Occupational, dietary, and other risk factors for myelodysplastic syndromes in Western Greece

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ABSTRACT

Purpose: We have observed an increasing incidence of myelodysplastic syndromes (MDS) in the geographic area of Western Greece during the past two decades. The objective of this study was to investigate potential risk factors for the manifestation of MDS in this area of Greece.

Methods: A hospital-based case–control study was conducted in the public hospitals of the region. Participants were interviewed based on a questionnaire regarding demographics, occupational exposures, smoking, alcohol consumption, dietary, and domestic factors.

Results: A total of 228 individuals (126 cases, 102 controls) were recruited in this study. Univariate analysis showed that risk of MDS was associated with a family history of hematologic malignancy or solid tumor, exposure to pesticides, insecticides, herbicides, increased weekly intake of meat and eggs, and increased alcohol intake, whereas fruit intake had a protective effect. Analysis by pesticide ingredient showed a weak association of exposure to paraquat and glyphosate with the occurrence of MDS. Multivariate analysis showed that independent risk factors for the manifestation of MDS were family history of solid tumor (OR 2.47, 95% CI 1.32–4.65), meat intake for ≥5 days/week (OR 2.67, 95% CI 1.05–6.80) and exposure to pesticides (OR 3.25, 95% CI 1.73–6.11).

Conclusions: Exposure to pesticides is a major risk factor of MDS in Western Greece. Family history of solid tumor and increased meat intake also appear to play a role in the pathogenesis of MDS. Public health authorities should implement policies to advise and protect farmers from the harmful effects of agrochemicals. Emphasis should also be given to health promotion advice including healthy eating.

KEYWORDS
Myelodysplastic syndromes; risk factors; pesticides; glyphosate; paraquat; dietary factors; stressful life event; comorbidities

1. Introduction

The incidence of MDS increases with age and it varies significantly among different countries. Ageing carries an increased risk for different types of cancer, and it is well-recognized that previous chemotherapy or radiation therapy predispose to therapy-related MDS (t-MDS) [1]. Among other factors that have been studied, benzene and ionizing radiation have been clearly proven to be carcinogenic to the hematopoietic system [2]. Many other occupational exposures have been suspected to play a role, but most frequently data are insufficient for a definite conclusion. During the past years there has been an increasing interest in investigating the role of smoking, as well as the potential harm from the use of agricultural chemicals.

The administrative region of Western Greece consists of three prefectures: Achaia, Ilia, and Eotlia-Akarnania, and has a population of 679 796 inhabitants according to 2011 census. We have conducted a retrospective epidemiological study on the incidence of MDS in this region, during the period 1990–2009, which revealed an increasing trend for diagnosing an MDS. This was mainly attributed to an increase of RA and RARS, whereas the incidence of RAEB and CMML remained rather stable over the study period [3]. The observed increasing trend in the incidence of MDS in Western Greece led us to search for potential risk factors in this particular region. Therefore, the objective of the present study was to investigate the role of occupational, environmental, dietary, and lifestyle factors in the pathogenesis of MDS in this geographic area.

2. Patients and methods

2.1. Study population

A hospital-based case–control study was conducted for the purposes of this research. The group of cases consisted of prevalent de novo MDS patients, who attended the Hematology outpatient clinic at the University Hospital of Patras and at ‘St Andrew’ General Hospital of Patras in Western Greece. Only patients with a confirmed diagnosis of MDS, according to FAB...
classification [4] after bone marrow examination, were included in the study. Patients with a previous history of chemotherapy or radiation therapy were not included.

The group of controls consisted of patients admitted to the Ophthalmology Department of the University Hospital of Patras, to undergo elective operation for cataract. Patients with a history of hematological disorder and/or previous chemotherapy or radiotherapy were excluded from the group of controls. Proportional matching of cases and controls was performed by gender and age.

Both cases and controls were interviewed based on the same questionnaire. Interviews were conducted in hospital by medical doctors, between November 2009 and July 2013. The questionnaire included:

(i) Demographic data, such as gender, age, area of residence, years of education, marital status, and profession
(ii) Family history of hematologic malignancy or solid tumor in the first degree relatives
(iii) Agricultural activities, exposure to agricultural chemicals, i.e. pesticides, insecticides, herbicides, fertilizers, and frequency of exposure. As regularly exposed were considered those who were using agrochemicals regularly as part of their routine agricultural practice. Rarely exposed were those who did not make use of pesticides routinely but only occasionally or under special circumstances. Indirectly exposed were those who did not use agrochemicals themselves but had been working with somebody else using them. When the individual reported exposure to pesticides, they were asked to recall brand names of the products they had been exposed to.
(iv) Exposure to a list of occupational risk factors
(v) Nutritional factors
(vi) Smoking and alcohol intake
(vii) Domestic factors
(viii) Leisure activities and hobbies, and
(ix) Exposure to ionizing radiation for diagnostic purposes.

All individuals gave their informed consent to participate in the study. The protocol was approved by the Scientific and Ethical Committees of the two participating hospitals.

3. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 22.0. T-test was used for the comparison of means and independent samples t-test for the comparison between groups. Pearson’s chi-square test was used for the comparison of percentages among groups. Logistic regression was performed to assess the impact of different variables on the risk for MDS, by calculating odds ratio (OR) and its 95% confidence intervals (95% CI). Univariate analysis was initially performed for each factor separately. Variables with a p value <0.10 as well as matching variables (age and gender) were finally included in the multivariate analysis (via forward conditional method). P < 0.05 was considered to be statistically significant unless otherwise specified.

4. Results

4.1. Demographic data

Totally 228 subjects participated in the study (126 cases and 102 controls). Mean age at the time of interview and gender distribution were not significantly different between the two groups. Cases and controls did not differ significantly by years of education (reflecting socio-economic status), residence in a rural or urban area or marital status. More than half of the individuals in both groups were farmers (66% of cases and 56% of the controls) (primary or secondary occupation) (Table 1).

| Variable                  | Group            | n  | Controls | Cases | p value |
|---------------------------|------------------|----|----------|-------|---------|
| Gender                    | Men              | 159| 69       | 90    | 0.537 (ns) |
|                           | Women            | 69 | 33       | 36    |         |
| Area of residence         | Rural            | 125| 54       | 71    | 0.607 (ns) |
|                           | Urban            | 103| 48       | 55    |         |
| Years of education        | 0                | 14 | 7        | 7     | 0.985 (ns) |
|                           | 1–6              | 127| 57       | 70    |         |
|                           | 7–9              | 31 | 13       | 18    |         |
|                           | 10–12            | 27 | 13       | 14    |         |
|                           | >12              | 26 | 12       | 14    |         |
|                           | Unknown          | 3  | 0        | 3     |         |
| Marital status            | Married          | 173| 81       | 92    | 0.505 (ns) |
|                           | Single           | 8  | 2        | 6     |         |
|                           | Divorced         | 4  | 1        | 3     |         |
|                           | Widower          | 43 | 18       | 25    |         |
| Profession                | Farmer (1st occupation) | 92 | 31      | 61    |         |
|                           | Farmer (2nd occupation) | 48 | 26      | 22    |         |
|                           | Farmers (total)  | 140| 57       | 83    | 0.123 (ns) |
|                           | Non-farmers      | 88 | 45       | 43    |         |
| Mean age (standard deviation) | (range)             |    | 75.3 (6.69) | 75.2 (7.98) | 0.915 (ns) |
| Total                     |                  | 228| 102      | 126   |         |
5. Exposure to potential risk factors – univariate analysis

5.1. Family history of cancer

Patients with MDS reported a family history of hematologic malignancy (OR 3.56, 95% CI 1.15–11.02) or solid tumor (OR 2.46, 95% CI 1.39–4.36) more often than controls (Table 2).

5.2. Occupational risk factors

Patients with MDS were more frequently exposed to pesticides, compared to controls (OR 2.47, 95% CI 1.44–4.24). In particular, they were more frequently exposed to insecticides (OR 3.34, 95% CI 1.62–6.90) and herbicides (OR 2.27, 95% CI 1.14–4.51), whereas exposure to fungicides was not significantly different between cases and controls. Patients were

