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Recurrent antibiotic exposure may promote cancer formation – Another step in understanding the role of the human microbiota?

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Abstract ***Background:*** Bacterial dysbiosis was previously described in human malignancies. In a recent animal model, tumour susceptibility was transmitted using faecal transplantation. Our aim was to evaluate possible association between antibiotic exposure and cancer risk.
Methods: We conducted nested case–control studies for 15 common malignancies using a large population-based electronic medical record database. Cases were defined as those with any medical code for the specific malignancy. Individuals with familial cancer syndromes were excluded. For every case, four eligible controls matched on age, sex, practice site and duration of follow-up before index-date were selected using incidence-density sampling. Exposure of interest was antibiotic therapy >1 year before index-date. Adjusted odds-ratios (AORs) and 95% confidence intervals (CIs) were estimated for each antibiotic type using conditional logistic regression.
Results: 125,441 cases and 490,510 matched controls were analysed. For gastro-intestinal malignancies, the use of penicillin was associated with an elevated risk of oesophageal, gastric and pancreatic cancers. The association increased with the number of antibiotic courses and reached 1.4 for gastric cancers associated with >5 courses of penicillin (95% CI 1.2–1.8). Lung cancer risk increased with the use of penicillin, cephalosporins, or macrolides (AOR for >5

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courses of penicillin: 1.4 95% CI 1.3–1.6). The risk of prostate cancer increased modestly with the use of penicillin, quinolones, sulphonamides and tetracyclines. The risk of breast cancer was modestly associated with exposure to sulphonamides. There was no association between the use of anti-virals and anti-fungals and cancer risk.

Conclusion: Recurrent exposure to certain antibiotics may be associated with cancer risk in specific organ sites.

1. Introduction

Antibiotic therapy is commonly used with up to 15% of the western population receiving at least one antibiotic course per-year [1]. In addition to targeting pathogenic bacteria, antibiotics alter the composition and decrease the diversity of human microbiota [2,3].

Bacterial dysbiosis has been described in gastrointestinal [4–6], genito-urinary [7] and breast cancers [8] as well as pre-malignant lesions in the colon [5]. Numerous mechanisms have been proposed to explain the association between bacterial dysbiosis and cancer risk, including induction of chronic inflammation; changes in the normal tissue metabolism; direct genotoxic effects; and weakening of the immune response [5,9–13].

Previous epidemiologic studies in humans evaluated the possible impact of antibiotic exposure on cancer risk in the lung [14], breast [15], prostate [16], colon [17] and skin [17] with conflicting results. Important limitations of these studies included lack of adjustment for common cancer risk factors, reverse causality (cancer patients are at higher risk for infections), confounding by indication (infection may be a risk factor for cancer), protopathic bias (medication was prescribed due to symptom of undiagnosed cancer) and failure to account for changes in trends of antibiotic prescription over time as well as changes in antibiotic types used.

In a recent study in mice that were genetically susceptible to CRC, a distinct microbiota composition following high fat diet had a causative role in tumour progression. This phenotype could be transmitted to healthy mice using faecal samples while antibiotics were able to block tumour progression [18]. In addition, we recently reported a higher risk of colorectal cancer (CRC) associated with penicillin use >1 year before diagnosis date. The risk increased with increasing number of antibiotic courses prescribed (>10 courses, adjusted odds-ratio (AOR) 1.2, 95% confidence interval (CI) 1.1–1.3) [19]. These data suggest the possibility that repeated antibiotic exposure and a subsequent change in microbiota diversity, both in the gut as well as in other body sites may promote cancer formation.

The current study aims to further evaluate the association between antibiotic exposure and cancer risk in multiple organ sites including the lung, breast, skin, gastrointestinal and genitourinary tract. As possible negative controls for this association, we selected melanoma (associated with exposure to ultraviolet radiation) and cervical cancer (associated with human papilloma virus). By analysing different time intervals of prescriptions, detailed information regarding previous infectious events and thorough cancer risk factors, we tried to avoid the bias that impaired the conclusions of previous studies.

2. Methods

2.1. Study design

We conducted nested case-control studies for 15 different epithelial, mesenchymal and haematologic malignancies using The Health Improvement Network (THIN) database. This design is computationally more efficient than a cohort-study, and produces odds-ratios (ORs) that are unbiased estimates of incidence-rate-ratios [20]. The study was approved by the Institutional Review Board at the University of Pennsylvania and by the Scientific Review Committee of THIN.

2.2. Data source

THIN is a large population-based electronic medical record database from the United Kingdom (UK) that contains data on approximately eleven million patients treated by general practitioners (http://www.thin-uk.com/). THIN includes information on patient demographics, socioeconomic status, medical diagnoses, lab results and drug prescriptions. Registration date is defined as the date when patients were first registered with a practice in THIN and Vision date is the date that a practice began using in-practice Vision software that collects information for the THIN database [21]. Data quality is monitored through routine analysis of the entered data [22]. The database has been previously used for pharmaco-epidemiology studies, showing excellent quality of information [23].

2.3. Study cohort

All people receiving medical care from 1995 to 2013 from a THIN practitioner were potentially eligible for inclusion. Patients without acceptable medical records (i.e., incomplete documentation or out of sequence date of birth, registration date, date of death, or date of exit