region while the specific component of melanoma the coastal area and Trieste. The estimate of the δ parameter is 0.45 (95% CrI 0.28, 0.65) suggesting that the unobserved risk factors shared by the two diseases are more associated with lip cancer than melanoma.

Ecological regression models

Table 4 shows the maximum, median and minimum values for covariates considered, by ASS in FVG. In Figure 6, we reported the spatial distribution of the three covariates in the region. Incidence of cutaneous melanoma (Figure 2) and altitude exhibit a completely different spatial distribution, while is similar with that of solar radiation. More confusing is the relationship with material deprivation. The solar irradiation distribution by municipalities was obtained by means of a Bayesian model, while for other covariates we have empirical data for each municipality. The results of the ecological regression models are shown in Table 5. A modest inverse association is observed with the material deprivation index (-0.048; 95%CrI: -0.02; 0.04). The results are consistent in both models with and without the clustering random term. Altitude and irradiation have a spatial structure, which is strongly related to the geographical distribution of cutaneous melanoma leading to over-adjustment when the clustering term is in the model. The results of the models without clustering showed a decreased risk of 15% for one standard deviation above sea level, and an increase of 5% for unit of standard deviation in solar irradiation.

Results by site

We focused on the analysis of standardised rates per unit of body surface area and on the relative tumour density (RTD), by dividing the incident cases of melanoma by site, separately for 3 different areas: area of Trieste (ASS1), coastal area (ASS2 and ASS5) and the rest of the region (ASS3, ASS4 and ASS6).

Table 6 shows, separately by sex and by area, the percentage of body surface area, the standardised rate, the standardised rate per unit area and the relative tumour density in the locations considered.

Table 2. Standard deviation of the two random terms of Besag York and Mollié model, heterogeneity and clustering, reporting incidence of cutaneous melanoma in Friuli Venezia Giulia (1995-2005).

	Total		0-64 years		65+ years	
	Male	Female	Male	Female	Male	Female
Heterogeneity (SD)	0.08 (0.05)	0.11 (0.06)	0.12 (0.06)	0.12 (0.07)	0.07 (0.04)	0.10(0.06)
Clustering (SD)	0.31 (0.08)	0.17 (0.07)	0.42 (0.12)	0.28 (0.10)	0.28 (0.10)	0.12 (0.08)
Ratio (clustering/heterogeneity)	3.9	1.5	3.5	2.3	4.0	1.2

SD, standard deviation.

Table 3. Number of cases, crude and standardised rate, and standardised incidence ratio for lip cancer in Friuli Venezia Giulia (1995-2005), by gender.

ASS	Male				Female			
	Cases	Crude rate	Standardised rate°	SIR	Cases	Crude rate	Standardised rate°	SIR
ASS 1 (Triestina)	35	2.80	1.60	0.58	9	0.64	0.19	0.48
ASS 2 (Isontina)	45	6.23	3.98	1.47	13	1.67	0.73	1.45
ASS 3 (Alto Friuli)	12	2.96	2.24	0.75	3	0.70	0.16	0.60
ASS 4 (Medio Friuli)	57	3.21	2.14	0.80	15	0.78	0.25	0.74
ASS 5 (Bassa Fiulana)	42	7.37	4.90	1.84	12	2.01	0.72	2.04
ASS 6 (Friuli Occidentale)	67	4.35	3.20	1.18	23	1.43	0.60	1.43
Total	258	4.12	2.71	1.00	75	1.11	0.40	1.00

ASS, *azienda per l'assistenza sanitaria* (healthcare assistance company); SIR, standardised incidence ratio. °Direct standardisation on European population.

Table 4. Maximum, median and minimum values of covariates included in the ecologic regression: altitude, material deprivation index, solar irradiation (average values, 1994-1999).

ASS	Altitude (m)			Deprivation (z)			Irradiation (Mj/m^2)		
	Max	Median	Min	Max	Median	Min	Max	Median	Min
ASS 1 (Triestina)	418	125	2	0.39	-1.41	-2.04	4834	4819	4806
ASS 2 (Isontina)	276	32	2	3.17	-0.63	-2.21	4869	4783	4751
ASS 3 (Alto Friuli)	1400	492	184	7.9	0.83	-2.02	4885	4804	4691
ASS 4 (Medio Friuli)	663	135	18	3.66	-0.71	-2.76	4836	4726	4594
ASS 5 (Bassa Fiulana)	43	9	2	3.85	0.59	-1.82	4829	4736	4669
ASS 6 (Friuli Occidentale)	830	116	11	3.42	-0.13	-2.9	4856	4808	4718
Total	1400	113	2	7.9	-0.26	-2.9	4885	4799	4594

ASS, *azienda per l'assistenza sanitaria* (healthcare assistance company).

