**SUPPLEMENTAL DIGITAL CONTENT**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Appendix Table 1: ICD-O-3 topography and morphology code mappings for microbial cancers | | | | |
| Cancer type description | | **Related microbial condition** | **ICD-O-3 topography code** | **ICD-O-3 morphology** |
|  | Oral cavity and pharynx SCC | Human papillomavirus | C01.9 base of tongue  C02.4 lingual tonsil  C09.0-C09.9 tonsil  C10.0 vallecula  C10.2-C10.9 oropharynx, except anterior surface of epiglottis  C14.0 pharynx NOS  C14.2 Waldeyer ring | 8050-8084, 8094 SCC  8121 Schneiderian carcinoma  8123 basaloid carcinoma  8010 carcinoma, NOS |
|  | Anal SCC | Human papillomavirus | C21.0-C21.8 anus and anal canal  C20.9 rectum | 8050-8084, 8094 SCC  8123 basaloid carcinoma  8124 cloacogenic carcinoma  8010 carcinoma, NOS\* |
|  | Liver hepatocellular carcinoma | Hepatitis C virus, hepatitis B virus | C22.0 liver | 8170-8180 hepatocellular carcinoma |
|  | Lung and bronchus | Pneumonia | C34.0-C34.9 | Excluding 9050-9055, 9140, 9590-9992 |
|  | Vagina SCC | Human papillomavirus | C52.9 vagina | 8050-8084, 8094 SCC  8123 basaloid carcinoma  8010 carcinoma, NOS |
|  | Vulva SCC | Human papillomavirus | C51.0-C51.9 vulva | 8050-8084, 8094 SCC  8123 basaloid carcinoma  8010 carcinoma, NOS |
|  | Penis SCC | Human papillomavirus | C60.0-C60.9 penis | 8050-8084, 8094 SCC  8123 basaloid carcinoma  8010 carcinoma, NOS |
|  | Non-Hodgkin lymphoma | Epstein-Barr virus |  | 9590-9597, 9670-9671, 9673, 9675, 9678-9680, 9684, 9687-9691, 9695, 9698-9702, 9705, 9708-9709, 9712, 9714-9719, 9724-9729, 9735, 9737-9738, 9811-9818, 9823, 9827, 9837 Non-Hodgkin lymphoma |
|  | Hodgkin lymphoma | Epstein-Barr virus |  | 9650-9667 Hodgkin lymphoma |
|  | Kaposi sarcoma | Kaposi sarcoma herpesvirus |  | 9140 Kaposi sarcoma |
| ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; NOS = not otherwise specified; SCC = squamous cell carcinoma  \* Only for anal sites (C21.0-C21.8), not rectum (C20.9). | | | | |

**Appendix Table 2. Variables considered for propensity score model. X indicates included in final model.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **Variable** | **HIV model** | **Uninfected model** |
|  | Calendar year | X | X |
| Demographics | Age (linear and quadratic) | X | X |
|  | Sex | X | X |
|  | Race/ethnicity | X | X |
| Healthcare utilization | Medicare utilization |  |  |
|  | Hospitalizations | X | X |
|  | Clinic visits | X | X |
| Comorbid conditions | Diabetes | X | X |
|  | Hepatitis C virus | X | X |
|  | Hepatitis B virus | X | X |
|  | BMI | X | X |
|  | Smoking status |  |  |
| Laboratory tests | ALT |  |  |
|  | AST |  |  |
|  | Hemoglobin | X | X |
|  | Platelets |  |  |
|  | Creatinine |  |  |
|  | eGFR |  |  |
|  | CD4 | X |  |
|  | CD8 |  |  |
|  | CD4/CD8 ratio |  |  |
|  | HIV RNA (viral load) | X |  |
|  | FIB-4 | X | X |
|  | Total cholesterol | X | X |
|  | LDL cholesterol | X | X |
|  | HDL cholesterol | X | X |
|  | Triglyderides | X | X |
|  | Fasting glucose | X | X |
|  | Blood pressure | X | X |
| Medications | Anti-hypertensives | X | X |
|  | Diabetes |  | X |
|  | Benzodiazepine |  |  |
|  | Epilepsy |  |  |
|  | Other lipid lowering drugs |  |  |
| Interactions | LDL\*HIV-RNA | X |  |
|  | LDL\*HCV | X |  |
|  | Diabetes\*LDL |  | X |
| Facility level | Prescription patterns | X | X |

