Exposure to Per- and polyfluoroalkyl substances (PFASs) and melanoma: a retrospective study on prognosis and histological features

P101

Paolo Del Fiore[1,*], Francesco Cavallin[2], Marcodomenico Mazza[1], Clara Benna[3], Irene Russo[1], Saveria Tropea[1], Alessandra Buja[4], Claudia Cozzolino[1], Rocco Cappellesso[5], Vanna Chiarion-Sileni[6], Antonella Vecchiato[1], Chiara Menin[7], Franco Bassetto[8], Angelo Paolo Dei Tos[5], Mauro Alaibac[9], Simone Mocellin[1,3]

* Correspondence: paolo.delfiore@iov.veneto.it

Objective

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made organic chemicals that are persistent environmental contaminants (1). PFAS have been manufactured since the 1940s and widely used in a variety of consumer and industrial products (such as carpeting, clothing, upholstery, food paper wrappings, fire-fighting foams). Previous studies have associated PFAS with several health conditions such as hepatotoxicity, dyslipidemia, endocrine outcomes, and immunotoxicity outcomes (2,3). Cancer is one of the health effects of interest in relation to PFAS exposure (4).

As regards cutaneous melanoma, even if its development is multifactorial and mainly related to ultraviolet light exposure and genetic susceptibility, several studies pointed out significant correlations between chemical exposure and melanoma incidence

In 2013, the Italian National Research Center (IRSA-CNR), triggered by the outcomes of the European PERFORCE project, found a high presence of PFAS in water and soil of large areas of North-eastern Italy. In the Veneto region, the main source of contamination was a chemical plant in the Province of Vicenza, which had produced PFAS compounds since early 60s. The contaminated area includes 30 towns, with 140,000 people directly exposed to the PFAS pollution (5,6). We hypothesized that PFAS exposure might affect the biological aggressiveness of melanoma. Hence, we compared melanoma patients stratified by the potential exposure to PFAS, to investigate differences in terms of tumor histological characteristics and prognosis between patients exposed and those unexposed to PFAS.

Materials and Methods

This investigation is a retrospective cohort study on PFAS exposure All patients who were diagnosed and/or treated for primary melanoma in 1998-2014 at Veneto Institute of Oncology and at the University Hospital of Padua (Italy) were considered for this study. Main inclusion criteria were age ≥15 years and living in the Veneto Region. Subjects living in PFAS areas constituted the exposed cohort, while patients living outside PFAS areas in the province of Venice were defined as the unexposed cohort. All data were extracted from a local database. The available variables included demographics (residence at diagnosis, age at diagnosis, sex) and tumor characteristics (subtype of melanoma, primary site, Breslow thickness, ulceration, number of mitoses, pTNM stage). Follow-up data were also extracted from scheduled visits. Overall survival (OS) was calculated from date of diagnosis to date of death or last visit. Disease-specific survival (DSS) was calculated from date of diagnosis to date of disease-related death, or date of last visit/disease-unrelated death. Disease-free survival (DFS) was calculated from date of diagnosis to date of recurrence, or date of last visit/death.

Continuous data were summarized as median and interquartile range (IQR). Comparisons between exposed and unexposed cohorts were performed using the Chi Square test or Fisher's exact test (categorical data), and Mann–Whitney test (continuous data). Survival estimates were calculated using the Kaplan-Meier method and compared between exposed and unexposed cohorts using log-rank test (unadjusted analysis) and Cox regression models with unbalanced baseline characteristics as additional independent variables (adjusted analysis). Effect sizes were reported as hazard ratio (HR) with 95% confidence interval (CI).

