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## Cancer and risk of Alzheimer’s disease: Small association in a nationwide cohort study

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### Abstract

**INTRODUCTION:** Small observational studies with short-term follow-up suggest cancer patients are at reduced risk of Alzheimer’s disease (AD) compared to the general population.

**METHODS:** Nationwide cohort study using Danish population-based health registries (1980–2013) with cancer patients (n=949,309) to identify incident diagnoses of AD. We computed absolute reductions in risk attributed to cancer and standardized incidence rate ratios (SIRs) accounting for survival time, comparing observed to expected number of AD cases.

**RESULTS:** During up to 34 years of follow-up of cancer survivors, the attributable risk reduction was 1.3 per 10,000 person-years, SIR=0.94 (95% confidence interval 0.92, 0.96). SIRs were similar after stratification by sex, age and cancer stage, and approached the general population for those surviving >10 years.

**DISCUSSION:** Inverse associations between cancer and AD were small and diminished over time. Incidence rates in cancer survivors approached those of the general population, suggesting limited association between cancer and AD risk.

### Keywords

Neoplasms; Alzheimer Disease; Dementia; Epidemiology; Risk

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None.

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## BACKGROUND

Several observational studies have shown reductions in risk for Alzheimer's disease (AD) or dementia subsequent to a cancer diagnosis [1–9]. An intriguing explanation involves opposing pathological processes, from uncontrolled cell proliferation in malignancy to neuronal cell death in AD and dementia [10–13]. An alternative explanation for the inverse association is failure to consider the competing risk of death among cancer patients, whose mortality rates are higher compared with individuals without cancer [14]. Moreover, clinicians may be less likely to pursue a dementia diagnosis in patients with life-threatening illness and shortened life expectancy, leading to an inverse detection bias.

A recent cohort study conducted in the state Washington found mixed evidence for an association between cancer and subsequent AD [hazard ratio (HR)=0.95 (95% confidence interval (CI): 0.77–1.17) for prevalent cancer at study inclusion and 0.73 (95% CI: 0.55–0.96) for incident cancer diagnosed during follow-up, with similar results before and after adjustment for a variety of potentially confounding factors [15]. The investigators stratified their analyses by prevalent cancer at study entry, by incident cancer diagnosed during follow-up, and by cancer stage; power was low due to a relatively small sample (n=4,357 participants aged 65+ years) [15]. Other studies have reported similar findings or even greater risk reductions but have also had parallel limitations, lacking stratification by dementia subtypes or cancer stage or including no information on relevant comorbidities [1–7,9,15].

In this nationwide cohort study with 34 years of follow-up, we examined the risk for AD, vascular dementia (VaD), and all-cause dementia in patients with a first primary cancer diagnosis and within specific primary cancer sites and stages compared to risk within the entire Danish general population.

## METHODS

### Setting and data sources

The Danish health care system provides tax-supported health care to all residents. Nationwide registries track diagnoses, procedures, and vital status for the entire population. These registries can be linked accurately using the unique civil personal registration number assigned to all Danish residents at birth or upon immigration. The Civil Registration System (CRS) records emigration and vital status [16].

The Danish Cancer Registry (DCR) maintains information on all incident cancers diagnosed in Denmark since 1943, including morphology, histology, and stage at diagnosis [17]. The Danish National Patient Registry (DNPR) has recorded all inpatient discharge diagnoses given to patients since 1977 and diagnoses made at hospital outpatient clinics since 1995 [18]. The Psychiatric Central Research Registry (PCRR) has similarly recorded inpatient psychiatric diagnoses given to patients since 1969 and diagnoses made at psychiatric outpatient visits since 1995 [19]. These registries coded diagnoses according to the *Eighth Revision* of the *International Classification of Diseases* (ICD-8) until 1993 and according to

the ICD-10 starting in 1994 [18]. The diagnostic codes used in this study are provided in Appendix Table A.

### Design and study population

We established a cohort of patients with a first incident primary cancer diagnosed during 1980—2013 recorded in the DCR. While benign neoplasms were not regarded as cancer, benign neoplasms of the brain and meninges were included in the analysis, because these conditions may cause neurologic symptoms similar to those caused by malignancy. We excluded patients with prevalent dementia diagnosed in an inpatient or outpatient setting up to and including the date of cancer diagnosis. We first analyzed all cancer sites in aggregate. We then selected some of the most common cancer sites and those that have been associated with dementia in previous studies [2,4,7,9,15,20]-- bladder, brain, breast, colon, kidney, leukemia, lung, melanoma, non-melanoma skin cancer, pancreatic, and prostate cancer--for separate analysis because of varying biology and prognosis. The large size of the Danish data is a notable strength of this study because it permits analysis by cancer type. Specificity of associations with only some types of cancer might give insight into the biological phenomena underlying the association or implicate particular types of bias, but prior studies have generally been too small to provide statistically precise estimate for particular cancer types. Information on cancer stage at diagnosis was collected for solid tumors. In total 15,270 cancer patients were excluded from the study due to dementia or a diagnosis likely to represent prodromal dementia (mild cognitive impairment or amnesic syndrome) before or on the cancer diagnosis date, leaving 949,309 cancer patients for analysis.

For patients with the selected cancer types (n=679,122), we also included a general population comparison cohort without any prevalent cancer diagnosis and dementia, mild cognitive impairment, or amnesic syndrome and matched them up to 5:1 within one year of birth, sex, and exact index year of cancer diagnosis.

We obtained information on inpatient and outpatient hospital diagnoses of comorbidities included in the Charlson Comorbidity Index (CCI) that were diagnosed before the cancer diagnosis date and information on receipt of chemotherapy within 3 months after cancer diagnosis [21].

### Endpoints and follow-up

Patients and their comparators were followed from their cancer diagnosis/index date until a record of incident dementia (either AD, VaD, or all-cause dementia [including unspecified dementia, Pick's disease, Creutzfeld-Jakob disease, Huntington's disease, HIV dementia, Parkinson's disease dementia, Lewy body dementia, progressive supranuclear palsy, and other specified and unspecified diseases]) recorded in the DNPR or the PCRR, death, emigration from Denmark, or 31 December 2013, whichever occurred first.

### Analytic variables

Age on the index date was categorized (<50, 50–59, 60–69, 70–79, and 80 years) and comorbidity burden was classified using the CCI [21], excluding malignancy and dementia. An individual's score weights were defined as total scores of 0, 1, 2–3, and 4, and

conditions comprising the CCI were also examined individually. Cancer was analyzed as all types combined and by the predefined specific cancer sites. Stage at diagnosis for solid tumors was categorized as localized, regional, distant and missing/unknown. Dementia was classified as AD, VaD, and all-cause dementia.

### Statistical analysis

We characterized cancer patients according to baseline characteristics. The potential reduction in dementia cases per 10,000 person-years was computed as the expected minus the observed number of cancer cases divided by the person time in days. We calculated standardized incidence rate ratios (SIRs) as a measure of relative risk by comparing observed dementia incidence among cancer patients with that expected, based on single years of age-, sex-, and single calendar-year-standardized incidence in the general population, and stratified by baseline characteristics. Associated 95% CIs were derived using Byar's approximation, assuming that the observed number of cases in a specific category followed a Poisson distribution. We used exact 95% CIs when the observed number of cancers was less than ten. Analyses were then stratified for cancer survivors by 0–1 year, >1–5 years, >5–10 years, >10–20 years, and >20–34 years of follow-up. To examine potential effects of chemotherapy or radiotherapy, we repeated the analysis for cancer patients diagnosed in 2004 or later receiving any type of chemotherapy by follow-up periods.

A Cox proportional hazard regression analysis was conducted using patients with the pre-specified cancer types separately and compared with their matched general population comparators in a stratified Cox analysis within the matched factors and follow-up periods as described above.

We conducted a number of sensitivity analyses. Our initial coding classified senile dementia (ICD-8) and unspecified dementia (ICD-10) as all-cause dementia. To account for potential miscoding, we conducted sensitivity analyses that re-categorized these as AD rather than all-cause dementia, with no effect on our results. We also conducted an analysis that only included inpatient diagnoses of dementia. We then repeated the analysis including mild cognitive dementia or amnesic syndrome in the dementia outcome. Finally, for the overall estimates we calculated E-values for dementia SIRs using the formula for HRs with rare outcomes (< 15%) [22]. The E-value describes the strength that an unmeasured confounder or set of confounders would need to have with both the exposure and outcome (assuming these two associations were equal) to fully explain the observed-exposure-outcome association [22].

