Spatial variation of mortality for common and rare cancers in Piedmont, Italy, from 1980 to 2000: a Bayesian approach

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A Bayesian hierarchical model was used to study the spatial variation in mortality risk from lung and pleural cancer in both sexes, and breast and soft tissue sarcoma (STS) in women in Piedmont (north-west Italy, average population 4 349 411) from 1980 to 2000. Of these four neoplasms, two are common (lung and breast) and two rare (pleura and STS); two have well recognized risk factors (lung and pleura) while the other two (breast and STS) have no single strong risk factor. Data were analysed at a small-area level (1206 municipalities, population 39 to 989 663), using both standardized mortality ratios and Bayesian-estimated mortality risks. The Bayesian model allowed for both heterogeneity (through spatially independent random effects) and clustering (through spatially correlated random effects) and, by borrowing information from neighbouring areas, provided stable estimates for areas with sparse data. The aim was to reduce the noise in the disease maps to highlight the true underlying mortality distribution. Lung cancer in men showed strong spatial structure with a marked east–west gradient, but no appreciable urban–rural differences . In contrast, high mortality areas for female lung cancer were observed around conurbations. Female breast cancer and STS appeared to be spread uniformly across the region. Pleural cancer mortality clusters were evident around areas with major asbestos manufacturers, or natural asbestiform fibre pollution. Maps of Bayesian-estimated mortality risk provided appreciably clearer pictures of risk distribution than did maps of the standardized mortality ratio.
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Introduction

Disease mapping is an efficient way to summarize spatial and spatio-temporal variations in risk. Besides simple descriptive purposes, it can contribute to the identification of risk factors by comparison of exposure patterns and incidence or mortality maps, and to the decision-making processes associated to resource-allocation policies in public health.

Two main problems slowed down the availability of spatial analyses: the lack of appropriate statistical methods and, especially, the lack of data (Pickle, 2002). Nowadays, however, both health statistics data and population estimates at a small-area level have been produced in many countries. The conventional approach is to produce maps of standardized rates based on Poisson inference. However, this does not take into account the presence of extra-Poisson variation (over dispersion) and of spatial patterns in disease distribution. Such problems are particularly serious when dealing with small geographical areas and small population numbers. Several methods based on Bayesian inference have been developed to tackle them (Besag, 1974; Clayton and Kaldor, 1987; Besag *et al.*, 1991; Cressie, 1993; Bernardinelli *et al.*, 1995; Besag and Kooperberg, 1995; Best *et al.*, 1999; Lawson *et al.*, 1999; Elliott *et al.*, 2000; Spiegelhalter *et al.*, 2002).

The aim of this work is to analyse mortality data in Piedmont in the period 1980–2000 for two common neoplasms, lung and breast, and for two rare ones, pleura and soft tissue sarcoma (STS). Of these, two were expected to exhibit strong spatial clustering (lung and pleural cancer) while the geographical distribution of the other two was more difficult to predict.

Lung cancer in men and breast cancer in women are the two most common neoplasms in Italy. In the Italian areas served by a cancer registry, the age-standardized incidence rates (world standard) were 61.1 and 71.3/100 000 in 1993–1998, respectively. Lung cancer incidence rate in women was 10.5/100 000. Pleural cancer and STS are, in contrast, rare neoplasms, with incidence rates 1.5 and 2.2/100 000 in men, respectively, and 0.5 and 1.7/100 000 in women (Zanetti *et al.*, 2002). Further, while lung and pleural cancer have well recognized risk factors (namely, cigarette smoking and asbestos exposure), breast cancer and STSs have no single strong risk factors. The main environmental risk factors for breast cancer are reproductive behaviour and hormonal pattern. Exposure

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Fig. 1

Location of Piedmont, Italy.

to dioxin-contaminated chlorophenoxyacetic acid in herbicides and chlorophenols is a possible risk factor of STSs (Adami *et al.*, 2002).

