**Table 1 Overview of studies investigating the association between cancer and dementia**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study design** | | | | **Cancer type** | | **Dementia type** | | **Study participants** | | **Age at inclusion** | | **Mean follow-up (years)** | **Effect estimate (95% CI)** | | **Controlling for bias** | | | **Time 0** | |
| **Studies investigating the risk of dementia in patients with cancer/cancer survivors** | | | | | | | | | | | | | | | | | | | | |
| **Yamada et al. (1999)** | Prevalence study in atomic bomb survivor cohort | | Cross-sectional | | Any cancer type | | AD | | Total N=2,222 (28.7% men). 230 participants had (a history of) cancer. 74 participants had AD. Unknown how many AD patients had a history of cancer. | | ≥ 60 | | NA | OR 0.3 (0.05-0.98)  Multiple logitistic regression | | None  Adjustment  \*\* Mention survival bias | | | **How many history of cancer in those with and without dementia among those who were alive in 1992-1996 (time is fixed at outcome measurement)** | |
| **Realmuto et al. (2012)** | Case control study | | Cross-sectional | | Any cancer type | | AD | | Total N=378 (28.6% men). 84 participants had (a history of) cancer. 126 participants had AD, of whom 23 with a history of cancer (18.3%). | | No criterion | | NA | OR 0.6 (0.4-1.1)  2x2 OR | | - Different cancer types  \*\* NO Mention survival bias | | | **Case control design. Selected based on outcome 🡪 selected those who were still alive at time of dementia assessment.**  **RS: median age dementia = 83.4**  **Median age cancer = 74.1**  **86.8% of those with cancer is diagnosed with cancer before median age dementia diagnosis**  **72.6% of those with cancer who died, died before median age dementia diagnosis** | |
| **White et al. (2013)** | Population-based cohort study | | Longitudinal  October 1993 and December 2009.  Average of 3.7 years, median of 3.0 years (maximum 15.5 years). | | NMSC | | AD | | Total N=1,102 (39.3% men). 141 participants had (a history of) NMSC (109 prev, 32 inc). 100 participants developed AD, of whom 6 with prevalent NMSC (6.0%).  From the 32 incident, 8 (25) died, from the 109 26 (23.9% died), from the NMSC-free 311 (31.3%) died | | ≥ 70 | | 3.7 | HR 0.47 (0.21-1.09)  Cox proportional hazard models.  these 141 individuals  contributed a total of 509 NMSC-positive person-years to the NMSC history cohort, and 993  individuals contributed 3,543 NMSC-negative person-  years to the cohort. | | None  Adjusting for multiple confounders  \*\* NO mention survival bias | | | **Cancer was modelled as time-dependent. Included prevalent cases.** | |
| **Nudelman et al. (2014)**  **Ever vs never** | Case control study  ADNI recruited individuals with specific AD-spectrum diagnosis. | | Cross-sectional  Follow up until M96 (high LTFU) | | Any cancer type | | AD | | Total N=1,609 (51.3% men). 503 participants had (a history of) cancer. 446 participants had AD, of whom 83 with a history of cancer (18.6%) | | ≥ 50 | | NA | OR 1.5 (1.3-1.8)\*  Chi-Square test  Cox using age as time to AD (AD at baseline)  Other diagnostic groups were censored  Small death # | | - Different cancer types  - Age of AD onset  \*\* No Mention survival bias | | | **History of cancer yes/no in those with AD, MCI, SMC and CN.**  **Analysis of age of AD onset by cancer history.** | |
| **Frain et al. (2017)** | Retrospective cohort study of US veterans | | Longitudinal  1996 and 2011 | | Exclusion of NMSC | | AD | | Total N=3,499,378 (98.0% men). 771,285 participants had (a history of) cancer. 82,998 participants developed AD. Unknown how many AD patients had a history of cancer. | | ≥ 65 | | 5.7 | HR 1.00 (0.97-1.03)  Cause-specific hazard  models for analysis, cancer exposure and  treatment as time-varying covariates. | | - Risk over four time intervals following cancer diagnosis  - Negative control diseases  - Different cancer types  \*\* Mention survival bias | | | **History vs no history of cancer and subsequent risk of dementia.**  **Patients were followed from entry age. Cancer exposure was modelled as time-varying covariate. Not sure what they did with prevalent cancers.**  **RS: those with cancer, fup time with cancer:**  **0-1 yr: 799 (49.6% died during follow-up)**  **1-2 yr: 279 (14.6% died during follow-up)**  **2-3 yr: 156 (7.6% died during follow-up)**  **>3 yr: 930 (28.2% died during follow-up)** | |