## RESULTS

### Characteristics of the cancer cohort

A total of 949,309 cancer patients were included in the study (48.3% male), involving 5,242,643 person-years of observation. Median age at cancer diagnosis was 67 years (interquartile range (IQR): 57–76 years). The median follow-up was 3.1 (IQR: 0.70–8.1)

years for cancer patients and 7.2 (IQR: 3.3–13.2) years for population comparisons. The majority of cancer patients had no comorbidities at diagnosis (74%) (Table 1).

### Risk of dementia after cancer

Table 2 shows the observed and expected number of dementia cases with corresponding SIRs and the absolute reduction in risk attributed to cancer per 10,000 person-years by descriptive characteristics and by follow-up period. During 34 years of follow-up, the observed to expected number was 10,048/10,725 cases of AD, 3598/3930 cases of VaD, and 28,544/29,723 cases of all-cause dementia.

After any cancer diagnosis, we observed a modestly reduced SIR for all-cause dementia (SIR: 0.96, 95% CI: 0.95–0.97). The absolute reduction in dementia risk attributed to cancer was 2.2 per 10,000 persons. Similar reductions were observed for AD and VaD and for males and females. SIRs for all-cause dementia and AD were above 1.0 for individuals with higher CCI scores and for individuals with most individual comorbid conditions, but were under 1.0 (SIR=0.91 [ 95% CI: 0.84–0.99]) for patients with comorbidity scores of 2–3. Stratified by age group at cancer diagnosis or cancer treatment with chemotherapy or radiotherapy, the risks for all-cause dementia, AD, or VaD were near unity (Table 2). When stratified by follow-up period, the long-term (34-year) relative risk of dementia among cancer survivors approached a null association for AD and all-cause dementia, although not for VaD. The inverse associations between cancer and AD and all-cause dementia were somewhat more pronounced for a cancer diagnosis in recent years (from 1995 onwards) than in earlier years (Table 2). In a sensitivity analysis including only inpatient diagnoses, the SIR for all-cause dementia was 0.94 (95% CI: 0.93–0.95), compared to 0.96 (95% CI: 0.95–0.97) in the primary analysis. In the analysis that added mild cognitive impairment and amnesic syndrome to the definition of dementia the number of observed all-cause dementia cases increased to 29,745 from 28,544 in our primary analysis and the association between cancer and dementia was similar to the primary analysis (SIR=0.97; 95% CI: 0.96–0.98).

Based on SIRs for the primary analysis, we estimate E-values as 1.32 for AD, 1.39 for VaD, and 1.25 for all-cause dementia.

We found diverging results by specific cancer sites, though the stage stratified analyses were restricted by low number of dementia cases. The SIRs were elevated for all types of dementia after brain cancer; increased for all-cause dementia but null or reduced for AD and VaD after lung cancer; and reduced or similar to that of the general population for most of the remaining cancer sites (Table 3).

Results from the Cox regression analysis of the matched cohorts (i.e., using both the cancer cohort and the general population comparison cohort) and stratified by years of follow-up resembled that of the SIR analysis (data not shown).

## DISCUSSION

In this large nationwide cohort study—which involved 34 years (5,242,643 person-years) of follow-up—we observed a 6% lower incidence rate for diagnosis of AD, and 4% for all-

cause dementia associated with prior cancer diagnosis. The magnitude of the association was closer to the null than previously reported and further attenuated after 10 years, approaching that of the general population.

During 34 years of follow-up of cancer survivors, the reduction in the number of AD cases attributed to cancer was only 1.3 AD cases per 10,000 person-years. We observed similar associations for VaD, where the primary underlying etiology is less likely to be neurodegenerative, and for dementia of any cause. The magnitude of these associations was considerably less than previously reported, as discussed below.

### Strengths and weaknesses

Strengths of this population-based cohort study include its large size and length of follow-up. Furthermore, all Danish hospitals and hospital clinics report data on diagnoses including dementia to the DNPR and the PCRR [18,19]. Data in the DCR are nearly complete and valid due to compulsory reporting except for non-melanoma skin cancer. Most tumors are histologically confirmed since 2009 [17]. Follow-up of all study participants was virtually complete, as patients were identified using comprehensive hospital-based registries in a healthcare system providing free access to health care, and as patients could be tracked easily through the CRS [16,18]. The positive predictive value of the dementia diagnosis in the DNPR overall has been shown to be 89% and is higher for AD than for other dementia types [23]. As many patients with dementia have mixed pathologies, including those of both AD and VaD [24], any misclassification may result in a bias with an unknown direction on the study results for individual causes of dementia, but not for all-cause dementia. To account for potential inaccurate coding, we conducted sensitivity analyses that included the ICD-8 code for senile dementia and the ICD-10 code for dementia unspecified as AD, with no effect on our results. Unfortunately, we did not have information on biomarkers relevant to diagnosis of dementia types.

Several limitations should be considered. As cancer diagnostics and treatment changed over the study period, cancer survivorship may have differed by calendar year of inclusion. However, we stratified our results by calendar year of cancer diagnosis and by follow-up period without changing the results. We excluded cancer patients with a baseline diagnosis of mild cognitive impairment or amnesic syndrome to reduce inclusion of patients with prodromal dementia. Dementia and cancer are both associated with a latency and prodromal period before diagnosis [25]. For AD, the prodromal period may be as long as 25 years [26]. The temporal indeterminacy of disease onset is a concern for shorter-term associations. Although competing risk of death is a concern when comparing cumulative risk of dementia among individuals with a cancer history to cumulative risk of dementia among individuals without a cancer history, it is unlikely to explain our results because our analyses are based on incidence rates, which intrinsically correct for differences in time at risk. Residual confounding is a possible explanation and -- unlike in typical studies focused on causal effects of an exposure on an outcome-- would be an important explanation in this case. A confounder-based explanation of the inverse association between cancer and dementia implies that there is an unmeasured factor that increases cancer risk but decreases dementia risk (or vice-versa). This is an important possible finding, and would justify further research



on what that unmeasured factor might be. Diagnostic bias is also a possible explanation for our results. Recent work in a large population-based cohort found that individuals subsequently diagnosed with cancer had slightly better memory functioning even prior to cancer diagnosis [27]. This would imply that the diagnostic bias, if relevant, results from individuals with higher cognitive function having increased chance of cancer diagnosis. We consider this most plausible for cancers that are often undiagnosed or diagnosed upon screening, such as prostate and breast cancer.

### Previous literature

Most studies that assessed the risk for AD or dementia after cancer were conducted in the United States, were limited to study populations aged 65+ years, and were not population based [1–7,9,15]. The reported inverse associations between cancer and dementia is stronger for AD than for other dementia types. For example, Roe *et al.* reported that cancer was associated with a reduced risk for AD (HR= 0.57, 95% CI: 0.36–0.90) after adjustment for a number of factors, including *APOE* genotype, over a median of 5.4 years of follow-up. No association was found between cancer and VaD [4]. Driver *et al.* found a reduced risk of probable AD (HR=0.67, 95% CI: 0.47–0.97) following a cancer diagnosis, particularly for survivors of lung cancer and other smoking-related cancer (HR=0.26, 95% CI 0.08–0.82) [2]. Freedman *et al.* similarly reported a decreased risk for AD within 10 years of follow-up after diagnosis of cancer at different sites [7]. In a study with 21 years follow-up Bowles *et al.* reported a HR for AD of 0.95 (95% CI: 0.77–1.17) for patients with prevalent cancer and 0.73 (95% CI: 0.55–0.96) for patients with incident cancer [15]. Findings from Frain *et al.* based on data from the US Veteran Healthcare System including patients age 65+ years, support previous studies of an inverse association between some cancer types and subsequent AD [9]. A study conducted in Italy reported similar findings in a population aged 60+ years [3]. However, a study based on data from the Utah Population Database and argue that such associations arise from bias due to the competing risk of dying [14]. Both for AD and for VaD, we found a lower relative risk associated with some smoking- and alcohol-related cancers such as those of the lung and colon, but not for other smoking or alcohol-related cancers (bladder, breast, kidney, pancreatic cancer), and not for long-term cancer survivors.

