

Special article

Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design

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ABSTRACT

Introduction: We present the protocol of a large population-based case-control study of 5 common tumors in Spain (MCC-Spain) that evaluates environmental exposures and genetic factors.

Methods: Between 2008-2013, 10,183 persons aged 20-85 years were enrolled in 23 hospitals and primary care centres in 12 Spanish provinces including 1,115 cases of a new diagnosis of prostate cancer, 1,750 of breast cancer, 2,171 of colorectal cancer, 492 of gastro-oesophageal cancer, 554 cases of chronic lymphocytic leukaemia (CLL) and 4,101 population-based controls matched by frequency to cases by age, sex and region of residence. Participation rates ranged from 57% (stomach cancer) to 87% (CLL cases) and from 30% to 77% in controls. Participants completed a face-to-face computerized interview on sociodemographic factors, environmental exposures, occupation, medication, lifestyle, and personal and family medical history. In addition, participants completed a self-administered food-frequency questionnaire and telephone interviews. Blood samples were collected from 76% of participants while saliva samples were collected in CLL cases and participants refusing blood extractions. Clinical information was recorded for cases and paraffin blocks and/or fresh tumor samples are available in most collaborating hospitals. Genotyping was done through an exome array enriched with genetic markers in specific pathways. Multiple analyses are planned to assess the association of environmental, personal and genetic risk factors for each tumor and to identify pleiotropic effects.

Discussion: This study, conducted within the Spanish Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP), is a unique initiative to evaluate etiological factors for common cancers and will promote cancer research and prevention in Spain.

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Abbreviations: CLL, Chronic Lymphocytic Leukaemia; FFQ, Food Frequency Questionnaire; EBV, Epstein-Barr Virus.

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Estudio multicaso-control de base poblacional de tumores comunes en España (MCC-Spain): razón y diseño del estudio

R E S U M E N

Introducción: Presentamos el protocolo del estudio caso-control de base poblacional de 5 tumores comunes en España (MCC-Spain) que evalúa factores ambientales y genéticos.

Métodos: Durante 2008-2013, se reclutaron 10.183 sujetos entre 20-85 años en 23 hospitales de 12 provincias españolas, incluyendo 1.115 casos de cáncer de próstata, 1.750 de mama, 2.171 colorrectal, 492 gastro-esofágicos, 554 de leucemia linfática crónica (LLC) y 4.101 controles poblacionales emparejados por frecuencia por edad, sexo y región de residencia. Las tasas de participación varían del 57% (cáncer de estómago) al 87% (casos de LLC) y del 30% al 77% en controles. Los participantes respondieron una entrevista personal informatizada sobre factores socio-demográficos, exposiciones ambientales, ocupación, medicación, estilos de vida, e historia médica personal y familiar. Además, cumplieron un cuestionario alimentario y realizaron entrevistas telefónicas. Se recogió sangre del 76% de los participantes y saliva para los casos de LLC y participantes que rechazaron la donación de sangre. En los casos, se recogió información clínica y se dispone de muestras de tumor fresco o parafinado a través de los biobancos de los hospitales. Se realizó el genotipado con un array de exoma suplementado con marcadores en pathways específicos. Se han planificado diversos análisis para evaluar la asociación de factores genéticos, personales y ambientales para cada tumor e identificar efectos pleiotrópicos.

Discusión: Este estudio, desarrollado en el Consorcio de Investigación Biomédica de Epidemiología y Salud Pública (CIBERESP), es una iniciativa única para evaluar factores etiológicos de tumores comunes y promoverá la investigación en cáncer y prevención en España.

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INTRODUCTION

A population-based multicase-control study (MCC-Spain) was launched in 2007 by the Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP) to evaluate the influence of environmental exposures and their interaction with genetic factors in three of the most common tumours in Spain (prostate, female breast, colorectal),¹ in which etiological causes remain largely unknown. Gastric cancer was also included due to its large geographical variation within Spain,² which points to the not well identified persistent environmental exposure in high risk areas (i.e. Castilla y León). A fifth neoplasm, chronic lymphocytic leukaemia (CLL) was included later, as a result of the collaboration with the International Cancer Genome Consortium (ICGC).