Abbreviations: BMI = body mass index, ALT = alanine aminotransferase , AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, FIB-4 = fibrosis-4 index, HCV = hepatitis C virus

**Appendix Figure 1. Study inclusion criteria**

**Exclusion reasons:**

* Rare regimens: pitavastatin (n = 63), cerivastatin (n = 10) and nicostatin (n = 4)
* Uncertain statin exposure: “placebo/statin” records)
* Pre-2002: (for adequate history)
* No second statin prescription fill
* Gap > 180 days between first and second prescription fills
* No visits in one of the following clinics: general internal medicine, cardiology, endocrinology, diabetes, gastroenterology, hypertension, infectious disease, pulmonary, renal/nephrology, geriatrics, women’s clinic, primary care, and hepatology

**Appendix Figure 2: Propensity score density plot for PWH and uninfected statin-exposed and unexposed patients before and after matching**

|  |  |  |
| --- | --- | --- |
|  | **PWH** | **Uninfected** |
| **Before matching** |  |  |
| **Matched** |  |  |
|  |  | |

**Appendix Table 3. Baseline characteristics among statin-exposed persons in the pre-matched, propensity score-matched, and unmatched patients**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | All patients (pre-matched) | | | | Propensity score matched | | | | Unmatched | | | |
|  |  | **PWH** | | **Uninfected** | | **PWH** | | **Uninfected** | | **PWH** | | **Uninfected** | |
|  |  | **N=**12,153 | | **N=**34,561 | | **N=**7,335 | | **N=**16,635 | | **N=**3,741 | | **N=**15,113 | |
|  |  | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Age | Mean +/-st dev (years) | 54.0 | 9.4 | 53.1 | 9.2 | 53.8 | 9.5 | 53.2 | 9.8 | 54.4 | 9.1 | 53.0 | 8.5 |
| Race/ethnicity | Non-Hispanic white | 5,467 | 45.0 | 13,967 | 40.4 | 3,114 | 42.5 | 6,705 | 40.3 | 2,353 | 48.8 | 7,262 | 40.5 |
|  | Non-Hispanic black | 5,369 | 44.2 | 16,343 | 47.3 | 3,419 | 46.6 | 7,932 | 47.7 | 1,950 | 40.5 | 8,411 | 46.9 |
|  | Hispanic | 949 | 7.8 | 3,086 | 8.9 | 580 | 7.9 | 1,459 | 8.8 | 369 | 7.7 | 1,627 | 9.1 |
|  | Other/unknown | 368 | 3.0 | 1,165 | 3.4 | 222 | 3.0 | 539 | 3.2 | 146 | 3.0 | 626 | 3.5 |
| Sex | Female | 327 | 2.7 | 876 | 2.5 | 216 | 2.9 | 478 | 2.9 | 111 | 2.3 | 398 | 2.2 |
|  | Male | 11,826 | 97.3 | 33,685 | 97.5 | 7,119 | 97.1 | 16,157 | 97.1 | 4,707 | 97.7 | 17,528 | 97.8 |
| Hepatitis C\* | HCV negative | 8,991 | 74.0 | 25,948 | 75.1 | 5,158 | 70.3 | 11,997 | 72.1 | 3,833 | 79.6 | 13,951 | 77.8 |
|  | Chronic HCV | 2,122 | 17.5 | 3,281 | 9.5 | 1,547 | 21.1 | 2,019 | 12.1 | 575 | 11.9 | 1,262 | 7.0 |
|  | HCV exposure | 735 | 6.0 | 1,160 | 3.4 | 464 | 6.3 | 591 | 3.6 | 271 | 5.6 | 569 | 3.2 |
|  | Never tested in the VA | 305 | 2.5 | 4,172 | 12.1 | 166 | 2.3 | 2,028 | 12.2 | 139 | 2.9 | 2,144 | 12.0 |