### Potential Mechanism

Neurodegenerative diseases and carcinogenesis may share several molecular signaling pathways and factors involved in cell cycle dysfunction [8,13,28–33]. Though still controversial, chemotherapeutic agents may affect cognition, ranging from maintaining cognitive function through suppressed inflammation and blocked cell cycles, on the one hand [8], to potential peripheral neurotoxic effects, on the other hand [12]. As well, specific comorbidities may lead to differing diagnostic procedures and treatment choices [8,34,35]. We found inverse associations between cancer and AD across all comorbidity levels, but increased risk for VaD and all-cause dementia among cancer patients with increasing CCI scores.

We also found an initial inverse association between some smoking- and alcohol-related cancers and AD and VaD, which diminished during follow-up for cancer survivors. Patients

with disseminated cancer are likely to have died from their disease in the first decade after diagnosis, leaving disease-free cancer patients for the long-term analysis. Misclassification of mild AD or mild dementia as no-dementia in patients with cancer also could explain the small, early inverse association. We found an increased risk of dementia after diagnosis of both benign and malignant brain tumor, consistent with the well-known increase in dementia and cognitive dysfunction associated with all types of brain tumors.

Our overall results for AD and VaD, which are largely similar, contrast with evidence that separated AD from other types of dementia, such as the results of Roe [4] Driver [2] and Freedman [7], although other studies have reported a decreased risk for all-cause dementia after cancer [1,6]. It is possible that neurodegeneration among cancer patients with comorbid cardiovascular conditions tended to be classified as VaD rather than AD, especially since the dementia diagnoses were not supported by brain imaging for the majority of our registry-defined cohort. Therefore, some patients classified as having VaD may have had Alzheimer's pathology or a combination of vascular and AD pathologies [36]. When we stratified results by cancer stage, we also found largely similar results by stage category within each dementia subtype. This suggests that dementia is not underdiagnosed in patients with metastatic cancer who have poorer survival prospects than the general population.

### Conclusions and implications

The evidence presented here augments recent reports showing that cancer patients may have decreased relative and absolute risks for AD after standardization to the general population. However, the magnitude of the association was much less than previously reported and diminished after 10 years, approaching that found in the general population. This study does not indicate a clinically relevant association between cancer and risk of AD, VaD, or all-cause dementia. Interest in the association is largely because it suggests the possibility of a physiologic process or risk factor that increases cancer risk but decreases dementia risk, i.e., a potential confounder with biological relevance; identifying such a potential confounder might provide novel insight into the mechanisms of dementia. When interpreting the strength of the observed inverse association, it is therefore valuable to assess how strong the effects of such a potential confounder or set of confounders would have to be in order to account for the association. The E-value provides such an estimate: under the assumption that the confounder has equally strong (but inverse) associations with cancer and dementia, the confounder or set of confounders would need to increase dementia risk by roughly 25% to account for the observed inverse association. The modest effect estimates are not as large as for single major risk factors such as *APOE*- $\epsilon$ 4 allele but are in line with estimates related to some cardiovascular risk factors, for example. Such small effects may be of biological interest if they relate to pathological cascade that culminate in dementia, but could also plausibly be explained by detection bias. We also note that the major advantages of our use of administrative records, which provides a much larger sample size than ever previously evaluated, also introduces potential biases that may underestimate the association between cancer and dementia, for example due to non-differential misdiagnoses.



## Contributorship statement

HTS conceived the study idea and designed the study together with AGO and VWH. EHP and KV carried out the analyses. AGO organized the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. AGO is the guarantor.

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## Abbreviations

|             |   |
|-------------|---|
| <b>AD</b>   | Alzheimer's disease                     |
| <b>HR</b>   | Hazard ratio                            |
| <b>VaD</b>  | Vascular dementia                       |
| <b>CRS</b>  | Civil Registration System               |
| <b>DCR</b>  | Danish Cancer Registry                  |
| <b>DNPR</b> | Danish National Patient Registry        |
| <b>PCRR</b> | Psychiatric Central Research Registry   |
| <b>ICD</b>  | International Classification of Disease |
| <b>CCI</b>  | Charlson comorbidity Index              |
| <b>SIR</b>  | Standardized incidence rate ratio       |
| <b>CI</b>   | Confidence interval                     |
| <b>IQR</b>  | Interquartile range                     |

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**Table 1.**

Characteristics of 949,309 Danish cancer patients diagnosed between 1980 and 2013, and matched cohort of cancer patients and cancer free Danish residents.

|   | All cancer patients |     | Matched cohorts                      |     |                                |     |
|---|---------------------|-----|--------------------------------------|-----|--------------------------------|-----|
|   | N                   | %   | Patients with specific cancer types* |     | Matched population comparisons |     |
|   | N                   | %   | N                                    | %   | N                              | %   |
| <b>Total</b>                            | 949,309             | 100 | 679,122                              | 100 | 3,395,597                      | 100 |
| <b>Gender</b>                           |                     |     |                                      |     |                                |     |
| Female                                  | 490,351             | 52  | 344,842                              | 51  | 1,724,208                      | 51  |
| Male                                    | 458,958             | 48  | 334,280                              | 49  | 1,671,389                      | 49  |
| <b>Median age (interquartile range)</b> | 67 (57, 76)         |     | 68 (58, 76)                          |     | 68 (58, 76)                    |     |
| <b>Age group, years</b>                 |                     |     |                                      |     |                                |     |
| <50                                     | 134,602             | 14  | 84,021                               | 12  | 420,889                        | 12  |
| 50–59                                   | 157,616             | 17  | 111,176                              | 16  | 555,402                        | 16  |
| 60–69                                   | 255,269             | 27  | 186,794                              | 28  | 934,335                        | 28  |
| 70–79                                   | 254,144             | 27  | 187,990                              | 28  | 939,871                        | 28  |
| 80+                                     | 147,678             | 16  | 109,141                              | 16  | 545,100                        | 16  |
| <b>Year of diagnosis</b>                |                     |     |                                      |     |                                |     |
| 1980–1994                               | 346,494             | 37  | 232,586                              | 34  | 1,162,921                      | 34  |
| 1995–2001                               | 183,789             | 19  | 128,478                              | 19  | 642,388                        | 19  |
| 2002–2009                               | 267,059             | 28  | 200,955                              | 30  | 1,004,773                      | 30  |
| 2010–2013                               | 151,967             | 16  | 117,103                              | 17  | 585,515                        | 17  |
| <b>Charlson Comorbidity Index</b>       |                     |     |                                      |     |                                |     |
| No comorbidity (CCI= 0)                 | 706,123             | 74  | 501,106                              | 74  | 2,628,460                      | 77  |
| Mild comorbidity (CCI= 1)               | 154,049             | 16  | 112,705                              | 17  | 500,327                        | 15  |
| Moderate comorbidity (CCI=2–3)          | 75,150              | 7.9 | 55,192                               | 8.1 | 228,482                        | 6.7 |
| Severe comorbidity (CCI= 4)             | 13,987              | 1.5 | 10,119                               | 1.5 | 38,328                         | 1.1 |
| <b>Specific comorbid condition</b>      |                     |     |                                      |     |                                |     |
| Myocardial infarction                   | 39,099              | 4.1 | 29,546                               | 4.4 | 142,097                        | 4.2 |
| Congestive heart failure                | 31,901              | 3.4 | 23,559                               | 3.5 | 101,655                        | 3.0 |
| Peripheral vascular disease             | 34,456              | 3.6 | 25,828                               | 3.8 | 100,550                        | 3.0 |
| Cerebrovascular disease                 | 57,248              | 6.0 | 42,592                               | 6.3 | 200,994                        | 5.9 |
| Chronic pulmonary disease               | 61,189              | 6.4 | 46,446                               | 6.8 | 173,146                        | 5.1 |
| Connective tissue disease               | 22,618              | 2.4 | 16,602                               | 2.4 | 72,543                         | 2.1 |
| Ulcer disease                           | 38,399              | 4.0 | 26,798                               | 3.9 | 109,417                        | 3.2 |
| Mild liver disease                      | 9797                | 1.0 | 6462                                 | 1.0 | 20,312                         | 0.6 |
| Diabetes I and II                       | 38,505              | 4.1 | 27,746                               | 4.1 | 123,291                        | 3.6 |
| Hemiplegia                              | 1867                | 0.2 | 1309                                 | 0.2 | 6091                           | 0.2 |
| Moderate to severe renal disease        | 12,898              | 1.4 | 9398                                 | 1.4 | 32,469                         | 1.0 |