Diet, physical activity, obesity and family history are common risk factors for the tumours examined^{3,4}. Moreover, environmental and occupational factors have also been investigated in relation to these tumours,⁵⁻⁷ but not in the Spanish population. Regarding infectious hypothesis, the best established risk factor for stomach cancer is infection with *Helicobacter pylori* (*H. pylori*), while infectious mononucleosis and high levels of Epstein-Barr Virus (EBV) antibodies have been associated with CLL.⁸ Non-steroidal anti-inflammatory drugs (NSAIDs) and statins may be protective for several of the included tumours. Genome Wide Association Studies (GWAS) have identified numerous low penetrance variants for colorectal, breast, and prostate cancer and CLL.⁹⁻¹² However, in spite of all the research conducted so far, the causes of this group of tumours are not well understood.

The aim of this study is to assess the association between environmental exposures and individual factors, including genetic susceptibility, and the occurrence of these cancers in Spain. In summary, MCC-Spain intends to explore and combine different approaches in order to identify new risk factors of to provide new data that might help to prevent their occurrence in the future. The specific objectives of the study are related to: a) environmental exposures, including drinking water contaminants, heavy metals and endocrine disruptors exposure; b) socioeconomic factors and occupational exposures, including disruption of the circadian rhythm through shift work; c) lifestyle factors, smoking, nutrition, obesity and physical activity; d) medical history and

consumption of specific drugs; e) hormonal factors, including exposures in early stages of life; f) infectious agents; and g) family history of cancer and genetic variation. Main effects and interactions, specifically with genetic factors, will be analyzed together with an evaluation by tumour subphenotypes.

METHODS

Study design

MCC-Spain is a population-based multicase-control study carried out between September 2008 and December 2013 in 12 Spanish provinces (Asturias, Barcelona, Cantabria, Girona, Granada, Gipuzkoa, Huelva, León, Madrid, Murcia, Navarra and Valencia). Recruitment of cases and controls was performed simultaneously: study personnel contacted newly diagnosed cancer cases in the 23 collaborating hospitals, and invited through the telephone population controls, who had been randomly selected from the administrative records of selected primary care health centres located within these hospitals' catchment area. In total, the study recruited 10,183 subjects (Table 1). All participants had to be 20-85 years, to have resided in the catchment area for at least 6 months prior to recruitment, and to be able to answer the epidemiological questionnaire. Each province recruited cases of at least two different tumour sites. Cases were identified, as soon as possible after the diagnosis was made, through active search that included periodical visits to the collaborating hospital departments (i.e. gynaecology, urology, gastroenterology, oncology, general surgery, radiotherapy, and pathology departments). We included histologically confirmed incident cases of cancer of the prostate (International Classification of Diseases 10th Revision [ICD-10]: C61, D07.5), breast (C50, D05.1, D05.7), colon or rectum (C18, C19, C20, D01.0, D01.1, D01.2), stomach (C16, D00.2), lower third of the oesophagus (C15.5), or chronic lymphocytic leukaemia and small lymphocytic lymphoma (C91.1), with no prior history of the disease, and diagnosed within the recruitment period, which differed by province; in CLL prevalent cases were also recruited. Controls were frequency-matched to cases, by age, sex and region, ensuring that in each region there was at least one control of the same sex and 5-year interval for each case. For each control needed, a total of five potential participants of

Table 1
Number of cases and controls with complete interviews by tumour type and geographic area.

Area (number of hospitals)	Controls	Colorectal	Breast	Prostate	Stomach/Oesophagus	CLL	Total	Start (month/year)	Finish (month/year)
Asturias (2)	232	77	70	16	15	53	463	11/08	2/12
Barcelona (4)	1,037	702	292	405	107	402	2,945	9/07	12/13
Cantabria (1)	378	151	142	175	26	22	894	4/10	7/12
Girona (2)	82		47			30	159	3/12	7/13
Granada (2)	187	166		65	5	47	470	4/10	6/13
Gipuzkoa (2)	362	119	226				707	2/08	7/10
Huelva (2)	178	74	115	52	16		435	4/10	5/13
León (1)	441	406	228		127		1,202	2/09	6/12
Madrid (2)	733	233	342	315	121		1,744	12/08	5/12
Murcia (1)	42	36			2		80	1/08	6/10
Navarra (2)	274	125	227		59		685	10/08	3/11
Valencia (2)	155	82	61	87	14		399	7/10	4/12
TOTAL	4,101	2,171	1,750	1,115	492	554	10,183	9/07	12/13

similar age, sex and hospital catchment area were randomly selected from the general practitioner lists. If contact with the first person of this list was not possible after a minimum of five tries at different times of the day, or if he/she refused to participate, the following person of the list was approached.

