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European multi-centre case–control study on risk factors for rare cancers of unknown aetiology

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Abstract

To search for occupational risk factors, we conducted a case–control study in nine European countries of cancers of the small intestine, male gall bladder, thymus, bone, male breast, melanoma of the eye, and mycosis fungoides. Recruitment was population based in Denmark, Latvia, France, Germany, Italy, and Sweden, from hospital areas in Spain and Portugal, and from one United Kingdom (UK) hospital. We recruited 1457 cases (84% interviewed). Numbers identified corresponded to those in the EUROCIM database for Denmark, but were below those observed for France, Italy and Sweden in the database. We recruited 3374 population (61% interviewed) and 1284 colon cancer controls (86% interviewed). It was possible to undertake this complicated study across Europe, but we encountered three main problems. It was difficult to ensure complete case ascertainment, for population controls, we found a clear divide in the response rate from 75% in the South to only 55% in the North, and a somewhat selective recruitment was noted for the colon cancer controls. The study showed there is a clear dose–response relationship between alcohol intake and the risk of male breast cancer, and an excess risk of mycosis fungoides among glass formers, pottery and ceramic workers. Further data are expected.

Keywords: Case–control study; Rare cancer; Occupational risk factors; Methods; Multi-centric case–control study

1. Introduction

Some rare cancers are caused by mutations in a single gene, like retinoblastoma of the eye [1]. Other rare cancers are closely associated with a specific exposure, like adenocarcinoma of the vagina in daughters of mothers using diethylstilbestrol during pregnancy [2]. Several

Abbreviation: ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; NA, Not available; NOS, Not otherwise specified; UK, United Kingdom.

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rare cancers are known to be caused by occupational exposures, such as pleural mesothelioma in asbestos workers [3], bone sarcoma in radium dial painters [4], and liver angiosarcoma in vinyl chloride workers [5]. Historically, the term "signal cancer" has been used for rare cancers clustering in specific occupations, like nasal adenocarcinoma in furniture-makers in Buckinghamshire, in the United Kingdom (UK), in the early 1960s [6].

However, little is known about the aetiology of most rare cancers, and these cancers are difficult to study on a national basis due to the small numbers seen. We therefore conducted a case–control study in nine European countries of cancers of the small intestine, male gall bladder and bile ducts, thymus, bone, male breast, eye melanoma, and mycosis fungoides. Before initiation of the study, we conducted a literature review [7], and showed that occupational risk factors could be involved in the aetiology of these cancers. The review resulted in some specific hypotheses and data were collected to test these. However, the primary aim of the study was to undertake a systematic search for occupational risk factors. We report here on the design and organisation of the study, ascertainment of cases and controls, and participation in the interviews.

2. Patients and methods

2.1. Definition of diseases and study base

The cancers were defined by topography and morphology codes according to International Classification of Diseases for Oncology [8,9] (Table 1). Only invasive malignancies with behaviour code "3" were included. Exceptions were carcinoids with behaviour code "1" located in the gallbladder, extrahepatic bile duct and small intestine, and thymoma with code "0". Topographically, eye melanoma was restricted to the eyeball, choroid, and eye not otherwise expected (NOS). Morphologically, bone cancer was restricted to osteosarcoma and chondosarcoma, and small intestine cancer to adenocarcinoma and carcinoid.

A population-based recruitment scheme was set up in Denmark and Latvia, in ten areas in France, five in Germany, three in Italy, and four in Sweden. Recruitment was based on hospital referral areas in three places in Spain and two in Portugal. A small non-representative sample of eye melanoma patients was recruited from a UK hospital. Data collection was started, but could not be completed in Lithuania. The study base comprised 37 million. We aimed at recruiting all incident cases aged 35–69 years and diagnosed from 1 January, 1995 to 31 December, 1996. Due to the waiting time involved to obtain local funding, the period had to be adjusted locally (Table 2).

2.2. Ascertainment of cases and controls

To ensure rapid contact with newly diagnosed patients, case identification was based on regular contacts to clinical and pathology departments. A computerised identification procedure was set up in areas with registers of pathology, hospital discharges and/or cancer. Ascertainment was made elsewhere by manual search of files in the collaborating hospitals, (Table 2). The same procedures were used for recruitment of cancer controls, see below. For each of the seven cancer sites, one expert pathologist reviewed the pathology report and one representative, haematoxylin–eosin stained slide and classified the case as definite, possible or non-eligible. For melanoma of the eye, the review could be based on the ophthalmological report only. Other cancers without slides could be classified as possible based on the pathology report.

Before selection of controls, the expected number of cases was estimated from local or nearby cancer registers. The controls were frequency matched with the expected number of cases by region, gender and 5-year age group. Within each stratum, we aimed to select a number of controls that was four times the number of the most "frequent" of the seven rare cancers.

Controls were selected randomly at specific points in time during case recruitment from population registers in Denmark, Italy, and Sweden, and from electoral rolls in France. In Germany, population controls were selected from municipality registers. As this was relatively expensive, a large pool of potential controls was selected at the beginning of the study, and controls were subsequently selected from this pool. In the UK, one control per case was selected from the list of the general practitioner (GP) of the case.

Where population controls could not be selected, colon cancer patients were regarded as appropriate alternatives, as the only known occupational risk for colon cancer is sedentary work [10]. Population-based colon cancer controls were selected randomly in Latvia. Hospital-based cancer controls were selected randomly among the incident colon cancer patients in two areas in Spain, and among the colon and a few stomach cancer patients in Portugal. Patients attending the emergency ward were selected as controls in one area in Spain. To provide data for a validity study, population-based colon cancer controls were selected as a second control group in Denmark [11].

2.3. Data collection

A questionnaire was developed in English, and translated into the other eight national languages, and for quality control back-translated in part. It included demographic variables, characteristics such as eye colour, medical and X-ray history, use of drugs, to-