| Hepatitis B\* | HBV negative | 10,280 | 84.6 | 18,737 | 54.2 | 6,177 | 84.2 | 9,146 | 55.0 | 4,103 | 85.2 | 9,591 | 53.5 |
|  | HBV positive | 424 | 3.5 | 134 | 0.4 | 284 | 3.9 | 72 | 0.4 | 140 | 2.9 | 62 | 0.3 |
|  | HBV acute resolved | 140 | 1.2 | 78 | 0.2 | 94 | 1.3 | 43 | 0.3 | 46 | 1.0 | 35 | 0.2 |
|  | Unconfirmed HBV | 81 | 0.7 | 53 | 0.2 | 49 | 0.7 | 20 | 0.1 | 32 | 0.7 | 33 | 0.2 |
|  | Never tested in the VA | 1,228 | 10.1 | 15,559 | 45.0 | 731 | 10.0 | 7,354 | 44.2 | 497 | 10.3 | 8,205 | 45.8 |
| BMI | Under/normal weight (<30) | 8,668 | 71.3 | 16,596 | 48.0 | 5,348 | 72.9 | 8,848 | 53.2 | 3,320 | 68.9 | 7,748 | 43.2 |
|  | Overweight (30-34.9) | 2,152 | 17.7 | 9,964 | 28.8 | 1,283 | 17.5 | 4,449 | 26.7 | 869 | 18.0 | 5,515 | 30.8 |
|  | Obese ( 35) | 1,027 | 8.5 | 7,003 | 20.3 | 562 | 7.7 | 2,892 | 17.4 | 465 | 9.7 | 4,111 | 22.9 |
|  | Unknown | 306 | 2.5 | 998 | 2.9 | 142 | 1.9 | 446 | 2.7 | 164 | 3.4 | 552 | 3.1 |
| Smoking | Non-smoker | 3,583 | 29.5 | 10,194 | 29.5 | 2,068 | 28.2 | 4,905 | 29.5 | 1,515 | 31.4 | 5,289 | 29.5 |
|  | Current | 6,031 | 49.6 | 16,746 | 48.5 | 3,826 | 52.2 | 8,312 | 50.0 | 2,205 | 45.8 | 8,434 | 47.0 |
|  | Former | 2,385 | 19.6 | 7,267 | 21.0 | 1,352 | 18.4 | 3,245 | 19.5 | 1,033 | 21.4 | 4,022 | 22.4 |
|  | Unknown | 154 | 1.3 | 354 | 1.0 | 89 | 1.2 | 173 | 1.0 | 65 | 1.3 | 181 | 1.0 |
| Diabetes | No | 9,509 | 78.2 | 24,281 | 70.3 | 5,920 | 80.7 | 13,283 | 79.8 | 3,589 | 74.5 | 10,998 | 61.4 |
|  | Yes | 2,644 | 21.8 | 10,280 | 29.7 | 1,415 | 19.3 | 3,352 | 20.2 | 1,229 | 25.5 | 6,928 | 38.6 |
| Year of | 2002-2003 | 1,852 | 15.2 | 6,339 | 18.3 | 818 | 11.2 | 2,094 | 12.6 | 1,034 | 21.5 | 4,245 | 23.7 |
| Index visit | 2004-2006 | 2,905 | 23.9 | 10,482 | 30.3 | 1,506 | 20.5 | 4,068 | 24.5 | 1,399 | 29.0 | 6,414 | 35.8 |
|  | 2007-2009 | 2,861 | 23.5 | 8,495 | 24.6 | 1,641 | 22.4 | 4,119 | 24.8 | 1,220 | 25.3 | 4,376 | 24.4 |
|  | 2010-2012 | 2,554 | 21.0 | 5,658 | 16.4 | 1,713 | 23.4 | 3,492 | 21.0 | 841 | 17.5 | 2,166 | 12.1 |
|  | 2013-2015 | 1,981 | 16.3 | 3,587 | 10.4 | 1,657 | 22.6 | 2,862 | 17.2 | 324 | 6.7 | 725 | 4.0 |
| HIV-RNA | ≤ 400 | 7,343 | 60.4 |  |  | 4,577 | 62.4 |  |  | 2,766 | 57.4 |  |  |
|  | >400 | 1,536 | 12.6 |  |  | 1,054 | 14.4 |  |  | 482 | 10.0 |  |  |
|  | Unknown | 3,274 | 26.9 |  |  | 1,704 | 23.2 |  |  | 1,570 | 32.6 |  |  |
| CD4 | ≥500 | 4,317 | 35.5 |  |  | 2,754 | 37.5 |  |  | 1,563 | 32.4 |  |  |
|  | 350-499 | 2,006 | 16.5 |  |  | 1,263 | 17.2 |  |  | 743 | 15.4 |  |  |
|  | 200-349 | 1,658 | 13.6 |  |  | 1,025 | 14.0 |  |  | 633 | 13.1 |  |  |
|  | 0-199 | 851 | 7.0 |  |  | 557 | 7.6 |  |  | 294 | 6.1 |  |  |
|  | Unknown | 3,321 | 27.3 |  |  | 1,736 | 23.7 |  |  | 1,585 | 32.9 |  |  |