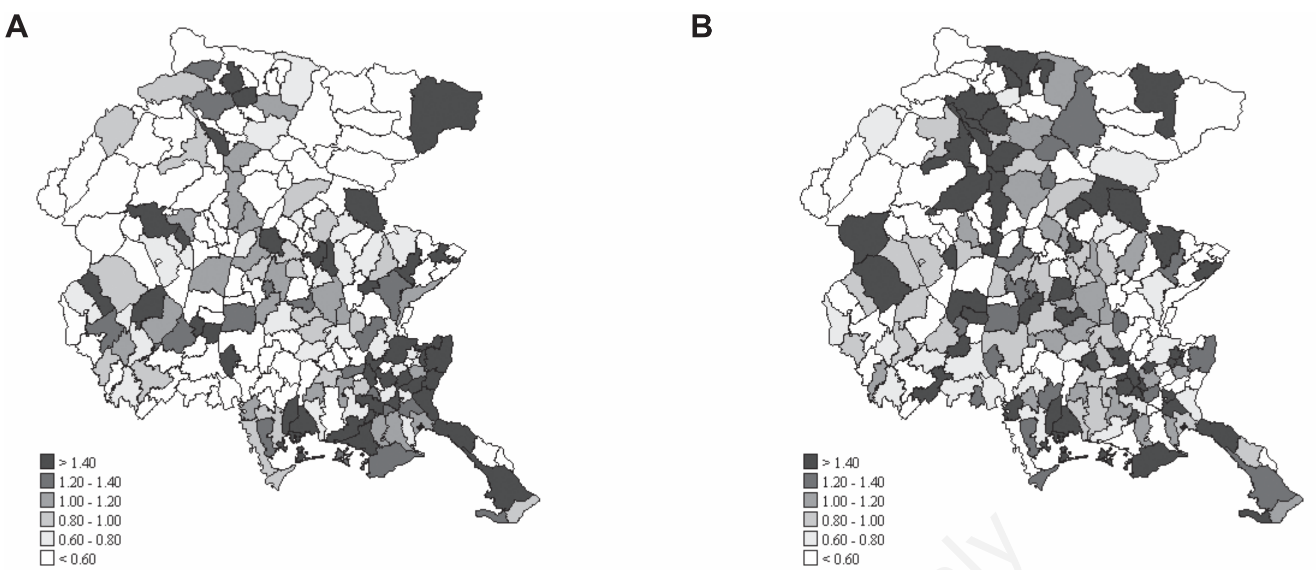

Figure 1. Standardised incidence ratio of males (A and females (B) by municipalities in Friuli Venezia Giulia (1995-2005).