| Variable                          | Category          | n  | Controls | Cases | OR   | 95% CI          | p value |
|-----------------------------------|-------------------|----|----------|-------|------|-----------------|---------|
| Family history of hematologic malignancy | No                | 208| 98       | 110   | 1.00 | (Ref.)         | 0.027   |
|                                   | Yes               | 20 | 4        | 16    | 3.56 | 1.15–11.02     |         |
| Family history of solid tumor     | No                | 147| 77       | 70    | 1.00 | (Ref.)         | 0.002   |
|                                   | Yes               | 81 | 25       | 56    | 2.46 | 1.39–4.36      |         |
| Agricultural activities           | No                | 71 | 36       | 35    | 1.00 | (Ref.)         | 0.224   |
|                                   | Yes               | 157| 66       | 91    | 1.42 | 0.81–2.49      |         |
| Pesticides                        | No                | 122| 67       | 55    | 1.00 | (Ref.)         | 0.001   |
|                                   | Yes               | 106| 35       | 71    | 2.47 | 1.44–4.24      |         |
| Frequency of exposure to pesticides | Never             | 122| 67       | 55    | 1.00 | (Ref.)         | 0.005   |
|                                   | Rarely/indirectly | 30 | 10       | 20    | 2.44 | 1.05–5.64      |         |
|                                   | Regularly         | 76 | 25       | 51    | 2.48 | 1.37–4.51      |         |
| Fungicides                        | No                | 172| 75       | 97    | 1.00 | (Ref.)         | 0.541   |
|                                   | Yes               | 26 | 13       | 13    | 0.77 | 0.34–1.77      |         |
| Insecticides                      | No                | 148| 76       | 72    | 1.00 | (Ref.)         | 0.001   |
|                                   | Yes               | 50 | 12       | 38    | 3.34 | 1.62–6.90      |         |
| Herbicides                        | No                | 148| 73       | 75    | 1.00 | (Ref.)         | 0.019   |
|                                   | Yes               | 50 | 15       | 35    | 2.27 | 1.14–4.51      |         |
| Fertilizers                       | No                | 152| 72       | 80    | 1.00 | (Ref.)         | 0.073   |
|                                   | Yes               | 49 | 16       | 33    | 1.86 | 0.94–3.65      |         |
| Glyphosate                        | No                | 162| 77       | 86    | 1.00 | (Ref.)         | 0.060   |
|                                   | Yes               | 23 | 6        | 17    | 2.57 | 0.96–6.84      |         |
| Paraquat                          | No                | 172| 81       | 91    | 1.00 | (Ref.)         | 0.043   |
|                                   | Yes               | 13 | 2        | 11    | 4.90 | 1.05–22.75     |         |
| Propineb                          | No                | 171| 74       | 97    | 1.00 | (Ref.)         | 0.138   |
|                                   | Yes               | 14 | 9        | 5     | 0.42 | 0.14–1.32      |         |
| Deltamethrin                      | No                | 176| 80       | 96    | 1.00 | (Ref.)         | 0.480   |
|                                   | Yes               | 9  | 3        | 6     | 1.67 | 0.40–6.88      |         |
| Colors                            | No                | 202| 93       | 109   | 1.00 | (Ref.)         | 0.273   |
|                                   | Yes               | 26 | 9        | 17    | 1.61 | 0.69–3.79      |         |
| Dyes                              | No                | 203| 94       | 109   | 1.00 | (Ref.)         | 0.180   |
|                                   | Yes               | 25 | 8        | 17    | 1.83 | 0.76–4.44      |         |
| Veneers                           | No                | 213| 95       | 114   | 1.00 | (Ref.)         | 0.876   |
|                                   | Yes               | 15 | 7        | 8     | 0.92 | 0.32–2.63      |         |
| Glues                             | No                | 219| 99       | 120   | 1.00 | (Ref.)         | 0.487   |
|                                   | Yes               | 9  | 3        | 6     | 1.65 | 0.40–6.77      |         |
| Gasoline                          | No                | 198| 91       | 107   | 1.00 | (Ref.)         | 0.342   |
|                                   | Yes               | 30 | 11       | 19    | 1.47 | 0.66–3.25      |         |
| Oil                               | No                | 205| 90       | 115   | 1.00 | (Ref.)         | 0.451   |
|                                   | Yes               | 23 | 12       | 11    | 0.72 | 0.30–1.70      |         |
| Greases                           | No                | 204| 89       | 115   | 1.00 | (Ref.)         | 0.329   |
|                                   | Yes               | 24 | 13       | 11    | 1.65 | 0.28–15.37     |         |
| Heavy metals                      | No                | 221| 98       | 123   | 1.00 | (Ref.)         | 0.507   |
|                                   | Yes               | 7  | 4        | 3     | 0.60 | 0.13–2.73      |         |
| Plastics                          | No                | 221| 99       | 122   | 1.00 | (Ref.)         | 0.919   |
|                                   | Yes               | 7  | 3        | 4     | 1.08 | 0.24–4.95      |         |
| Welding fumes                     | No                | 225| 101      | 124   | 1.00 | (Ref.)         | 0.692   |
|                                   | Yes               | 3  | 1        | 2     | 1.56 | 0.15–18.22     |         |
| Wood processing                   | No                | 226| 99       | 123   | 1.00 | (Ref.)         | 0.793   |
|                                   | Yes               | 6  | 3        | 3     | 0.77 | 0.16–4.07      |         |
| Carbon                            | No                | 226| 101      | 125   | 1.00 | (Ref.)         | 0.881   |
|                                   | Yes               | 2  | 1        | 1     | 0.81 | 0.05–13.08     |         |
| Sulphuric acid                    | No                | 225| 101      | 124   | 1.00 | (Ref.)         | 0.692   |
|                                   | Yes               | 3  | 1        | 2     | 1.63 | 0.15–18.22     |         |
| Carbon tetrachloride              | No                | 226| 101      | 125   | 1.00 | (Ref.)         | 0.881   |
|                                   | Yes               | 2  | 1        | 1     | 0.81 | 0.05–13.08     |         |
| Acetone                           | No                | 225| 101      | 124   | 1.00 | (Ref.)         | 0.692   |
|                                   | Yes               | 3  | 1        | 2     | 1.63 | 0.15–18.22     |         |
| Turpentine                        | No                | 224| 101      | 123   | 1.00 | (Ref.)         | 0.438   |
|                                   | Yes               | 4  | 1        | 3     | 2.46 | 0.25–24.05     |         |
| Textile industry                  | No                | 222| 98       | 124   | 1.00 | (Ref.)         | 0.289   |
|                                   | Yes               | 6  | 4        | 2     | 0.39 | 0.07–2.20      |         |
consequently stratified into three groups, according to the frequency of their general exposure to pesticides (never, rarely, regularly exposed). People who were rarely (n = 23) or indirectly exposed (n = 7) were grouped together in stratified univariate analysis. The association was statistically significant, both in the group of low frequency and in the group of high frequency. There was also weak evidence suggesting that use of fertilizers may be associated with MDS (Table 2). The use of protective measures during application did not seem to modify the risk of MDS among the exposed (p = 0.254).

