

RESEARCH ARTICLE

Influence of Residential Environment and Lifestyle on Multiple Primary Malignancies in Taiwan

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Abstract

Background: Multiple primary malignancies (MPM) have become increasingly prevalent worldwide. This investigation was aimed at establishing the clinicopathological characteristics of MPM patients and evaluating the impact of the living environment on MPM in the Taiwanese population. **Materials and Methods:** From January 2009 to December 2013, a total of 8,268 cancer patients were identified in our institutional center. Of these, 125 were diagnosed as MPM and thus enrolled. Data for clinicopathological features and treatment approaches for these MPM patients living in urban or suburb zone were obtained. Findings for the air pollution status in Taiwan were also collected. **Results:** The most common cancer match of MPM was esophageal cancer with hypopharyngeal cancer (12.8%), followed by colorectal cancer with gastric cancer (6.4%) and colorectal cancer with breast cancer (5.6%). The air quality was significantly worse in the urban than in the suburban zone and there was a remarkably higher portion of MPM patients in the urban zone suffering from grade III and IV post-chemotherapeutic neutropenia (30.8% vs 15.1%, $P=0.036$). **Conclusions:** The tumor frequency and site distribution should be taken into the clinical evaluation because there is a relatively high risk of developing MPM. This study also highlighted the potential influence of environmental factors on post-chemotherapeutic neutropenia for patients with MPM.

Keywords: Air pollution - lifestyle - multiple primary malignancies - post-chemotherapeutic neutropenia

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Introduction

The prevalence of multiple primary malignancies (MPM) has been rising worldwide, according to advancing medical management of chronic diseases and subsequently the increasing life span. To present, it was reported the incidence of MPM varied from 0.7% to 18% in all cancer patients, owing to different populations (Luciani et al., 2009; Gursel et al., 2011; Travis et al., 2013). Although it required further investigation to disclose the precise pathogenesis of MPM, several etiological factors were found and stratified (Wood et al., 2012; Takalkar et al., 2013). The main causes of MPM could be categorized as: *i*) chemoradiation-affiliated; *ii*) syndromic; *iii*) genetically predisposed; *iv*) lifestyle and environmental exposure-related. Of these, environmental and lifestyle influences, including tobacco use, excess alcohol consumption, dietary pattern and residential area, were considered one of the major causes leading to increasing risk of developing MPM. It was observed that tobacco use was strongly associated with MPM involving lung and upper aerodigestive organs (Begg et al., 1995; Krishna Rao et al., 2013). The relationship between excess alcohol intake

and the occurrence of cancers in liver (Grewal P et al., 2012), breast (Brooks and Zakhari, 2013) and digestive tract (Haas et al., 2012) was also recognized. Additionally, obesity with physical inactivity was associated with a myriad of cancers such as breast cancer (Jain et al., 2013), thyroid cancer (Marcello et al., 2014), colorectal cancer (De Pergola and Silvestris, 2013) and gynecologic cancers (McTiernan et al., 2010; Schmandt et al., 2011). It was also reported that environmental exposure to air contamination increased the incidence of lung cancer (Dales; 2008; Park et al., 2008). Nevertheless, limited study regarding MPM and environmental exposure was under investigation. Therefore, our study was aimed to clarify the association between MPM and environmental exposure as well as attributive risk factors.

Materials and Methods

Between January 2009 and December 2013, a total of 8268 cancer patients were clinically diagnosed and pathologically proven at the Far Eastern Memorial Hospital (FEHM) in New Taipei city, Taiwan. Among these patients, 125 patients with MPM were identified

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by pathological verification and thus enrolled. Patients found with a second cancer due to recurrence or metastasis were excluded. Patients with MPM were divided into the groups living in urban zone (Banqiao city) and suburb zone (Tucheng, Zhonghe, Shulin, etc.). The clinical data during admission and out-patient department follow-up were collected via charts review, including age, gender, living area, family history of cancer, history of tobacco use and alcohol intake, tumor site distribution, TNM tumor stage and underlying comorbidities such as hypertension (HTN), cardiovascular diseases (CVD), obstructive lung diseases (OLD), peptic ulcer disease (PUD), hepatitis B and C, chronic kidney disease (CKD), diabetes mellitus (DM) and stroke events. The laboratory data after patients received chemotherapy were acquired including white blood cell count (WBC), absolute neutrophil count (ANC), hemoglobin (Hb), aspartate aminotransferase (AST), alanine transaminase (ALT), creatinine, blood urea nitrogen (BUN), albumin, fasting blood glucose (FBG), cholesterol, high density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP). All laboratory values were obtained by the automatic analyzer with standard operating procedures.

