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Research Paper

Identification of Associations Between Prescribed Medications and Cancer: A Nationwide Screening Study

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ABSTRACT

Purpose: We present a systematic screening for identifying associations between prescribed drugs and cancer risk using the high quality Danish nationwide health registries.
Methods: We identified all patients (cases) with incident cancer in Denmark during 2000–2012 (n = 278,485) and matched each case to 10 controls. Complete prescription histories since 1995 were extracted. Applying a two-phased case–control approach, we first identified drug classes or single drugs associated with an increased or decreased risk of 99 different cancer types, and further evaluated potential associations by examining specificity and dose–response patterns.
Findings: 22,125 drug–cancer pairs underwent evaluation in the first phase. Of 4561 initial signals (i.e., drug–cancer associations), 3541 (78%) failed to meet requirements for dose–response patterns and specificity, leaving 1020 eligible signals. Of these, 510 signals involved the use of single drugs, and 33% (166 signals) and 67% (344 signals) suggested a reduced or an increased cancer risk, respectively. While a large proportion of the signals were attributable to the underlying conditions being treated, our algorithm successfully identified well-established associations, as well as several new signals that deserve further investigation.
Conclusion: Our results provide the basis for future targeted studies of single associations to capture novel carcinogenic or chemopreventive effects of prescription drugs.
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1. Introduction

Identification of unintended effects of drug therapy is an essential part of post-marketing drug surveillance (pharmacovigilance), as knowledge of rare side-effects is limited at the time of marketing of new medications (Strom et al., 2012). Unintended effects of drugs may involve an increase or a reduction in cancer risk (International Agency for Research on Cancer, 2012; Umar et al., 2012). Although systematic and comprehensive testing of genotoxicity and carcinogenicity is performed for any new drug prior to marketing (Brambilla and Martelli, 2009), both these laboratory assays and the premarketing phase-3 trials are disadvantaged by the typically long latency period of cancer development in humans (Umar et al., 2012; Burstein and Schwartz, 2008). For example, the excess risk of breast cancer induced by use of menopausal or contraceptive hormone therapy first becomes apparent after 5–10 years of continued use (Howell and Evans, 2011; Zhu et al., 2012), and the protective effect of aspirin against colorectal cancer requires at least five years of regular use (Chan et al., 2012; Cuzick et al., 2015). Traditional approaches in pharmacovigilance (based primarily on spontaneous reporting of adverse events) rarely detect drug–cancer associations, primarily due to the long induction time of most cancer types, which separate the use of the drug from the diagnosis by several years. As most individual cancer types are rare and have a long latency, pre-marketing clinical trials are unlikely to detect carcinogenic or chemopreventive effects of drugs due to the typically small size and short follow-up of these trials. Since neither spontaneous reporting nor clinical trials would be effective in capturing signals, the primary tool in surveillance of drugs for unintended carcinogenic or cancer preventive effects would be analyses of large administrative databases. Such studies have been instrumental in the identification of carcinogenic effects of several drugs, e.g., female hormone therapy and phenacetin (International Agency for Research on Cancer, 2012).

Denmark has a long history of establishing nationwide health care registries and databases with information on all Danish residents (Thygesen and Ersbøll, 2014). Two of the nationwide registries with the highest data quality, the Danish Prescription Registry (initiated in 1995 (Kildemoes et al., 2011)) and the Danish Cancer Registry (established in 1943 (Gjerstorff, 2011)), hold virtually complete data

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on drug prescriptions and incident cancer cases and thus provide a unique setting for active surveillance of cancer risk associated with the use of prescription drugs.

We established a system to screen for associations between prescription drug use and cancer risk, based on a multiple case–control design. In the present paper, we describe (i) the source population and data sources, (ii) the initial screening process, (iii) the strategy for internal validation of signals, and (iv) initial results from the nationwide screening.

2. Setting and Data Sources

2.1. Data Sources

The entire Danish population is provided free tax-supported medical care by the National Health Service (Thygesen and Ersbøll, 2014). For administration and maintenance of this health care system, numerous administrative and health registries have been established. In addition to supporting high quality service in the health care system, these registries allow population-based studies covering all residents in Denmark (approximately 5.6 millions).

The main data sources for our screening system include the Danish Cancer Registry (Gjerstorff, 2011), the Danish Prescription Registry (Kildemoes et al., 2011), the Danish National Patient Registry (Lynge et al., 2011), and the Danish Civil Registration System (Pedersen, 2011).