Piedmont is a region situated in north-west Italy, which covers an area of 25 399 km^2 and comprises 1206 municipalities (Fig. 1). The average annual population in 1980–2000 was 4 349 411 inhabitants. In Italy, municipalities are the smallest administrative units for which routine disease data are available, and in Piedmont they range from small rural or mountain villages to the large urban area of Turin.

A fully Bayesian approach is used in the present work to analyse mortality in Piedmont municipalities in 1980–2000 for lung and pleural cancer and STSs in both sexes, and female breast cancer. The method is aimed at producing maps as clean as possible from random noise and artefacts of population variation so that the 'true' underlying distribution of the four neoplasms of interest can be assessed.

Materials and methods

Data

Data have been extracted from the Mortality Data Bank of Piedmont (Dalmasso *et al.*, 2004), based on the Italian Institute of Statistics Census of 1981, 1991 and 2001, and the Dynamic Demographic Data Bank of Piedmont, which provides annual updates on the population residing in Piedmont since 1991 (http://www.regione.piemonte.it/stat/bdde/).

The causes of death considered are neoplasms of the lung (ICD IX 162; 44 169 deaths in men and 8397 in women during the 21 years covered by the study), breast in women (ICD IX 174; 21 623 deaths), pleura (ICD IX 163; 1503 deaths in men and 988 in women) and soft tissue sarcomas (ICD IX 171; 399 deaths in men and 399 in women).

The population is heterogeneously distributed in the 1206 municipalities of Piedmont. In the study period the smallest village and Turin had average annual populations of 39 and 989 663 inhabitants, respectively; 10% of municipalities had fewer than 250, 50% fewer than 1000 and 90% fewer than 5000 inhabitants. Besides Turin, which, with its surroundings, represents the only real urban area of Piedmont, only another town (Novara) reached 100 000 inhabitants (Table 1).

Estimation of mortality risk

The study region is divided into n contiguous areas (1206 municipalities) labeled $i = 1,\ldots n,$. Let $\mathbf{y} = (y_1,\ldots y_n)$ denote the number of deaths from the disease of interest during the period of observation. Expected number of deaths $\mathbf{e} = (e_1,\ldots e_n)$ is supposed to be constant during periods of 4 years and is calculated by applying the overall sex-, age- and period-specific death rates to the population at risk in each area. Independently, in each area i the number of deaths y_i follows a Poisson distribution with mean $e_i r_i$, where $\mathbf{r} = (r_1,\ldots r_n)$ are the unknown area-specific relative risks of mortality. These are estimated by the standardized mortality ratios (SMRs), calculated in each area i as the ratio between the number of observed and expected deaths: $SMR_i = y_i/e_i$. SMR standard errors are inversely dependent on the number expected: $s_i = \sqrt{y_i}/e_i$ (Breslow and Day, 1987). Thus, the most extreme SMRs occur in small population areas and are based only on a few cases, while the most extreme P values associated to the SMRs simply identify areas with large populations. Instability of estimates is a relevant problem in studies on rare diseases or small areas, making the interpretation of SMR maps difficult and even misleading (see, for example, Clayton and Kaldor, 1987). The relative risk of death was estimated separately for men and women in every municipality through a Bayesian approach. This combines two types of information: the observed deaths in each area described by the Poisson likelihood $[\mathbf{y}|\mathbf{r}]$, and some information on the relative risks summarized by their prior distribution $[\mathbf{r}]$, which reflects general beliefs about their variation in the region. Bayesian inference about the unknown relative risks $\mathbf{r}$ is based on the marginal posterior distribution

Table 1 Distribution of the average annual population in the 1206 municipalities and average annual population of the major towns of Piedmont between 1980 and 2000

Number of municipalities	Average annual population
627	<1000
456	1000–5000
93	5000–20 000
23	20 000–50 000
5	50 000–100 000
2	100 000–1 000 000
Total: 1206	
Percentile	**Average annual population**
0	39
0.10	243
0.25	450
0.50	950
0.75	2128
0.90	5101
1	989 663
Town	**Average annual population**
Verbania	31 053
Casale Monferrato	39 293
Biella	49 647
Vercelli	49 893
Cuneo	55 442
Asti	74 671
Alessandria	93 342
Novara	101 909
Turin	989 663