The report of air quality status in Taiwan for the year 2009 to 2013 was referred to the Taiwan Air Quality Monitoring Network (TAQMN) manipulated by the Environmental Protection Administration (EPA). The parameters of air quality encompassed the annually average levels of particulate matter with aerodynamic diameter less than 10 and 2.5 mm (PM10 and PM2.5), nitrogen dioxide (NO₂) and sulfur dioxide (SO₂). The data of air quality were recorded by a network of 12 monitoring stations spreading in New Taipei city.

Statistical analyses were performed using The SPSS (version 15.0; SPSS Inc., Chicago, USA) statistical software in the present study. All data were expressed as the mean \pm standard deviation or number with percentage (%). For categorical data, Chi-square test was applied and for continuous data, student's t test was used for statistical analyses. Statistical significance was considered if a P value was less than 0.05.

Results

Out of these 8,268 cancer-bearing patients registered in our hospital over the 5-year period, 125 (1.5%) were diagnosed as MPM. Among the 125 patients with MPM, 52 lived in urban zone and 73 lived in suburb zone. Most of them had second primary cancers and merely 2 had third primary cancers. The clinical manifestations of these patients were shown in Table 1. The average age of MPM patients at first diagnosed was 62.47 \pm 1.00 years old. There was no significance between urban zone group and suburb zone group. Of these patients, 68% was male. There was no significant gender difference between both groups. 15 patients living in urban zone and 13 living in suburb zone had a family history of cancer. Approximately half of MPM patients had tobacco use and excess alcohol consumption in our study (tobacco use: 58.3% vs 49.3%, $P=0.617$; alcohol use: 42.3% vs 42.5%, $P=0.986$). Among these patients with MPM, 22 were stage I, 19 stage II,

32 was stage III and 32 was stage IV in the urban zone group; 38 was stage I, 37 was stage II, 37 was stage III and 34 was stage IV in the suburb zone group. There was no significant difference between both groups. Notably, a significantly higher portion of MPM patients living in urban zone had HTN than those living in suburb zone (53.8% vs 27.4%, $P=0.003$). Twenty-three MPM patients had cardiovascular diseases (CVD), 6 had obstructive lung diseases (OLD), 16 had peptic ulcer diseases (PUD), 32 had hepatitis B or C, 6 had chronic kidney disease (CKD), 32 had diabetes mellitus (DM) and 7 had stroke history. There was no remarkable difference of the underlying comorbidities mentioned above between both groups. Treatment approaches of patients with MPM were listed in Table 2. Most of patients with MPM had received chemotherapy (88.5% vs 79.5%, $P=0.184$) and surgical intervention (75.0% vs 78.1%, $P=0.687$). Moreover, about half of them had received radiotherapy (55.8% vs 52.1%, $P=0.681$), without significant difference regarding to living zones.

The tumor site and frequency of MPM patients were shown in Figure 1. The most common neoplasm in MPM

Table 1. Clinical Characteristics of Patients with Multiple Primary Malignancies Living in Urban Zone and Suburb Zone

