Age-related Diseases of Inflammation in Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

Supplemental Methods

Data Source

SEER-Medicare. We used linked data from SEER-Medicare to identify cases of adults aged 66 and older with MDS or CMML diagnosed between 2002 and 2015. SEER-Medicare includes data from population-based registries representing approximately 28% of all cancer patients in the United States and permits access to clinical information through Medicare enrollment and claims files.

Selection of Study Population

An MDS/CMML population (cases) were compared to two distinct control populations: 1) patients diagnosed with invasive solid tumors and 2) a representative Medicare population. Malignancies in the MDS/CMML and solid tumor populations were identified from cancer registry files using International Classification of Diseases for Oncology, third edition codes (*see table below*). Patients ≥ 66 years of age were included ensure at least 1 year of claims prior to malignancy diagnosis (US Medicare eligibility begins at age 65 years). Patients diagnosed between January 1, 2002 and December 31, 2015 with MDS, CMML or non-hematologic invasive cancer were included in the MDS/CMML and the solid tumor groups, respectively (*see flow diagram below*). Patients were excluded if they had any interruptions in Medicare Part A and B coverage or had any Health Maintenance Organization (HMO) coverage during the period extending from month -13 to month +12 relative to index malignancy diagnosis. Patients for whom index malignancy was diagnosed at autopsy or time of death or who died within 1 year of index malignancy diagnosis were also excluded.

The representative Medicare population was derived from a file containing a random sample of 5% of Medicare recipients provided by SEER-Medicare [the summarized denominator, SUMDENOM file].

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Patients with a history of hematologic malignancy as well as individuals with any HMO coverage or who lacked 3 years of continuous part A and B coverage were excluded from analysis as indicated in the flow diagram below.

MDS/CMML cases were matched in a 1:2 ratio to solid tumor and representative Medicare controls based on calendar year of diagnosis (+/- 2 years), sex, age (+/-2 years) and registry location. Representative Medicare controls were given their matched case's MDS/CMML diagnosis date as a pseudo-diagnosis date and matching was restricted to patients who survived ≥ 12 months after their assigned pseudo-diagnosis date.

Variables of Interest

<u>Prevalent Diseases of Inflammaging.</u> Prevalent conditions were defined as those occurring in the period up to 5 years antecedent to MDS/CMML diagnosis. Months 0 to -6 were excluded from our analysis to limit ascertainment bias. We used international classification of diseases codes to identify diseases of inflammaging from Medicare OUTPAT, NCH and MEDPAR claims files and the specific codes used can be found in Supplemental Table 2. Diseases of inflammaging were defined as diseases with strong associations with inflammaging as alluded to in the literature[1-18] and included: the cardiovascular diseases[8-10] – atherosclerosis, myocardial infarction (MI), stroke or transient ischemic attack and cardiomyopathy (heart failure); the pulmonary diseases[11] – chronic obstructive pulmonary disease, chronic bronchitis, and asthma; the metabolic diseases[2,12-14] – type 2 diabetes mellitus (T2DM), insulin resistance, fatty liver disease and chronic kidney disease (CKD) the bone and joint diseases[5-7]– osteoarthritis, osteoporosis, rheumatoid arthritis and gout; and the neurologic diseases[15-18] - Alzheimer's dementia, Parkinson's disease, other dementias (includes other age-related dementias and vascular dementia), amyotrophic lateral sclerosis (ALS) multiple sclerosis (MS) and age-related macular

generation. Conditions with two or more claims during the 54 month observation period were considered valid.

Other Variables of Interest. Baseline demographic data for SEER-Medicare cases and controls included age at diagnosis, sex, race, ethnicity, cancer diagnosis date, and registry location. To make a general comparison of comorbidity burden and engagement with healthcare, the median number of outpatient claims and National Cancer Institute (NCI) comorbidity index[19] were calculated using physician claims within the 6 months prior to diagnosis/pseudodiagnosis date.