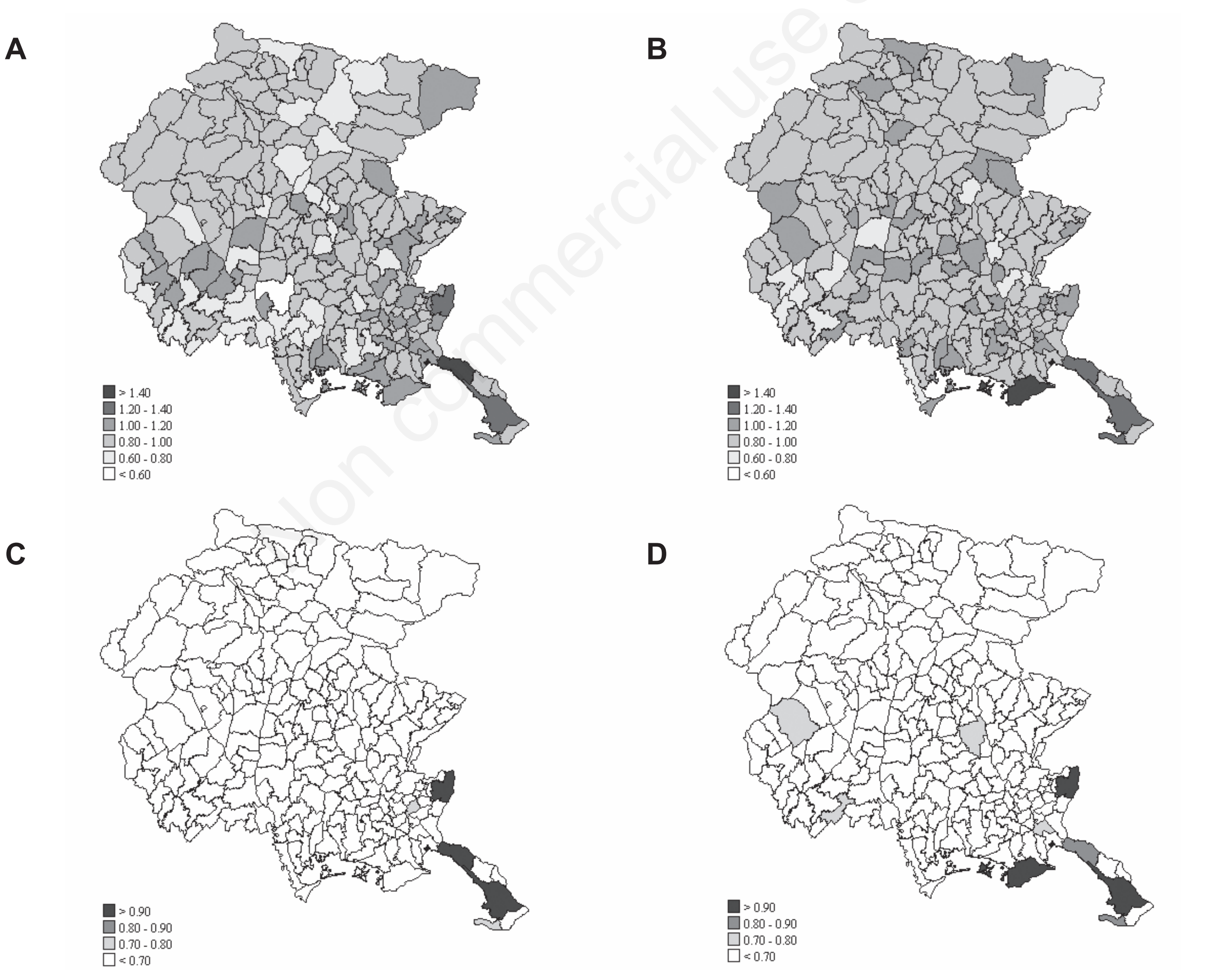

Figure 2. A, B) Bayesian relative risks by municipality; C, D) Bayesian posterior probabilities of each municipality to be in excess with respect to the regional mean. Values for males are in A) and C), and for females in B) and D). Poisson-Gamma model. Friuli Venezia Giulia (1995-2005).

In males, the standardised rate is around 18 per 100,000 for both Trieste and the coastal area, while it is around 10 per 100,000 in the rest of the region. The distribution by site, however, is very different: in the area of Trieste is the trunk to show the highest rate (33 per 100,000 unit area with RTD 1.78), while in the coastal area is the face (152 per 100,000 unit area with RTD 8.45). In women, the standardised rate is around 18 per 100,000 in the area of Trieste, while the rest of the region has values around 10/12 per 100,000. The distribution by site is very different: in the area of Trieste is still the trunk to show the highest rates per unit area (22 per 100,000 units of surface and RTD 1.28) against high values (between 18 and 26 per 100,000 units of surface with RTD between 1.7 and 2.4) for the face in the remaining areas.

Table 7 shows the analysis of the relative tumour density by site and age (<50, 50-64, 65+ years). In men, trunk show higher values in younger age groups in all areas. On the other hand, the face tends to show very high values of RTD in the older age classes, especially in coastal and mountain areas. In women, we find the trunk with a high RTD at a young age, the upper and lower limbs in old age in the area of Trieste. In the coastal area, as in Trieste, upper and lower limbs in old age show high RTD, and face with high RTD. In the remaining area, only the face shows high values of RTD, in old age.

Table 5. Regression coefficients with 90% credible interval, with and without clustering in Friuli Venezia Giulia (1995-2005).

	With clustering	Without clustering
Irradiation	-0.208 (-0.42, -0.11)	0.046 (0.0001, 0.14)
Deprivation	-0.048 (-0.02, 0.04)	-0.0578 (-0.02, 0.01)
Altitude	-0.047 (-0.04, 0.04)	-0.171 (-0.26, -0.11)

