Weiderpass E, Hemminki K, Tamaro S, Chia KS, Pompe-Kirn V, Kliewer EV, Tonita JM, Martos C, Jonasson JG, Dresler CM, Boffetta P and Brennan P: Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev *17*: 1543-1549, 2008.

6 Chuang SC, Scelo G, Tonita JM, Tamaro S, Jonasson JG, Kliewer EV, Hemminki K, Weiderpass E, Pukkala E, Tracey E, Friis S, Pompe-Kirn V, Brewster DH, Martos C, Chia KS, Boffetta P, Brennan P and Hashibe M: Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J Cancer *123*: 2390-2396, 2008.

7 Dong C and Hemminki K: Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer *85*: 997-1005, 2001.

8 Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, Seddon J, Tarbell N and Boice JD Jr.: Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst *85*: 1121-1128, 1993.

9 Garipidou V, Vakalopoulou S and Tziomalos K: Development of multiple myeloma in a patient with chronic myeloid leukemia after treatment with imatinib mesylate. Oncologist *10*: 457-458, 2005.

10 Jawed I, Lee M, Tward JD, Macdonald OK, Martincic D, Vudarla N and Fairbanks HK: Survival outcomes for multiple myeloma over three decades: A Surveillance, Epidemiology, and End Results (SEER) analysis. J Clinic Oncol *25 [18S(20 Suppl)]*: 8019, 2007.

11 Karahalios E, English D, Thursfield V, Simpson J, Farrugia H, and Giles G: Second Primary Cancers in Victoria. pp. 1-116. 2009. Melbourne, Victoria. Australia, Victorian Cancer Registry, Cancer Epidemiology Centre, Cancer Council Victoria. Ref Type: Serial (Book, Monograph).

12 Khadilkar U, Prasad K, Gupta S and Prabhu GL: Synchronous RCC with NHL: a case report. Kathmandu Univ Med J (KUMJ) *5*: 417-420, 2007.

13 Kristinsson SY, Bjorkholm M, Goldin LR, Blimark C, Mellqvist UH, Wahlin A, Turesson I and Landgren O: Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden. Int J Cancer *125*: 2147-2150, 2009.

14 Luca DC and Almanaseer IY: Simultaneous presentation of multiple myeloma and acute monocytic leukemia. Arch Pathol Lab Med *127*: 1506-1508, 2003.

15 Muir CS and Percy C: Cancer registration: principles and methods. Classification and coding of neoplasms. IARC Sci Publ pp. 64-81, 1991.

16 Nishikubo CY, Kunkel LA, Figlin R, Belldegrun A, Rosen P, Elashoff R, Wang H and Territo MC: An association between renal cell carcinoma and lymphoid malignancies. A case series of eight patients. Cancer *78*: 2421-2426, 1996.

17 Noura S, Ohue M, Seki Y, Tanaka K, Motoori M, Kishi K, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Tsukuma H, Murata K and Kameyama M: Second primary cancer in patients with colorectal cancer after a curative resection. Dig Surg *26*: 400-405, 2009.

18 Okamoto N, Morio S, Inoue R and Akiyama K: The risk of a second primary cancer occurring in five-year survivors of an initial cancer. Jpn J Clin Oncol *17*: 205-213, 1987.

19 Renshaw C, Ketley N, Moller H and Davies EA: Trends in the incidence and survival of multiple myeloma in South East England 1985-2004. BMC Cancer *10*: 74, 2010.

20 Satram-Hoang S, Ziogas A and nton-Culver H: Risk of second primary cancer in men with breast cancer. Breast Cancer Res *9*: R10, 2007.

21 Shukla J, Patne SC and Singh NK: Simultaneous appearance of dual malignancies of hematopoietic system-multiple myeloma and acute myeloid leukemia. Indian J Pathol Microbiol *51*: 118-120, 2008.

22 Stewart AK, Freedman J and Garvey MB: Acute leukemia evolving from multiple myeloma and co-expressing myeloid and plasma cell antigens. Am J Hematol *34*: 210-214, 1990.

23 Storm HH and Prener A: Second cancer following lymphatic and hematopoietic cancers in Denmark, 1943-80. Natl Cancer Inst Monogr *68*: 389-409, 1985.

24 Turesson I, Velez R, Kristinsson SY and Landgren O: Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol *28*: 830-834, 2010.

25 Waxman AJ, Mink PJ, Devesa SS, Anderson WF, Weiss BM, Kristinsson SY, McGlynn KA and Landgren O: Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood *116*: 5501-5506, 2010.

26 Wirtschafter SK and Rapaport SI: The familial occurrence of chronic lymphocytic leukemia and multiple myeloma. Calif Med *92*: 165-166, 1960.

Received August 20, 2012
Accepted September 12, 2012