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|   | All cancer patients |     | Matched cohorts                      |     |                                |     |
|---|---------------------|-----|--------------------------------------|-----|--------------------------------|-----|
|   |                     |     | Patients with specific cancer types* |     | Matched population comparisons |     |
| Diabetes with end organ damage                                | 14,642              | 1.5 | 10,689                               | 1.6 | 49,085                         | 1.4 |
| Moderate to severe liver disease                              | 2674                | 0.3 | 1795                                 | 0.3 | 4668                           | 0.1 |
| AIDS  | 647                 | 0.1 | 232                                  | 0.0 | 709                            | 0.0 |
| <b>Cancer stage<sup>†</sup></b>                               |                     |     |                                      |     |                                |     |
| Localized   | 298,538             | 31  | 298,538                              | 44  |                                |     |
| Regional  | 69,692              | 7.3 | 69,692                               | 10  |                                |     |
| Distant   | 54,675              | 5.8 | 54,675                               | 8.1 |                                |     |
| Missing/Unknown   | 526,404             | 56  | 256,217                              | 38  |                                |     |
| Receipt of any radiotherapy <sup>‡</sup>                      |                     |     | 51,512                               | 14  |                                |     |
| Receipt of any chemotherapy <sup>‡</sup>                      |                     |     | 76,079                               | 21  |                                |     |
| <b>Median age at dementia diagnosis (interquartile range)</b> |                     |     | 83.1 (77.9, 87.5)                    |     | 83.5 (78.6, 87.7)              |     |
| <b>Median follow-up time (interquartile range)</b>            | 2.8 (0.60, 8.0)     |     | 3.1 (0.70, 8.1)                      |     | 7.2 (3.3, 13.2)                |     |

\* Prostate cancer (n=68,895), Lung cancer (n=103,428), colon cancer (n=67,315), pancreatic cancer (n=22,114), breast cancer (n=109,755), non-melanoma skin cancer (n=195,899), brain cancer (n=12,433), leukemia (n=21,660), melanoma (n=30,586), liver cancer (n=7,824), kidney cancer (n=15,728), bladder cancer (n=23,485).

<sup>†</sup> Only solid cancer. Other cancer types are included in the missing/unknown category.

<sup>‡</sup> Received within three months of cancer diagnosis. Restricting to patients diagnosed from 2004 onwards due to data availability.

**Table 2.**

Age, sex, and calendar-year standardized incidence rate ratios (SIRs) with 95% confidence intervals (CIs) and absolute reduction in dementia risk attributed to cancer per 10,000 person-years by descriptive characteristic for in 949,309 Danish cancer patients diagnosed between 1980 and 2013.

|                                | Alzheimer's disease |                 |                   |                         | Vascular dementia |                 |                   |                         | All-cause dementia |                 |                    |                         |
|--------------------------------|---------------------|-----------------|-------------------|-------------------------|-------------------|-----------------|-------------------|-------------------------|--------------------|-----------------|--------------------|-------------------------|
|                                | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number   | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI)       | Absolute risk reduction |
| All                            | 10,048              | 10,725          | 0.94 (0.92, 0.96) | 1.3                     | 3598              | 3930            | 0.92 (0.89, 0.95) | 0.6                     | 28,544             | 29,723          | 0.96 (0.95, 0.97)  | 2.2                     |
| <b>Sex</b>                     |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                    |                         |
| Female                         | 6121                | 6601            | 0.93 (0.90, 0.95) | 1.6                     | 1904              | 2076            | 0.92 (0.88, 0.96) | 0.6                     | 16,823             | 17,649          | 0.95 (0.94, 0.97)  | 2.7                     |
| Male                           | 3927                | 4124            | 0.95 (0.92, 0.98) | 0.9                     | 1694              | 1853            | 0.91 (0.87, 0.96) | 0.7                     | 11,721             | 12,073          | 0.97 (0.95, 0.99)  | 1.6                     |
| <b>CCI score</b>               |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                    |                         |
| None (CCI=0)                   | 7951                | 8424            | 0.94 (0.92, 0.96) | 1.1                     | 2441              | 3065            | 0.80 (0.77, 0.83) | 1.4                     | 21,513             | 23,294          | 0.92 (0.9 to 0.94) | 4.0                     |
| Low (CCI=1)                    | 1454                | 1595            | 0.91 (0.87, 0.96) | 2.6                     | 713               | 597             | 1.19 (1.11, 1.28) | -2.1                    | 4668               | 4457            | 1.05 (1.02, 1.08)  | -3.9                    |
| Moderate (CCI=2-3)             | 573                 | 626             | 0.91 (0.84, 0.99) | 2.7                     | 383               | 238             | 1.61 (1.46, 1.78) | -7.4                    | 2068               | 1753            | 1.18 (1.13, 1.23)  | -16.0                   |
| High (CCI=4+)                  | 70                  | 79              | 0.89 (0.69, 1.12) | 3.5                     | 61                | 30              | 2.03 (1.55, 2.61) | -12.2                   | 295                | 218             | 1.35 (1.20, 1.52)  | -30.2                   |
| <b>Age at cancer diagnosis</b> |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                    |                         |
| 0-49                           | 117                 | 149             | 0.78 (0.65, 0.94) | 0.2                     | 56                | 65              | 0.86 (0.65, 1.12) | 0.1                     | 571                | 527             | 1.08 (1.00, 1.18)  | -0.3                    |
| 50-59                          | 752                 | 725             | 1.04 (0.96, 1.11) | -0.2                    | 253               | 298             | 0.85 (0.75, 0.96) | 0.4                     | 2162               | 2100            | 1.03 (0.99, 1.07)  | -0.5                    |



|                                 | Alzheimer's disease |                 |                   |                         | Vascular dementia |                 |                   |                         | All-cause dementia |                 |                   |                         |
|---------------------------------|---------------------|-----------------|-------------------|-------------------------|-------------------|-----------------|-------------------|-------------------------|--------------------|-----------------|-------------------|-------------------------|
|                                 | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number   | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI)      | Absolute risk reduction |
| 60-69                           | 2353                | 2414            | 0.97 (0.94, 1.02) | 0.4                     | 975               | 995             | 0.98 (0.92, 1.04) | 0.1                     | 6812               | 6809            | 1.00 (0.98, 1.02) | 0.0                     |
| 70-79                           | 4250                | 4485            | 0.95 (0.92, 0.98) | 2.4                     | 1482              | 1623            | 0.91 (0.87, 0.96) | 1.4                     | 11,433             | 11,904          | 0.96 (0.94, 0.98) | 4.7                     |
| 80+                             | 2576                | 2953            | 0.87 (0.84, 0.91) | 10.2                    | 832               | 948             | 0.88 (0.82, 0.94) | 3.1                     | 7566               | 8382            | 0.90 (0.88, 0.92) | 22.0                    |
| <b>Year of cancer diagnosis</b> |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                   |                         |
| 1980 - 1994                     | 5059                | 5076            | 1.00 (0.97, 1.02) | 0.1                     | 1516              | 1657            | 0.91 (0.87, 0.96) | 0.6                     | 12,786             | 12,958          | 0.99 (0.97, 1.00) | 0.7                     |
| 1995 - 2001                     | 2124                | 2285            | 0.93 (0.89, 0.97) | 1.3                     | 1028              | 1093            | 0.94 (0.88, 1.00) | 0.5                     | 7480               | 7759            | 0.96 (0.94, 0.99) | 2.3                     |
| 2002 - 2009                     | 2447                | 2832            | 0.86 (0.83, 0.90) | 3.0                     | 940               | 1033            | 0.91 (0.85, 0.97) | 0.7                     | 7157               | 7756            | 0.92 (0.90, 0.94) | 4.7                     |
| 2010 - 2013                     | 418                 | 531             | 0.79 (0.71, 0.87) | 4.6                     | 114               | 147             | 0.78 (0.64, 0.93) | 1.3                     | 1121               | 1250            | 0.90 (0.85, 0.95) | 5.3                     |
| <b>Year of follow-up</b>        |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                   |                         |
| 0-1                             | 1294                | 1348            | 0.96 (0.91, 1.01) | 0.7                     | 405               | 453             | 0.89 (0.81, 0.99) | 0.6                     | 3446               | 3346            | 1.03 (1.00, 1.07) | -1.3                    |
| >1-5                            | 2964                | 3517            | 0.84 (0.81, 0.87) | 2.9                     | 1080              | 1219            | 0.89 (0.83, 0.94) | 0.7                     | 8102               | 9137            | 0.89 (0.87, 0.91) | 5.5                     |
| >5-10                           | 2495                | 2602            | 0.96 (0.92, 1.00) | 0.8                     | 898               | 963             | 0.93 (0.87, 1.00) | 0.5                     | 7033               | 7308            | 0.96 (0.94, 0.99) | 2.1                     |
| >10-20                          | 2446                | 2406            | 1.02 (0.98, 1.06) | -0.4                    | 994               | 1004            | 0.99 (0.93, 1.05) | 0.1                     | 7648               | 7572            | 1.01 (0.99, 1.03) | -0.7                    |

