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Morbidity risks among older adults with pre-existing age-related diseases

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ABSTRACT

Multi-morbidity is common among older adults; however, for many aging-related diseases there is no information for U.S. elderly population on how earlier-manifested disease affects the risk of another disease manifested later during patient's lifetime. Quantitative evaluation of risks of cancer and non-cancer diseases for older adults with pre-existing conditions is performed using the Surveillance, Epidemiology, and End Results (SEER) Registry data linked to the Medicare Files of Service Use (MFSU). Using the SEER-Medicare data containing individual records for 2,154,598 individuals, we empirically evaluated age patterns of incidence of age-associated diseases diagnosed after the onset of earlier manifested disease and compared these patterns with those in general population. Individual medical histories were reconstructed using information on diagnoses coded in MFSU, dates of medical services/procedures, and Medicare enrollment/disenrollment. More than threefold increase of subsequent diseases risk was observed for 15 disease pairs, majority of them were i) diseases of the same organ and/or system (e.g., Parkinson disease for patients with Alzheimer disease, HR = 3.77, kidney cancer for patients with renal failure, HR = 3.28) or ii) disease pairs with primary diseases being fast-progressive cancers (i.e., lung, kidney, and pancreas), e.g., ulcer (HR = 4.68) and melanoma (HR = 4.15) for patients with pancreatic cancer. Lower risk of subsequent disease was registered for 20 disease pairs, mostly among patients with Alzheimer's or Parkinson's disease, e.g., decreased lung cancer risk among patients with Alzheimer's (HR = 0.64) and Parkinson's (HR = 0.60) disease. Synergistic and antagonistic dependences in geriatric disease risks were observed among US elderly confirming known and detecting new associations of wide spectrum of age-associated diseases. The results can be used in optimization of screening, prevention and treatment strategies of chronic diseases among U.S. elderly population.

1. Introduction

Approximately 96% of Medicare expenditures were accounted for by the 2/3 of beneficiaries with multiple chronic conditions (Anderson et al., 2004). At advanced ages, people are at their highest multi-morbidity risks that also lead to growing medical expenditures. The risks of different diseases may be not independent: disease that has occurred earlier can increase or decrease the probability of occurrence of the disease that will be diagnosed later. To evaluate these relationships, two types of disease risks should be distinguished: conditional (calculated for cohort of the patients who have the disease of interest) and unconditional (calculated for the general population). The conditional risk reflects the interrelations between an earlier occurred (pre-existing) disease and a subsequent disease (manifested later in time), while the unconditional risk of disease occurrence does not depend on the presence of other diseases in the patient. The conditional risk of a certain disease could be higher (in this case pre-existing disease is a risk factor for this disease) or lower (in this case pre-existing condition possesses certain protective effect against this disease) than the unconditional risk. Understanding and evaluation of relationships between the aging-associated diseases risks are important for both public health and clinical practice –– i.e., at the population and individual patient's levels. The detailed information on dependent risks helps to develop the prognoses of population morbidity (including disease incidence and prevalence) and mortality with a better accuracy; specifically, the effects of pre-existing diseases on risks of later-in-life diagnosed diseases can be incorporated into disease incidence prognosis and into the health forecasting models for specific population groups. Also, understanding the possible underlying causes of observed phenomena of dependence between disease risks (e.g., the effects of treatment of earlier occurred disease that can increase or decrease the risk of later occurred disease, shared behavioral risks, pleotropic effects of genes) can be used for developing new preventive strategies and therapeutic approaches. Recently, several pairs of diseases whose risks

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were influenced by the presence of another pre-existing disease have been described: e.g., cancer and circulatory diseases, cancer and Parkinson's disease, stroke and Alzheimer's disease, cancer and diabetes, and asthma and cancer (Tabarés-Seisdedos et al., 2011; Ukraintseva et al., 2010).

However, systematic information about disease dependence is largely lacking. We considered 21 diseases representing various systems of human organism and evaluated the conditional and unconditional disease risks using empirical methods and more formal approaches based on the proportional hazard models. Specific attentions were paid to pairs of diseases of the same organ, the same system, and diseases for which a pre-existent condition decreased or substantially increased their risks.

The Medicare-based datasets provide an excellent, underexplored opportunity for systematic investigation of the mutual dependence of aging-associated diseases risks at the national level. The progress in this area became possible after development and validation of a computational approach allowed for identifying the date of onset of cancer and non-cancer diseases for Medicare beneficiaries using longitudinal information from Medicare Files of Service Use (MFSU) (Akushevich et al., 2012; Yashin et al., 2010). The Surveillance, Epidemiology, and End Results (SEER) Registry data linked to MFSU is one of the largest sources of such information for cancer and non-cancer diseases. Accordingly, the SEER-Medicare data are used in analyses presented this paper.

1.1. Data and methods

1.1.1. SEER-Medicare data

The expanded SEER registry covers approximately 26% of the U.S. population. In total, the Medicare records for 2,154,598 individuals are available in SEER-Medicare including individuals i) with diagnosed cancers of breast (n = 353,285), colon (n = 222,659), lung (n = 342,961), prostate (n = 448,410) and skin melanoma (n = 101,123); and ii) from a random 5% sample of Medicare beneficiaries residing in the SEER areas who had none of the above mentioned cancers. For the majority of patients, we have continuous records of Medicare services use from 1991 (or from the time the person has passed the age of 65 after 1990) until his/her death. A small fraction of individuals (e.g., new patients diagnosed with cancer in 2003–2005) has Medicare records from 1998. Medicare records are available for each institutional (MedPAR, outpatient, hospice, or home health agency HHA) and non-institutional (Carrier–Physician–Supplier and Durable Medical Equipment Providers) claim type.

