Pergamon

European Journal of Cancer Vol. 31A, No. 2, pp. 193–197, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(94)00474-9

The Mortality Rate of the Province of Birth as a Risk Indicator for Lung and Stomach Cancer Mortality Among Genoa Residents Born in Other Italian Provinces

M. Ceppi, M. Vercelli, A. Decarli and R. Puntoni

This study analyses the relationship between migration and mortality for lung and stomach cancer, these diseases being those considered susceptible to changes in environmental conditions and individual habits that usually follow migration. Mortality rate of the province of birth was used as the index of risk related to migration. Data were analysed using the Poisson regression model for grouped data. Results indicate that migration determines modifications in the mortality rates of the migrant populations for the diseases under study. For lung cancer, the analysis showed a greater risk for migrants originating from areas with high rates and that migrants had a reduced risk in comparison with natives of Genoa. With regard to stomach cancer, the study revealed that migrants originating from high risk areas had higher relative risks than the Genoa natives, even if these were lower than expected when compared to the risks of the populations in the regions from which the migrants originated.

Key words: cancer, migration, Poisson regression
Eur J Cancer, Vol. 31A, No. 2, pp. 193–197, 1995

INTRODUCTION

NUMEROUS epidemiological studies have documented stomach and lung cancer mortality in Italian emigrants now resident in other countries [1–11]. However, internal Italian migration also seems to provide a viable source for insight into the relationship between cancer risk and migration, particularly in light of the internal, predominantly northward migratory flow of nearly 1 450 000 persons-year between 1951 and 1965 [12], and the great variability in the geographic distribution of mortality rates in Italy.

Mortality studies among southern Italians who emigrated to the northern regions show death rates between those observed in southern (the lowest) and northern (the highest) Italian regions [13–15]. Incidence data from the Cancer Registry of the Province of Varese (northern Italy) revealed reduced risks for lung and stomach cancers among people born in southern regions [16]. A case control study on the effect of birthplace on cancer risk conducted in the province of Florence showed that men born in southern Italy had a significantly lower risk than men born in northern regions [17].

All of these studies used a geographical index to classify the migrants with respect to their original mortality risk for some cause of death. Since the large geographical areas, i.e. northwestern, northeastern, central and southern Italy, are not intrinsically homogeneous with regard to the cancer risks under investigation [18], the mortality rate of the province of birth was used in this work as the index of risk related to migration. This investigation concerns residents in the town of Genoa born elsewhere in Italy dying from either lung cancer (ICD 162, males only) or stomach cancer (ICD 151, both sexes) during the period 1984–1987, these cancers normally being considered susceptible to changes in environmental conditions and to individual habits that usually follow migration.

MATERIALS AND METHODS

Data for each migrant (date and province of birth, sex, date of registration in Genoa, date of death) were provided by municipal records of the City of Genoa. The analysis concerned the mortality rates of the provinces of birth as well as the risk factor of interest, age at migration and length of residence as possible confounders. All variables were categorised according to their frequency distribution quartiles. Data were analysed using the Poisson regression method for grouped data, incorporating external standard rates in the multiplicative model [19]. The model is

$$\log (Y_{ij}) = \log (E_j) + \mu + \beta_i X_{ij} + e_{ij}$$

where Y_{ij} are the observed deaths in the j age and sex stratum and with i explanatory variables; E_j are the baseline expected deaths, for age and sex stratum, according to mortality rates of

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Revised 24 Oct. 1994, accepted 1 Nov. 1994.
This work was conducted within the framework of the CNR (Italian National Research Council). Applied project 'Clinical Applications on Oncological Research' (Contract No. 94.01119. PF39).

