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Perinatal and childhood factors and risk of prostate cancer in adulthood: MCC-Spain case-control study

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ABSTRACT

Background: In utero and early-life exposures are suspected to modulate the risk of prostate cancer. This study examines the influence of certain perinatal and childhood-related factors on prostate cancer risk overall and by Gleason score at biopsy.

Methods: MCC-Spain is a multicase-control study where 1088 histologically-confirmed incident prostate cancer cases (aged 42–85 years) and 1345 population-based controls (aged 38–85 years), frequency matched by age and province of recruitment, were recruited in 7 Spanish provinces. Self-reported perinatal and childhood-related characteristics were directly surveyed by trained staff. The association with prostate cancer risk, globally and according to Gleason score at biopsy, was evaluated using logistic and multinomial regression mixed models, adjusting for age, family history of prostate cancer, educational level and body mass index one year before the interview, and including the province as a random effect term.

Results: Most perinatal factors were not related to prostate cancer risk, with the exception of middle-high socioeconomic level at birth (OR for high grade tumors = 1.36; 95%CI = 1.09–1.68). Regarding puberty, risk rose by 6% for each year of delayed onset (OR = 1.06; 95%CI = 1.01–1.10; p trend = 0.016), with a clear excess

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of risk in men who reached puberty after age 15 (OR:1.35; 95%CI = 1.08–1.68). A borderline significant positive association with prepubertal height was also observed (p trend = 0.094).
Conclusion: Some exposures experienced in utero and during adolescence, when the prostate is still maturing, might be relevant for prostate cancer risk in adulthood.

1. Introduction

Prostate cancer (PC), with an estimated 278,500 new cancer cases in Spain in 2012 [1], has registered a dramatic rise in incidence from 1990 onwards. This was particularly marked among men aged 45–64 years, and has mainly been attributed to opportunistic screening [2]. Regarding the clinical profile of newly diagnosed cases, data from a nationwide hospital-based registry showed that, in 2010, the mean age at diagnosis was 69 years and 56.5% of patients had a Gleason score $\leq$6 [3]. This tumor is the third cause of death by cancer in Spain, accounting for 8.8% of all cancer-related deaths in 2013 [4].

As in other hormone-dependent tumors, pre- and perinatal periods might constitute a "time window" of major importance for future PC risk [5–7]. However, epidemiological evidence on this hypothesis is still scarce and contradictory. Birthweight has been positively associated with the risk of PC in some studies [8–10], mainly with more aggressive tumors [9,10], although other studies described no association [11–13]. Longer gestational age [14], pre-eclampsia and eclampsia [15] have been associated with reduced PC risk, whereas advanced paternal [16], but not maternal [15–17], age at birth has been related to an increased risk.

There is strong evidence that developmental factors in childhood and adolescence that influence growth are linked to an increased risk of PC [7]. Although the association between PC and early life body size seems to be weak [18], recent studies have described a positive association with childhood obesity [19] and with childhood stature [20,21], as well as no association with energy restriction [22]. Puberty is also a critical period for prostate gland development. The increase in testosterone production is accompanied by a rapid growth and development of the prostate until the end of puberty, when it reaches approximately adult size and morphology [23].

The Gleason grading system—initially developed by Donald Gleason in 1966 [24] and afterwards revised by the International Society of Urological Pathology in 2005 [25] and 2014 [26], is the most common pathology scoring system used to classify prostate cancer according to its aggressiveness and prognosis. Low grade tumors ($<$ = 6) tend to grow slowly, while intermediate and high grade tumors (>6) tend to be fast-growing and aggressive cancers with worse prognosis. Epidemiologic studies have observed different associations of some risk factors between localized/non aggressive and advanced/aggressive tumors, suggesting etiologic heterogeneity [27]. This study sought to investigate whether perinatal and childhood sociodemographic and anthropometric factors influence the risk of adult PC by Gleason score in a large multicase control study in Spain.

2. Materials and methods

2.1. Study population

Multicase Control Spain (MCC-Spain) is a research project carried out between September 2008 and December 2013 to explore environmental and genetic factors associated with the risk of colorectal, breast, prostate, gastric tumors and chronic lymphocytic leukemia. It is a multicase-control study, with incident cases treated in the oncologic units of 23 hospitals and population-based controls recruited in 12 Spanish provinces (Barcelona, Madrid, Navarra, Gipuzkoa, León, Asturias, Murcia, Huelva, Cantabria, Valencia, Granada and Girona). Participants had to be aged 20–85, should have resided in the catchment area for at least 6 months prior to recruitment, and had to be able to answer the epidemiological questionnaire. Each provincial research group recruited cases of two or more of the selected cancers and a single set of controls for all of them. We made an initial estimate of the expected age-sex distribution that cases, all combined, would have in each region, according to the tumors they recruited and to the cancer incidence rates from cancer registries. We applied these estimates to predefine age-sex distribution of our population-based controls, which were selected randomly from the general practitioner lists of the hospital catchment area. Research personnel invited potential controls via telephone, and those who agreed attended a personal interview. When the recruitment of cases ended, we compared, once again, the age-sex distribution of cases and controls. If needed, we recruited new participants to ensure that for each case in each region there was at least one control of the same 5-year age interval and sex. PC cases were recruited in Barcelona, Madrid, Asturias, Huelva, Cantabria, Valencia and Granada. For this purpose, our research personnel reviewed the hospital admission registries weekly and periodically (weekly or even daily) went to the collaborating hospital departments (i.e. urology, oncology, radiotherapy, and pathology) to find new cases and invite them to participate. The study was approved by the Ethics Committee of all hospitals and participant primary care centers. All participants signed an informed consent form. More details regarding the design of the study are provided elsewhere [28,29].

Fig. 1 shows a flow chart displaying the selection process of PC cases and their controls. Response rates were 52.2% for controls and 67.4% for PC cases respectively. We recruited a total of 1112 histologically-confirmed incident PC cases (International Classification of Diseases 10th Revision [ICD-10]: C61, D07.5) with no prior history of the disease, and diagnosed within the recruitment period, which differed by province. For this analysis, we selected male controls from our pool of controls, and excluded those with personal history of PC, those who resided in provinces that had not recruited PC cases, and in each province, those that were more than 5 years younger than the youngest PC case. In addition, we excluded both cases and controls with missing information of key covariates (body mass index (BMI) one year before the interview and family history of PC). Finally, a total of 1088 cases and 1345 male controls were included for the analyses.

2.2. Data collection

Trained interviewers administered a structured computerized epidemiological questionnaire in a face-to-face interview, including sociodemographic data, self-reported height and weight one year prior to the interview, family and personal history of cancer, medical, residential and occupational history, smoking and physical activity.

With respect to perinatal factors, our questionnaire used a series of comprehensive questions to collect self-reported information on relative socioeconomic status of the participants' parents at their birth, birthweight, maternal and paternal age at