IMPACT OF SOCIO-ECONOMIC STATUS AND DISTRICT OF RESIDENCE ON CUTANEOUS MALIGNANT MELANOMA PROGNOSIS: SURVIVAL STUDY ON INCIDENT CASES BETWEEN 1991-2011 IN THE PROVINCE OF FERRARA, NORTHERN ITALY

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ABSTRACT

Objectives: To analyse the impact of socio-economic status (SES) on the prognosis of patients with invasive malignant melanoma (MM) incident from 1991 to 2011 in the province of Ferrara, northern Italy.

Methods: 750 patients provided by the Area Vasta Emilia Centrale Cancer Registry were included in this retrospective cohort study. Prognosis was analysed in terms of overall (OS) and specific survival (SS). The study determinants were the patients' SES and district of residence. The confounding effect of gender, age, period ad TNM stage at diagnosis was evaluated.

Results: In the study population, neither OS nor SS showed significant differences among different layers of SES and districts of residence. The risk of death from MM was lower for the female gender (HR 0.68, IC95% 0.50-0.94), and for diagnoses made in the most recent period (2005-2011: HR 0.56, IC95% 0.36-0.89 with respect to 1991-1997). A worse prognosis was observed in patients older than 70 years at diagnosis (HR 2.33, IC95% 1.39-3.91 with respect to the <40-year group) and in >pT1 tumours (up to 20 times for pT4 tumours).

Conclusions: SES and district of residence did not constitute prognostic factors for MM patients residing in the province of Ferrara. Homogeneity in MM staging, treatment and follow up strategies due to the relatively small extent of the study area and the presence of a single University Hospital of reference, as well as less marked social and economic differences among the study patients in comparison with other previously analysed populations may account for this finding.

Key words: socio-economic status, district of residence, melanoma, prognosis, survival, staging

INTRODUCTION

Malignant melanoma (MM) is the most aggressive skin cancer and is responsible for 75% of deaths from skin tumors [1]. Its incidence has considerably risen worldwide during the recent decades [2]. Increasing incidence has been attributed, at least in part, to an increase in spontaneous skin screening, whereas early detection of MM with low metastatic potential seems to account for the relatively stable mortality trends [3].

About 13,800 subjects were expected to be diagnosed with melanoma in Italy in 2016, of whom 47.8% were expected to be women [4]. Among the new diagnoses of cancer, MM is the ninth most common malignancy in male patients, the second most commonly diagnosed cancer among 0-49 year-old males, and the seventh in females (the third among female subjects younger than age 50). In 2013, the Italian statistical institute (ISTAT) recorded 1948 deaths in Italy due to MM (43.0% in females) [4].

Evidence on the impact of social determinants, such as both socioeconomic status (SES) and lifestyle factors, on the outcome of MM is increasing [5]. In particular, the relationship between SES and melanoma incidence and prognosis has been acknowledged. Overall, melanoma incidence increases in populations with higher SES, whereas its death rate is lower in such populations, because of early diagnosis. On the contrary, melanoma mortality rates are usually greater among lower SES populations due to advanced stages of the disease at the time of diagnosis. Lifestyle factors are related to SES as well [6].

This study aimed to assess the prognostic weight of socio-economic deprivation on melanoma survival among cases incident from 1991 to 2011 in the province of Ferrara, which is located in Emilia-Romagna Region (ER) in the north Italy. In ER (about 4,500,000 inhabitants) about 1,150 new MM cases were expected in 2016 (44.8% in females) and 142 deaths were recorded in 2015. Ferrara province showed lower incidence than other areas of ER, in line with an overall lower SES [7]. The study provided an overview of the territorial reality that highlighted results partially in

contrast with the available findings of the literature. Understanding the impact of social determinants in the outcome of MM can lead to targeted interventions potentially improving patient survival.

MATHERIALS AND METHODS

The present study was developed according to a retrospective cohort model. It considered all the patients with invasive cutaneous melanoma diagnosed between 1991 and 2011 in the Province of Ferrara and provided by the cancer registry of Area Vasta Emilia Centrale.

Data were collected and recorded in accordance with codified international rules by the International Agency for Research on Cancer (IARC) in Lyon and the Italian Cancer Registries (AIRTUM) [8,9]. Lesions were selected by ICD-O 3 codes (C44.0-C44.9, M-8720-8790, behavioural code 3) [10]. Patients with diagnoses obtained only from the death certification (Death Certification Only -DCO) were excluded from the study as well as those with multiple invasive tumors, synchronous or metachronous. The vital status of patients was verified by the archive of the Ferrara local health unit, with follow-up extended to 31 December 2013. The cause of death of the study patients was obtained from the Mortality Archives (ReNCaM) of the Ferrara local health unit, which collects the causes of death of all residents, as provided by the flow of ISTAT death certificates (Law 675/1996) [11].