|  | Alzheimer's disease |                 |                   |                         | Vascular dementia |                 |                   |                         | All-cause dementia |                 |                   |                         |
|--|---------------------|-----------------|-------------------|-------------------------|-------------------|-----------------|-------------------|-------------------------|--------------------|-----------------|-------------------|-------------------------|
|  | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number   | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI)      | Absolute risk reduction |
| >20-34                                   | 849                 | 852             | 1.00 (0.93, 1.07) | 0.1                     | 221               | 291             | 0.76 (0.66, 0.87) | 2.8                     | 2315               | 2361            | 0.98 (0.94, 1.02) | 1.8                     |
| <b>Specific comorbidities in the CCI</b> |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                   |                         |
| Myocardial infarction                    | 358                 | 411             | 0.87 (0.78, 0.97) | 4.4                     | 201               | 167             | 1.20 (1.04, 1.38) | -2.8                    | 1142               | 1182            | 0.97 (0.91, 1.02) | 3.3                     |
| Congestive heart failure                 | 231                 | 288             | 0.80 (0.70, 0.91) | 8.4                     | 136               | 107             | 1.27 (1.07, 1.50) | -4.3                    | 832                | 820             | 1.01 (0.95, 1.09) | -1.8                    |
| Peripheral vascular disease              | 250                 | 281             | 0.89 (0.78, 1.01) | 3.6                     | 140               | 107             | 1.30 (1.10, 1.54) | -3.8                    | 859                | 779             | 1.10 (1.03, 1.18) | -9.2                    |
| Cerebrovascular disease                  | 560                 | 599             | 0.93 (0.86, 1.02) | 2.4                     | 532               | 223             | 2.39 (2.19, 2.60) | -18.9                   | 2250               | 1686            | 1.33 (1.28, 1.39) | -34.5                   |
| Chronic pulmonary disease                | 385                 | 461             | 0.83 (0.75, 0.92) | 4.5                     | 153               | 171             | 0.89 (0.76, 1.05) | 1.1                     | 1247               | 1251            | 1.00 (0.94, 1.05) | 0.2                     |
| Connective tissue disease                | 220                 | 250             | 0.88 (0.77, 1.00) | 3.7                     | 103               | 88              | 1.16 (0.95, 1.41) | -1.8                    | 691                | 692             | 1.00 (0.93, 1.08) | 0.2                     |
| Ulcer disease                            | 384                 | 365             | 1.05 (0.95, 1.16) | -1.6                    | 177               | 142             | 1.24 (1.07, 1.44) | -2.8                    | 1220               | 1051            | 1.16 (1.10, 1.23) | -13.7                   |
| Mild liver disease                       | 34                  | 35              | 0.98 (0.68, 1.37) | 0.3                     | 20                | 13              | 1.49 (0.91, 2.29) | -2.7                    | 165                | 97              | 1.70 (1.45, 1.98) | -28.1                   |
| Diabetes I and II                        | 314                 | 310             | 1.01 (0.91, 1.13) | -0.4                    | 192               | 110             | 1.74 (1.50, 2.01) | -7.4                    | 1085               | 822             | 1.32 (1.24, 1.40) | -23.8                   |
| Hemiplegia                               | 5                   | 13              | 0.40 (0.13, 0.93) | 13.8                    | <5                | 4               | NA                | 0.5                     | 29                 | 33              | 0.88 (0.59, 1.27) | 7.0                     |
| Moderate to severe renal disease         | 81                  | 92              | 0.88 (0.70, 1.09) | 2.9                     | 51                | 35              | 1.46 (1.09, 1.92) | -4.3                    | 285                | 256             | 1.11 (0.99, 1.25) | -7.6                    |

|   | Alzheimer's disease |                 |                   |                         | Vascular dementia |                 |                   |                         | All-cause dementia |                 |                   |                         |
|---|---------------------|-----------------|-------------------|-------------------------|-------------------|-----------------|-------------------|-------------------------|--------------------|-----------------|-------------------|-------------------------|
|   | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number   | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI)      | Absolute risk reduction |
| Diabetes with end organ                   | 101                 | 105             | 0.96 (0.79, 1.17) | 1.0                     | 87                | 40              | 2.19 (1.76, 2.71) | -12.6                   | 397                | 287             | 1.38 (1.25, 1.52) | -29.2                   |
| Moderate to severe liver disease          | <5                  | 7               | NA                | NA                      | <5                | 3               | NA                | NA                      | 26                 | 20              | 1.29 (0.84, 1.90) | -10.7                   |
| AIDS                                      | <5                  | 1               | NA                | NA                      | <5                | 0               | NA                | NA                      | 5                  | 2               | 2.57 (0.83, 5.98) | -14.3                   |
| <b>Cancer stage*</b>                      |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                   |                         |
| Localized                                 | 733                 | 824             | 0.89 (0.83, 0.96) | 2.8                     | 253               | 272             | 0.93 (0.82, 1.05) | 0.6                     | 1910               | 2156            | 0.89 (0.85, 0.93) | 7.5                     |
| Regional                                  | 6912                | 7195            | 0.96 (0.94, 0.98) | 0.8                     | 2452              | 2670            | 0.92 (0.88, 0.96) | 0.6                     | 19,503             | 20,192          | 0.97 (0.95, 0.98) | 1.9                     |
| Distant                                   | 585                 | 691             | 0.85 (0.78, 0.92) | 2.7                     | 176               | 243             | 0.73 (0.62, 0.84) | 1.7                     | 1677               | 1812            | 0.93 (0.88, 0.97) | 3.4                     |
| Missing                                   | 1818                | 2014            | 0.90 (0.86, 0.94) | 2.1                     | 717               | 745             | 0.96 (0.89, 1.04) | 0.3                     | 5454               | 5562            | 0.98 (0.95, 1.01) | 1.2                     |
| <b>Radiotherapy by follow-up period †</b> |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                   |                         |
| >3 months-10 years                        | 165                 | 220             | 0.75 (0.64, 0.87) | 4.1                     | 55                | 70              | 0.79 (0.60, 1.03) | 1.1                     | 494                | 545             | 0.91 (0.83, 0.99) | 3.8                     |
| >3months-1 year                           | 23                  | 42              | 0.55 (0.35, 0.82) | 6.5                     | 12                | 15              | 0.80 (0.41, 1.39) | 1.1                     | 98                 | 111             | 0.88 (0.72, 1.08) | 4.5                     |
| >1-5 years                                | 95                  | 129             | 0.74 (0.60, 0.90) | 4.1                     | 38                | 41              | 0.92 (0.65, 1.26) | 0.4                     | 293                | 322             | 0.91 (0.81, 1.02) | 3.6                     |
| >5-10 years                               | 47                  | 49              | 0.96 (0.70, 1.27) | 0.9                     | 5                 | 13              | 0.38 (0.12, 0.89) | 3.4                     | 103                | 113             | 0.91 (0.75, 1.11) | 4.0                     |
| <b>Chemotherapy by follow-up period †</b> |                     |                 |                   |                         |                   |                 |                   |                         |                    |                 |                   |                         |