The Danish Cancer Registry (Gjerstorff, 2011) has recorded incident cancer cases on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cases (Gjerstorff, 2011; Statens Serum Institute and Danish Cancer Society, n.d.). Approximately 90% of cancer cases in the registry are histologically verified, while the remaining are mainly represented by brain tumours and cancers in very old and/or frail patients. Cancer diagnoses are recorded using the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-3).

The Danish National Prescription Registry (Kildemoes et al., 2011) contains data on all prescription drugs dispensed to Danish residents since 1995. The data include the type of drug, date of dispensing, and quantity dispensed. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO (WHO Collaborating Centre for Drug Statistics Methodology, 2014).

The Danish National Patient Register (Lynge et al., 2011) contains nationwide data on all non-psychiatric hospital admissions since 1977 and all outpatient specialist contacts in hospital setting since 1995. Discharge/contact diagnoses are coded using ICD-8 (1977–1993) and ICD-10 (1994–).

The Danish Civil Registration System (Pedersen, 2011) contains data on vital status (date of death) and migration to and from Denmark, allowing sampling of general population controls and complete tracking of study subjects.

2.2. Data Linkages

Data sources were linked by the civil registry number, a unique identifier assigned to all Danish residents since 1968 (Pedersen, 2011). Linkage was performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes (Thygesen et al., 2011a).

2.3. Identification of Cancer Cases

From the Danish Cancer Registry, we identified all individuals in Denmark with incident cancers diagnosed between January 1, 2000 and December 31, 2012. We defined the index date as the date of diagnosis. Cases were restricted to histologically verified cancers (except for tumours of the central nervous system, of which some are based on clinical and imaging findings only, and haematological malignancies).

Exclusion criteria were age outside 18–85 years at index date and migration to or from Denmark anytime during the 10 years prior to index date. This ensured at least 10 years of complete follow-up prior to sampling for all study subjects and a minimum of five years of prescription data (available from 1995). We excluded the youngest since both drug use and cancer incidence are low among children and adolescents. We further excluded individuals with a previous history of cancer (except non-melanoma skin cancer) thus focusing on primary incident cancers.

Based on ICD-O topography and morphology codes for 34 cancer sites, we restricted the cancer outcomes to 99 cancer subtypes. For a complete list of the included cancers and their definitions within the Cancer Registry, see Appendix A.

2.4. Selection of Controls

Controls were selected using risk set sampling. For each case, we randomly selected 10 controls from all Danish citizens applying the same exclusion criteria as for cases and with the same sex and birth year as the case. Controls were assigned an index date identical to that of the corresponding case. Each subject was eligible for sampling as a control before becoming a case and could be sampled as a control more than once. Thereby, the calculated odds ratios (ORs) provide unbiased estimates of the corresponding incidence rate ratios (IRRs) that would have emerged from cohort studies conducted in the underlying source population (Rothman et al., 2008).

2.5. Approvals and Funding

The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board (Thygesen et al., 2011a). The study was funded by the Danish Council for Independent Research (grant 4004-00234B). The funder had no role in the study conduct, interpretation of data, or reporting of the findings.

3. Initial Screening Process

The process consisted of two stages. In the first stage, we identified potential signals, i.e., drug–cancer associations. Those associations meeting our strength criteria qualified for further evaluation of causation in the second stage (see “Evaluation of Signals” below).

3.1. Classification of Drug Exposures

For each cancer or cancer subtype in the screening process, we included all drugs and drug classes that either had 10 observed long-term users (defined as ≥8 prescriptions) among the cases or where 10 cases were expected to be long-term users based on drug exposure among the controls given no drug–cancer association. Single drugs were defined by the fifth level of the ATC-system (e.g., C07AB02, metoprolol), and drug classes were analysed at both the second (e.g., C07, all beta-blockers) and fourth level (e.g., C07AB, selective beta-blockers).

Exposure to a specific drug or drug class was assessed from prescription fills recorded in the Prescription Registry prior to the index date for cases and controls. We classified use as non-use (0–1 prescription), intermediate use (2–7 prescriptions), and long-term use (≥8 prescriptions). Eight prescriptions was chosen as a cut-off as drugs for chronic treatment are typically supplied for 3 months use for each dispensing in Denmark, whereby our definition of long-term use would correspond to two years' cumulative treatment.

In all assessments of primary drug exposures or confounders, we disregarded prescriptions redeemed within one year prior to the index date. This was done for two reasons. First, such recent exposure is unlikely to be associated with cancer development (International Agency for Research on Cancer, 2012; Umar et al., 2012). Secondly, drug use has been shown to increase in the year prior to cancer

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