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Spatial variation in mortality risk for hematological malignancies near a petrochemical refinery: A population-based case-control study

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ABSTRACT

Introduction: The study investigated the geographic variation of mortality risk for hematological malignancies (HMs) in order to identify potential high-risk areas near an Italian petrochemical refinery.
Material and methods: A population-based case-control study was conducted and residential histories for 171 cases and 338 sex- and age-matched controls were collected. Confounding factors were obtained from interviews with consenting relatives for 109 HM deaths and 267 controls. To produce risk mortality maps, two different approaches were applied and compared. We mapped (1) adaptive kernel density relative risk estimation for case-control studies which estimates a spatial relative risk function using the ratio between cases and controls' densities, and (2) estimated odds ratios for case-control study data using Generalized Additive Models (GAMs) to smooth the effect of location, a proxy for exposure, while adjusting for confounding variables.
Results: No high-risk areas for HM mortality were identified among all subjects (men and women combined), by applying both approaches. Using the adaptive KDE approach, we found a significant increase in death risk only among women in a large area 2–6 km southeast of the refinery and the application of GAMs also identified a similarly-located significant high-risk area among women only (global p-value < 0.025). Potential confounding risk factors we considered in the GAM did not alter the results.
Conclusion: Both approaches identified a high-risk area close to the refinery among women only. Those spatial methods are useful tools for public policy management to determine priority areas for intervention. Our findings suggest several directions for further research in order to identify other potential environmental exposures that may be assessed in forthcoming studies based on detailed exposure modeling.

1. Introduction

Worldwide, on an annual basis, more than 850,000 patients are diagnosed with hematological malignancies (HMs) (Ferlay et al., 2010). HMs are a heterogeneous group of diseases classified according to international classification of disease, IX revision (World Health Organization, 1977) that includes Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, and leukemia, and account for 6–8%, 40–44%, 15–16%, and 34–36% of total incident HMs in developed countries, respectively (GLOBOCAN, 2012). Little is known about the etiological mechanism of leukemias and lymphoma. Genetics factors, infectious disease, ionizing radiation, and smoking have been described in relation to leukemias (Rodriguez-Abreu et al., 2007). Emissions from petroleum refineries are considered one of the putative environmental risk factors in hematological cancers investigated. Those emissions include substances such as benzene, recognized as a carcinogen by the International Agency for Research on Cancer (IARC, 1987). Effects modulated by benzene-induced oxidative stress, aryl hydrocarbon receptor dysregulation and reduced immunosurveillance may lead to the generation of leukemic stem cells and subsequent clonal evolution to leukemia (McHale et al., 2012).

Effects of occupational benzene exposure and of emissions from refineries on cancer have been widely investigated with different results both in terms of occurrence and mortality. Some

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studies have showed evidence that occupational exposure to benzene leads to an increased risk for acute myeloid leukemia (Schnatter et al., 2005), chronic lymphocytic leukemia (Khalade et al., 2010) and non-Hodgkin lymphoma (Steinmaus et al., 2008). Evidence of an association between emissions from refineries and HMs is weaker. A recent study in Sweden did not show any excess of incidence for leukemia or lymphoma (Axelsson et al., 2010). In Italy a case-control study showed a moderate, but not significant, risk of mortality for lymphohematopoietic neoplasms among residents living within 2 km from a petrochemical plant (Belli et al., 2004). In another case-control study, authors showed a 90% increased NHL risk of incidence associated with 10 years of proximity to petroleum refineries (OR=1.9, 95% C.I: 1.0–3.6) (De Roos et al., 2010).

Recently, in a population-based case-control study, we found a significant excess of HM-related death risk for women and participants who spent most of their time at their home resident in an area surrounding an Italian petrochemical refinery (Micheli et al., 2014). In that study, we combined distances and residency duration as a proxy of residential exposure for a long period of life before the event to analyze HMs death risk using conditional logistic regression. Participants who spent most of their time at home were identified using information on occupational status from interviews with consenting relatives. However, we were not able to specifically identify those areas (possibly influenced by the prevalent winds) where the risk was the highest.

In this paper, we conducted spatial analyses in order to detect geographic variation of risk for HMs mortality and to identify potential high-risk areas near the refinery. To reach the aim, we applied and compared two methods: (1) smoothing of location using Generalized Additive Models (GAMs) to produce risk maps adjusted for potential confounders (Vieira et al., 2002; Webster et al., 2006) and (2) adaptive kernel density relative risk estimation (KDE) (Davies and Hazelton, 2010).