Variables	Total	Urban zone	Suburb zone	P value
Age (y)	62.47 \pm 1.00	61.69 \pm 1.43	63.03 \pm 1.38	0.513
Gender				0.889
Male	85 (68.0%)	35 (67.3%)	50 (68.5%)	
Female	40 (32.0%)	17 (32.7%)	23 (31.5%)	
FHC				0.145
Yes	28 (22.4%)	15 (28.8%)	13 (17.8%)	
No	97 (77.6%)	37 (71.2%)	60 (82.2%)	
Tobacco use	64 (51.2%)	28 (58.3%)	36 (49.3%)	0.617
Alcohol use	53 (42.4%)	22 (42.3%)	31 (42.5%)	0.986
Stage				
I	60 (23.9%)	22 (21.0%)	38 (26.0%)	0.133
II	46 (18.3%)	19 (18.1%)	37 (25.3%)	0.117
III	69 (27.5%)	32 (30.5%)	37 (25.3%)	0.229
IV	66 (26.3%)	32 (30.5%)	34 (23.3%)	0.096
Comorbidities				
HTN	48 (38.4%)	28 (53.8%)	20 (27.4%)	0.003
CVD	23 (18.4%)	12 (23.1%)	11 (15.1%)	0.254
OLD	6 (4.8%)	2 (3.8%)	4 (5.5%)	0.674
Pul TB	4 (3.2%)	1 (1.9%)	3 (4.1%)	0.494
PUD	16 (12.8%)	8 (15.4%)	8 (11.0%)	0.465
Hepatitis B/C	32 (25.6%)	10 (19.2%)	22 (30.1%)	0.168
CKD	6 (4.8%)	3 (5.8%)	3 (4.1%)	0.669
DM	32 (25.6%)	14 (26.9%)	18 (24.7%)	0.775
Stroke	7 (5.6%)	3 (5.8%)	4 (5.5%)	0.945

Table 2. Treatment of Patients with Multiple Primary Malignancies Living in Urban Zone and Suburb Zone

Treatment types	Total	Urban zone	Suburb zone	P value
Chemotherapy	104 (83.2%)	46 (88.5%)	58 (79.5%)	0.184
Surgical intervention	96 (76.8%)	39 (75.0%)	57 (78.1%)	0.687
Radiotherapy	67 (53.6%)	29 (55.8%)	38 (52.1%)	0.681

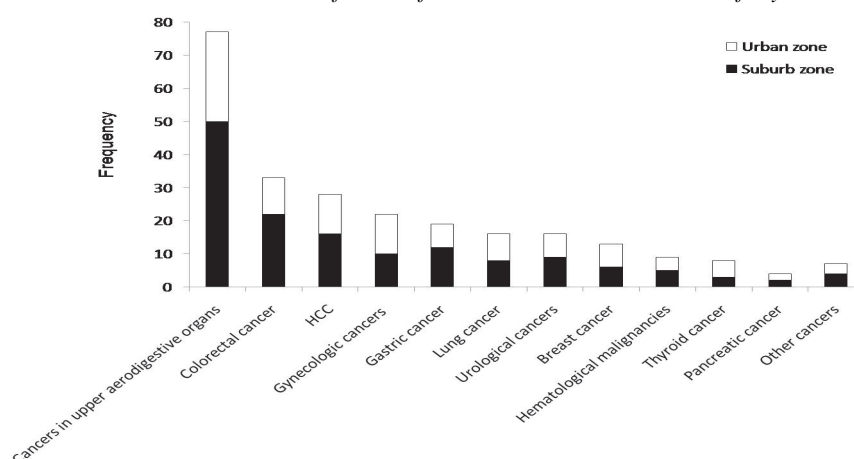


Figure 1. The Frequency of Tumor Site Distribution in Patients with Multiple Primary Malignancies Living in Urban Zone and Suburb Zone