In Table 2 we present the main characteristics of the study population.

Response rates

Response rates were calculated using subjects interviewed in the numerator, and all subjects including refusals in the denominator.^{13,14} For cases, these response rates were 68% for colorectal cancer cases, 71% for breast, 72% for prostate, 57% for gastric and 87% for CLL. In controls, mean participation rate of controls was 53% and varied by region. For 22% of the subjects the phone contact was not possible due wrong phone number or no-answer.

Questionnaires, biological samples, hospital records and anthropometric measurements

A structured computerized epidemiological questionnaire was administered by trained personnel in a face-to-face interview (<http://www.mccspain.org>). The average duration of the interview was 70 minutes (range 30-130). Information was collected on socio-demographic factors, residential history, lifelong retrospective environmental exposures, including water consumption and use (showering, bathing, swimming in pools), occupational history -including night shift-, medication, lifestyles-smoking, alcohol consumption, physical activity, use of cosmetic products-, sun-bathing and sleeping habits, personal/family medical history and quality of the interview. Missing values on key variables and specific questions on additional study objectives (e.g. questions on disruption of the circadian rhythm) were completed through subsequent telephone contact. The main characteristics of the study population are presented in Table 2. After the interview, biological samples and anthropometric data were obtained following the study protocol. Height and weight at different ages were self-reported and waist and hip circumference were measured with a tape. Subjects were provided a semi-quantitative Food Frequency Questionnaire (FFQ), which was a modified version from a previously validated instrument in Spain¹⁵ to include regional products. It included 140 food items, and assessed usual dietary intake during the previous year. Portion sizes were specified for each item, and photographs were used to define degrees of doneness. Information on consumption of vitamin and mineral supplements and on important changes on dietary habits in the past 5 years were also collected. The FFQ was self-administered and returned by mail or filled out face to face (global response rate 88%).

When feasible, 27 ml of peripheral blood was drawn from participants, which were aliquoted in whole blood, plasma, cellular fraction for DNA extraction, and serum and stored at -80 °C. Saliva was collected for subjects refusing to donate blood and for all CLL cases, with the Oragene® DNA Kit and stored at room temperature until DNA extraction. We collected biological samples for DNA extraction for 96% of participants with interview (76% blood and 27% saliva) as well as toenail and hair samples were taken from participants (79% and 84% respectively). In 4 centres (Madrid, Cantabria, Asturias and Huelva, which include approximately 1/3 of the study participants) cases and controls also donated urine samples (60 ml) that were aliquoted and frozen at -80 °C. Fresh tumour biopsies or paraffin embedded samples are available in all participating hospitals.

Standardised basic clinical and pathological information on the diagnosis and treatment of tumours was collected from hospital records using a predefined format.

Sociodemographic, lifestyle and environmental factors

MCC-Spain will examine the **Socioeconomic status** will be examined using multilevel approaches that allow the evaluation of the role of structural socioeconomic factors on health. Environmental justice, proximity to green spaces and environmental pollution will be assessed through an evaluation of exposures proximate to the place of residence.

Lifestyle exposures are one of the main objectives of this study. **Diet** is examined through summary intakes of relevant food groups based on reported intake frequencies and portion size information. Food composition tables were developed and will be combined with reported intake frequencies and cooking method preferences to estimate intakes of nutrients, food contaminants (e.g. polycyclic aromatic hydrocarbons) and food properties (e.g. total antioxidant capacity). An *a priori* Mediterranean diet score, alternative diet patterns and a factor-analysis derived diet pattern will be examined. General and central **obesity** is examined together with leisure time **physical activity** and sedentary lifestyle. Numerous other potential risk factors that could be associated with the cancers investigated are examined. These include, among others, smoking habits, exposure to medical radiation, use of cosmetics, use of tight clothes and belts, exposure to sun or sleeping patterns.