2. Material and methods

Details on the study area and participants in this spatial analysis are described in a previous paper (Micheli et al., 2014).

2.1. Study area and population

Briefly, the petrochemical refinery is located in the Municipality of Falconara Marittima (Province of Ancona, Region of the Marches, Central Italy) and has been operating since the early 1950s. A study funded by the Region of the Marches in 2003 found that mortality from leukemia and other HMs increased (non-significantly) from 1984 to 2000 in the municipality of Falconara and the adjacent municipality of Chiaravalle, in contrast to decreased or stable HM mortality in the Province of Ancona and Region of the Marches (Baili et al., 2007). However, monitoring data during that time period showed that known carcinogens, were present in the atmosphere, and with support from the Region of the Marches (Giunta Regionale, 2004), an additional study was initiated to investigate mortality risk for leukemia, non-Hodgkin lymphoma, and other HMs (Micheli et al., 2014).

The study area included three municipalities (Falconara, Chiaravalle, Montemarciano) near the refinery with a geographic extent of approximately 65 km^2 (Fig. 1). Only cancer mortality can be investigated and not incidence because no population-based cancer registry is available in this region. Deaths for HM occurring between January 1, 1994 and December 31, 2003 were identified from death certificates, provided by the Italian National Institute of Statistics (ISTAT). A total of 177 deaths for HM (89 males and 88 females) were identified (Micheli et al., 2014).

For each case two controls were sampled from municipal records using the risk set sampling method (Rothman et al., 2008). Eligible controls (risk set) were identified among residents in the study area with the same sex and age ($\pm$2.5 years) and alive at the date of case death (index date).

2.2. Data collection

A complete residential history was traced for all 177 cases, and for 349 matched controls. The address with the longest residency duration (main residence) over a 15-year interval (time window) was used in the analysis. The time window was defined as the period preceding the index date by no more than 20 years to take into account latency between exposure and cancer mortality observed for workers exposed to benzene, and excluding the 5 years prior to the index date for persons $\geq$25 years (or 2 years prior to cancer death for 4 cases and index data for 8 controls under 25

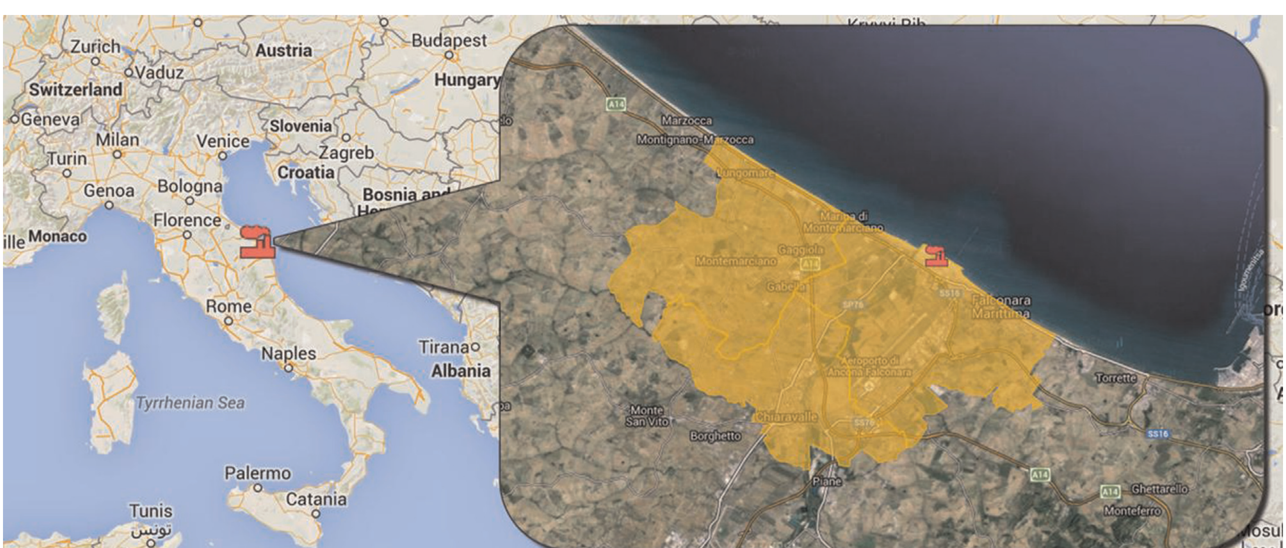

Fig. 1. Map showing the location of the refinery (in red) and the study area in yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)