Among the 228 individuals, it was possible to identify status of exposure to certain pesticides in 185 of them. After analyzing these qualitative data we managed to match reported brand names to a list of pesticide ingredients (Table 3). In certain cases the individuals could not recall the actual names, therefore analysis was restricted to the ones that were confirmed.

Analysis by name of pesticide was done only for those encountered more frequently. Exposure to paraquat dichloride (Gramoxone) was associated with MDS (OR 4.90, 95% CI 1.05–22.75). There was also weak evidence that exposure to glyphosate (Roundup) may be associated with MDS (OR = 2.57, 95% CI 0.96–6.84) (Table 2).

All cases and controls were interviewed, regarding exposure to dyes, colors, glues, veneers, greases, oil, gasoline, heavy metals, plastics, welding fumes, wood processing, carbon, sulfuric acid, carbon tetrachloride, acetone, turpentine, textile industry, and other occupational risk factors, but none of them was found to differ significantly between the two groups. However, for the majority of the above occupational factors the number of exposed individuals was very low (Table 2). In particular, the OR of exposure to tar, liquid gas, asbestos, steel dust, dry cleaning fumes, methanol, ionizing radiation, and electromagnetic radiation could not be calculated because the number of exposed individuals was 0 in either group of cases or controls.

### 5.3. Dietary factors

Diagnosis of MDS was associated with the consumption of meat for ≥5 days a week (OR 3.20, 95% CI 1.39–7.41) and of >2 eggs per week (OR 2.09, 95% CI 1.08–4.05). There was also weak evidence suggesting that consumption of dairy products more often than 5 days a week may be associated with MDS (OR 1.65, 95% CI 0.92–2.97). On the other hand, consumption of fruit more often than 5 days a week had a protective effect (OR 0.56, 95% CI 0.31–0.99). Finally, no difference in the weekly consumption of vegetables, fish, legumes and coffee between cases and controls was observed (Table 4).

### 5.4. Smoking and alcohol consumption

In the present study, no significant association between smoking and risk of MDS was found, even when current and former smokers were grouped together as ever-smokers (Table 5).

Regarding alcohol consumption, it was shown that the risk of MDS for those consuming ≥15 drinks (alcohol equivalents) per week was two-fold higher, in comparison to those who consumed 0–14 drinks per week (OR 2.06, 95% CI 1.13–4.11). There was not sufficient evidence to prove any association between MDS and the kind of drink that had been consumed (wine, beer, or spirits). Further analysis of a possible interaction between smoking and alcohol consumption did not show any significant results. However, a joint effect of smoking with exposure to pesticides was observed (OR 2.89, 95% CI 1.35–6.22) (Table 6).

### 5.5. Domestic, environmental risk factors, leisure activities, and stressful life events

The participants of the study were interviewed on hair dye use, type of residence, proximity of residence with petrol station, with a mobile antenna, use of microwave oven, cordless or mobile phone, and use of computer, but none of these factors was significantly different.

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**Table 3.** Pesticide ingredients and number of individuals who reported a specific exposure in our study.

| Ingredient                     | IARC classification | n   |
|-------------------------------|---------------------|-----|
| **Herbicides**                |                     |     |
| Glyphosate                    | Group 2A             | 23  |
| Paraquat                      | Not listed           | 13  |
| Fluazifop-P-butyl             | Not listed           | 1   |
| Simazine                      | Group 3              | 1   |
| Propanil                      | Not listed           | 2   |
| **Insecticides**              |                     |     |
| 0.05% Pyrethrins, 0.4% Permethrin, 0.1% Pyriproxyfen | Permethrin classified in Group 3 (other ingredients not listed) | 5 |
| Deltamethrin                  | Group 3              | 9   |
| DDT (dichlorodiphenyltrichloroethane) | Group 2A         | 2   |
| Methamidophos                 | Not listed           | 4   |
| Endosulfan                    | Group 2A             | 1   |
| Demeton-O + demeton-S         | Not listed           | 2   |
| mercaptobenzimidhe            | Not listed           | 1   |
| Sodium arsenate               | Group 1              | 2   |
| Morphothion (organophosphate) | Not listed           | 3   |
| Dimethoate (organophosphate)  | Not listed           | 2   |
| Fenthion (organophosphate)    | Not listed           | 1   |
| Malathion (organophosphate)   | Group 2A             | 1   |
| Carbofuran (carbamate)        | Not listed           | 1   |
| Methylnyl (carbamate)         | Not listed           | 1   |
| Lindane (organochlorine)      |                     | 1   |
| Aldrin (organochlorine)       |                     | 3   |
| Fungicides                    |                     |     |
| Propeineb                     | Not listed           | 14  |
| Metalaxyl-M, mancobeze        | Not listed           | 5   |