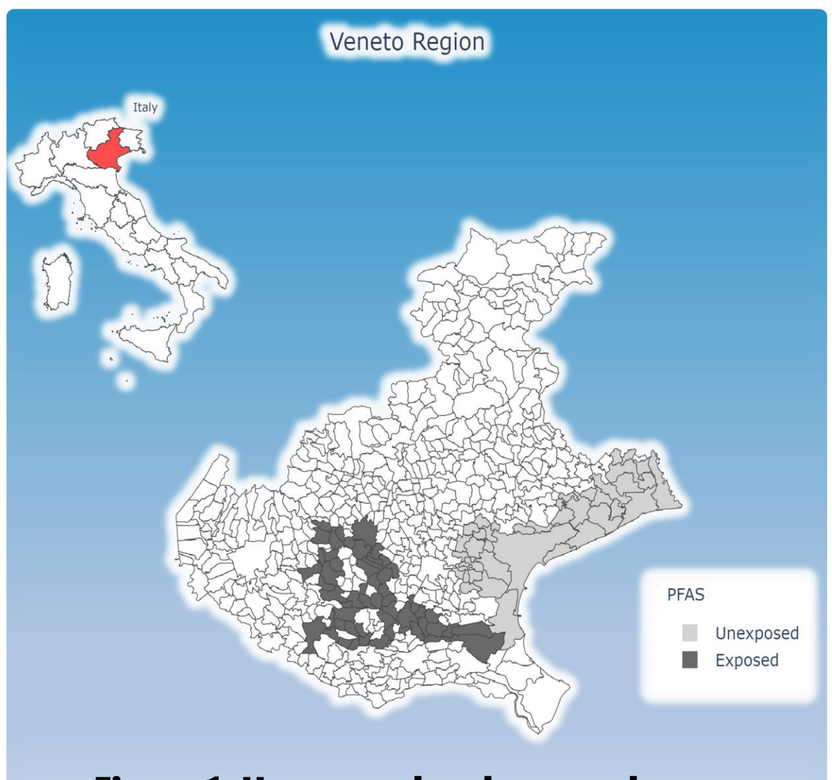

Figure 1. Unexposed and exposed area in Veneto Region.

Results

The number of mitoses per mm2 was higher in exposed vs. unexposed patients (p=0.005), while no other statistically significant differences were found in the two cohorts. 5-year OS was 83.7% in exposed patients and 88.0% in unexposed patients (p=0.20); 5-year DSS was 88.0% in exposed patients and 90.9% in unexposed patients (p=0.50); 5-year DFS was 83.8% in exposed patients and 87.3% in unexposed patients (p=0.20). Survival was not statistically different between exposed and unexposed patients (OS: HR 1.11, 95% CI 0.77 to 1.60, p=0.55; DSS: HR 0.98, 95% CI 0.61 to 1.57, p=0.93; DFS: HR 1.04, 95% CI 0.68 to 1.57, p=0.86), while higher number of mitoses per mm2 was associated with impaired OS (HR 1.13, 95% CI 1.10 to 1.16; p<0.0001), DSS (HR 1.13, 95% CI 1.09 to 1.16; p<0.0001) and DFS (HR 1.14, 95% CI 1.11 to 1.17; p<0.0001).

Characteristic	Exposed cohort (n=194)	Unexposed cohort (n=488)	p-value
Age, years	50 (37-62)	49 (38-61)	0.90
Males	96 (49.5)	227 (46.5)	0.54
Primary site:			
Acral	12 (6.2)	28 (5.7)	0.93
Head/neck	18 (9.3)	40 (8.2)	
Upper limb	43 (22.2)	120 (24.6)	
Trunk	92 (47.4)	235 (48.2)	
Lower limb	29 (14.9)	65 (13.3)	
Breslow thickness, mm	0.9 (0.5-2.0)	0.8 (0.4-1.8)	0.23
Ulceration:			
Absent	144 (76.6)	372 (79.3)	0.51
Present	44 (23.4)	97 (20.7)	
Presence of Mitoses	134 (70.5)	284 (58.7)	**0.005**
pTNM:			
I	116 (59.8)	325 (66.6)	0.22
II	43 (22.2)	85 (17.4)	
III	35 (18.0)	78 /16.0)	
Melanoma Subtype:			
Acral Lentiginous	4 (2.0)	14 (3.0)	0.78
Lentigo Maligna	5 (2.7)	7 (1.5)	
Nodular	33 (17.6)	85 (18.1)	
Superficial Spreading	141 (75.0)	347 (73.8)	
Other	5 (2.7)	17 (3.6)	

Table 1. Demographics and tumor characteristics according to the geographical area of residency.