Use of **medical drugs** was collected through personal interviews, mainly by indication. Information was coded (Anatomical Therapeutic Chemical-ATC code) to assess individual exposure to different drugs including statins and anti-inflammatory drugs, analgesics, hormones, antihypertensives, beta-blockers, bisphosphonates and corticosteroids.

Hormonal factors and endocrine disruption are also examined. Sex dimorphic phenotypes (finger ratio and anogenital

Table 2
Main characteristics of the population of the MCC-Spain study.

	Controls N = 4101	Colorectal N = 2171	Breast N = 1750	Prostate N = 1115	Stomach/Oesophagus N = 492	CLL N = 554
Area						
Asturias	232 (5.7%)	77 (3.5%)	70 (4%)	16 (1.4%)	15 (3%)	53 (9.6%)
Barcelona	1037 (25.3%)	702 (32.3%)	292 (16.7%)	405 (36.3%)	107 (21.7%)	402 (72.6%)
Cantabria	378 (9.2%)	151 (7%)	142 (8.1%)	175 (15.7%)	26 (5.3%)	22 (4%)
Girona	82 (2%)		47 (2.7%)			30 (5.4%)
Granada	187 (4.6%)	166 (7.6%)		65 (5.8%)	5 (1%)	47 (8.5%)
Gipuzkoa	362 (8.8%)	119 (5.5%)	226 (12.9%)			
Huelva	178 (4.3%)	74 (3.4%)	115 (6.6%)	52 (4.7%)	16 (3.3%)	
León	441 (10.8%)	406 (18.7%)	228 (13%)		127 (25.8%)	
Madrid	733 (17.9%)	233 (10.7%)	342 (19.5%)	315 (28.3%)	121 (24.6%)	
Murcia	42 (1%)	36 (1.7%)			2 (0.4%)	
Navarra	274 (6.7%)	125 (5.8%)	227 (13%)		59 (12%)	
Valencia	155 (3.8%)	82 (3.8%)	61 (3.5%)	87 (7.8%)	14 (2.8%)	
Sex						
Men	2063 (50.3%)	1387 (63.9%)		1115 (100%)	336 (68.3%)	334 (60.3%)
Women	2038 (49.7%)	784 (36.1%)	1750 (100%)		156 (31.7%)	220 (39.7%)
Age, mean(sd)	62.9 (12.1)	67.0 (10.8)	56.4 (12.6)	66.1 (7.33)	66.2 (12.3)	66.1 (10.3)
Education						
Less than primary school	753 (18.4%)	696 (32.1%)	271 (15.5%)	261 (23.4%)	147 (29.9%)	147 (26.5%)
Primary school	1307 (31.9%)	822 (37.9%)	567 (32.4%)	441 (39.6%)	186 (37.8%)	160 (28.9%)
Secondary school	1182 (28.8%)	429 (19.8%)	579 (33.1%)	242 (21.7%)	106 (21.5%)	149 (26.9%)
University	859 (20.9%)	224 (10.3%)	333 (19.0%)	171 (15.3%)	53 (10.8%)	98 (17.7%)
Race						
White	4034 (98.4%)	2147 (98.9%)	1703 (97.3%)	1099 (98.6%)	474 (96.3%)	549 (99.1%)
Non-white	67 (1.63%)	24 (1.11%)	47 (2.69%)	16 (1.43%)	18 (3.66%)	5 (0.90%)

CLL: lymphocytic leukaemia.

distance) will be evaluated in relation to the development of breast and prostate cancer. The ratio of the length of the index finger and middle finger of both hands (2D: 4D) were measured using callipers with a resolution of 0.05 mm,¹⁶ a validation study has shown a good repeatability of finger measurements.¹⁷ Anogenital distance was assessed in a subgroup of prostate cancer cases and controls.¹⁸ The influence of reproductive history, hormonal treatments (contraceptives, hormone replacement therapy) and influence of hormonal development (pattern of fat distribution at different ages, and height) will be examined. Endocrine disruptors (xenoestrogens and other persistent organic pollutants) will be measured in serum through a determination of the global xenoestrogenic burden (TEXB).¹⁹

Among **environmental pollutants**, evaluation of **drinking water contaminants** focuses on disinfection by products (such as trihalomethanes and haloacetic acids), nitrates and metals. Exposure data from water companies and municipalities, national surveillance data and new water analyses has been gathered,^{20,21} and modelled to estimate historical levels of pollutants in drinking water and combined with individual data from the questionnaire. Urinary trichloroacetic acid was measured in a subset of controls. MCC-Spain will also study environmental exposure to different **metals**, including Cd, Ni, Cr, As, Pb, Se, and Zn in relation to the five combining biomarker-based estimations with information based on the epidemiological information.