IARC Classification groups: Group 1: carcinogenic to humans; Group 2A: probably carcinogenic to humans; Group 2B: possibly carcinogenic to humans; Group 3: not classifiable as to its carcinogenicity to humans; Group 4: probably not carcinogenic to humans.
between cases and controls. We also studied the use of domestic insecticides, as well as hobbies (gardening, wood preservation, preservation of car or motorbike, amateur use of coloring), but no significant difference was shown between cases and controls. Individuals were also interviewed briefly on their experience of any stressful life events. The prevalence of stressful life events in general was not different between cases and controls. There was weak evidence of an increased risk of MDS in those who had experienced loss or severe illness of a child, and reduced risk in those who had lost their spouse (Table 7).

5.6. Exposure to ionizing radiation for diagnostic purposes

No difference was shown between cases and controls regarding exposure to X-rays, computerized tomography (CT) scan, scintigram, mammogram, angiography, barium swallow, barium enema, and intravenous pyelogram (Table 7).

6. Multivariate analysis of risk factors for MDS

In the multivariate analysis we included the matching variables (gender and age), as well as all variables for

| Table 4. Nutritional factors (univariate analysis). |
|-----------------------------------------------|
| Food | Frequency | n   | Controls | Cases | OR | 95% CI | p value |
|------|-----------|-----|----------|-------|----|--------|---------|
| Meat | 0–4 days/week | 193 | 94       | 99    | 1.00 | (Ref.) | 0.006   |
|      | 5–7 days/week | 35  | 8        | 27    | 3.20 | 1.39–7.41 | 0.029   |
| Eggs | 0–2/week    | 176 | 86       | 90    | 1.00 | (Ref.) |        |
|      | 3–7/week    | 51  | 16       | 35    | 2.09 | 1.08–4.05 | 0.091   |
| Dairy products | 0–5 days /week | 63 | 34       | 29    | 1.00 | (Ref.) |        |
|      | 6–7 days /week | 164 | 68       | 96    | 1.65 | 0.92–2.97 |        |
| Fruit | 0–5 days /week | 71  | 25       | 46    | 1.00 | (Ref.) | 0.048   |
|      | 6–7 days /week | 156 | 77       | 79    | 0.56 | 0.31–0.99 |        |
| Vegetables | 0–5 days /week | 94 | 37       | 57    | 1.00 | (Ref.) | 0.157   |
| Fish  | 0–2 days /week | 194 | 90       | 104   | 1.00 | (Ref.) | 0.287   |
| Legumes | 0–1 days /week | 163 | 70       | 93    | 1.00 | (Ref.) | 0.389   |
| Coffee | 0–1/day | 134 | 57       | 77    | 1.00 | (Ref.) | 0.045   |
|      | ≥2/day    | 94  | 45       | 49    | 0.81 | 0.47–1.37 |        |

| Table 5. Smoking and alcohol consumption (univariate analysis). |
|-----------------------------------------------|
| Variable | Category | n   | Controls | Cases | OR | 95% CI | p value |
|----------|----------|-----|----------|-------|----|--------|---------|
| Smoking (1) | Never | 91  | 43       | 48    | 1.00 | (Ref.) | 0.521   |
|          | Current smokers | 45  | 22       | 23    | 0.94 | 0.46–1.91 | 0.74–2.39 |
|          | Ex-smokers | 92  | 37       | 55    | 1.33 | 0.74–2.39 | 0.019   |
| Smoking (2) | Never | 91  | 43       | 48    | 1.00 | (Ref.) | 0.334   |
|          | Ever-smokers | 137 | 59       | 78    | 1.18 | 0.69–2.02 | 0.019   |
| Alcohol use | 0–14 drinks/week | 173 | 85       | 88    | 1.00 | (Ref.) | 0.748   |
| Wine | No | 58  | 27       | 31    | 1.00 | (Ref.) | 0.657   |
|          | Yes | 170 | 75       | 95    | 1.10 | 0.61–2.01 | 0.685   |
| Beer  | No | 184 | 81       | 103   | 1.00 | (Ref.) | 0.914   |
|          | Yes | 44  | 21       | 23    | 0.86 | 0.44–1.66 | 0.894   |
| Spirits | No | 164 | 72       | 92    | 1.00 | (Ref.) | 0.914   |
| Kind of drink | No alcohol | 47  | 20       | 27    | 1.00 | (Ref.) | 0.914   |
| Wine only | 94  | 42       | 52    | 0.92 | 0.45–1.86 | 0.894   |
| Beer only | 3   | 2        | 1     | 0.37 | 0.03–4.37 | 0.894   |
| Spirits only | 6   | 4        | 2     | 0.37 | 0.06–2.22 | 0.894   |
| Wine + beer | 20  | 8        | 12    | 1.11 | 0.38–3.22 | 0.894   |
| Wine + spirits | 37  | 15       | 22    | 1.09 | 0.45–2.60 | 0.894   |
| Beer + spirits | 2   | 1        | 1     | 0.74 | 0.09–12.57 | 0.894   |
| Wine + beer + spirits | 19  | 10       | 9     | 0.67 | 0.23–1.84 | 0.894   |