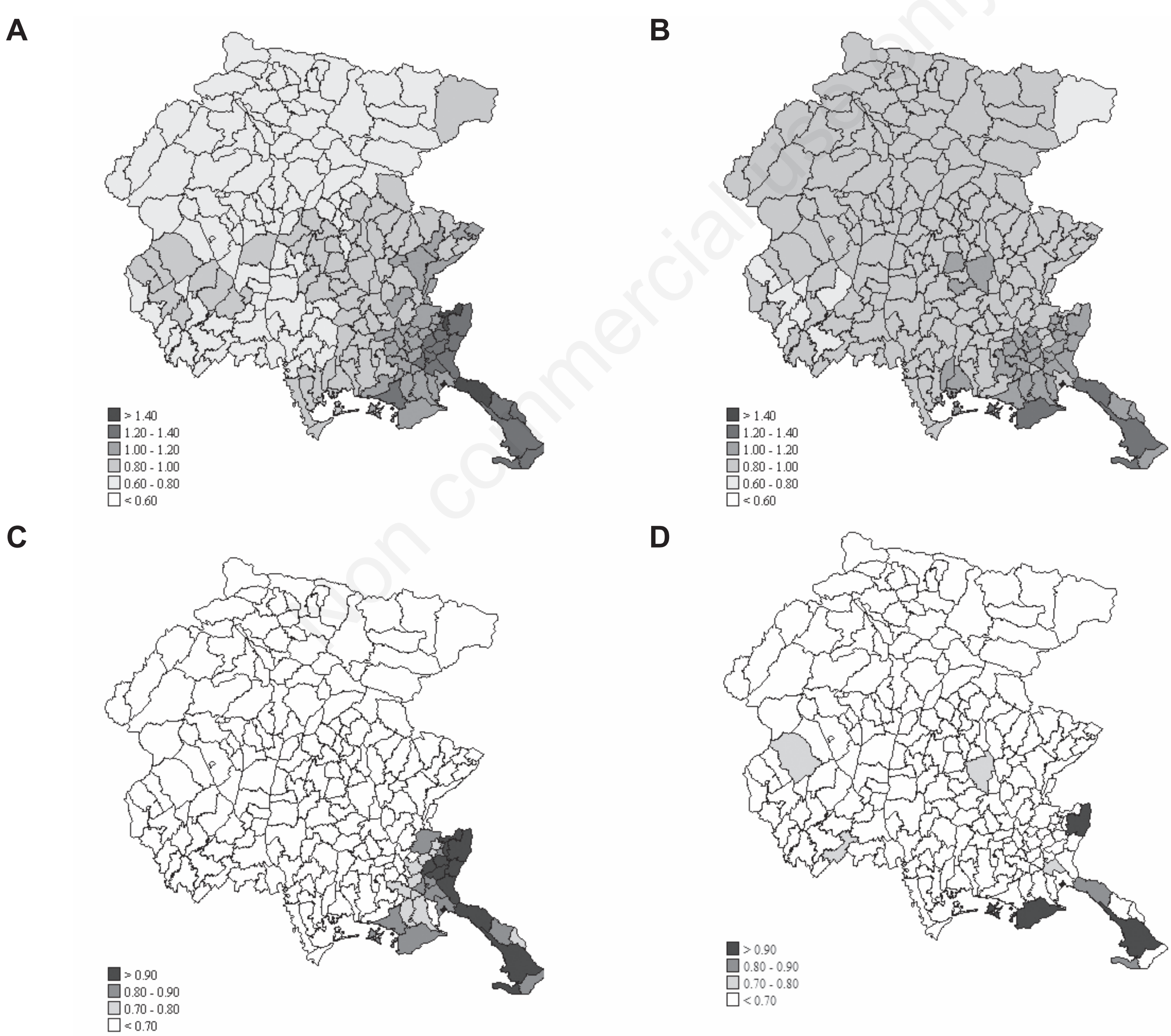

Figure 3. A, B) Bayesian relative risks by municipality; C, D) Bayesian posterior probabilities of each municipality to be in excess with respect to the regional mean. Values for males are in A) and C), and for females in B) and D). Besag York and Mollié model. Friuli Venezia Giulia (1995-2005).

Table 6. Standardised rates, standardised rates per unit of body surface, relative tumour density by site of cutaneous melanoma, separately by gender and areas in Friuli Venezia Giulia (1995-2005).

ASS	Gender	Sites	Body surface (%)	Standardised rates	Standardised rates per unit of body surface	RTD
ASS 1	Male	Face	2.9	0.62	21.23	1.15
		Ears	0.6	0.07	12.46	0.67
		Scalp, neck	5.5	1.08	19.59	1.06
		Trunk	32	10.57	33.02	1.78
		Upper	19	3.74	19.68	1.06
		Lower	40	2.45	6.13	0.33
		Total		18.52		
	Female	Face	2.9	0.37	12.67	0.74
		Ears	0.6	0.05	7.57	0.44
		Scalp, neck	5.5	0.71	12.87	0.76
		Trunk	32	7.00	21.87	1.28
		Upper	19	3.92	20.62	1.21
		Lower	40	7.30	18.25	1.07
		Total		17.02		
ASS 2, ASS 5	Male	Face	2.9	4.43	152.62	8.45
		Ears	0.6	0.18	29.79	1.65
		Scalp, neck	5.5	1.11	20.26	1.12
		Trunk	32	7.71	24.10	1.33
		Upper	19	2.32	12.16	0.67
		Lower	40	2.32	5.80	0.32
		Total		18.06		
	Female	Face	2.9	0.74	25.52	2.03
		Ears	0.6	0.07	11.67	0.93
		Scalp, neck	5.5	0.46	8.36	0.66
		Trunk	32	1.38	4.32	0.34
		Upper	19	3.15	16.58	1.32
		Lower	40	5.99	14.98	1.19
		Total		12.58		
ASS 3, ASS 4, ASS 6	Male	Face	2.9	0.71	24.56	2.42
		Ears	0.6	0.07	11.32	1.11
		Scalp, neck	5.5	0.81	14.67	1.45
		Trunk	32	5.63	17.61	1.73
		Upper	19	1.64	8.63	0.85
		Lower	40	1.33	3.33	0.33
		Total		10.15		
	Female	Face	2.9	0.52	17.79	1.70
		Ears	0.6	0.07	10.86	1.03
		Scalp, neck	5.5	0.22	4.06	0.39
		Trunk	32	3.16	9.86	0.94
		Upper	19	2.12	11.15	1.06
		Lower	40	4.41	11.04	1.05
		Total		10.49		

ASS 1, Trieste; ASS 2,5, coastal area; ASS 3,4,6, other; RTD, relative tumour density.