Data Analysis and Statistics

Descriptive statistics were used to describe patient baseline characteristics (SEER-Medicare and HMDR). Categorical variables were compared using the Cochran-Armitage test or Fisher's exact test. Wilcoxon rank-sum test was used to compare continuous variables. Odds ratios (and 95% confidence intervals [CI]) comparing SEER-Medicare MDS/CMML cases to controls were obtained using univariable and multivariable logistic regression, adjusted for NCI comorbidity index calculated as a measure of baseline "sickness" for each cohort. Calculated variance inflation factors did not indicate significant multicollinearity concerns for use of the comorbidity index in our models. These are included below.

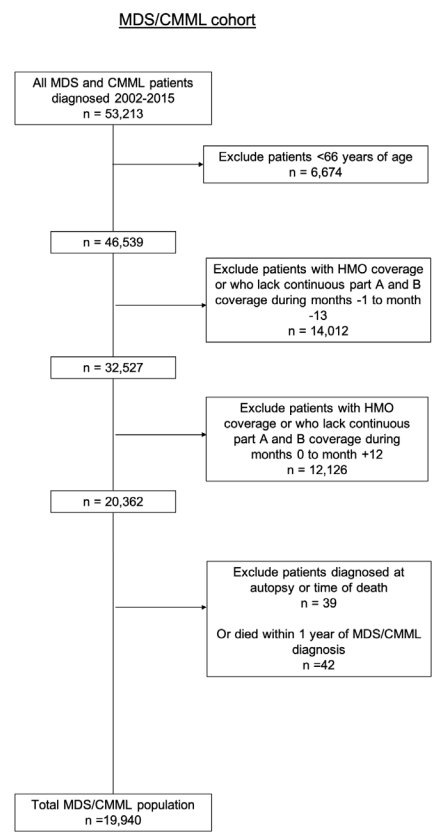| Variance Inflation Factors Calculated for NCI Comorbidity Index and Logistic Regression Models of Inflammaging Disease Prevalence		
	Solid cohort	Rep 5%
All Conditions of Inflammaging	1.024986	1.027909
Cardiovascular Diseases	1.017584	1.017641
Pulmonary Diseases	1.030571	1.027919
Metabolic Diseases	1.008798	1.006276
Neurologic Diseases	1.036611	1.035929
Bone and Joint Diseases	1.031059	1.035448

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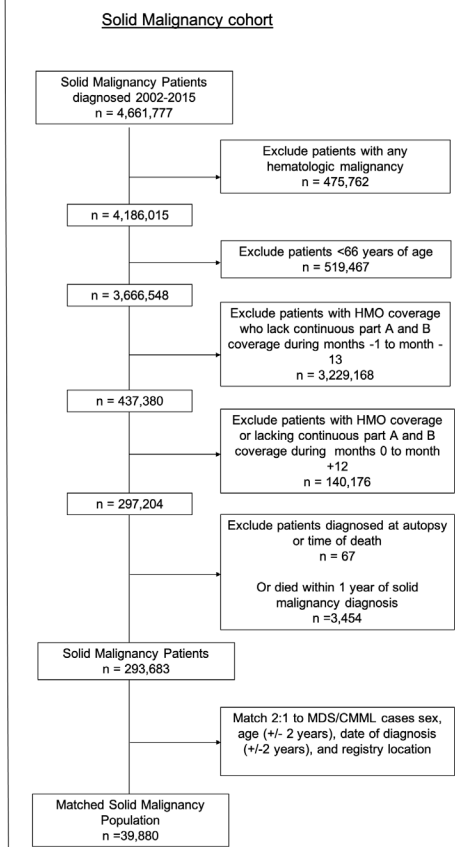
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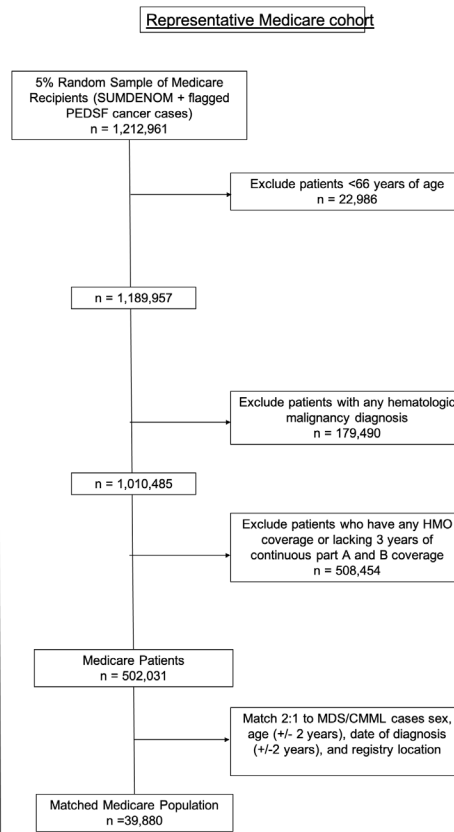
Supplemental Methods: Cohort assembly diagrams.