| Table 6. Exploring the joint effect smoking/alcohol consumption and smoking/pesticide exposure (univariate analysis). |
|-----------------------------------------------|
| Variable | Category | n   | Controls | Cases | OR | 95% CI | p value |
|----------|----------|-----|----------|-------|----|--------|---------|
| Smoking and alcohol use | Never smoker and no alcohol | 29  | 14       | 15    | 1.00 | (Ref.) | 0.093   |
|          | Never smoker and 1–14 drinks per week | 51  | 27       | 24    | 0.83 | 0.33–2.07 | 0.33–2.07 |
|          | Never smoker and ≥15 drinks per week | 11  | 2        | 9     | 4.20 | 0.77–22.91 | 0.056   |
|          | Ever smoker and no alcohol | 15  | 6        | 9     | 2.57 | 0.66–9.96 | 0.66–9.96 |
|          | Ever smoker and 1–14 drinks per week | 78  | 40       | 38    | 0.88 | 0.38–2.08 | 0.38–2.08 |
|          | Ever smoker and ≥15 drinks per week | 44  | 15       | 29    | 1.80 | 0.69–4.71 | 0.69–4.71 |
| Smoking and pesticide exposure | Never smoker and not exposed to pesticides | 50  | 29       | 21    | 1.00 | (Ref.) | 0.011   |
|          | Never smoker and exposed to pesticides | 41  | 14       | 27    | 2.66 | 1.13–6.27 | 0.13–6.27 |
|          | Ever smoker and not exposed to pesticides | 72  | 38       | 34    | 1.24 | 0.60–2.56 | 0.60–2.56 |
|          | Ever smoker and exposed to pesticides | 65  | 21       | 44    | 2.89 | 1.35–6.22 | 1.35–6.22 |
which p value was <0.10 in the univariate analysis. Hence, the following parameters were included in the analysis: gender, age, family history of hematologic malignancy, family history of solid tumor, exposure to pesticides, exposure to fertilizers, alcohol consumption, weekly consumption of meat, eggs, dairy products, fruit, and vegetables. Types of agricultural chemicals (i.e. herbicides, insecticides) as well as the frequency of exposure were not included in the multivariate analysis, because they had already been taken into account by including general exposure to pesticides.

Multivariate analysis showed that the following three variables were independently associated with the risk of MDS: family history of solid tumor (OR 2.47, 95% CI 1.32–4.65), consumption of meat ≥5 days a week (OR 2.67, 95% CI 1.05–6.80), and exposure to pesticides (OR 3.25, 95% CI 1.73–6.11) (Table 8).

7. Myelodysplastic syndromes and comorbidities

Presence of other comorbid conditions was retrieved from medical records and confirmed during the interview. Such data were available for 200/228 participants (88%), and were missing for 11/126 cases (9%) and 17...
102 controls (17%). Remarkably, history of osteoarthritis (OR 0.20, 95% CI 0.09–0.46), allergy (OR 0.20, 95% CI 0.08–0.54) and hypertension (OR 0.44, 95% CI 0.24–0.77) appeared to have a negative association with MDS (Table 9).

8. Discussion

The etiology of de novo MDS is unknown and probably multifactorial. This study attempted to investigate a wide spectrum of potential risk factors, most but not all of which had previously been reported in the literature.

Few studies have demonstrated an association of MDS with family history of hematologic malignancy [5,6] or other cancer [7]. In the present study we did find a significant association between MDS and family history of hematologic malignancy or solid tumor. Notably, the latter was confirmed as an independent risk factor in multivariate analysis. This finding implies the importance of genetic predisposition for cancer and deserves further investigation in large epidemiological studies.

Whereas cases and controls were similarly involved in farming and other agricultural activities, exposure to pesticides (and particularly herbicides and insecticides) was significantly associated with MDS, and this proved to be an independent risk factor in multivariate analysis. Exposure to agricultural chemicals has been studied extensively as a risk factor, and most studies indicate a positive association with MDS [6–12], although in some others, no significant association was found [13,14]. A recent meta-analysis of 11 case-control studies confirmed a significant association between MDS and exposure to pesticides. Increased risk was also associated with exposure to insecticides, but not to herbicides or fungicides [15]. In another meta-analysis, exposure to pesticides was associated with the manifestation of other hematologic malignancies, and, in a stratified analysis, association was only found with non-Hodgkin lymphoma (NHL), whereas results for leukemia and multiple myeloma were borderline significant [16]. In addition, another meta-analysis has also shown a significant association between occupational exposure to pesticides and myeloid leukemia [17]. Apart from hematologic malignancies, exposure to pesticides has been associated with solid tumors, such as brain, breast, pancreatic, prostate, and stomach cancer [18].