Both overall survival (OS) and specific survival (SS), i.e. the probability of surviving MM in the absence of other causes of death, of the study subjects were considered in the study. Survival time was calculated as the difference between the date of diagnosis and the date of death.

SES and districts of residence were considered as determinants for patient survival. SES has been defined through a deprivation index (DI) calculated on an ecological basis [12]. For each patient, DI was obtained by five echological indicators, based on his own residence census block (Italian Institute of Statistic 2001 Census of Population and Housing [13]). The SES domains synthetized

for each census block were education, unemployment, residence in a house not owned, single-parent families and overcrowding, according to a validate algorithm [14].

The provincial district of residence for each patient was assumed as configured by the organization of the Ferrara local health unit: West District, North-Central District (including Ferrara town and its University-Hospital) and South-East District.

Gender; age at MM diagnosis; year of diagnosis, divided into three periods (1991-1997; 1998-2004; 2005-2011); MM stage at diagnosis, according to the TNM system; and histological type of MM were considered as possible confounders. Across the long period of observation, MM were staged according to three different editions of the TNM system (V, VI and VII [15, 16, 17]). So, a transcoding from V and VI to VII version was performed. The following histological types and combinations were considered: superficial spreading, malignant lentigo melanoma, nodular, acro-lentiginous, desmoplastic, epithelioid cells, spindle cell and epithelioid + spindle, other/ not otherwise specified (NOS).

Statistical analysis was realized through the packages SPSS Statistics rel. 20 and Stata rel. 12.1. Ten years survival analysis was performed using actuarial method and Cox proportional hazards model. Confidence intervals were calculated at 95% probability, according to Poisson distribution.

RESULTS

Based on the study eligibility criteria, from the 875 overall incident cases in the studied period, 750 cases of invasive melanoma which were followed up to the end of 2013 were included. The details of the included patients and MM are reported in Table 1.

Patients belonging to high and medium-high SES represented 43.7% of the patients in the Centre-North district, 37.4% in the West district and 19.6% in the South-East district; patients with medium-low or low SES were 37.7%, 41.2% and 57.6% respectively. In 4.9% of the study patients SES was impossible to determine. While in the Center-North and West districts, where high and

medium-high SES were more represented, MM occurred mostly in the high and medium-high SES population strata (43.7% and 37.4%, respectively), the opposite occurred in the South-East district, where mainly the lower SES population developed MM (57.6%).

Ex-post reconstruction of MM stage at diagnosis across the three study periods revealed several problems. So in 56.4% of cases in 1991-97, 29.5% in 1998-2004, and 30.9% in 2005-11 this information was impossible to obtain. Stages I and II accounted for 24.8% of all MM diagnosed in the first period, whereas they represented 50.2% and 48.7% of the cases diagnosed during the second and third periods, respectively. This suggests an increase of stage I and II diagnosis from the early 90s to today.

Table 2 shows the distribution for SES and MM stage at diagnosis. Patients with stage I showed a uniform distribution for SES; among stage II patients, 29.1% belonged to high or medium-high SES subgroups and 56.3% to medium-low or low SES ones. The imbalance was even greater among stage IV patients, of whom 20.0% had high or medium-high SES, 47.7% had medium-low or low SES and 18.5% had missing values. Thus, almost half of the patients diagnosed with stage II and IV MM belonged to the most deprived layers of the population.

Ten-years survival analysis by SES illustrates the trend of patients' SS during the follow up (Figure 1). The disadvantage of people with undetermined SES (black line), which was statistically significant, may be observed, although the gap was amplified by the low number of patients included in this group. The most noteworthy aspect is that there were not significant differences in terms of SS among the different SES subgroups. The OS curves (not shown) had a trend that was perfectly superimposable to those of SS for all SES subgroups.

Data from univariate and multivariate analyses of the melanoma-specific mortality are reported in Table 3. These data show that neither the SES nor the district of residence, significantly influenced the risk of death from MM among the study patients, although a light trend may be pointed out.