Table 7. Relative tumour density by sites, separately by gender, areas and age, in Friuli Venezia Giulia (1995-2005).

ASS	Sites	Male			Female		
		<50 years	50-64 years	65+ years	<50 years	50-64 years	65+ years
ASS 1	Face	1.9	0.3	1.3	0.0	1.1	2.1
	Scalp, neck	0.5	1.2	1.3	0.8	0.4	1.2
	Trunk	1.8	1.8	1.7	1.5	1.2	0.9
	Upper	0.9	1.1	1.1	1.0	1.3	1.6
	Lower	0.4	0.3	0.3	0.9	1.0	1.7
ASS 2, ASS 5	Face	3.7	8.2	9.9	0.7	0.4	5.3
	Scalp, neck	0.8	0.5	2.1	0.5	0.7	0.8
	Trunk	1.7	1.2	1.1	0.4	0.3	0.2
	Upper	0.7	0.8	0.5	1.0	1.4	1.8
	Lower	0.4	0.3	0.2	1.1	1.0	1.5
ASS 3, ASS 4, ASS 6	Face	0.4	1.5	4.3	1.0	0.4	4.0
	Scalp, neck	1.4	0.8	3.5	0.3	0.3	0.7
	Trunk	1.8	1.8	1.6	1.2	1.0	0.4
	Upper	0.8	1.0	0.8	0.9	1.3	1.1
	Lower	0.5	0.2	0.2	1.0	1.1	1.2

Discussion

The spatial distribution of the incidence of cutaneous melanoma in FVG region is very marked. The Cancer Registry has been active for many years and incompleteness of registration for selective areas of the province of Pordenone and Udine seems unlikely. In fact, the percentage of histological verification is 93% for men and 97% for women, the DCO is equal to 0% for both sexes, the ratio M/I is 0.25 for males and 0.18 for females (Bidoli *et al.*, 2007).

A different diagnostic assessment in the area of Trieste and in the coastal area could lead to a more accurate recognition, while elsewhere some cases may not be recognised. An effect of *screening* on prevalent cases is not sustainable for a period of 11 years. In addition, the differences by ASS have been documented since the birth of cancer registry and were also present in the atlas of cancer mortality in the eighties (Bidoli *et al.*, 1999). If a phenomenon of early diagnosis exists, this would be relative to superficial spreading type (Golger *et al.*, 2007). In the FVG registry, however, the percentage of classified as malignant melanoma (ICD-O-3M=M8720/3) is 47.3%, making it impossible to verify. The age-specific rate curve could involve some cohort trends. For example, among males, in Trieste, high rates for people less than fifty

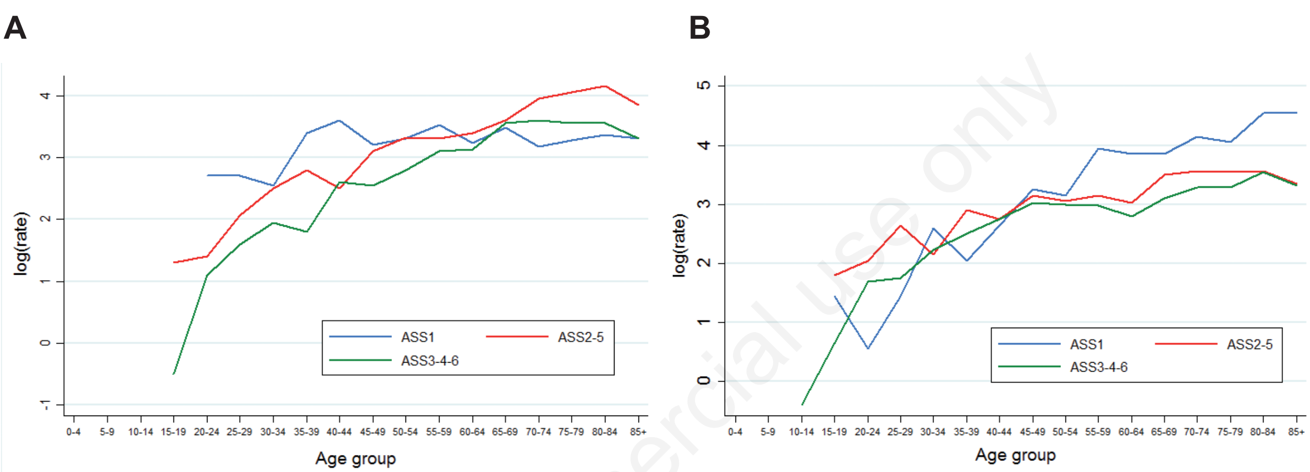

Figure 4. Age specific rate curve. Rates are on logarithmic scale. Areas are denoted respectively by 1 (Trieste), 2-5 (coastal area) and 3-4-6 (other). Values for males are in A) and for females in B). Friuli Venezia Giulia (1995-2005).