$[\mathbf{r}|\mathbf{y}] \propto [\mathbf{y}|\mathbf{r}] \times [\mathbf{r}]$. A point estimate of the relative risk (Bayesian-estimated mortality relative risk, BMR) is given by a measure of location of this distribution, typically the posterior mean or median. Usually direct evaluation of these parameters through analytical or numeric integration is not possible, and Monte Carlo methods are used to draw samples from the posterior distribution (Gilks *et al.*, 1996). Monte Carlo integration was carried out using BayesX 0.9 (11 09 2002) (Brezger *et al.*, 2002).

Prior information indicates unstructured heterogeneity or local spatially structured variation of the relative risks (for example, geographically close areas may tend to have similar relative risks). An intermediate distribution proposed by Besag *et al.* (1991) assumes that the log relative risks are the sum of two independent components (random effects): $\mathbf{x} = \mathbf{u} + \mathbf{v}$, where $\mathbf{v}$ is a normal model describing the unstructured heterogeneity, and $\mathbf{u}$ is an intrinsic Gaussian auto-regression representing local spatially structured variation. This approach overcomes the problem of overdispersion of standard SMRs, providing smooth estimates which preserve the most reliable data based on areas with sufficiently large populations.

For every cause of deaths considered, the presence of extra-Poisson variation was evaluated through an appropriate statistical test (Biggeri *et al.*, 2000), and found statistically significant ($P < 0.001$) in both sexes for all neoplasms except for STSs.

Relevant risk factor exposure

No information was available on tobacco smoking and reproductive factors at the municipality level. It is known, however, that in the past smoking was more common and average parity was lower in urban than in rural areas (ISTAT, 1986).

With reference to asbestos exposure, in the alpine valleys in the west of the region there are areas where asbestos-containing rocks are naturally surfacing (Mirabelli and Cadum, 2002). In one of these valleys was located the Italian asbestos mine of Balangero (Piolatto *et al.*, 1990). More important, the industrial area around Turin has had several asbestos manufacturing activities. Furthermore, an important factory of asbestos cement had been operating from 1907 to 1985 in Casale Monferrato (Magnani *et al.*, 1991, 1995, 2001).

Rice has been grown extensively in the east of the region, around Vercelli and Novara. When manual rice weeding ceased, soon after World War II, extensive use of phenoxy herbicides started, making these high-exposure areas (Vineis *et al.*, 1987; Donna *et al.*, 1989; Gambini *et al.*, 1997). There are no single major sources of dioxin emissions in Piedmont. However, sources of dioxin-contaminated emissions are common: steel mills, iron foundries and, no less important, motor vehicle traffic.

Results

Figure 2 shows SMR and BMR maps. Along the 21 years covered by the study, only 21 (1.7%) and 92 (7.6%) municipalities recorded no deaths from lung cancer in men and breast cancer in women, respectively. No deaths from lung cancer in women were recorded in 279 municipalities (23.1%). No deaths from pleural cancer and STS were recorded in 795 (65.9%) and 1015 (84.2%) in men, and 908 (75.3%) and 1008 (83.6%) in women, respectively. Such large zero counts make SMR estimates unstable.

Lung cancer in men showed a strong north-east–south-west gradient, already visible in the SMR map and much more evident in the BMR one. The metropolitan area of Turin did not emerge as a high-risk area. For women, the SMR map showed an unstructured, fragmentary picture of difficult interpretation. In contrast, the BMR map showed distinctively identifiable high-risk patterns around urban areas (mainly Turin, but also other main towns such as Alessandria, Novara, Biella and Verbania).