Univariate and multivariate analyses of the risk of death from MM showed the following findings as well: lower survival in males and in the elderly population, increase in specific survival across the study period, stage at diagnosis in inverse proportion to the specific survival. Nodular, desmoplastic and NOS types of MM are associated to higher mortality risk in univariate analysis, but not in multivariate approach.

Similar data were found regarding the all-cause mortality (not shown).

DISCUSSION

The main topic of the present study was the analysis of the impact of SES and district of residence on survival in a cohort of patients resident in the province of Ferrara with malignant melanoma developed between 1991 and 2011.

In this retrospective cohort study, 750 cases of invasive melanoma followed until the end of 2013 were included. Several findings of the study were in agreement with the literature, such as the protective role of female gender, the inverse correlation between patient age and survival, and the progressive increase in survival during the period considered. The latter finding suggests a gradual improvement in MM early diagnosis leading in turn to an improvement of prognosis.

On the other hand, with specific reference to the main topic of the study, our findings surprisingly deviate from data previously provided by other research. In fact, the most striking result of our study is that neither SES nor district of residence significantly affected survival, both general and specific. The most relevant studies concerning this issue found that the most deprived populations tend to get sick less than wealthier ones. On the other hand, mortality had been shown to be greater in the most deprived subjects because of the late diagnosis and because of the potential differences in terms of treatment [18,19]. Differences between incidence and mortality may also be influenced by the district of residence [20].

Two main reasons may be hypothesized to warrant this trend in our study population. First, efficiency of management and therapy might minimize the modest diagnostic delay, with a consequently more advanced stage in the most deprived population in comparison with higher SES subgroups. Secondly, in the geographical area considered in this study, social and economic differences among people are less marked than those found in more heterogeneous populations previously investigated [21]. In these latter, social differences seem to have a relevant impact on different possibilities of access to health facilities and care, which may account for different prognosis among MM patients. It may be expected that in the province of Ferrara people may undergo similar staging, treatment and follow up strategies, due to both its relatively small area and the presence of a single University Hospital of reference.

The main limitations of the study regard some problems that emerged during the data collection and analysis. It was not possible to collect the stage at diagnosis in about one third of the patients. This gap depended on several factors, including: a) three different editions of the TNM staging used in the study period and traced back to the seventh edition [15,16,17]; b) cases of diagnosis and therapy carried out in extra-provincial structures; c) multi-specialty diagnostic and therapeutic pathways. It should be noticed that this gap mostly affects elderly patients and MM occurred in the earlier period. Nevertheless as seen in Table1 information completeness about stage at diagnosis did not differed by SES status, our main exposure.

SES was not determined in less than 5% of patients. Patients' high residential mobility was the main cause of undetermined SES. It is worthy of note that patients without SES determination showed the worse MM survival.

On the other hand, these issues represent a main strength of the study, considering that all these cases with missing information about MM staging or SES were included in the analyses in order to estimate their distortive effect.

Another strength of the study is the type of casuistry. The study cases were provided by the Cancer Registry of the province of Ferrara and they represent all cutaneous MM diagnosed among people resident in the province of Ferrara during a 21-year period. The archive of a cancer registry ensures a high number of good quality diagnostic data, in the absence of selection bias that can characterize the clinical series. Moreover, the study cases have a microscopic confirmation in 99.9% of cases, and the proportion of patients lost to follow-up is negligible (1.5%).

Even with some minimal, not significant differences, the study did not identify specific obstacles taking in charge MM patients in relation to their SES or district of residence.

In conclusion, based on the findings provided by the present study, SES and place of residence seem not to represent a prognostic bottom line for people living in the province of Ferrara affected with cutaneous melanoma. The opportunity to organize a formalized diagnostic, therapeutic and care pathway for this cancer appears to improve, in the short term, traceability and comprehensiveness of the diagnostic information, and the biological characterization, the therapeutic approach and the follow-up, allowing better control of risk factors and a more efficient management of this disease and its epidemiological characteristics within the province of Ferrara.