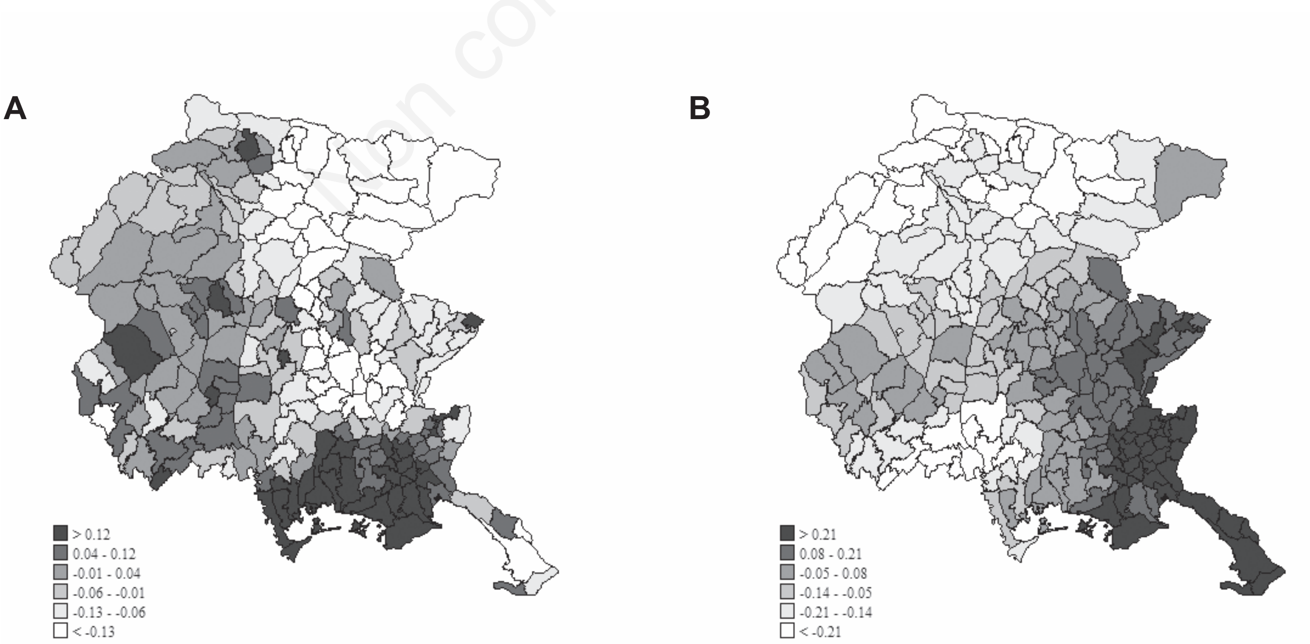

Figure 5. Shared (A) component with the lip cancer and specific (B) component of relative risk for cutaneous melanoma, by municipality. Bivariate hierarchical Bayesian model. Friuli Venezia Giulia (1995-2005).

years old could be a symptom of a much greater risk for cohorts born after World War II that have probably been sun intermittently exposed (seaside holidays) from childhood. This may be a characteristic for the richest area in the region where occupational exposure is less prevalent. Among females, the pattern shows high rates for the Trieste population in older age groups comparing to other regional areas.

Lip cancer has been associated with occupational exposure and solar radiation (Moore *et al.*, 1999). The shared model shows that a small portion of the spatial distribution for melanoma is explained by common factors with lip cancer. The results suggest occupational exposures in the municipalities of the coastal zone.

Ecological regression analysis shows that actually solar radiation is higher in the coastal area and in Trieste, and lesser in other areas. A work on data from the Styria cancer registry (Richting *et al.*, 2007) reported lower incidence rates in mountain areas. The FVG data are consistent with that observation and with lower levels of solar radiation in that area.

As regards the analysis by site, the number of unspecified sites could affect it. However, for the FVG registry, this number is limited (9.4% at regional level). In our data we do not have a detailed classification of site and it is thus not possible to split the trunk in the front, back or abdominal area, or split limbs. This leads to a certain misclassification: the back part of the trunk has typically intermittent exposures and the front part for man but not for the woman. The upper limb, the hand and wrist have a chronic exposure, while the shoulder is the most affected by intermittent exposure. The lower limb, in the woman, is typically intermittent exposed, in particular the thigh and the hip areas (Bulliard *et al.*, 2007). The face is typical site of higher cumulative exposures, even of chronic type.