The SMR for breast cancer mortality in women showed no clear patterns, with high and low-risk areas being scattered across the region, likely reflecting random variation. Smoothing made the risk picture uniform with only a slightly higher mortality in the central band of the region, mainly in the mountainous north-west areas.

Pleural cancer in men showed five well-defined spatial aggregations: a small mountain area in the west (Fig. 2: 1M), a circular cluster around Turin (2M), a smaller cluster around Biella (3M), a large elongated area in the south-east (around Casale Monferrato, 4M) and a small area in the centre of the region, north of Cuneo (5M). The pattern was detectable in both SMR and BMR maps, but more clearly identifiable in the latter. A similar picture characterized pleural cancer in women, although spatial aggregations did not entirely coincide with those of men: the mountain cluster in the west (1W) was maintained (although less evident), and so the ones around Turin (2W), Biella (3W, more pronounced), and Casale Monferrato (4W); the spatial aggregation close to Cuneo is not present, but there is another one in a mountainous area at the southern boundaries (5W); finally, a small cluster appears around Verbania (6W). Like for men, the distribution was already detectable in the SMR but more apparent in the BMR map.

For STS, the SMR maps for men (not shown) and women were very similar, dominated by scattered black and white areas, showing how estimates for rare diseases are sensitive to random fluctuations. The BMR maps substantially reduced the range of variation, flattening the whole spatial distribution towards the null: risk estimates varied between 0.94 and 1.09 for men (not shown) and between 0.97 and 1.04 for women, respectively.

The range of variation of mortality indicators is reported in each map. Large ranges of variation in SMRs indicate conspicuous risk differences between areas (when counts are large and estimates robust), or high instability of estimates (when counts are small and estimates unreliable). In the latter case, the smoothing algorithm reduces the range of variation of risk by removing some within-area variability. Maximum shrinkage was observed for STS in women, and minimum for pleural cancer in men (ratio between standard deviations of SMR and BMR distributions: 447.6 and 1.6, respectively).

Variation analysis of the posterior distributions of the two random effects of the model ($\mathbf{v}$ representing heterogeneity, and $\mathbf{u}$ clustering) allows the detection of spatially structured patterns. Evidence of spatial aggregation emerged for lung cancer in men and pleural cancer in both sexes: the relative weights of heterogeneity versus clustering were 1 : 3 for lung, 1 : 11 and 1 : 14 for pleura in men and women, respectively. The other neoplasms appeared uniformly distributed. The number of significant BMR estimates at credibility levels of 80 and 95% is given in Table 2. No significant estimates were obtained for STS, reflecting data sparseness. The largest number was for lung cancer in men.