Abbreviations: HCV = hepatitis C virus, HBV = hepatitis B virus, BMI = body mass index

\*Definitions: HCV negative, negative HCV antibody test result(s) only; Chronic HCV, positive HCV RNA test; HCV exposure, positive HCV antibody test, but negative or unknown HCV RNA test; Never tested in the VA, no HCV laboratory test results available from the VA (it is possible that some of these patients were tested for HCV outside the VA)

HBV negative, negative HBV surface antigen test result(s) only; HBV positive, at least two positive HBV surface antigen tests over 6 months apart; HBV acute resolved, positive HBV surface antigen test followed by only negative test results; Unconfirmed HBV, one positive HBV surface antigen test not confirmed with additional testing; Never tested/unknown, no HBV laboratory test results available.

**Appendix Table 4. Hazard ratiosfrom propensity score-matched sample (statin-exposed versus unexposed) for microbial and non-microbial cancer groups with and without lung cancer**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Statin exposed** | **Unexposed** | **Statin HR** | | | |
|  | **# cancers** | **# cancers** | **HR** | **95% CI** | | **p-value** |
| Lung cancer as microbial |  |  |  |  |  |  |
| Microbial cancers | 620 | 726 | 0.76 | 0.69 | 0.85 | <.0001 |
| Non-microbial cancers | 1,110 | 988 | 1.00 | 0.92 | 1.09 | 0.97 |
| Lung cancer as non-microbial |  |  |  |  |  |  |
| Microbial cancers | 349 | 424 | 0.74 | 0.64 | 0.85 | <.0001 |
| Non-microbial cancers | 1,397 | 1,304 | 0.96 | 0.89 | 1.03 | 0.24 |
| Lung and Bronchus | 323 | 335 | 0.86 | 0.74 | 1.00 | 0.053 |

Abbreviations: HR = hazard ratio, 95% CI = 95% confidence interval

**Appendix Figure 3. Initial statin type by year**



**Appendix Figure 4. Hazard ratios from propensity score-matched sample (statin-exposed versus unexposed) for any statin, initiated Simvastatin, and initiated other statin types combined**

A screenshot of a computer

Description automatically generated

\* Microbial cancers include: human papillomavirus (HPV)-related oral cavity and pharynx squamous cell carcinoma (SCC), anal SCC, hepatocellular carcinoma (HCC); cancers of the stomach, lung, cervix, vulva, vagina, and penis; Hodgkin lymphoma, non-Hodgkin lymphoma, and Kaposi sarcoma