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Risk of subsequent cancers in renal cell carcinoma survivors with a family history

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Abstract ***Background:*** This study aimed at elucidating the effect of family history on the development of subsequent cancers in renal cell carcinoma (RCC) survivors and aimed at assessing whether the interactions between risks of subsequent cancers in RCC survivors and familial risk of subsequent cancer are additive or multiplicative interactions.
Methods: A population-based cohort (Swedish Family-Cancer Database) of 14,267 RCC patients diagnosed in 1990–2010 was followed for cancer incidence. Standardised incidence ratios (SIRs) were calculated for subsequent cancers in RCC survivors and in RCC survivors with a family history of subsequent cancer. Familial risk of subsequent cancer was calculated for individuals with family history of specific cancer, compared to those without.
Results: For subsequent hemangioblastoma (HB) in RCC survivors, drastically elevated risk was observed for the effect of family history of HB [SIR = 777 (95% confidence interval (CI): 160–2270)] and of family history of RCC [378 (46–1367)]. Colorectal, lung, prostate and RCCs favoured additive interactions between risk of subsequent cancers in RCC survivors and familial risk, while endocrine glands, nervous system and urinary bladder cancers favoured multiplicative interactions.
Conclusions: Risks of subsequent HB in RCC survivors were tremendously modified by family history of RCC or HB, which may resemble characteristics of von Hippel–Lindau syndrome and show the power of present approach to detect heritable cancer clusters. Additive or multiplicative interactions found for colorectal, lung, prostate, endocrine glands, nervous system, urinary bladder and RCCs might raise awareness among clinicians and RCC survivors with a family history of seven cancers about elevated risks of subsequent those cancers.

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1. Introduction

The number of cancer survivors has steadily increased due to improvement in early detection, treatment and supportive care [1,2]. Although in Sweden the incidence of renal cell carcinoma (RCC) has decreased since 1980 with a transition towards lower tumour stages [3], increasing proportions of kidney tumours are found incidentally because of improved imaging technologies and these tumours tend to be smaller than symptomatic tumours [4]. Standard treatment for kidney cancer has been surgery, and recently, antiangiogenic drugs have been introduced to metastatic kidney cancer [4]. Substantial improvements in survival for kidney cancer patients have been observed in all Nordic countries from the period 1964–1968 to the period 1999–2003, e.g. for Swedish men, the age-standardised 5-year relative survival increased from 27% to 52%; while for Swedish women, it increased from 31% to 57% [5,6]. Survivors of kidney cancer have an elevated risk of development of many second primary cancers, including bladder, prostate, colorectal, lung and nervous system cancers, melanoma and non-Hodgkin lymphoma [7]. Plausible aetiologies for second primary cancer could be intensive medical surveillance after the diagnosis of the first primary cancer, therapy for the first cancer, shared genetic or non-genetic factors between the first and second cancer or the interaction between them [8,9].

Family history has been fundamental to the understanding of heritable components in the aetiology of cancer [10]. Multiple primary cancers have been proposed to be a possible indicator of familial risk between cancer sites [11]. Population-based assessment of familial clustering of multiple primary cancers may facilitate identification of common aetiological factors, including susceptibility genes. However, population-based data on the risk of subsequent cancer in RCC survivors with family history are not available. This study aimed at elucidating the effect of family history on the development of subsequent cancers in RCC survivors and aimed at assessing whether the interactions between risks of subsequent cancers in RCC survivors and familial risk of subsequent cancer are additive or multiplicative interactions. To our knowledge, both of these aims are novel.

2. Materials and methods

The nationwide Swedish Family-Cancer Database (FCD) is the largest family-cancer database in the world [12]. We used the latest version of the FCD (FCD2010, updated in 2013), with separately recorded information on up to five invasive cancers per patient and/or up to five in situ carcinomas per patient by linking to Swedish Cancer Registry for the years 1958–2010. Cancer cases were retrieved from the Swedish Cancer Registry, relying on separate compulsory notifications from clinicians, pathologists and cytologist [12]. Close to 100% of registered cancers were histologically verified and the Swedish Cancer Registry only records primary tumours as metastasised tumours to other sites were only registered at primary sites [13]. For multiple primary tumours occurring in same organ or same organ system, only clearly separated malignancies were accepted as multiple primaries and registered in Swedish Cancer Registry; approximately 98% of diagnoses of second neoplasms were correctly verified according to a re-evaluation study of 209 multiple primary tumours [14]. FCD2010 comprises over 14.7 million individuals and about two million patients with any tumours (invasive and/or in situ), including the first and multiple primaries.

Data on family relationships were obtained from the multigeneration register with high quality and practically complete coverage [15], thus minimising biases related to reporting of family history, selection and recall. Family history information was obtained on all (and only) first-degree relatives (FDRs), including parents, siblings and children. Two types of family history were investigated in this study, i.e. a family history of RCC and of subsequent cancer in the same site, which is called concordant cancer in this paper.

We included only invasive cancers diagnosed during 1990–2010 and included only RCC cases (with 4-digital International Classification of Diseases (ICD)-7 code 180.0) as RCCs account for the majority (80–85%) of kidney cancers [13,16]. Nevertheless, for ensuring large sample size to assess the effect of family history, family history of RCC and of concordant subsequent cancer was based on cancer cases diagnosed during the entire period of cancer registration, 1958–2010. Hemangioblastoma (HB) was defined as tumours of central nervous system (CNS), with ICD-7 code 193 and with pathological anatomic diagnosis (PAD) code 501 and 511 (including hemangioma).

We employed standardised incidence ratios (SIRs) to estimate the relative risk. We first calculated the risk of any subsequent cancer in RCC survivors and then assessed to what extent family history of RCC and of the subsequent cancer modified the risk (Fig. 1). Calculations were also performed in a reverse order by assessing the risk of second RCC in any first cancer survivors and further assessing the risk for patients who had family history of RCC or of the first primary cancer (Fig. 1).

SIRs were calculated as the ratio of observed to expected numbers of cases. For SIR of subsequent cancer in RCC survivors, the expected numbers of second cancer in RCC survivors were calculated from the strata-specific first cancer incidence rate in the Swedish general population, multiplied by the corresponding person-years for second cancer in RCC survivors. Person-years at risk were accumulated for each patient, starting at the date of diagnosis of the first primary cancer or 1st January 1990 (start of the study) and

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