|                    | Alzheimer's disease |                 |                   |                         | Vascular dementia |                 |                   |                         | All-cause dementia |                 |                   |                         |
|--------------------|---------------------|-----------------|-------------------|-------------------------|-------------------|-----------------|-------------------|-------------------------|--------------------|-----------------|-------------------|-------------------------|
|                    | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number   | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI)      | Absolute risk reduction |
| >3 months-10 years | 130                 | 170             | 0.76 (0.64, 0.91) | 2.2                     | 30                | 55              | 0.55 (0.37,0.78)  | 1.4                     | 342                | 425             | 0.80 (0.72, 0.89) | 4.6                     |
| >3months-1 year    | 18                  | 41              | 0.44 (0.26, 0.70) | 5.2                     | <10               | 15              | 0.20 (0.04,0.60)  | 2.7                     | 70                 | 107             | 0.65 (0.51-0.83)  | 8.4                     |
| >1-5 years         | 75                  | 98              | 0.77 (0.60, 0.96) | 2.1                     | 20                | 32              | 0.63 (0.38, 0.97) | 1.1                     | 197                | 245             | 0.80 (0.70-0.92)  | 4.5                     |
| >5-10 years        | 37                  | 32              | 1.16 (0.82, 1.60) | -1.8                    | <10               | 9               | 0.82 (0.33, 1.68) | 0.6                     | 75                 | 73              | 1.02 (0.81-1.28)  | 0.6                     |

CCI: Charlson comorbidity index.

\* Only solid tumors

<sup>†</sup>Treatment received within three months of cancer diagnosis, starting follow-up at this date. Restricting to patients diagnosed from 2004 onwards due to data availability.

**Table 3.**

Standardized incidence rate ratios (SIRs) with 95% confidence intervals (CIs) and absolute reduction in dementia risk attributed to cancer per 10,000 person-years for any dementia, in 679, 122 Danish cancer patients with specific cancer sites diagnosed between 1980 and 2013, by stage.

|                       | Alzheimer's disease |                 |                   |                         |                 |                 | Vascular dementia |                         |                 |                 |                   |                         | All-cause dementia |                 |              |                         |  |  |
|-----------------------|---------------------|-----------------|-------------------|-------------------------|-----------------|-----------------|-------------------|-------------------------|-----------------|-----------------|-------------------|-------------------------|--------------------|-----------------|--------------|-------------------------|--|--|
|                       | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI) | Absolute risk reduction |  |  |
| <b>Bladder cancer</b> | 227                 | 242             | 0.94 (0.82, 1.07) | 1.6                     | 98              | 97              | 1.01 (0.82, 1.23) | -0.1                    | 640             | 662             | 0.97 (0.89, 1.04) | 2.3                     |                    |                 |              |                         |  |  |
| Localized             | 135                 | 148             | 0.91 (0.77, 1.08) | 2.1                     | 59              | 60              | 0.99 (0.75, 1.28) | 0.1                     | 385             | 403             | 0.96 (0.86, 1.06) | 3.0                     |                    |                 |              |                         |  |  |
| Regional              | 28                  | 23              | 1.23 (0.81, 1.77) | -5.2                    | 17              | 9               | 1.90 (1.11, 3.05) | -8.1                    | 67              | 60              | 1.11 (0.86, 1.41) | -6.8                    |                    |                 |              |                         |  |  |
| Distant               | <5                  | 3               | NA                | 12.9                    | <5              | 1               | NA                | 7.6                     | 8               | 7               | 1.08 (0.47, 2.13) | -3.9                    |                    |                 |              |                         |  |  |
| Missing/Unknown       | 63                  | 69              | 0.92 (0.70, 1.17) | 2.5                     | 22              | 28              | 0.79 (0.50, 1.20) | 2.5                     | 180             | 192             | 0.94 (0.81, 1.09) | 5.0                     |                    |                 |              |                         |  |  |
| <b>Brain cancer</b>   | 13                  | 8               | 1.62 (0.86, 2.77) | -1.6                    | 10              | 3               | 2.90 (1.39, 5.33) | -2.1                    | 91              | 24              | 3.77 (3.03, 4.63) | -21.1                   |                    |                 |              |                         |  |  |
| <b>Breast cancer</b>  | 1495                | 1569            | 0.95 (0.91, 1.00) | 0.8                     | 486             | 492             | 0.99 (0.90, 1.08) | 0.1                     | 4129            | 4132            | 1.00 (0.97, 1.03) | 0.0                     |                    |                 |              |                         |  |  |
| Localized             | 899                 | 901             | 1.00 (0.93, 1.07) | 0.0                     | 276             | 285             | 0.97 (0.86, 1.09) | 0.2                     | 2403            | 2385            | 1.01 (0.97, 1.05) | -0.4                    |                    |                 |              |                         |  |  |
| Regional              | 419                 | 471             | 0.89 (0.81, 0.98) | 1.7                     | 148             | 147             | 1.01 (0.85, 1.18) | 0.0                     | 1176            | 1214            | 0.97 (0.91, 1.03) | 1.2                     |                    |                 |              |                         |  |  |
| Distant               | 30                  | 38              | 0.79 (0.53, 1.12) | 4.3                     | 10              | 11              | 0.90 (0.43, 1.66) | 0.6                     | 94              | 95              | 0.99 (0.80, 1.21) | 0.4                     |                    |                 |              |                         |  |  |
| Missing/unknown       | 147                 | 158             | 0.93 (0.78, 1.09) | 1.9                     | 52              | 50              | 1.05 (0.78, 1.37) | -0.4                    | 456             | 438             | 1.04 (0.95, 1.14) | -3.0                    |                    |                 |              |                         |  |  |
| <b>Colon cancer</b>   | 833                 | 944             | 0.88 (0.82, 0.94) | 3.6                     | 279             | 337             | 0.83 (0.73, 0.93) | 1.9                     | 2343            | 2598            | 0.90 (0.87, 0.94) | 8.4                     |                    |                 |              |                         |  |  |
| Localized             | 207                 | 253             | 0.82 (0.71, 0.94) | 6.0                     | 71              | 86              | 0.83 (0.64, 1.04) | 1.9                     | 585             | 668             | 0.88 (0.81, 0.95) | 10.8                    |                    |                 |              |                         |  |  |
| Regional              | 93                  | 104             | 0.90 (0.73, 1.10) | 3.0                     | 22              | 34              | 0.64 (0.40, 0.98) | 3.4                     | 231             | 266             | 0.87 (0.76, 0.99) | 9.9                     |                    |                 |              |                         |  |  |