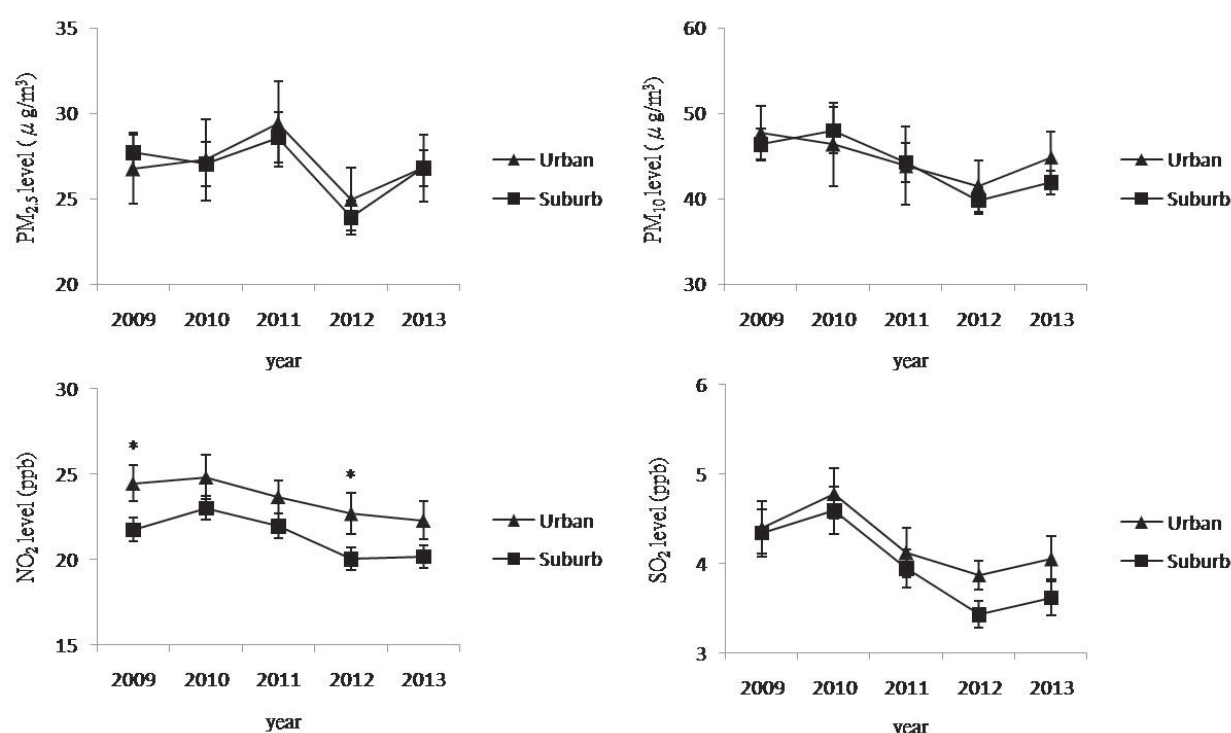


Figure 2. The air Quality Status in Northern Taiwan for the year 2009 to 2013, cited and analyzed from the Taiwan Air Quality Monitoring Network (TAQMN) of Environmental Protection Administration (EPA)

Table 3. The Top 5 Cancer Matches in Patients with Multiple Primary Malignancies

Cancer matches	Total
Esophageal cancer & hypopharyngeal cancer	16 (12.8%)
Colorectal cancer & gastric cancer	8 (6.4%)
Colorectal cancer & breast cancer	7 (5.6%)
Esophageal cancer & laryngeal cancer	6 (4.8%)
Ovarian cancer & endometrial cancer	6 (4.8%)

was malignancies in upper aerodigestive tract, followed by colorectal cancer, hepatocellular carcinoma, gynecological cancers, gastric cancer, lung cancer, urological cancers, breast cancer, hematological malignancies, thyroid cancer, pancreatic cancer and other cancers. There was no significant distribution of tumor site and frequency in patients with MPM living in urban zone and suburb zone. The top 5 cancer matches in patients with MPM

were listed in Table 3. The most common cancer matches was esophageal cancer and hypopharyngeal cancer (n=16, 12.8%), followed by colorectal cancer and gastric cancer (n=8, 6.4%), colorectal cancer and breast cancer (n=7, 5.6%), esophageal cancer and laryngeal cancer (n=6, 4.8%), and ovarian cancer and endometrial cancer (n=6, 4.8%).

The parameters of air contamination in urban zone and suburb zone for 5 consecutive years were shown in Figure 2. There was no significant difference between urban zone and suburb zone in PM₁₀ and PM_{2.5} levels. Both NO₂ and SO₂ levels in urban zone were higher than in suburb zone for 5 consecutive years, with statistical significance for NO₂ levels in the year 2009 and 2012 ($P=0.046$ and 0.047 , respectively).