Among types of pesticides associated with carcinogenesis are the following [19]:

(i) Organochlorine insecticides, such as:
   (a) DDT (4,4′-dichlorodiphenyltrichloroethane): classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic (Class 2B) since 1991 but recently upgraded to Class 2A (probably carcinogenic) [20,21].
   (b) Chlordane: classified as Class 2B (possibly carcinogenic) [20].
   (c) Lindane: recently reviewed by IARC and upgraded from Class 2B (possibly carcinogenic) to Class 1 (carcinogenic) [21], linked specifically to NHL [22].

Table 9. Comorbidities in cases and controls (univariate analysis).

| Comorbidity Category       | n  | Controls | Cases | OR    | 95% CI  | p value |
|----------------------------|----|----------|-------|-------|---------|---------|
| Allergy                    |    |          |       |       |         |         |
| No                        | 176| 67       | 109   | 1.00  | (Ref.)  | 0.001   |
| Yes                       | 24 | 18       | 6     | 0.20  | 0.08–0.54 |         |
| Autoimmune disease         |    |          |       |       |         |         |
| No                        | 188| 82       | 106   | 1.00  | (Ref.)  | 0.218 (ns) |
| Yes                       | 12 | 3        | 9     | 2.32  | 0.61–4.83 |         |
| Hypertension               |    |          |       |       |         |         |
| No                        | 94 | 30       | 64    | 1.00  | (Ref.)  | 0.005   |
| Yes                       | 106| 55       | 51    | 0.44  | 0.24–0.77 |         |
| Ischemic heart disease     |    |          |       |       |         |         |
| No                        | 171| 76       | 95    | 1.00  | (Ref.)  | 0.181 (ns) |
| Yes                       | 29 | 9        | 20    | 1.78  | 0.77–4.13 |         |
| Heart failure              |    |          |       |       |         |         |
| No                        | 187| 82       | 105   | 1.00  | (Ref.)  | 0.156 (ns) |
| Yes                       | 13 | 3        | 10    | 2.60  | 0.69–9.77 |         |
| Stroke                     |    |          |       |       |         |         |
| No                        | 190| 82       | 108   | 1.00  | (Ref.)  | 0.418 (ns) |
| Yes                       | 10 | 3        | 7     | 1.77  | 0.44–7.06 |         |
| Atrial fibrillation        |    |          |       |       |         |         |
| No                        | 175| 79       | 96    | 1.00  | (Ref.)  | 0.052   |
| Yes                       | 25 | 6        | 19    | 2.61  | 0.90–6.84 |         |
| Diabetes mellitus          |    |          |       |       |         |         |
| No                        | 154| 65       | 89    | 1.00  | (Ref.)  | 0.878 (ns) |
| Yes                       | 46 | 20       | 26    | 0.95  | 0.49–1.85 |         |
| Thyroid disease            |    |          |       |       |         |         |
| No                        | 178| 75       | 103   | 1.00  | (Ref.)  | 0.766   |
| Yes                       | 22 | 10       | 12    | 0.87  | 0.36–2.13 |         |
| Peptic ulcer               |    |          |       |       |         |         |
| No                        | 184| 78       | 106   | 1.00  | (Ref.)  | 0.916 (ns) |
| Yes                       | 16 | 7        | 9     | 0.95  | 0.34–2.65 |         |
| Osteoarthritis             |    |          |       |       |         |         |
| No                        | 166| 60       | 106   | 1.00  | (Ref.)  | <0.0001 |
| Yes                       | 34 | 25       | 9     | 0.20  | 0.09–0.46 |         |
| Parkinson’s disease        |    |          |       |       |         |         |
| No                        | 195| 82       | 113   | 1.00  | (Ref.)  | 0.432 (ns) |
| Yes                       | 5  | 2        | 3     | 0.48  | 0.08–2.96 |         |
| Psychiatric disease        |    |          |       |       |         |         |
| No                        | 176| 74       | 102   | 1.00  | (Ref.)  | 0.725 (ns) |
| Yes                       | 24 | 11       | 13    | 0.86  | 0.36–2.02 |         |
| Neoplasm                   |    |          |       |       |         |         |
| No                        | 185| 81       | 104   | 1.00  | (Ref.)  | 0.155 (ns) |
| Yes                       | 16 | 4        | 12    | 2.34  | 0.73–7.51 |         |
| COPD                       |    |          |       |       |         |         |
| No                        | 182| 80       | 102   | 1.00  | (Ref.)  | 0.193 (ns) |
| Yes                       | 18 | 5        | 13    | 2.04  | 0.70–5.96 |         |
(ii) Herbicides such as 2,4-d (2,4-dichlorophenoxyacetic acid), recently classified as possibly carcinogenic (class 2B) [21], and glyphosate (isopropylamine salt); recently classified by IARC as Class 2A (probably carcinogenic) [20].

In our study we found an increased risk of MDS in subjects exposed to glyphosate, although not statistically significant. We also found an association of MDS with exposure to paraquat. A prospective cohort in the US reported an association between exposure to paraquat and NHL, as well as a non-significantly elevated relative risk for leukemia [23].