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Table 1. Study patient and melanoma characteristics

Variables		**cases**	**%**
Gender	Male	361	48.1%
	Female	389	51.9%
Age classes	0-39 years	134	17.9%
	40-49 years	120	16.0%
	50-64 years	288	38.4%
	70+ years	208	27.7%
Years of incidence	1991-1997	165	22.0%
	1998-2004	271	36.1%
	2005-2011	314	41.9%
District of residence	North-central	414	55.2%
	West	131	17.5%
	Southeast	205	27.3%
Anatomic site of MM	External ear	17	2.3%
	Face	45	6.0%
	Head and neck	33	4.4%
	Trunk	263	35.1%
	Upper limb	97	12.9%
	Legs	243	32.4%
	Neighbouring sites	2	0.3%
	Unspecified skin	50	6.7%
MM histotype	Superficial spreading	325	42.3%
	In lentigo maligna	27	3.6%
	Nodular	120	15.9%
	Acral lentiginous	10	1.3%
	Desmoplastic	7	0.9%
	Epithelioid and spindle cells	20	2.7%
	Epithelioid cells	98	13.1%
	Spindle cells	8	1.1%
	Other/ not otherwise specified	136	18.1%
Basis of MM diagnosis	Clinical	1	0.1%
	Cytological	1	0.1%
	Primary histology	713	95.1%
	Metastases histology	35	4.5%
Stage	I	275	36.7%
	II	55	7.3%
	III	85	11.3%

	IV	65	8.7%
	Missing	270	36.0%
Ulceration	No	229	30.5%
	Yes	154	20.5%
	Missing	367	48.9%
Breslow's depth	Up to 1 mm	229	39.9%
	1.01 - 2mm	149	19.9%
	2.01 - 4 mm	108	14.4%
	Over 4 mm	74	9.9%
	Missing	120	16.0%
Clark level	II	212	28.3%
	III	188	25.1%
	IV	202	26.9%
	V	30	4.0%
	Missing	118	15.7%
Socio- economic status	High	157	20.9%
	Medium-high	113	15.1%
	Medium	115	15.3%
	Lower middle	160	21.3%
	Low	168	22.4%
	Missing	37	4.9%

Table 2. Distribution by SES and stage at diagnosis

		Stage at diagnosis										Total	
		Stage I		*Stage II*		*Stage III*		*Stage IV*		*Missing*			
Socio-economic status	*high*	59	*21.5%*	9	*16.4%*	26	*30.6%*	6	*9.2%*	57	*21.1%*	157	*20.9%*
	medium-high	40	*14.5%*	7	*12.7%*	12	*14.1%*	7	*10.8%*	47	*17.4%*	113	*15.1%*
	medium	60	*21.8%*	6	*10.9%*	8	*9.4%*	9	*13.8%*	32	*11.9%*	115	*15.3%*
	lower-middle	52	*18.9%*	18	*32.7%*	15	*17.6%*	17	*26.2%*	58	*21.5%*	160	*21,3%*
	low	58	*21.1%*	13	*23.6%*	19	*22.4%*	14	*21.5%*	64	*23.7%*	168	*22.4%*
	missing	6	*2.2%*	2	*3.6%*	5	*5.9%*	12	*18.5%*	12	*4.4%*	37	*4.9%*
Total		275	*100.0%*	55	*100.0%*	85	*100.0%*	65	*100.0%*	270	*100.0%*	750	*100.0%*

% for column (by stage)

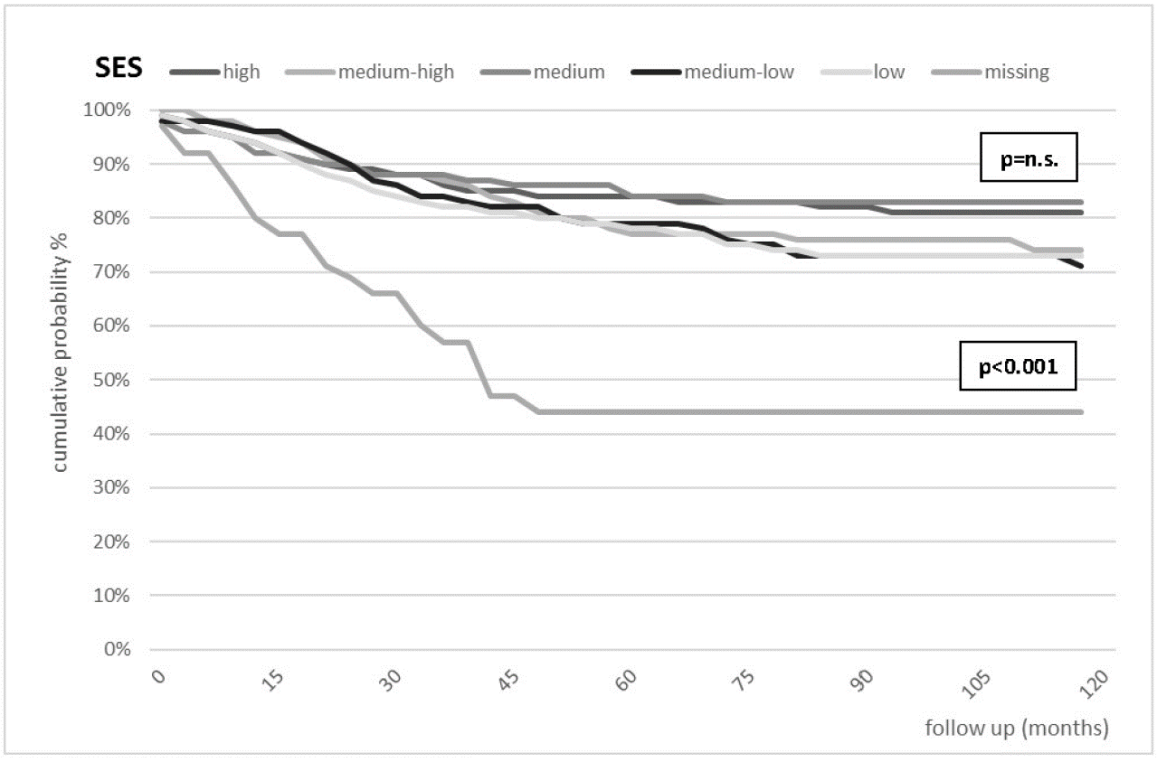
Table 3. Analysis of prognostic determinants (risk of death) - 10-years specific mortality