EJC 31:2-0

Genoa natives; X_{ij} is the vector of the explanatory variables in the model; exp (μ) is the Standardised Mortality Ratio (SMR) for the migrant reference group ($X_{ij} = 0$) versus Genoa natives and is reported in the first line of the RR2 column of Tables 3 and 4; exp (β_i) are the relative risk estimates for other migrants versus the migrant reference group: these are shown in the RR1 column of Tables 3 and 4; e_{ij} are the random errors. If the effect of risk factors is constant over the age and sex strata, the regression coefficients β_i show how the log (SMR) varies according to exposure levels. Thus, combining exp (μ) with exp (β_i) we obtained the SMR for all migrants versus Genoa natives (RR2 column in Tables 3 and 4). To evaluate the statistical significance of the variables in the models and to test the hypothesis of homogeneity between strata, we analysed the scaled deviance [20] of each model. This statistic expresses the variability of the dependent variable unexplained by the model and asymptotically has a chi-square distribution with n-p-1 degrees of freedom where n is the number of cells with non-zero person-years and p is the number of parameters estimated by the model. A scaled deviance value close to its degrees of freedom provides a good description of the data. The difference between the scaled deviances of two hierarchical models, e.g. the first with k parameters and the second with $k + p$ parameters, also follows a chi-square distribution with p degrees of freedom; this difference is the Log-likelihood Ratio Test Statistic (LRTS) that compares the two models. If the LRTS exceeds the critical value of the chi-square distribution at fixed α and with p degrees of freedom, the null hypothesis of no effect of p parameters can be rejected. The data have been fitted to the models using the GLIM statistical package [21]. To verify the possible changes in mortality rates after migration, we estimated the death risk of populations from which migrants originated relative to Genoa natives, by computing the ratio of the directly standardised rates of the two cohorts, using Italy 1981 as the standard population [19]. These estimates are reported in the RR3 column of Tables 3 and 4.

RESULTS

Figure 1 illustrates the subdivision of Italy into its four classical geographical areas, and Table 1 reports the population resident in Genoa from these respective areas of birth. The

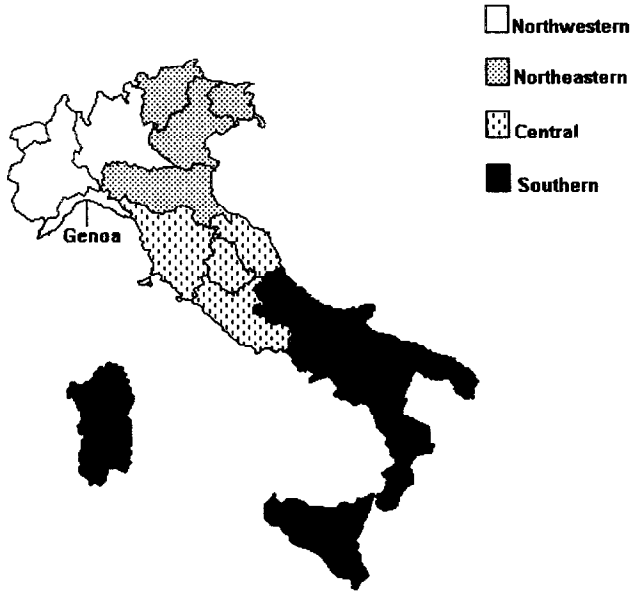

Figure 1. Italy subdivided into its principal geographical areas.

Table 1. Structure of the population resident in the Municipality of Genoa by area of birth in Italy (at 30 June 1986)

Zone of birth	Males	(%)	Females	(%)
Town of Genoa ("native")	205 645	63.4	215 064	59.7
Northwestern	35 998	11.1	52 649	14.6
Northeastern	5 035	1.6	8 230	2.3
Central	37 900	11.7	45 832	12.7
Southern	39 517	12.2	38 518	10.7
Total	324 095		360 293	

Table 2. Mortality for lung and stomach cancer among residents in the Municipality of Genoa (period 1984–87)

Site of cancer	Natives	(%)*	Migrants	(%)*
Lung (males)	832	32.1	871	30.1
Stomach (both sexes)	278	12.6	473	18.8

* Percentages calculated on overall cancer deaths.

migratory flow from southern regions is more recent (chiefly after World War II) than others from elsewhere in Italy (e.g. the northeastern migratory flow which occurred prior to World War II). Table 2 shows the number of deaths from lung and stomach cancer for the period 1984–1987 among natives and migrants.

Lung cancer

The mortality rate for lung cancer of Genoa male natives is among the highest in Italy (95.68 per 100 000 inhabitants). Figure 2 shows the distribution of SMRs for lung cancer (males)