The laboratory characteristics of MPM patients were shown in Table 4. Both WBC and ANC were found lower

Table 4. Laboratory Data of Patients with Multiple Primary Malignancies Living in Urban Zone and Suburb Zone

Variables	Total	Urban zone	Suburb zone	P value
WBC (x10 ³ /μL)	3.40±0.19	3.03±0.24	3.67±0.28	0.103
ANC (x10 ³ /μL)	2.02±0.14	1.76±0.17	2.19±0.20	0.125
Hb (g/dL)	9.05±0.15	8.84±0.24	9.20±0.20	0.249
AST (IU/L)	57.07±4.71	61.81±8.87	53.70±5.02	0.398
ALT (IU/L)	49.41±3.84	53.21±5.58	46.70±5.24	0.405
BUN (mg/dL)	24.60±1.77	26.10±2.80	23.54±2.29	0.478
Creatinine (mg/dL)	1.84±0.53	1.45±0.10	2.12±0.91	0.537
Albumin (g/dL)	2.92±0.10	3.09±0.17	2.80±0.12	0.047
FBG (mg/dL)	122.86±5.19	127.98±9.93	119.18±5.40	0.384
Cholesterol (mg/dL)	178.41±9.38	183.52±12.16	173.52±13.31	0.295
HDL-C (mg/dL)	47.44±3.45	46.21±4.88	48.52±4.85	0.631
Triglyceride (mg/dL)	172.27±17.79	198.98±31.70	146.76±18.37	0.164
CRP (mg/dL)	9.54±0.92	7.79±1.28	10.61±1.25	0.151

*WBC, white blood cell count; ANC, absolute neutrophil count; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine transaminase; BUN, blood urea nitrogen; FBG, fasting blood glucose; HDL-C, high density lipoprotein cholesterol; CRP, C-reactive protein

Table 5. The Absolute Neutrophil Count of Patients with Multiple Primary Malignancies Living in Urban Zone and Suburb Zone

ANC level	Urban zone	Suburb zone	P value
Normal	19 (36.5%)	34 (46.6%)	
<2,000/μL	33 (63.5%)	39 (53.4%)	0.263
<1,500/μL	19 (36.5%)	28 (52.1%)	0.836
<1,000/μL	16 (30.8%)	11 (15.1%)	0.036
<500/μL	10 (19.2%)	7 (9.6%)	0.121

in MPM patients living in urban zone than those in suburb zone (WBC: $3.03 \pm 0.24 \times 10^3/\mu\text{L}$ vs $3.67 \pm 0.28 \times 10^3/\mu\text{L}$, $P=0.103$; ANC: $1.76 \pm 0.17 \times 10^3/\mu\text{L}$ vs $2.19 \pm 0.20 \times 10^3/\mu\text{L}$, $P=0.125$), which were not significant. The albumin level was significantly higher in MPM patients living in urban zone than those in suburb zone (3.09 ± 0.17 g/dL vs 2.80 ± 0.12 g/dL, $P=0.047$). There was no statistical difference in other laboratory parameters between both groups. We further evaluated the ANC in MPM patients living in urban zone and suburb zone. The result indicated there was a significantly higher portion of patients with MPM living in urban zone than those living in suburb zone at a cut-off of 1,000/μL (30.8% vs 15.1%, $P=0.036$).

Discussion

Our main finding in the present study indicated the most frequent tumor site distribution in patients with MPM was malignancies in upper aerodigestive tract, subsequently colorectal cancer, hepatocellular carcinoma, gynecological cancers and gastric cancer. The most common cancer matches in MPM patients were esophageal cancer accompanied with hypopharyngeal cancer, followed by colorectal cancer accompanied with gastric cancer, colorectal cancer accompanied with breast cancer, esophageal cancer accompanied with laryngeal cancer, and ovarian cancer accompanied with endometrial cancer. The ANC after chemotherapy was lower in MPM patients living in urban zone than those in suburb zone, with statistical significance at a cut-off level of 1,000/μL. To our best knowledge, the current study should be the first episode to investigate the association between environmental exposure and post-chemotherapeutic

neutropenia in patients carrying second primary malignancies.