| **Bowles et al. (2017)** | Prospective population-based cohort study | | Longitudinal | | Exclusion of NMSC | | AD | | Total N=4,357 (41.3% men). 756 participants had prevalent cancer. 583 participants developed incident cancer. 877 participants developed AD, of whom 126 with prevalent cancer (14.4%) and73 with (a history of) incident cancer (8.3%). | | ≥ 65 | | 6.4 (median) | Prevalent cancer:  HR 0.95 (0.77-1.17)  Incident cancer:  HR 0.73 (0.55-0.96) | | - Risk of dementia per cancer stage  - Analysis in participants who survived at least to age 80  - Different cancer types | | | **Categorized participants as having prevalent, incident, or no cancer diagnosis. Incident cancer was timevarying exposure.**  ***‘If a person had a cancer diagnosis before ACT study enrollment, they were counted as having a prevalent cancer through the end of follow-up unless they developed a second cancer after ACT study enrollment; thereafter, they were counted as having an incident cancer.’***  **Study entry was at age of study entrollment.**  **Relation was only sign with incident cancer, not prevalent cancer. Maybe because prevalent cancer = more favourable cancer because participants survived until study entry.**  **They report % alive**  **In RS: total dataset 🡪 18.1% has cancer, 12.3% has dementia. Limited to >=80 years 🡪 13.0% has cancer, 26.7% has dementia!** | |
| **Studies investigating both the risk of dementia in patients with cancer/cancer survivors and the risk of cancer in patients with dementia** | | | | | | | | | | | | | | | | | | | | |
| **Roe et al. (2005)** | Prospective cohort study | Longitudinal | | Any cancer type | | AD | | Total N=594 (35.7% men). 50 participants had (a history of) cancer. It is unknown how many participants developed AD. | | ≥ 47 | | 4.0 in patients with cancer | | | HR 0.34 (0.10-1.12) | | None | **Cancer was used as time-varying variable.**  **Cancer survival time**  **for participants not receiving a cancer diagnosis during the study**  **were considered censored on the date of their last assessment**  **session in the analyses. ??--> cancer diagnoses only possible during assessments?** | |
|
| **Roe et al. (2010)** | Prospective cohort study | Longitudinal | | Any cancer type | | AD | | Total N=2,151 (unknown % men). 390 participants had (a history of) cancer. It is unknown how many participants developed AD. | | ≥ 65 | | 5.4 | | | HR 0.72 (0.52-1.00) | | None | **Baseline history of cancer and risk of AD. Participants without a prevalent cancer history, but who later**  **had an incident cancer hospitalization, were included in the**  **baseline “no cancer history” group. DID THEY NOT INCLUDE CA INC?? NOTE: Results**  **were generally similar for the analyses excluding**  **incident cancer cases from the baseline no cancer groups**  **(table e-3).** | |
|
| **Driver et al. (2012)** | Prospective population-based cohort study | Longitudinal | | Exclusion of NMSC | | AD | | Total N=1,278 (38.8% men). 423 participants had (a history of) cancer. 256 participants developed AD. Unknown how many AD patients had a history of cancer. | | ≥ 65 | | 10 | | | HR 0.81 (0.59-1.11) | | - Different cancer types  - Analysis in participants who survived at least to age 80: If the association was predominantly due to the death  of cancer survivors, then it should be diminished when these  patients were excluded  - Negative control disease | **The cancer history variable**  **was updated to include cases of incident cancer that occurred**  **during follow-up after baseline.** | |
|
| **Musicco et al. (2013)** | Prospective/ retrospective historical cohort study | Longitudinal | | Any cancer type | | AD | | Total N=21,451 (57.0% men). All of these participants had (a history of ) cancer. 161 participants developed AD of whom 68 with (a history of) cancer (42.2%) | | ≥ 60 | | 101,317.9 person years | | | RR 0.64 (0.50-0.81) | | - Retrospective and prospective follow-up  - Separate analyses for persons surviving or dying during follow-up (If the occurrence  of AD dementia (or cancer) in persons with cancer (or AD dementia)  was less than in the general population due to reduced survival or  competing causes of death, we expected to find differences between  observed and expected cases mainly in nonsurvivors.) 🡪 *they did not find this.*  - Different cancer types | **The retrospective followup period started on January 1, 2004, for persons who were 601 on that date, or at the completion of this age for those who were**  **younger, and ended at the date of diagnosis of AD dementia or cancer, respectively. The prospective period started with the diagnosis**  **of cancer or AD dementia and ended with death or on December 31,**  **2009. No time varying??** | |
|
| **Freedman et al. (2016)** | Prospective cohort study in Medicare population | Longitudinal | | Any cancer type | | AD | | Total N=1,163,327 (50.4% men). 742,809 participants had (a history of) cancer. 21,526 developed AD of whom 11,812 with (a history of) cancer (54.9%) | | ≥ 66 | | 1.9 in patients with cancer | | | HR 0.87 (0.84-0.90) | | - Negative control disease  - Different cancer types | **For the cancer cases, follow-up**  **began at the age at cancer diagnosis, and for the comparison group, at the age at selection.**  **We accounted for left truncation due to late age at entry**  **using the entrytime statement in proc phreg, SAS 9.2.** | |
|

\* Cancer history positive is used as reference

CI = confidence interval, AD = Alzheimer dementia; OR = odds ratio; HR = hazard ratio; MCI = mild cognitive impairment; RR = risk ratio; SIR = standardised incidence ratio; NMSC = non-melanoma skin cancer; NA = not applicable