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Environmental exposure to pesticides and cancer risk in multiple human organ systems

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HIGHLIGHTS

- Data on non-occupational exposure to pesticides and cancer are scarce.
- A population-based case–control study estimated the risk of cancer at different sites.
- Prevalence of cancer at most organ sites was higher in areas of greater pesticide use.
- The risk of cancer at most organ sites was higher in areas of greater pesticide use.
- Environmental exposure to pesticides may be a risk factor for different cancer sites.

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ABSTRACT

There is growing evidence on the association between long-term exposure to pesticides in occupational settings and an elevated rate of chronic diseases, including different types of cancer. However, data on non-occupational exposures are scarce to draw any conclusion. The objective of this study was to investigate the putative associations of environmental pesticide exposures in the general population with several cancer sites and to discuss potential carcinogenic mechanisms by which pesticides develop cancer. A population-based case–control study was conducted among people residing in 10 Health districts from Andalusia (South Spain) to estimate the risk of cancer at different sites. Health districts were categorized into areas of high and low environmental pesticide exposure based on two quantitative criteria: number of hectares devoted to intensive agriculture and pesticide sales per capita. The study population consisted of 34,205 cancer cases and 1,832,969 age and health district matched controls. Data were collected by computerized hospital records (minimum dataset) between 1998 and 2005. Prevalence rates and the risk of cancer at most organ sites were significantly higher in districts with greater pesticide use related to those with lower pesticide use. Conditional logistic regression analyses showed that the population living in areas with high pesticide use had an increased risk of cancer at all sites studied (odds ratios between 1.15 and 3.45) with the exception of Hodgkin's disease and non-Hodgkin lymphoma. The results of this study support and extend previous evidence from occupational studies indicating that environmental exposure to pesticides may be a risk factor for different types of cancer at the level of the general population.

1. Introduction

Pesticides are widely used throughout the world because of their benefits for humans in agriculture (maintaining high product quality and quantity) and public health. World pesticide amount used was approximately 2.4 million tonnes in both 2006 and 2007, with herbicides accounting for the largest portion of total use, followed by other pesticides, insecticides and fungicides (US-EPA, 2011). Herbicides remained the most widely used type of pesticide in the agricultural market sector. In Spain, pesticide sales for the year 2008 reached a total amount of 94,549 tonnes, of which one third was used in Andalusia (South Spain) representing the highest amount of pesticides sold nationwide. Distinct agriculture practices are observed in this region, with areas of intensive farming within plastic greenhouses (particularly near the coastline) and other of traditional open-air agriculture (in inland areas), which

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accounts for a heterogeneous pattern of pesticide use (Parrón et al., 2011).

As pesticides are intrinsically toxic, the potential health impact of using the aforementioned huge amounts has merit increasing concerns in the public opinion. The general population has been reported to show detectable levels of pesticide metabolites in urine (Barr et al., 2010, 2011) indicating potential exposure from indirect sources, including dietary (drinking water, food) and non-dietary (dust, breathing air) exposures. Long-term heavy use of pesticides in areas of intensive agriculture may lead to environmental contamination; thus, residential proximity to pesticide-treated farmland is an important pesticide exposure pathway that ultimately impacts the human health.

The increasing trend in cancer incidence over the last 50–60 years may be largely attributed not only to the ageing of the population but also to the diffusion of carcinogenic agents in occupational and general environments (Tebourbi et al., 2011). A growing body of epidemiological, molecular biology and toxicological evidence has shown that exposures to various environmental pollutants, including pesticides, are associated with increasing frequency of cancers. Besides known risk factors for cancer, such as smoking, excessive alcohol intake, sun exposure, consumption of an unhealthy diet, lack of physical activity and obesity, cancer caused by involuntary exposures (e.g., pesticides) has raised concern among the general public (Anand et al., 2008; Stewart, 2012). The major groups of insecticides (organophosphates, organochlorines, *N*-methylcarbamates and pyrethroids) have shown carcinogenic potential in various models (Alavanja et al., 2013; George and Shukla, 2011). Moreover, exposures to certain pesticides may interact with other chemical exposures, life circumstances (e.g. those causing a weakened immune system) and genetic factors to increase the risk of cancer. Likewise, there are studies supporting evidence that lifespan exposure to carcinogenic agents, beginning during developmental life, produces an overall increase in carcinogenic processes (Soffritti et al., 2008).