Occupational exposure to many other risk factors has been previously investigated, and MDS has been associated with exposure to radiation, organic substances, metals (copper) and hydrogen peroxide [13], exposure to organic solvents [5,6,24], petroleum and textile dust [5]. In the present study the participants were interviewed on history of exposure to potential occupational risks, but no significant association with MDS was observed. However, the total number of exposed persons was really low in the studied population, and it might not have been possible to reveal such an association even if it really existed. This is mainly explained by the fact that Western Greece is a rather agricultural than industrial region.

The role of diet in MDS is still obscure. In our study cases consumed meat and eggs more often than controls, and controls consumed fruit more often than cases. Among these, only consumption of meat for ≥5 days a week proved to be an independent risk factor in multivariate analysis. A large cohort study revealed obesity as a risk factor for MDS, whereas participation in vigorous physical activity had a protective role. In the same cohort, no association was found between MDS and meat, fruit or vegetable intake [25]. Another study found a positive association of MDS with coffee intake [7], whereas coffee intake was not different between cases and controls in our study. A case-control study conducted in Thessaly, central Greece, it was shown that smoking during pesticide application increased the risk of MDS and other hematologic malignancies [12].

Smoking is considered to be the main non-occupational source of exposure to benzene, which is long-time known for its leukemogenic effect in humans [33,34]. A number of studies have investigated the impact of smoking on the cytogenetics of patients with MDS, and some of them have found a positive association between smoking and abnormal karyotype [6,35]. Abnormal karyotype has also been investigated in relation to occupational exposure in some studies [35–37].

In the present study the consumption of ≥15 drinks-alcohol equivalents per week was associated with increased risk of MDS. Alcohol consumption has been addressed as a risk factor for MDS, with some studies showing a positive association [7,30] and some others not [38].

Hair dye use has been reported to be associated with a significantly increased risk of MDS in some [9,24] but not all [36] studies, but no association was confirmed in our study. Among the leisure activities studied, none was found to be associated with an increased risk of MDS. West et al. studied the role of ionizing radiation for diagnostic purposes and found that exposure to dental X-rays and possibly bone X-rays was associated with MDS [13]. On the contrary, Nisse et al. did not find such an association [5]. In our study we did not find a significant impact of the number of radiology investigations, however the sample was small and this question is probably subject to recall bias.

To our knowledge, the role of stressful life events in MDS has not been explored. Stressful life events have been linked with other types of cancer (e.g. breast cancer [39]). Stress can affect different pathways of the immune system [40]. In our study we did not find an overall difference in reported stressful life events between cases and controls. However, cases had more frequently suffered loss or severe illness of their child, whereas controls had experienced more often death of their spouse. A study with a larger number of participants and more detailed interrogation on perceived stress could probably shed more light on this unexplored aspect of MDS pathogenesis.

Finally, multivariate analysis showed that exposure to pesticides, increased meat intake and family history of cancer were independent risk factors for MDS in Western Greece.

Despite the small number of participants, we attempted to compare comorbidities between cases and controls. We found a higher prevalence of hypertension, allergy and osteoarthritis in the group of controls.
Few studies have studied the association of MDS with other diseases. Dalamaga et al. found an association between MDS and autoimmune thyroid disease [41], and another study with data from the General Practice Research Database showed a slightly increased risk of MDS in patients diagnosed with any autoimmune disorder more than 10 years before diagnosis of MDS [42]. MDS have also been associated with other comorbid conditions, such as Crohn’s disease [43], Helicobacter pylori infection [44] and HIV infection [45,46].

The limitations of the present study are mainly related to its nature. As a case–control study, information was collected retrospectively and there may be a recall bias, as many exposures happened decades before. One methodological pitfall in similar studies is that MDS patients may try harder than controls to attribute their disease to some factors, thus increasing the recorded exposure rate in the group of cases. Additionally, the interviewer was not blinded as to the case/control status of the participants. The number of participants was relatively small. A larger number of participants would increase statistical power and it might have allowed more associations to be revealed. Prevalent (not incident) cases of MDS were recruited and some of the conditions may have slightly changed since the date of diagnosis. For instance, the nutrition of patients with MDS may have been modified due to anemia or other laboratory findings, and the answers given may not reflect their dietary habits before diagnosis. Finally, information was obtained in a face-to-face interview and not by a self-administered questionnaire. Therefore, it is not known whether the participants replied honestly, especially regarding alcohol consumption or stressful life events. However, the present study could not have been realized otherwise, given that patients were elderly and more than half of them had only primary education.

All of the above underline the complexity of mechanisms involved, and imply that the pathogenesis of MDS is multifactorial. Given the increasing bulk of evidence, it is mandatory to minimize occupational and environmental exposure to agrochemicals. Public health authorities should implement policies in order to advise and protect farmers from the harmful effects of exposure to pesticides. Emphasis should be given on health promotion, smoking cessation, maintaining a healthy diet and psychological well-being.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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