Discussion

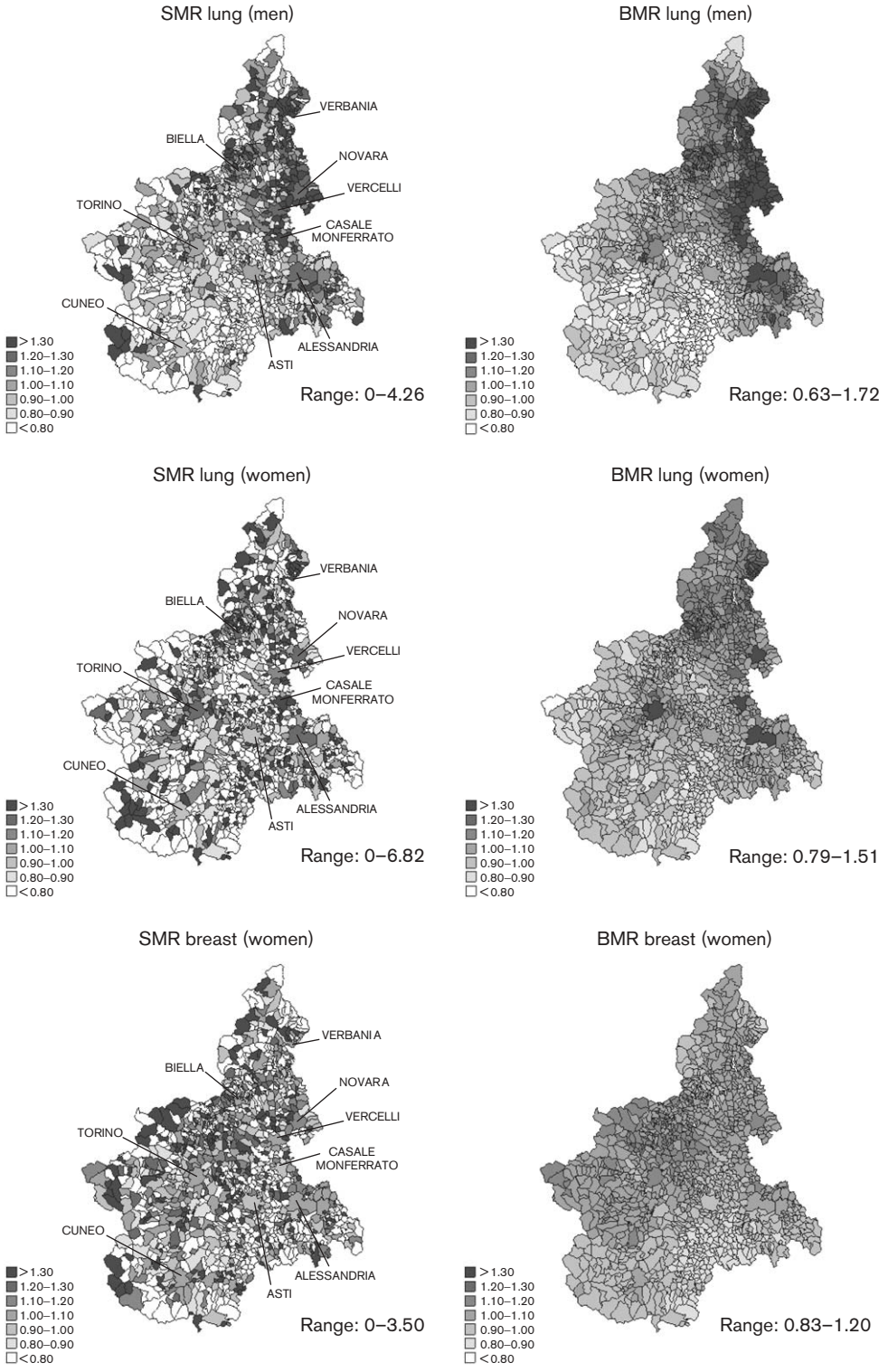
The present analysis of spatial variation of mortality from selected neoplasms in Piedmont shows a clear advantage of Bayesian methods as compared to standard SMRs. BMRs, in fact, were able to identify patterns of mortality for lung cancer in men and women which were not identifiable using SMRs. They also indicated that the apparent variation in mortality from female breast cancer and STS are attributable to random fluctuations, and made more clearly identifiable the clusters of pleural cancer mortality around asbestos polluted areas.

A number of possible biases have to be considered in interpreting our results. The statistical power of the spatial analyses carried out is limited, especially for diseases as rare as STSs (798 deaths in 91 337 633 person-years of observation): this is reflected by the absence or the small number of statistically significant Bayesian-estimated mortality risks. It is also plausible that some heterogeneity in the accuracy of death certificates may have occurred, both in space (across Piedmont) and in time (along the period of the study), causing differential and non-differential misclassification of cases. This is especially true for the older age groups, where diagnoses are generally less accurate. Temporal heterogeneity has also characterized the composition of the region population, and major changes such as important migratory fluxes might have occurred at different times in different geographical areas.