The results of the present study are very informative and consistent with the literature. Surprisingly, in the area of Trieste, the RTD for the face is close to one. The standardised rates per unit of body surface area show values among the highest in the literature, above 33 per 100,000 unit area in men and around 20 in women. The coastal area shows typical trends by site of chronic exposures .The analysis of the RTD by ages confirm these findings.

In the literature, the ear is reported as a site with high rates per unit of body surface area. The values for the coastal zone are consistent with the literature and also those of the remaining FVG areas, while they are relatively low, such as those of the rest of the face, in the area of Trieste. We do not believe they are due to a different coding assessment, but may reflect a different type of exposure.

We have not information on nevi counts in Cancer Registry datasets, therefore we cannot further speculate on the so-called divergent pathway hypothesis (Whiteman *et al.*, 1998, 2003). However Whiteman *et al.* (2006) suggest divergent pathways from different exposure patterns analysing age and site-specific melanoma density distribution. A recent paper on this issue in Italy is (Chiarugi *et al.*, 2015).

Conclusions

This study documents a significant gradient in the incidence of cutaneous melanoma in FVG region in the years 1995-2005. The area of Trieste shows very high-standardised incidence rates, around 20 per 100,000 in both sexes. High rates are present also in the coastal area, with comparable values in males. The descriptive analysis by age group and by site shows risks associated with intermittent exposures in both genders. For the coastal area the risk is especially high for sites traditionally linked to high cumulative exposures (face and neck), especially among men. From public health point of view, the results suggest diagnostic preventive interventions in the populations living in the area of Trieste, given the high rates observed in the young age groups.

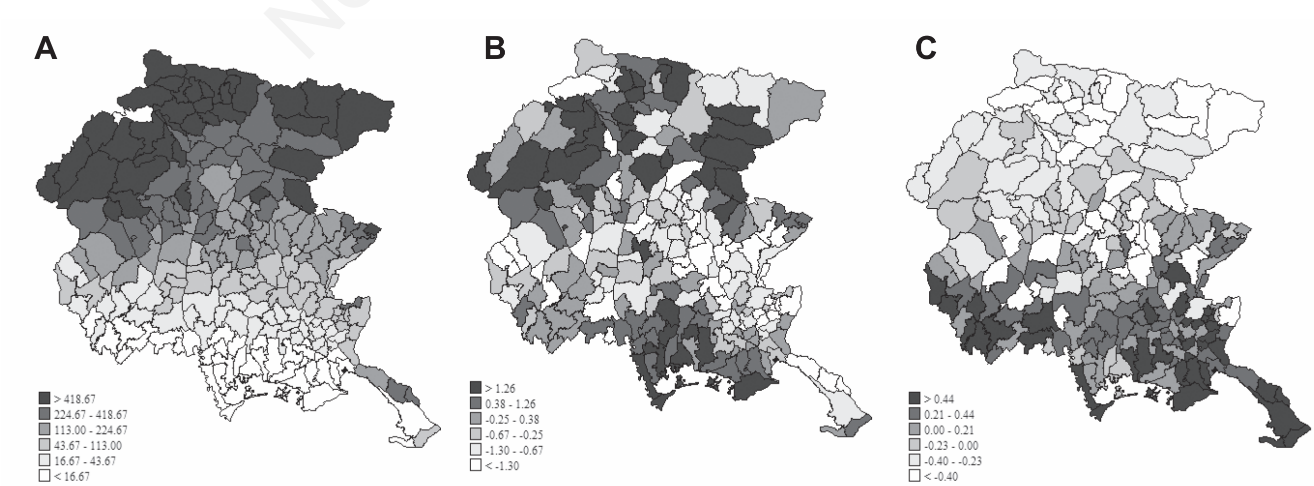

Figure 6. Spatial distribution of altitude (A), material deprivation index (B), and solar irradiation (C) in Friuli Venezia Giulia.

References

Adami HO, Hunter D, Trichopoulos D, 2002. Textbook of cancer epidemiology. Oxford University Press, Oxford, USA.

AIRTUM Working Group, 2009. I nuovi dati di incidenza e mortalità. Periodo 2003-2005. Associazione Italiana Registri Tumori, Florence, Italy.

Armstrong BK, Kricker A, 1996. Epidemiology of sun exposure and skin cancer. Cancer Surv 26:133-53.

Besag J, 1974. Spatial interaction and the statistical analysis of lattice systems (with discussion). J Roy Stat Soc B 36:192-236.

Besag J, York JC, Mollié A, 1991. Bayesian image restoration, with two applications in spatial statistics (with discussion). Ann I Stat Math 43:1-59.

Bidoli E, 1999. Atlante della mortalità per tumori nelle regioni e province del Nord-Est e in Italia. Centro di Riferimento Oncologico, Servizio di Epidemiologia, Aviano, Italy.