|                             | Alzheimer's disease |                 |                   |                         |                 |                 | Vascular dementia |                         |                 |                 |                   |                         | All-cause dementia |                 |              |                         |  |  |
|-----------------------------|---------------------|-----------------|-------------------|-------------------------|-----------------|-----------------|-------------------|-------------------------|-----------------|-----------------|-------------------|-------------------------|--------------------|-----------------|--------------|-------------------------|--|--|
|                             | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI) | Absolute risk reduction |  |  |
| Distant                     | 20                  | 27              | 0.75 (0.46, 1.16) | 5.8                     | <5              | 8               | NA                | 4.8                     | 54              | 64              | 0.85 (0.64, 1.11) | 8.3                     |                    |                 |              |                         |  |  |
| Missing/unknown             | 513                 | 561             | 0.91 (0.84, 1.00) | 2.6                     | 183             | 208             | 0.88 (0.76, 1.02) | 1.4                     | 1473            | 1601            | 0.92 (0.87, 0.97) | 7.0                     |                    |                 |              |                         |  |  |
| <b>Kidney cancer</b>        | 86                  | 110             | 0.78 (0.62, 0.96) | 3.7                     | 53              | 42              | 1.25 (0.94, 1.63) | -1.6                    | 286             | 303             | 0.95 (0.84, 1.06) | 2.5                     |                    |                 |              |                         |  |  |
| Localized                   | 62                  | 74              | 0.84 (0.65, 1.08) | 2.6                     | 43              | 29              | 1.48 (1.07, 2.00) | -3.1                    | 204             | 206             | 0.99 (0.86, 1.14) | 0.4                     |                    |                 |              |                         |  |  |
| Regional                    | 5                   | 9               | 0.56 (0.18, 1.30) | 8.1                     | <5              | 3               | NA                | NA                      | 17              | 24              | 0.72 (0.42, 1.15) | 13.4                    |                    |                 |              |                         |  |  |
| Distant                     | 6                   | 7               | 0.86 (0.31, 1.86) | 2.0                     | <5              | 3               | NA                | NA                      | 16              | 18              | 0.88 (0.50, 1.43) | 4.2                     |                    |                 |              |                         |  |  |
| Missing/unknown             | 13                  | 21              | 0.63 (0.33, 1.08) | 7.6                     | 8               | 8               | 1.06 (0.46, 2.08) | -0.4                    | 49              | 55              | 0.89 (0.66, 1.18) | 6.0                     |                    |                 |              |                         |  |  |
| <b>Leukemia</b>             | 150                 | 162             | 0.93 (0.78, 1.09) | 1.2                     | 51              | 60              | 0.85 (0.63, 1.11) | 0.9                     | 395             | 440             | 0.90 (0.81, 0.99) | 4.5                     |                    |                 |              |                         |  |  |
| <b>Lung cancer</b>          | 174                 | 207             | 0.84 (0.72, 0.97) | 2.5                     | 65              | 81              | 0.80 (0.62, 1.02) | 1.2                     | 613             | 546             | 1.12 (1.04, 1.22) | -5.1                    |                    |                 |              |                         |  |  |
| Localized                   | 83                  | 101             | 0.82 (0.66, 1.02) | 2.9                     | 38              | 41              | 0.93 (0.66, 1.28) | 0.5                     | 291             | 272             | 1.07 (0.95, 1.20) | -3.0                    |                    |                 |              |                         |  |  |
| Regional                    | 32                  | 43              | 0.75 (0.51, 1.06) | 3.2                     | 12              | 18              | 0.68 (0.35, 1.19) | 1.7                     | 124             | 115             | 1.07 (0.89, 1.28) | -2.6                    |                    |                 |              |                         |  |  |
| Distant                     | 25                  | 38              | 0.67 (0.43, 0.98) | 5.4                     | 8               | 14              | 0.58 (0.25, 1.14) | 2.5                     | 110             | 97              | 1.14 (0.93, 1.37) | -5.6                    |                    |                 |              |                         |  |  |
| Missing/unknown             | 34                  | 26              | 1.31 (0.91, 1.83) | -6.5                    | 7               | 9               | 0.82 (0.33, 1.68) | 1.3                     | 88              | 61              | 1.43 (1.15, 1.76) | -21.6                   |                    |                 |              |                         |  |  |
| <b>Melanoma skin cancer</b> | 284                 | 325             | 0.87 (0.78, 0.98) | 1.5                     | 92              | 124             | 0.74 (0.60, 0.91) | 1.2                     | 805             | 929             | 0.87 (0.81, 0.93) | 4.5                     |                    |                 |              |                         |  |  |
| Localized                   | 253                 | 285             | 0.89 (0.78, 1.00) | 1.3                     | 82              | 110             | 0.75 (0.59, 0.93) | 1.1                     | 715             | 820             | 0.87 (0.81, 0.94) | 4.2                     |                    |                 |              |                         |  |  |
| Regional                    | 9                   | 10              | 0.94 (0.43, 1.78) | 0.7                     | <5              | 4               | NA                | NA                      | 27              | 27              | 1.01 (0.66, 1.47) | -0.3                    |                    |                 |              |                         |  |  |
| Distant                     | <5                  | 2.8             | NA                | NA                      | <5              | 1               | NA                | NA                      | <5              | 7               | NA                | NA                      |                    |                 |              |                         |  |  |



|                                 | Alzheimer's disease |                 |                   |                         |                 |                 | Vascular dementia |                         |                 |                 |                   |                         | All-cause dementia |                 |              |                         |  |  |
|---------------------------------|---------------------|-----------------|-------------------|-------------------------|-----------------|-----------------|-------------------|-------------------------|-----------------|-----------------|-------------------|-------------------------|--------------------|-----------------|--------------|-------------------------|--|--|
|                                 | Observed number     | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number | Expected number | SIR (95% CI)      | Absolute risk reduction | Observed number    | Expected number | SIR (95% CI) | Absolute risk reduction |  |  |
| Missing/unknown                 | 20                  | 27              | 0.73 (0.44, 1.12) | 3.9                     | 9               | 10              | 0.91 (0.42, 1.74) | 0.4                     | 59              | 76              | 0.78 (0.59, 1.00) | 8.9                     |                    |                 |              |                         |  |  |
| <b>Non-melanoma skin cancer</b> | 3876                | 4005            | 0.97 (0.94, 1.00) | 0.8                     | 1366            | 1505            | 0.91 (0.86, 0.96) | 0.9                     | 10805           | 11479           | 0.94 (0.92, 0.96) | 4.3                     |                    |                 |              |                         |  |  |
| Localized                       | 3316                | 3384            | 0.98 (0.95, 1.01) | 0.5                     | 1171            | 1277            | 0.92 (0.87, 0.97) | 0.8                     | 9251            | 9725            | 0.95 (0.93, 0.97) | 3.6                     |                    |                 |              |                         |  |  |
| Regional                        | 16                  | 11              | 1.50 (0.86, 2.43) | -15.3                   | <5              | 4               | NA                | NA                      | 36              | 31              | 1.17 (0.82, 1.63) | -15.3                   |                    |                 |              |                         |  |  |
| Distant                         | 5                   | 2               | 2.48 (0.80, 5.77) | -35.6                   | <5              | 1               | NA                | NA                      | 9               | 6               | 1.60 (0.74, 3.05) | -40.5                   |                    |                 |              |                         |  |  |
| Missing/unknown                 | 539                 | 608             | 0.89 (0.81, 0.96) | 2.8                     | 190             | 223             | 0.85 (0.74, 0.98) | 1.3                     | 1509            | 1718            | 0.88 (0.83, 0.92) | 8.5                     |                    |                 |              |                         |  |  |
| <b>Pancreatic cancer</b>        | 19                  | 26              | 0.72 (0.43, 1.13) | 5.2                     | 4               | 9               | 0.45 (0.12, 1.15) | 3.5                     | 59              | 66              | 0.90 (0.69, 1.16) | 4.7                     |                    |                 |              |                         |  |  |
| Localized                       | 8                   | 7               | 1.19 (0.51, 2.34) | -3.4                    | <5              | 2               | NA                | NA                      | 17              | 17              | 1.00 (0.58, 1.60) | 0.1                     |                    |                 |              |                         |  |  |
| Regional                        | <5                  | 6               | NA                | NA                      | <5              | 2               | NA                | NA                      | 10              | 14              | 0.70 (0.34, 1.29) | 10.8                    |                    |                 |              |                         |  |  |
| Distant                         | <5                  | 5               | NA                | NA                      | <5              | 2               | NA                | NA                      | 14              | 11              | 1.22 (0.67, 2.05) | -8.3                    |                    |                 |              |                         |  |  |
| Missing/unknown                 | 6                   | 9               | 0.67 (0.25, 1.46) | 9.0                     | 2               | 3               | 0.66 (0.08, 2.39) | 3.2                     | 18              | 23              | 0.79 (0.47, 1.25) | 14.9                    |                    |                 |              |                         |  |  |
| <b>Prostate cancer</b>          | 779                 | 813             | 0.96 (0.89, 1.03) | 1.2                     | 325             | 340             | 0.96 (0.85, 1.07) | 0.5                     | 2175            | 2237            | 0.97 (0.93, 1.01) | 2.2                     |                    |                 |              |                         |  |  |
| Localized                       | 387                 | 399             | 0.97 (0.88, 1.07) | 0.8                     | 162             | 164             | 0.99 (0.84, 1.15) | 0.1                     | 1080            | 1077            | 1.00 (0.94, 1.06) | -0.2                    |                    |                 |              |                         |  |  |
| Regional                        | 29                  | 27              | 1.09 (0.73, 1.57) | -2.1                    | 10              | 11              | 0.91 (0.43, 1.67) | 0.9                     | 69              | 70              | 0.98 (0.76, 1.24) | 1.2                     |                    |                 |              |                         |  |  |
| Distant                         | 84                  | 94              | 0.90 (0.72, 1.11) | 3.1                     | 22              | 40              | 0.55 (0.35, 0.83) | 5.7                     | 217             | 258             | 0.84 (0.73, 0.96) | 13.0                    |                    |                 |              |                         |  |  |
| Missing/unknown                 | 279                 | 294             | 0.95 (0.84, 1.07) | 1.8                     | 131             | 125             | 1.05 (0.88, 1.24) | -0.7                    | 809             | 831             | 0.97 (0.91, 1.04) | 2.5                     |                    |                 |              |                         |  |  |

