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Original Research

Sex differences in cancer risk and survival: A Swedish cohort study

Cecilia Radkiewicz*, Anna L.V. Johansson, Paul W. Dickman, Mats Lambe, Gustaf Edgren

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, SE-171 77 Stockholm, Sweden

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Abstract ***Aim:*** The aim of this study is to firmly delineate temporal and age trends regarding sex discrepancies in cancer risk and survival as well as quantifying the potential gain achieved by eliminating this inequality.
Methods: We performed a population-based cohort study using data on all adult incident cancer cases (n = 872,397) recorded in the Swedish Cancer Register in 1970–2014. To assess the associations between sex and cancer risk and sex and survival, male-to-female incidence rate ratios (IRRs) and excess mortality ratios (EMRs) adjusted for age and year of diagnosis were estimated using Poisson regression.
Results: Men were at increased risk for 34 of 39 and had poorer prognosis for 27 of 39 cancers. Women were at increased risk for 5 of 39 and had significantly poorer survival for 2 of 39 cancers. IRRs among male predominant sites ranged from 1.05; 95% confidence interval (CI), 1.03–-1.1 (lung adenocarcinoma) to 8.0; 95% CI, 7.5–8.5 (larynx). EMRs among sites with male survival disadvantage ranged from 1.1; 95% CI, 1.03–1.1 (colon) to 2.1; 95% CI, 1.5–-2.8 (well-differentiated thyroid).
Conclusion: Male sex is associated with increased risk and poorer survival for most cancer sites. Identifying and eliminating factors driving the observed sex differences may reduce the global cancer burden.
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* *Corresponding author:* Fax: +46 8314975.
E-mail addresses: cecilia.radkiewicz@ki.se (C. Radkiewicz), anna.johansson@ki.se (A.L.V. Johansson), paul.dickman@ki.se (P.W. Dickman), mats.lambe@ki.se (M. Lambe), gustaf.edgren@ki.se (G. Edgren).

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1. Introduction

Despite evidence of sex differences in disease risk and prognosis, the sex of the patient is rarely considered in the clinical setting [1]. Data from different parts of the world have shown that men are both at increased risk and have a poorer prognosis compared with women for most cancers [2–7].

The observed discrepancy in cancer risk has been attributed to sex differences in exposures to environmental carcinogens such as smoking, alcohol consumption and occupational toxins [8,9]. However, recent studies have suggested that intrinsic biological factors could also play a prominent role [3,4,10,11]. Men have also been found to have a consistently poorer survival for most cancers [5–7]. The underlying reasons for the male survival disadvantage remain incompletely understood [12,13]. Male frailty is not only an oncological concern but it also appears that men die at a higher rate for virtually all of the most common causes of death [14]. Environmental factors contributing to sex differences in cancer incidence could also affect survival. Additional mechanisms may include sex differences in comorbidity, tumour biology, health awareness and utilisation, clinical management, as well as response and tolerance to oncologic therapy. To date, few comprehensive analyses of sex differences in cancer risk and survival based on robust data sources have been conducted.

With the underlying goal to delineate temporal and age trends regarding sex discrepancies in cancer risk and survival as well as quantifying the potential gain achieved by eliminating this inequality, we performed a nationwide cohort study to estimate sex differences in cancer risk and survival across a complete range of cancer sites.

2. Methods

2.1. Data sources and study design

The study was based on all incident primary cancer cases identified in the nationwide Swedish Cancer Register, which prospectively records details on virtually all cancer cases in Sweden since 1958. Reporting is mandatory, and the register covers over 95% of all incident cases [15].

We restricted the study period to year 1970–2014 to minimise potential biases due to under-diagnosis, under-reporting and misclassification in earlier years. Incidental autopsy findings were excluded, as were non-histopathology-verified cases and cases where emigration was recorded before date of diagnosis. We used the first recorded incident cancer and excluded subsequent registrations if the same site was recorded multiple times. Multiple primary cancers at different sites were included to avoid biased relative survival estimates. All analyses were restricted to adults, aged 15–84 years at diagnosis (Appendix Table A.1).

To estimate incidence, the cohort was compared with the general population of Sweden, utilising population counts from Statistics Sweden available by sex, age and calendar year. Deaths and emigration were ascertained by linking the study cohort, using the national registration number assigned to all Swedish residents, to the nationwide Cause of Death and Total Population Registers, ensuring a complete follow-up throughout 2014. We retrieved sex-, age- and calendar year-specific mortality in the general population from Statistics Sweden [16].

2.2. Tumour classification

The Swedish Cancer Register records all malignancies using current classification systems as well as the historical 7th revision of the International Classification of Diseases (ICD-7) for anatomical site, and the World Health Organisation Histological Classification of Neoplasms for morphology (CANC/24.1) [17,18]. We grouped all cancers (excluding genital and breast cancer) using the historical classification with a few exceptions. It was not feasible to subdivide leukaemias before 1980 and lung cancer before 1993 because of insufficient quality and substantial temporal changes in diagnostic techniques and criteria, respectively. Hence, the ICD-8 was used for leukaemias and the International Classification of Diseases for Oncology, second edition (ICD-O-2) was used to subdivide lung cancer [19,20]. Basalioma was not included, and squamous cell carcinoma was, therefore, the predominant histological subtype in non-melanoma skin cancer (Appendix Table A.2).

2.3. Statistical analyses

Sex-specific incidence rates (IRs) were computed as the number of new cancer cases per 100,000 person-years in the population. IRs were directly age-standardised to the Swedish population in 2014. Male-to-female incidence rate ratios (IRRs) with 95% confidence intervals (CIs), adjusted for age and year of diagnosis, were estimated using Poisson regression. To graph male-to-female IRRs together with IRs by sex over calendar year and age at diagnosis, we included restricted cubic splines with four degrees of freedom (three internal knots) in the Poisson regression models. Age- and year-specific estimates were compared graphically with spline estimates to ensure model validity. We calculated population attributable risk percent (PAR%), i.e. the fraction of incident cancers in the total population that can be attributed to sex differences, with CIs constructed using the substitution method [21].

The overall survival analyses were restricted to year 1995–2014 to reflect modern treatment guidelines. Survival was counted from date of diagnosis until date

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