With regard to specific problems related to the methodology used, the main difficulty of a fully Bayesian approach is the choice of an appropriate prior for the relative risks. This has been shown to have a large influence on the posterior estimates of parameters' variance components. However, if the main objective of the study is to obtain area-specific estimates of risk, such prior sensitivity may be of little importance (Mollié, 2000). Imprecision in risk estimates is more likely to arise in areas close to the boundaries of the region, where the number of neighbouring areas providing information on the spatial pattern is smaller. This problem may be particularly serious for irregularly shaped regions like Piedmont, and should therefore be kept in mind when maps are interpreted.

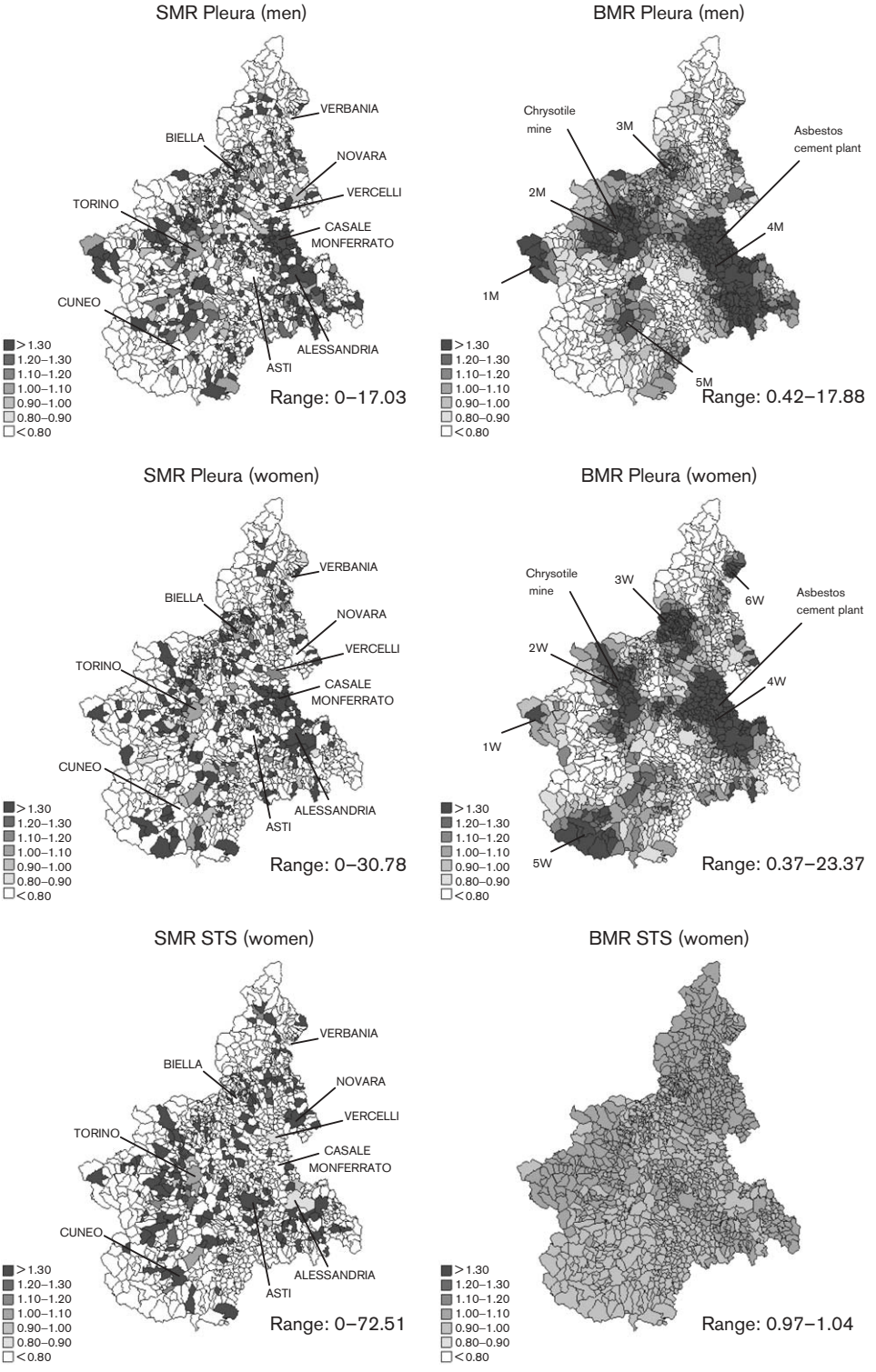
The primary goal of smoothing algorithms is to remove background noise from the data so that the underlying spatial pattern can emerge. This is a challenging task in Piedmont both because it is a complex and heterogeneous region from the point of view of geographic, demographic and social characteristics, and because mortality data on rare diseases such as STS and pleural cancer are sparse. On the other hand, one of the most attractive features of the fully Bayesian hierarchical–spatial model, including both fixed and random effects, is