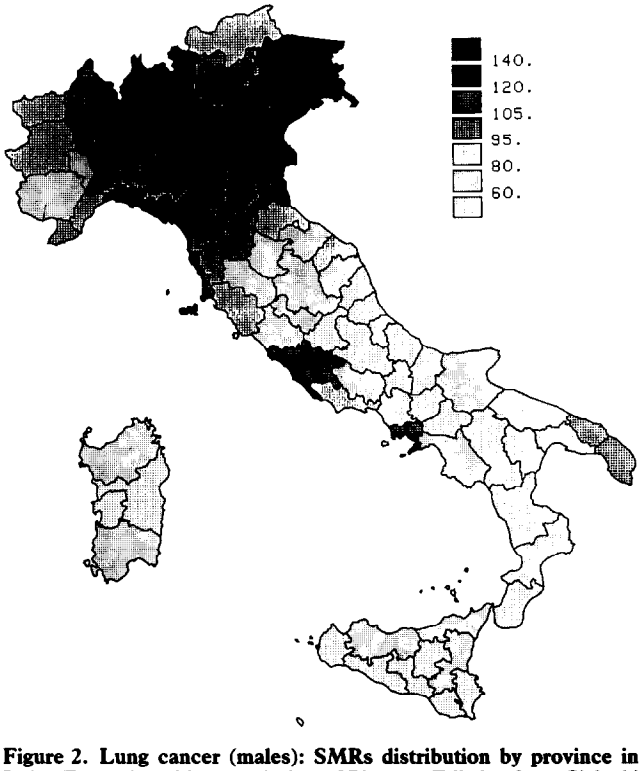

Figure 2. Lung cancer (males): SMRs distribution by province in Italy. (Reproduced by permission of Pitagora Editrice from Cislaghi C, Decarli A, La Vecchia C, Laverda N, Mezzanotte G, Smans M. *Dati indicatori e mappe di mortalitá tumorale, Italia 1975–1977.* 1986.)

Table 3. Lung cancer (males): relative risk estimates for the variable province of birth mortality rate adjusted for the effect of age at migration and length of residence

Province of birth mortality rate	RR1 (CI 95%)	RR2 (CI 95%)	RR3 (CI 95%)
<37.3	1.00	0.57	0.31
	–	(0.36–0.90)	(0.29–0.33)
37.3–54.4	1.27	0.73	0.46
	(0.98–1.66)	(0.47–1.12)	(0.43–0.49)
54.5–73.9	1.26	0.72	0.66
	(0.97–1.63)	(0.47–1.11)	(0.61–0.71)
>73.9	1.36	0.78	0.88
	(1.05–1.76)	(0.51–1.19)	(0.82–0.94)

Model deviance 108.9 with 138 df.

RR1, relative risk estimates of other migrants versus migrants reference level; RR2, SMR of all migrants versus Genoa natives; RR3, relative risk estimates of the populations from which migrants originate versus Genoa natives; CI 95%, Confidence intervals of the estimates.

by province in Italy. The highest risk provinces are located in geographically different areas (see Figure 1), especially in northern Italy. Central and southern Italy also have areas of high SMR.

Data analysis revealed no violations of the assumption of homogeneity between strata. Mortality rate of province of birth is the only variable that determined a significant decrease of deviance (9.48 with 3 df). Since model deviance is close to its degrees of freedom (108.9 with 138 df) and the addition of second order interaction factors did not significantly improve the fit of the model to the data, we report the estimates from the model based on the main effects of risk factor (Table 3). The analysis of RR1 shows a greater risk for migrants coming from areas with high rates. If we consider RR2 and RR3, we see that migrants have a reduced risk for lung cancer in comparison to Genoa natives, although this reduction appears to be of relatively minor importance for migrants whose original populations have low risk. However, the RR2 is generally greater than the RR3.

Stomach cancer

Stomach cancer rates among Genoa natives are very low (14.32 per 100 000 inhabitants for both sexes). Figure 3a and b show the distribution of SMRs for stomach cancer (males and females, respectively) by province in Italy. This distribution is quite similar for both sexes, with higher risk areas existing both in some northern provinces (where low risk areas are also present) and in most central provinces. The lowest SMRs are found in southern Italy.

Data reveal that mortality rate of province of birth is the only variable accounting for a strong decrease of deviance (30.1 with 3 df). Table 4 reports relative risk estimates for this variable adjusted for the effects of age at migration and length of residence. Model deviance (120.3 with 138 df) indicates a good fit of the model to the data. Migrants coming from high risk areas present higher relative risks, even if these are lower than expected considering the migrants' geographic origin.