1.1.2. Computation of dates of onsets and disease rates

Twenty one diseases of various systems were selected for analyses based on the following selection criteria: i) most common cancers (lung, colon, female breast, and prostate) and cancers with increasing incidence (skin melanoma, kidney, pancreatic); ii) highly prevalent diseases of cardio- (myocardial infarction, angina pectoris, heart failure) and cerebrovascular (stroke) systems, respiratory system (chronic obstructive pulmonary disease (COPD), asthma), and kidney and gastrointestinal tract (chronic renal disease/failure, ulcer); iii) highly prevalent (Parkinson's and Alzheimer's) neurodegenerative diseases; iv) highly prevalent endocrine disease (diabetes) or disorder with growing prevalence and public health concern (goiter); v) highly prevalent autoimmune disease with high disability (rheumatoid arthritis); and vi) trauma/injury associated with high medical costs and disabilities (hip fracture). The ages at disease onsets were reconstructed from the MSUF data using the scheme described in detail in Akushevich et al. (2012). In brief, individual medical histories for each selected disease were reconstructed from MFSU by combining all records with their respective ICD-9 codes (listed in Supplementary Table 1). Then, a special computational procedure was applied for individuals with the histories of considered disease to separate the incident and prevalent cases and to identify the age at the disease onset. An individual was treated as having a disease onset when he/she had two records (occurred during 0.3 year interval) with respective ICD-9 code as a primary diagnosis in one of four Medicare sources: inpatient care, outpatient care, physician services, and skilled nursing facilities. The first of these two records was interpreted as a preliminary diagnosis, and the second record provided a confirmation of the diagnosis. The date of the disease onset was the date of the first record.

Identified dates of disease onsets for all diseases were combined into the individual medical history containing information about the date of entry into the follow-up, the dates of disease onsets (if any), and the date of, and survival status at, the end of individual follow-up. This information was used for evaluation of age-patterns of unconditional and conditional disease incidences. Unconditional disease incidence was evaluated for each disease for the total population, and the conditional rates were evaluated for cohorts of individuals after another disease onset. The proportional hazard model of disease incidence with the age as the follow-up variable was used to estimate the hazard ratios of occurrence vs. non-occurrence of the disease with earlier onset (i.e., pre-existing disease). The model was applied for all individuals in the dataset. Since individual follow-up could start from different ages (e.g., because of relocation to the SEER areas after age 65), we used the proportional hazard model with left truncation. The dependent variable is the occurrence of the pre-existence condition. The binary indicator function is the respective time-dependent covariate. It equals 0 or 1 for time periods of individual follow-up before or after the onset of the earlier occurred disease.

2. Results

In total, 420 pairs of diseases were analyzed. For each pair, we calculated the age patterns of the unconditional incidence rates of the diseases, conditional rates of later-in-life diagnosed disease for individuals after onset of the earlier diagnosed disease, and the hazard ratios of onset of later occurred disease in the presence (or absence) of the pre-existing disease. The most interesting results are presented in Figs. 1 and 2, and all sets of plots are given in Supplementary Fig. 1. The three evaluated quantities, i.e., conditional and unconditional rates and hazard ratios, are presented in each cell of these Figs. We focused on identifying three groups of interrelations between the studied diseases: i) diseases whose risk became much higher when patients had certain pre-existed (earlier diagnosed) disease (Fig. 1); ii) diseases whose risk became lower than in the general population when patients had certain pre-existing conditions (so called “trade-off” effect between earlier and later occurred diseases) (Fig. 2); and iii) diseases for which “the two-tail” effects were observed: i.e., when the effects are significant for both orders of disease precedence; both effects can be direct (any of the disease from a disease pair increases the risk of another disease), inverse (any of the disease from a disease pair decreases the risk of another disease), or controversial (one disease increases the risk of another, but another disease decreases the risk of the second disease from a considered disease pair).

Fifteen pairs of diseases with high (above 3.0) and significant HRs ($p < 0.001$) were identified (Fig. 1). Three types of interrelations were detected. The first one comprises diseases pairs when the later diagnosed diseases (both cancers and non-cancers) occurred in patients who had earlier diagnosed cancers that are characterized by quick progression (i.e., cancers of lung, kidney, and pancreas): cancers of breast (HR = 3.3) and kidney (HR = 4.6) in lung cancer patients; cancers of lung (HR = 3.1) and pancreas (HR = 3.6), and chronic kidney disease (HR = 3.3) among kidney cancer patients; and cancers of lung (HR = 4.9), colon (HR = 3.4) and breast (HR = 3.8), melanoma (HR = 4.2), and peptic ulcer (HR = 4.7) among the patients with pancreas cancer. The second type of interrelations was when the later occurred disease was of the same organ/system: e.g., manifestation of Parkinson's disease after Alzheimer's disease (HR = 3.8), angina pectoris after myocardial