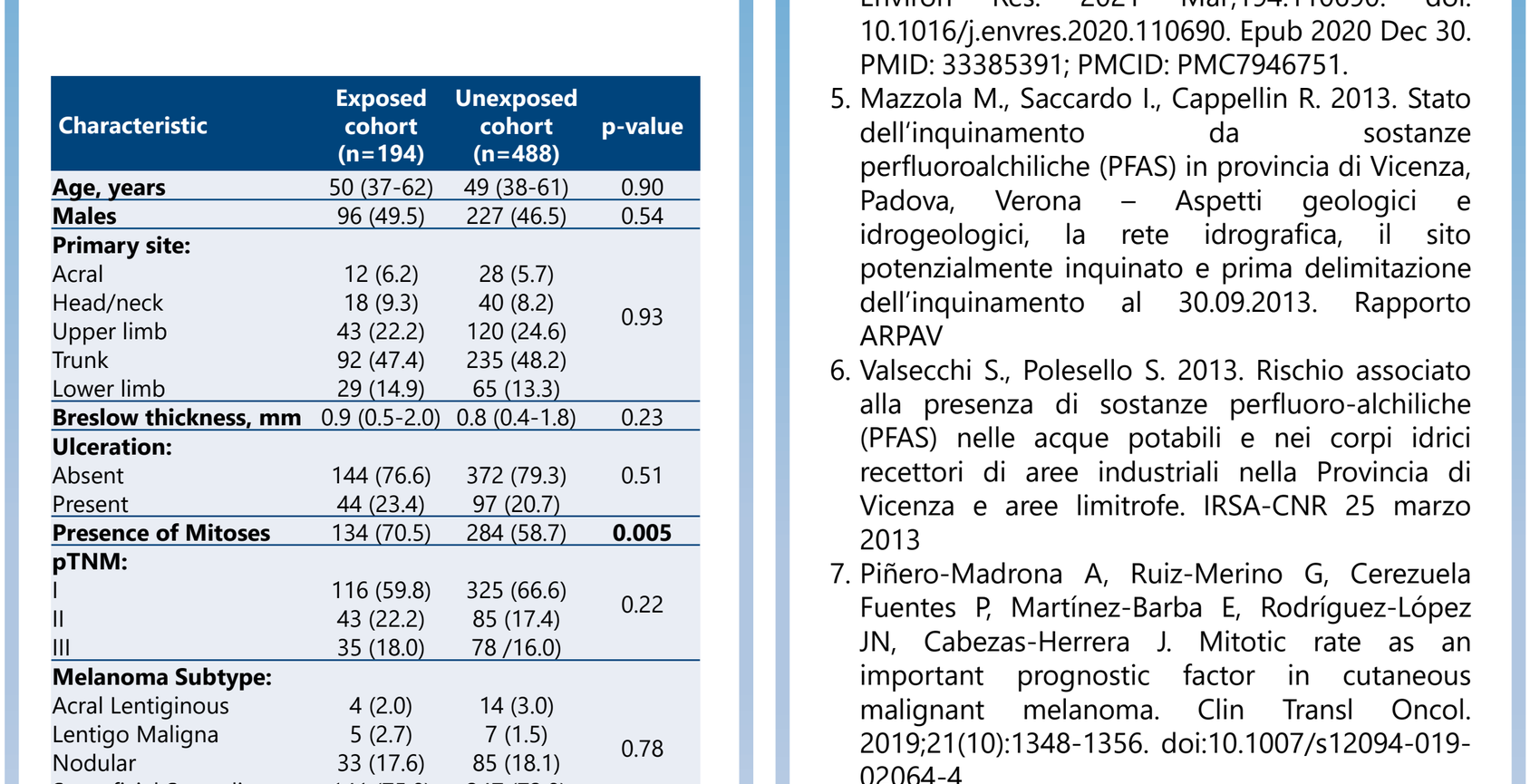

Figure 2. Overall survival, disease-specific survival, and disease-free survival: comparison between exposed and unexposed cohorts.

Conclusion

Our findings showed that melanoma patients living in PFAS-contaminated areas had higher number of mitoses compared to unexposed patients. However, the quantification of mitoses in cutaneous melanoma has been discharged from the main prognostic variables of the TNM classification, many recent studies (7,8) confirmed a clear association between an increasing mitotic rate (MR) and decreased overall, melanoma-specific, and recurrence-free survival, suggesting a reconsideration of MR prognostic role for future inclusion in the melanoma staging system. Our results prompt further studies aimed to investigate the impact of PFAS exposure on the biological aggressiveness of cutaneous melanoma, with special regard to the role of PFAS on vitamin D-related anticancer effects.

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