Fig. 2



Spatial variation in mortality from cancer of the lung, breast, pleura and soft tissue sarcoma (STS) in 1206 municipalities, Piedmont, Italy, 1980–2000. Maps are based on the standardized mortality ratio (SMR) and the Bayesian-estimated mortality risk (BMR).

Fig. 2 ***(Continued)***



that parameters can be estimated also for very small areas, for which data are usually too sparse to employ simple fixed effects approaches. By 'borrowing' information from neighbouring areas, risk estimates in small areas become more stable: within-area variability is reduced while between-area variability is enhanced (Pickle, 2002). This allows us to overcome the problem of overdispersion and unreliability of the classical SMRs, preserving the ones

Table 2 Bayesian-estimated mortality ratios (BMRs) of municipalities in Piedmont between 1980 and 2000: number of towns (out of 1206) in which the BMR was significantly different from 1, at credibility levels of 80 and 95%

Type of cancer	Statistically significant estimates (BMR) at two credibility levels	
	80%	95%
Lung		
Men	525	261
Women	46	8
Breast		
Women	171	16
Pleura		
Men	102	51
Women	75	39
Soft tissue sarcoma		
Men	0	0
Women	0	0

based on large populations and smoothing those based on sparse data (Lawson *et al.*, 1999; Elliott *et al.*, 2000).

The most striking feature of lung cancer mortality in men is that the metropolitan area of Turin did not emerge as a high-risk area. Case–control studies conducted in Turin (Simonato *et al.*, 2001; Richiardi *et al.*, 2004) have quantified the role of occupational exposure and tobacco smoking but the lack of geographical comparisons with the rest of the region does not help to explain this phenomenon. The absence of an urban excess can perhaps be related to the intense migratory fluxes which occurred from the end of the 1950s until the end of the 1970s from southern Italy to Piedmont, particularly to the urban industrialized areas. A substantially lower lung cancer mortality, due to lower smoking prevalence in the past, and perhaps to occupation and some aspect of diet (Franceschi *et al.*, 1995), was observed in southern Italian populations (Facchini *et al.*, 1985) as well as in migrant populations (Vigotti *et al.*, 1988). The distinct north-east–south-west gradient of lung cancer mortality in men is part of a wider east–west gradient affecting all northern Italy (Merletti *et al.*, 1999), possibly reflecting different smoking patterns in the past (ISTAT, 1986). In women, instead, lung cancer mortality is higher in urban areas: Turin and most of the other major towns emerge as high-risk areas, besides Cuneo and Asti, where the main economic activities have been linked to agriculture. The effects of urban lifestyle are thus more evident in women than in men, both because of smoking (almost absent in the past in women living in the countryside) and, perhaps, because of a smaller number of female migrants moving north (ISTAT, 1986). The excess in Casale Monferrato instead is likely to be due to the very high asbestos exposure (Magnani *et al.*, 1993; Magnani and Leporati, 1998; Mollo *et al.*, 2002). Although after smoking, asbestos is the most important cause of lung cancer, the distinctive geographical pattern observed for pleural cancer is not seen in lung cancer, due to the overwhelming importance of tobacco at the population level. The proportion of lung cancer attributable to asbestos exposure in men in Piedmont was around 4%, according to the most recent estimates (Martuzzi *et al.*, 1998).