Cox model

		univariate		multivariate*	
Risk of death		**HR**	***CR 95%***	**HR**	***CR 95%***
Socio-economic status	*High*	1.00	-	1.00	-
	Medium-high	1.22	*0.71; 2.08*	1.09	*0.62; 1.92*
	Medium	0.83	*0.46; 1.50*	1.02	*0.55; 1.89*
	Lower middle	1.34	*0.83; 2.17*	1.22	*0.73; 2.03*
	Low	1.36	*0.84; 2.19*	1.44	*0.86; 2.41*
	Missing	**3.73**	*2.07; 6.73*	2.18	*0.10; 4.32*
District of residence	*North-central*	1.00	-	1.00	-
	West	1.19	*0.79; 1.79*	1.38	*0.89; 2.12*
	Southeast	1.11	*0.78; 1.58*	1.02	*0.70; 1.49*
Gender	*Male*	1.00	-	1.00	-
	Female	**0.54**	*0.40; 0.74*	**0.68**	*0.50; 0.94*
Age at diagnosis	*<40 years*	1.00	-	1.00	-
	40-49 years	0.86	*0.44; 1.67*	1.10	*0.56; 2.18*
	50-69 years	1.63	*0.99; 2.68*	1.65	*0.99; 2.74*
	70+ years	**2.72**	*1.65; 4.50*	**2.33**	*1.39; 3.91*
Time at diagnosis	*1991-1997*	1.00	-	1.00	-
	1998-2004	0.73	*0.51; 1.04*	0.82	*0.54; 1.26*
	2005-2011	**0.53**	*0.36; 0.79*	**0.56**	*0.36; 0.89*
MM stage	*I*	1.00	-	1.00	-
	II	**11.76**	*5.24; 26.40*	**8.80**	*3.72; 20.83*
	III	**25.38**	*12.40; 51.96*	**21.57**	*10.08; 46.19*
	IV	**41.60**	*19.99; 86.58*	**20.17**	*8.77; 46.34*
	Missing	**7.88**	*3.90; 15.89*	**5.86**	*2.84; 12.06*
MM histotype	*Superficial spreading*	1.00	-	1.00	-
	Lentigo maligna	1.31	*0.47; 3.66*	0.94	*0.33; 2.70*
	Nodular	**4.67**	*3.08; 7.09*	1.49	*0.95; 2.33*
	Acral lentiginous	0.87	*0.12; 6.31*	0.44	*0.06; 3.25*
	Desmoplastic	**1.21**	*1.67; 8.30*	0.27	*0.04; 2.02*
	Epithelioid cells	1.70	*0.97; 2.98*	0.79	*0.44; 1.43*
	Spindle cells	2.05	*0.87; 4.84*	1.04	*0.42; 2.56*
	NOS	**3.85**	*2.52; 5.88*	1.59	*0.95; 2.66*

HR: Hazard risk; CR: Confidence Range; NOS: not otherwise specified; *adjusted for all the variables.

Figure 1 – 10-years melanoma-specific survival, actuarial curves



SES, socio-economic status; n.s., not significant