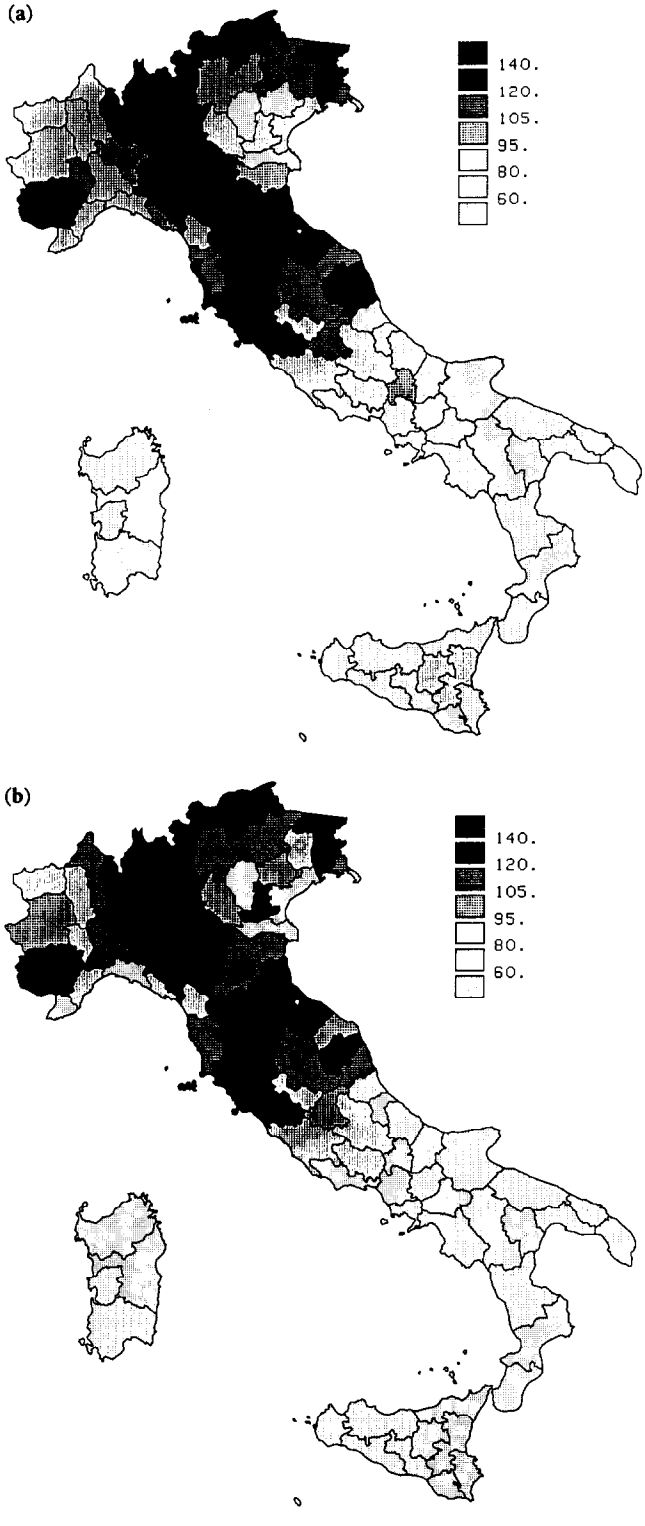

Figure 3. (a) Stomach cancer (males): SMRs distribution by province in Italy; (b) stomach cancer (females): SMRs distribution by province in Italy. (Reproduced by permission of Pitagora Editrice from Cislaghi C, Decarli A, La Vecchia C, Laverda N, Mezzanotte G, Smans M. *Dati indicatori e mappe di mortalitá tumorale, Italia 1975–1977*. 1986.)

DISCUSSION

Both analyses show that mortality rate of province of birth accounts for a significant part of the total variance of the data, thus prompting consideration of this variable as the most important to explain the risk related to migration for the cancers under study.

From an epidemiological and aetiological standpoint, our data seem to confirm the trend for an increase in lung cancer rates after migration to a high risk area [22], this tendency being

Table 4. Stomach cancer (both sexes): relative risk estimates for the variable province of birth mortality rate adjusted for the effect of age at migration and length of residence

Province of birth mortality rate		RR1 CI 95%	RR2 CI 95%	RR3 CI 95%
Males	Females	1.00	0.83	1.02
<22.3	<16.1	-	(0.51–1.34)	(0.91–1.16)
22.3–31.2	16.1–19.8	1.30	1.08	1.52
		(0.98–1.73)	(0.68–1.70)	(1.35–1.72)
31.3–45.0	19.9–28.5	1.16	0.96	2.08
		(0.87–1.54)	(0.61–1.52)	(1.85–2.35)
>45.0	>28.5	1.99	1.65	3.07
		(1.50–2.63)	(1.04–2.60)	(2.73–3.47)

Model deviance 120.3 with 138 df.
RR1, relative risk estimates of other migrants versus migrants' reference level; RR2, SMR of all migrants versus Genoa natives; RR3, relative risk estimates of the populations from which migrants originate versus Genoa natives; CI 95%, confidence intervals of the estimates.