According to the literature review, it was concluded the prevalence of MPM arranged from 0.7% to 11.3% (Demandante et al., 2003; Arpaci et al., 2013; Jiao et al., 2014). With the improvement of medical techniques and extended lifespan, the incidence of MPM had been increasing worldwide and been of great concern with public health. Although the pathogenesis of MPM had not been clearly illustrated, a myriad of risk factors were involved and the most common ones among these should be genetic predisposition, treatment-related chemoradiation and environmental exposure. In our results, over half portion of MPM patient had a history of tobacco use, receiving chemotherapy and radiotherapy, no matter living in which residential area. Also, approximately half as many patients with MPM had excess alcohol consumption. Interestingly, most of these patients did not have a family history of cancer. Therefore, lifestyle and environmental exposure should be the main influencing factors of developing MPM in our study. As previously reported, consumption of tobacco and alcohol was highly associated with the incidence of esophageal cancer (Mao et al., 2011) and the co-occurrence of esophageal cancer and other malignancies in upper aerodigestive organs (Zhu et al., 2012). Cigarette smoking was also considered one of the risk factors of developing colorectal malignancies (Cross et al., 2014). Additionally, it was observed that the most frequent sites of second primary cancer followed by colorectal cancer were stomach and breast (Ueno et al., 2003; Sun et al., 2014). These results aforementioned were similar with our observational findings, in which the most common cancer matches in MPM were esophageal cancer accompanied with malignancies in upper aerodigestive tract, colorectal cancer accompanied with gastric cancer and colorectal cancer accompanied with breast cancer.

It was believed that living in the metropolis could be stressful to human lifestyle and health, according to dense population, noise and air pollutions, and psychological stress (Huang WH et al., 2013). Exactly, a notably higher portion of MPM patient living in urban zone suffered from HTN than those in suburb zone in the present study. However, it had been complicated to evaluate the quality of living environment and thus

difficult to evaluate the impact of residential environment on human health efficiently. Air quality was one of the efficacious environmental indicators to be quantified. Air pollutants were commonly detected for estimating air quality, including particulate matter (PM), carbon monoxide (CO), sulfur dioxide (SO₂), nitrogen oxides (NO_x), ozone (O₃) and lead (Pb)(Samet JM, 2011). In our study, the analyzed data referred from Environmental Protection Administration indicated that air contamination was more deteriorated in urban zone than that in suburb zone. Accumulating evidence had demonstrated that poor air quality was remarkably associated to multitudinous comorbidities, particularly lung cancer, cerebrovascular and cardiopulmonary diseases (Dockery et al, 1993; Mateen and Brook, 2011). However, it was not apparent in our results because there was no significant difference between MPM patients accompanied with lung cancer living in urban and suburb zones. Previous studies also found that air contamination could lead to systemic inflammation (Bind et al., 2012; Rich et al., 2012). Our results indicated that air pollution was significantly associated with chemotherapy-induced neutropenia to grade III and IV in patients with MPM. In our opinion, persistent inflammatory response was not beneficial for human health, especially for some immunosusceptible populations such as cancer patients. Additionally, it was reported that episodes of neutropenia and overall mortality of cancer patients were significantly decreased in protective environment implementation (Stoll et al., 2013), which could further explain the relationship between air contamination and chemotherapy-related neutropenia in the cancer patients. Commensurately, it was deemed that urban population should possess better socioeconomic status and more sufficient nutritional support than rural one. And our result represented that MPM patients living in urban zone had a significantly higher albumin level than those living in suburb zone as well.

There were some limitations in our study. First, it was a retrospective study design with a small case number. However, MPM was still quite rare even numerous studies regarding with MPM were addressed and the incidence of MPM was on the rise. Second, the data bias could not be excluded for the geographically regional factors. Furthermore, some clinical data with prognostic significance were not obtained in detail, such as the amount and time of tobacco and alcohol use, making it difficult to conduct a dose-effect relationship survey. Additionally, it was difficult and complicated to compare the advantages and disadvantages of residential environments, especially with regard to cancer patients, who usually have long-term comorbid illness. Further research could be focused on the links among these variables to overall survival in patients with MPM.

In summary, our study showed the most common malignancy associations in MPM were esophageal cancer accompanied with malignancies in upper aerodigestive tract, colorectal cancer accompanied with gastric cancer and colorectal cancer accompanied with breast cancer. The present study also indicated that air contamination might increase the risk of chemotherapy-induced neutropenia, especially grade III and IV in MPM patients. Nevertheless,

the detailed etiology and mechanism remained to be elucidated. These observational results should be deliberated upon the risk evaluation and therapeutic strategy of the patients with MPM.

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