The higher breast cancer rates commonly seen in urban areas are related to reproductive factors, namely, lower parity in urban areas, mainly in the first half of the past century (ISTAT, 1986; Barbone *et al.*, 1996). However, women migrating from the south had maintained higher parity, and also lower baseline breast cancer risk, at least in the first generation (Vigotti *et al.*, 1988; Barbone *et al.*, 1996; Parkin, 2004). This may partly or largely explain the absence of urban–rural differences in female breast cancer risk in Piedmont. The somewhat higher risk in the mountains in the west of the region could be an artefact (boundary effect).

Mortality from pleural cancer appears to reflect available information on asbestos exposure (Adami *et al.*, 2002). The most striking mortality excess appears for both men and women in the area around Casale Monferrato (Fig. 2: 4M and 4W), where the largest Italian asbestos cement plant was active for decades (Magnani *et al.*, 1991, 1993, 2001). The clusters stretch south, in the surroundings of Alessandria, where occupational exposure to asbestos was mainly due to the chemical industry. For men, the cluster (4M) is more elongated and, without solution of continuity, reaches areas where it was common for workers to commute to and from Genoa to work in shipyards and steel mills. The high-risk areas around Turin (2M and 2W) are due to a wide range of asbestos manufacturers (mainly textile (Pira *et al.*, 2005), and the production of brakes and clutches) and industrial use of asbestos products. Although these activities account for the majority of cases for both men and women in these areas, the clusters reach the Lanzo Valley, where the biggest chrysotile mine in Europe ('Amiantifera' of Balangero, Fig. 2) was active until 1991 (Piolatto *et al.*, 1990). Manufacturing activities, mainly in the textile sector, characterize asbestos exposure in the surroundings of Biella (3M and 3W). Around Verbania (6W), mortality appears to be higher only in women: some asbestos-related industries operated in the area, two of which (a small cement plant and a foundry) employed mainly men, and a manufacturer of synthetic-fibre textiles, where women were largely employed. In men, the excess north of Cuneo (5M) can be attributed to the local construction of railway carriages. In women, the high-risk cluster is shifted south (5W), in a mountainous region where there is no obvious asbestos exposure: it should be noted that this is based on a limited number of deaths (13) and the maximum BMR is 1.93 (while the maximum BMR in 4W is 23.37 in Casale Monferrato, based on 162 deaths). Nevertheless, this spatial aggregation may

deserve attention. The presence of tremolite in soil in the Susa and Chisone Valleys (Western Alps) is a plausible explanation for the most western clusters (1M and 1W) identifiable from the BMR map (Mirabelli and Cadum, 2002), again based on a small number of deaths (six among men and two among women).

High STS risk was postulated in the rice-growing areas around Novara and Vercelli (north-east), characterized by high level of exposure to herbicides. Phenoxy herbicides and chlorophenols, in fact, are suspected risk factors for STSs (Adami *et al.*, 2002), and increased risk was found in a seasonal female working population employed in manual rice weeding in that area (Vineis *et al.*, 1987). However, the epidemiological evidence is still inconsistent. A cohort study of rice growers conducted in the same area found only a weak association with STS mortality (Gambini *et al.*, 1997). The spatial distribution of STS mortality was similar in both sexes and the choice of showing here only maps for women was due to the fact that exposure to herbicides was higher for women working in rice cultivars as rice weeders. The emerging pattern, however, is uniform, confirming the absence of major geographic clusters for this rare disease. In Piedmont there were very few incinerators, which are the major industrial source of exposure to dioxins, and no excess STS mortality has been observed around them. Many other industrial plants that emit dioxins were scattered across the whole region; the same is true for the many motorways and roads. Thus the absence of disease clustering may be due to the fact that relevant pollution sources were widespread. However, the interpretation of the risk estimates from the application of Bayesian methods to such sparse data remains open to discussion.

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