Most of the information about environmental cancer risk comes from epidemiological studies on long-term occupational exposures (Alavanja and Bonner, 2012; Bassil et al., 2007; Blair and Freeman, 2009; Jaga and Dharmani, 2005). Workers are at a greater risk as they show higher cumulative exposures than the general population; accordingly, potential associations are more easily observed. Major epidemiologic evidence related to occupational pesticide exposures and cancer incidence comes from the Agricultural Health Study (AHS) cohort. In the AHS, an excess incidence of cancer at different sites has been reported in pesticide applicators and farmers after exposure to specific pesticides (Alavanja et al., 2004; Alavanja and Bonner, 2012). Despite certain methodological drawbacks raised as to the associations found, in particular regarding the validity of the intensity-weighted exposure algorithm used (Weichenthal et al., 2010), AHS stands as the best epidemiological evidence linking pesticides and cancer. Outside the AHS, the evidence remains limited with respect to most of the observed associations.

In contrast to occupational settings, relatively little epidemiologic studies have been conducted to characterize the role that environmental exposures may have in cancer development (Alavanja et al., 2013). By assuming a non-threshold linear relationship between the size of exposure and cancer risk, a higher prevalence of cancer should be expected when a greater size of population is considered. Thus, this study was aimed to ascertain whether people living in close vicinity to high intensive agriculture areas, where pesticides are heavily used, show an increased prevalence and risk of cancer in various organ systems. Potential mechanisms by which these environmental contaminants develop cancer are also discussed.

2. Materials and methods

2.1. Design

A population-based case–control study was conducted in selected areas from Andalusia (South Spain) with different environmental exposure to pesticides as a result of a different patterns of pesticide use to test whether there are associations between exposure to these chemicals and cancer at different organ sites. Each study area corresponds to an administrative territorial division with a reference Hospital (referred to as health district).

2.2. Criteria for selecting the study areas and pesticide exposure

Andalusian health districts with high agriculture activity within plastic greenhouses were selected as target areas. Other health districts lacking intensive agriculture practices, but with extensive herbaceous crops, were selected for comparison purposes. Two agronomic criteria were used for the categorization of these geographical areas (health districts) as regard to pesticide exposure (Table 1). First, the study areas were classified into two groups based on the number of hectares devoted to intensive agriculture according to figures provided by the Andalusian Council of Agriculture. One thousand and two hundred hectares was used as a cut-off level for distinguishing areas of high and low pesticide use. Second, pesticide sales for the year 2001 allowed to estimate the average pesticide exposure in the study areas as this year represents the middle of the time period studied. Given that pesticide sales are available only at province level but not for health districts, the total amount of pesticides sold in each Andalusian province was divided by its total population and then multiplied by the population living in the selected health districts within each province (Parrón et al., 2011). Population data was obtained from the 2001 census. Areas of high exposure included the following health districts: West Almeria (Poniente), Centre of Almeria (Centro), South Granada and Huelva coastline. By contrast, low exposure areas were comprised by Axarquia (Malaga), Jerez coastline, East Almeria (Levante), Northeast Jaen, North Cordoba and North Seville (Fig. 1).

2.3. Study population and target diseases

The study population consisted of 34,191 cancer cases collected from the study areas between 1998 and 2005 using the place of residence in Andalusia as inclusion criteria (see distribution in Table 2). The above population was diagnosed with any of the following types of cancer: stomach, colorectal, liver, lung, skin, bladder, brain, leukaemia, multiple myeloma, non-Hodgkin lymphoma (NHL), Hodgkin's disease (HD), breast cancer, cervix, ovary, prostate and testicle. Cases were collected from computerized records of the Andalusian Health Service (referred to as Minimum Dataset) for the 8-year study period. The Andalusian Minimum Dataset (AMD) collects public hospital discharge information, including coded clinical data for inpatients. AMD is recorded when a patient is discharged from a hospital after staying for at least one night or more. The main cause for admission (major diagnosis) and other secondary medical diagnoses are routinely recorded in AMD as are also age, gender, race and place of residence. The validity of the data gathered in AMD is determined by the quality of the discharge report with respect to its inclusion of diagnoses and principal and secondary procedures and by exhaustiveness in the codification of hospital discharges.

The total number of control participants was 1,832,969 (both sexes, aged 37 years as an average), whom were matched by age to be comparable with the age distribution of the entire case group within each health district of residence. All controls were obtained from the 2001 census and were used to analyze data for each specific tumour type.

Table 1
Agronomic criteria to categorize health districts as areas with high and low use of pesticides in Andalusia (South Spain).

	High use of pesticides	Low use of pesticides
Population	800,017	1,032,952
Hectares of plastic greenhouses	30,291	2510
Total pesticides (tonnes used)	8883.74	6145.84
Insecticides	4777.50	2210.89
Fungicides	2228.81	1666.28
Herbicides	599.80	1380.02
Plant growth regulators	905.21	694.03
Other pesticides	462.48	235.36
Total pesticides (kg/person)	11.10	5.95
Insecticides	5.97	2.14
Fungicides	2.79	1.61
Herbicides	0.75	1.34
Plant growth regulators	1.13	0.67
Other pesticides	0.58	0.23