**Appendix Table A.**

Diagnostic codes and categorizations used in the study.

|  |   |
|--|---|
| <b>Dementia, overall</b>   |   |
| Alzheimer's disease  | ICD-8: 290.10, 290.09, ICD-10: F00, G30   |
| Vascular dementia  | ICD-8: 293.09, 293.19, ICD-10: F01  |
| Other dementias  | ICD-8: 094.19 and 292.09, 290.11, 290.18, 290.19, ICD-10: F02, F03, F1x.73 (F10.73 through F19.73), G23.1; G31.0, G31.0A, G31.0B, G31.1, G31.8B, G31.8E, G31.85 |
| <b>Charlson Comorbidity Index</b>  |   |
| <i>Score 1</i>   |   |
| Myocardial infarction  | ICD-8: 410; ICD-10: I21, I22, I23   |
| Congestive heart failure   | ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2   |
| Peripheral vascular disease  | ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77   |
| Cerebrovascular disease  | ICD-8: 430–438; ICD-10: I60–I69, G45, G46   |
| Dementia – excluded  | ICD-8: 290.09–290.19, 293.09; ICD-10: F00–F03, F05.1, G30   |
| Chronic pulmonary disease  | ICD-8: 490–493, 515–518, ICD-10: J40–J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3   |
| Connective tissue disease  | ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86   |
| Ulcer disease  | ICD-8: 530.91, 530.98, 531–534; ICD-10: K22.1, K25–K28  |
| Mild liver disease   | ICD-8: 571, 573.01, 573.04; ICD-10: B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0   |
| Diabetes type 1 and 2  | ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9   |
| <i>Score 2</i>   |   |
| Hemiplegia   | ICD-8: 344; ICD-10: G81, G82  |
| Moderate to severe renal disease   | ICD-8: 403, 404, 580–583, 584, 590.09, 593.19, 753.10–753.19, 792; ICD-10: I2, I13, N00–N05, N07, N11, N14, N17–N19, Q61  |
| Diabetes with end organ damage   | ICD-8: 249.01–249.05, 249.08, 250.01–250.05, 250.08; ICD-10: E10.2–E10.8, E11.2–E11.8   |
| Any tumor – excluded   | ICD-8: 140–194; ICD-10: C00–C75   |
| Leukemia – excluded  | ICD-8: 204–207; ICD-10: C91–C95   |
| Lymphoma – excluded  | ICD-8: 200–203, 275.59; ICD-10: C81–C85, C88, C90, C96  |
| <i>Score 3</i>   |   |
| Moderate to severe liver disease   | ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85                                |
| <i>Score 6</i>   |   |
| Metastatic solid tumor – excluded  | ICD-8: 195–198, 199; ICD-10: C76–C80  |
| AIDS   | ICD-8: 079.83; ICD-10: B21–B24  |
| <b>Cancers</b>   |   |
| <i>ICD-7 codes for exclusion of prevalent cancer</i>   | ICD-7: 140–205  |
| Hodgkin's lymphoma   | ICD-10: C81   |
| Non-Hodgkin's lymphoma (excl. leukemia, multiple myeloma, and types with cutaneous manifestations) | ICD-10: C82–86, C88 (excl. C826, C840, C841, C848, C863, C866, C884B)   |

|  |   |
|--|---|
| Multiple myeloma and malignant plasma cell neoplasms   | ICD-10: C90   |
| Leukemia   | ICD-10: C91-C95   |
| Malignant neoplasm of lymphoid, haematopoietic, and related tissues, unspecified                                       | ICD-10: C96   |
| Haematological cancer with cutaneous manifestations  | C826 (cutaneous follicle center lymphoma)<br>C840 (Mycosis fungoides)<br>C841 (Sézary's disease)<br>C848 (Cutaneous T-cell lymphoma, unspecified)<br>C863 (Subcutaneous panniculitis-like T-cell lymphoma)<br>C866 (Primary cutaneous CD30-positive T-cell proliferations)<br>C884B (Lymphoma of skin-associated lymphoid tissue (SALT-lymphoma)) |
| Liver including intrahepatic bile ducts*   | ICD-10: C22   |
| Malignant melanoma including those located in anus and anal canal (morphological codes 872-879)                        | ICD-10: C43   |
| Non-melanoma skin cancers  | ICD-10: C44   |
| Kaposi's sarcoma   | ICD-10: C46, B210   |
| Cervix   | ICD-10: C53   |
| Anus and anal canal excl. malignant melanomas (morphologic code 872-879) and basal cell cancers (morphologic code 809) | ICD-10: C21   |
| External female genitalia excluding basal cell carcinomas (morphological code 809)                                     | ICD-10: C51   |
| Lip  | ICD-10: C00   |
| Tongue   | ICD-10: C01-02  |
| Mouth  | ICD-10: C03-06  |
| Tonsil and pharynx   | ICD-10: C09-C13   |
| Other and poorly specified location in lip, oral cavity, and pharynx   | ICD-10: C14   |
| Larynx   | ICD-10: C32   |
| Other and poorly specified location in airways and respiratory organs  | ICD-10: C39   |
| Oesophagus   | ICD-10: C15   |
| Stomach  | ICD-10: C16   |
| Colon incl. rectosigmoid junction  | ICD-10: C18-C19   |
| Rectum   | ICD-10: C20   |
| Pancreas   | ICD-10: C25   |
| Lung, bronchus and trachea   | ICD-10: C33-C34   |
| Kidney   | ICD-10: C64   |
| Renal pelvis   | ICD-10: C65   |
| Ureter   | ICD-10: C66   |
| Urinary bladder  | ICD-10: C67   |
| Salivary gland   | ICD-10: C07-C08   |
| Small intestine  | ICD-10: C17   |
| Gallbladder and bile ducts   | ICD-10: C23-C24   |
| Other and ill-defined cancers of digestive organs  | ICD-10: C26   |
| Nasal cavity, middle ear and accessory sinuses   | ICD-10: C30-C31   |
| Thymus   | ICD-10: C37   |
| Heart and mediastinum  | ICD-10: C380-383, C388  |
| Pleura incl. mesothelioma pleura   | ICD-10: C384, C450  |

|   |  |
|---|--|
| Bone and articular cartilage  | ICD-10: C40-C41  |
| Mesothelioma  | ICD-10: C45.1-C45.9                                      |
| Peripheral nerves and autonomic nervous system  | ICD-10: C47  |
| Retroperitoneum and peritoneum, and malignant neoplasm of other connective and soft tissue                    | ICD-10: C48-C49  |
| Breast  | ICD-10: C50  |
| Vagina excluding basal cell carcinomas (morphological code 809)   | ICD-10: C52  |
| Uterus  | ICD-10: C54-C55  |
| Ovary and fallopian tube  | ICD-10: C56, C570-574                                    |
| Placenta  | ICD-10: C58  |
| Other and unspecified female genital organs   | ICD-10: C577-579   |
| Penis excluding basal cell carcinomas (morphological code 809)  | ICD-10: C60  |
| Prostate  | ICD-10: C61  |
| Testis  | ICD-10: C62  |
| Other and unspecified cancers in male genital organs excluding basal cell carcinomas (morphological code 809) | ICD-10: C63  |
| Other and unspecified urinary organs  | ICD-10: C68  |
| Eye and adnexa  | ICD-10: C69  |
| Meninges  | ICD-10: C70  |
| Brain including hypophysis, corpus pineale, and ductus craniopharyngealis                                     | ICD-10: C71  |
| Benign neoplasms of brain and meninges  | ICD-10: DD32, DD33, DD352, DD353, DD354                  |
| Spinal cord, cranial nerves and other parts of central nervous system   | ICD-10: C72  |
| Endocrine glands and related structure  | ICD-10: C73-C75  |
| Metastasis and unspecified cancer in lymph nodes (only if there is no primary tumor coded)                    | ICD-10: C77-79 (only if there is no primary tumor coded) |
| Malignant neoplasm of other, ill defined, or unspecified sites  | ICD-10: C76, C80   |

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