more evident for migrants with low "original" risks. Various hypotheses may be advanced to account for this increase. First, it is well known that cigarette consumption increases with urbanisation [22], and some epidemiological studies have related urban air pollution with lung cancer mortality [23]. Moreover, it should be kept in mind that surveys conducted by DOXA [24, 25] in 1958 and 1966, which chronologically encompass the largest migratory flows from southern Italy to Genoa, reveal only a slight excess of prevalence of smokers in southern males. As regards the influence of diet on lung cancer risk, a strong negative relationship with a vegetable- and fruit-rich diet has been irrefutably confirmed [26, 27]. Other hypotheses of a positive relationship with fatty acid and cholesterol intakes have been advanced, but still require confirmation [28]. Finally, a historically greater consumption of fresh fruits and vegetables and of unsaturated fats in dietary items by southern with respect to northern Italian populations has recently been confirmed [29], and might contribute to the difference in risk.

As regards stomach cancer mortality, our observations seem to uphold the findings within the literature that reveal slow changes in the mortality rates of populations migrating from high to low risk areas, although the rates of the migrants remain higher than those of local populations [3, 4, 11, 30]. There exist at least two hypotheses to account for the effect of migration on stomach cancer risk:

(1) the change in dietary habits, i.e. the principal risk factors for this neoplasm, is only partial subsequent to migration and, consequently, stomach cancer risk undergoes only a partial reduction;
(2) dietary habits in the first years of life induce an increase of absolute risk which cannot be reversed by successive dietary changes. Existing geographical patterns of risk would thus be due mainly to irreversible initiating factors that affect the early stages of carcinogenesis.

Admittedly, our present study is limited by the lack of information about the distribution of important aetiological factors (i.e. smoking habits, diet, alcohol consumption, occupation). Nevertheless, analysis using birthplace mortality rate as index of risk related to migration gives rise to findings which are consistent with current hypotheses on the relationship between lung and stomach cancers and migration and, moreover, substantiates the use of this covariable when analysing typical ecological studies.

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Pergamon

European Journal of Cancer Vol. 31A, No. 2, pp. 197–201, 1995

0959–8049/95 $9.50+0.00

0959-8049(94)00449-8

Detection by Polymerase Chain Reaction of BCR/ABL Transcripts in Myeloproliferative Diseases at Time of Diagnosis and for Monitoring Chronic Myelogenous Leukaemia Patients After Bone Marrow Transplantation

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The Philadelphia chromosome t(9;22)(q34;q11) is a cytogenetic marker for chronic myelogenous leukaemia (CML), and is also present in some acute leukaemias. The translocation in CML gives rise to two *BCR/ABL* chimeric transcripts (b3a2 and b2a2) encoding a 210-kD tyrosine kinase protein. These leukaemia-specific transcripts can be detected easily by the reverse transcriptase polymerase chain reaction (PCR). PCR has improved the possibility of detecting minimal residual leukaemia cells in Ph-positive patients, especially after bone marrow transplantation (BMT). With PCR, we looked for *BCR/ABL* transcripts in 30 patients with CML and 4 with essential thrombocythaemia at time of diagnosis, finding a significant difference in the platelet counts of CML patients carrying b3a2 or b2a2 transcripts. The *BCR/ABL* transcript was monitored by PCR in 6 CML patients after BMT. The usefulness of PCR in clinical practice at time of diagnosis, and the biological and clinical significance of positive/negative PCR results, in patients with transplants, are discussed.

Key words: Philadelphia chromosome, BCR-ABL, fusion proteins, polymerase chain reaction, chronic leukaemia, myeloid leukaemia, essential thrombocythaemia, platelet count, bone marrow transplantation, graft versus host disease

Eur J Cancer, Vol. 31A, No. 2, pp. 197–201, 1995

INTRODUCTION

THE PHILADELPHIA chromosome (Ph), a shortened long-arm chromosome 22 [1], is present in cells of more than 95% of patients with chronic myelogenous leukaemia (CML), approximately 25% of adult acute lymphocytic leukaemia (ALL) and a few (< 5%) with acute non-lymphocytic leukaemia and paediatric ALL [2]. The Ph abnormality is due to a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11). At the molecular level, the translocation involves the *ABL* gene on chromosome 9 and the *BCR* gene on chromosome 22 [2]. The c-abl proto-oncogene product belongs to the Abelson subfamily of non-receptor protein tyrosine kinases, defined by the products of human, murine, *Drosophila ABL* gene [3] and human *ARG* gene [4]. The *BCR* gene product is a serine/threonine kinase protein [5]. The rupture of the *ABL* gene is usually located in the intron 5′ of exon II [6]. In Ph-positive CML and in approximately half of the Ph-positive ALL, the

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Revised 29 July 1994; accepted 5 Sept. 1994.