Occupational exposures will also be studied. All **jobs** conducted for more than one year were recorded with information regarding specific tasks, exposures and timing of the job. Jobs were coded by two experts following the Spanish National Classification of Occupations (CNO-94). The Spanish JEM, MatEmEsp, will be applied.²² Detailed information on work shift (rotating and night) and **disruption of the circadian rhythm** was also collected.

Other possible etiological factors have also been included in the project. Among them, several **infections** will be evaluated in relation to colorectal and gastric tumours and CLL. The role of *H. pylori*

infection will be estimated using seroprevalence against several virulence antigens. In relation to CLL, seroprevalence of several polyomaviruses, herpesviruses, and *Chlamydia trachomatis* will be evaluated. Additionally the antibody response pattern to EBV will also be measured.

Extensive information on **family history** was collected to identify familial cases. This information will allow describing the typical family structure of study participants and, if genetic effects are identified, estimating their penetrance using Kin-cohort methods. In addition, genetic analyses will be carried out within MCC-Spain and also through participation in international consortia such as the prostate cancer consortium PRACTICAL (<http://ccge.medschl.cam.ac.uk/consortia/practical/>). The Infinium HumanExome BeadChip from Illumina was used to genotype >200,000 coding markers plus 6,000 additional custom variants on the pathways of interest such as inflammation, circadian rhythm or detoxification.

Ethics and availability of data

The protocol of MCC-Spain was approved by the Ethics committees of the participating institutions. All participants were informed about the study objectives and signed an informed consent. Confidentiality of data is secured removing personal identifiers in the datasets. The database was registered in the Spanish Agency for Data Protection, number 2102672171. Permission to use the study database will be granted to researchers outside the study group, after revision and approval of each request by the Steering Committee. More details on the organization of the project can be found online at <http://www.mccspain.org>.

DISCUSSION

Cancer locations and hypotheses examined in MCC-Spain were selected with a public health perspective to provide information

useful for cancer prevention. MCC-Spain also aims to foster a network of research in cancer epidemiology in Spain.

The option of a single set of population controls and a single questionnaire for all tumours has the main benefit of the optimization of the economic resources. This approach has been successfully used previously.²³ On the other hand, the main drawback is the need to use the same tools to gather the information regarding risk factors for all types of cases.

The advantages and problems of the selection of population versus hospital controls have been extensively discussed.^{24,25} The evaluation of a variety of exposures makes hospital controls less suitable given the potential association between multiple diseases and exposures of interest. As expected from other population-based studies, participation rates of cases were higher than those of controls. Selecting controls through lists of general practitioners provides a representative sampling frame given the almost universal public coverage of the national health system in Spain. However, errors in these lists concerning personal data resulted in a lower than expected response rate.¹⁴

The study is population-based since we intended to recruit all cases with a first diagnosis of the studied tumors in the selected health areas, using for this purpose the reference hospital/hospitals in each area and identifying every new diagnosis of the studied cancers. We could not use population cancer registries to ascertain the number of cases lost since in most of the regions included in the study there was not any such registry, but we can certainly assume to be few. Potential misclassification of exposure is a major limitation of case-control studies. The implementation of a computerized questionnaire, training and continuous feedback to interviewers, and repeated interviews to complete missing values is likely to reduce errors.

A challenge of current cancer epidemiology research is to accurately define the molecular phenotype of tumours so that specific risk factors can be identified for each molecular subtype. All tumours have pathology slides in the reference hospitals that can be retrieved and some hospitals also have tumour banks that have collected fresh tumour tissue for some cases.

Finally, networking is among the major achievements of the study. MCC-Spain includes 17 different centres and has followed organizational procedures to promote the exchange of knowledge and experiences between centres.

Editor in charge

Alberto Ruano-Ravina.

Statement of authorship

All authors have contributed to the conception and design of the study, and have acquired data, have been involved in drafting the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Annex 1.

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Annex 2.

BARCELONA

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