Bidoli E, De Dottori M, Serraino D, Vicario G, Zanier L, 2007. Registro tumori del Friuli Venezia Giulia. Dati di incidenza 1999-2003. Centro di Riferimento Oncologico, Aviano, Italy.

Bulliard JL, 2000. Site-specific risk of cutaneous malignant melanoma and pattern of sun exposure in New Zealand. Int J Cancer 85:627-32.

Bulliard JL, Cox B, Elwood JM, 1997. Comparison of the site distribution of Melanoma in New Zealand and Canada. Int J Cancer 72:231-5.

Bulliard JL, De Weck D, Fisch T, Bordoni A, Levi F, 2007. Detailed site distribution of melanoma and sunlight exposure: aetiological patterns from a Swiss series. Ann Oncol 18:789-94.

Catelan D, Biggeri A, Lagazio C, 2009. On the clustering term in ecological analysis: how do different prior specifications affect results? Stat Method Appl 18:49-61.

Chiarugi A, Quaglino P, Crocetti E, Nardini P, De Giorgi V, Borgognoni L, Brandani P, Gerlini G, Manganoni AM, Bernengo MG, Pimpinelli N, GIPMe Centres, 2015. Melanoma density and relationship with the distribution of melanocytic naevi in an Italian population: a GIPMe study. The Italian multidisciplinary group on melanoma. Melanoma Res 25:80-7.

Clayton DG, Kaldor J, 1987. Empirical Bayes estimates of age-standardized relative risks for use in disease mapping. Biometrics 43:671-81.

Costa G, Cislaghi C, Caranci N, 2009. Le disuguaglianze sociali di salute. Problemi di definizione e di misura. Franco Angeli, Milan, Italy.

Dal H, Boldemann C, Lindelöf B, 2007. Does relative melanoma distribution by body site 1960-2004 reflect changes in intermittent exposure and intentional tanning in the Swedish population? Eur J Dermatol 17:428-34.

Franceschi S, Levi F, Randimbison L, La Vecchia C, 1996. Site distribution of different types of skin cancer: new aetiological clues. Int J Cancer 66:1-5.

Golger A, Yoing DS, Ghazarian D, Neligan PC, 2007. Epidemiological features and prognostic factors of cutaneous head and neck melanoma: a population-based study. Arch Otolaryngol 133:442-7.

Green A, 1992. A theory of site distribution of melanoma: Queensland, Australia. Cancer Causes Control 3:513-6.

Held L, Natário I, Fenton SE, Rue H, Becker N, 2005. Towards joint disease mapping. Stat Methods Med Res 14:61-82.

Hughes J, Haran M, 2013. Dimension reduction and alleviation of confounding for spatial generalized linear mixed models. J Roy Stat Soc B 75:139-59.

Lee JAH, Merrill JM, 1970. Sunlight and the aetiology of malignant melanoma: a synthesis. Med J Australia 2:846-51.

Lunn DJ, Thomas A, Best N, Spiegelhalter D, 2000. WinBUGS. A Bayesian modelling framework: concepts, structure, and extensibility. Stat Comput 10:325-37.

Mackay J, Jemal A, Lee NC, Parkin DM, 2006. The cancer atlas. American Cancer Society, Atlanta, (GA), USA.

Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T, Ono T, Albertson DG, Pinkel D, Bastian BC, 2003. Determinants of BRAF mutations in primary melanoma. J Natl Cancer I 95:1878-90.

Moore S, Johnson N, Pierce A, Wilson D, 1999. The epidemiology of lip cancer: a review of global incidence and aetiology. Oral Dis 5:185-95.

Pearl DK, Scott EL, 1986. The anatomical distribution of skin cancers. Int J Epidemiol 15:502-6.

Richardson S, Thomson A, Best N, Elliott P, 2004. Interpreting posterior relative risk estimates in disease-mapping studies. Environ Health Persp 112:1016-25.

Richtig E, Berghold A, Schwantzer G, Ott A, Wölfelmaier F, Karner B, Ludwig R, Denk H, Stering R, Leitner G, Lax S, Okcu M, Gerger A, Kerl H, Smolle J, 2007. Clinical epidemiology of invasive cutaneous malignant melanoma in the Austrian province Styria in years 2001-2003 and its relationship with local geographical, meteorological and economic data. Dermatology 214:246-52.

Rivers JK, 2004. Is there more than one road to melanoma? Lancet 363:728-30.

Tanner MA, Wong WH, 1987. The calculation of posterior distributions by data augmentation. J Am Stat Assoc 82:528-40.

Whiteman DC, Parsons PG, Green AC, 1998. Expression and risk factors for cutaneous melanoma: a case-control study. Int J Cancer 77:843-8.

Whiteman DC, Stickley M, Watt P, Hughes MC, Davis MB, Green AC, 2006. Anatomic site, sun exposure, and risk of cutaneous melanoma. J Clin Oncol 24:3172-7.

Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC, 2003. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer I 95:806-12.