A.

MDS/CMML cohort

All MDS and CMML patients
diagnosed 2002-2015
n = 53,213

→ Exclude patients <66 years of age
n = 6,674

n = 46,539

→ Exclude patients with HMO coverage
or who lack continuous part A and B
coverage during months -1 to month
-13
n = 14,012

n = 32,527

→ Exclude patients with HMO
coverage or who lack continuous
part A and B coverage during
months 0 to month +12
n = 12,126

n = 20,362

→ Exclude patients diagnosed at
autopsy or time of death
n = 39

Or died within 1 year of MDS/CMML
diagnosis
n = 42

Total MDS/CMML population
n = 19,940

B.

Solid Malignancy cohort

Solid Malignancy Patients
diagnosed 2002-2015
n = 4,661,777

→ Exclude patients with any
hematologic malignancy
n = 475,762

n = 4,186,015

→ Exclude patients <66 years of age
n = 519,467

n = 3,666,548

→ Exclude patients with HMO coverage
who lack continuous part A and B
coverage during months -1 to month -
13
n = 3,229,168

n = 437,380

→ Exclude patients with HMO coverage
or lacking continuous part A and B
coverage during months 0 to month
+12
n = 140,176

n = 297,204

→ Exclude patients diagnosed at autopsy
or time of death
n = 67

Or died within 1 year of solid
malignancy diagnosis
n =3,454

Solid Malignancy Patients
n = 293,683

→ Match 2:1 to MDS/CMML cases sex,
age (+/- 2 years), date of diagnosis
(+/-2 years), and registry location

Matched Solid Malignancy
Population
n =39,880

C.

Representative Medicare cohort

5% Random Sample of Medicare
Recipients (SUMDENOM + flagged
PEDSF cancer cases)
n = 1,212,961

→ Exclude patients <66 years of age
n = 22,986

n = 1,189,957

→ Exclude patients with any hematologic
malignancy diagnosis
n = 179,490

n = 1,010,485

→ Exclude patients who have any HMO
coverage or lacking 3 years of
continuous part A and B coverage
n = 508,454

Medicare Patients
n = 502,031

→ Match 2:1 to MDS/CMML cases sex,
age (+/- 2 years), date of diagnosis
(+/-2 years), and registry location

Matched Medicare Population
n =39,880

Supplemental Methods, Table 1: Diseases of Inflammaging and ICD-09 codes used to identify claims in SEER-Medicare		
Diseases of Inflamamaging	ICD-09 codes to use for analysis by group	ICD-09 codes for specific diseases
Cardiovascular Diseases	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02, 410.01, 410.11, 410.21, 410.31, 410.41, 410.50, 410.51, 410.52, 410.61, 410.71, 410.81, 410.91, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.2, 414.3, 414.4, 414.8, 414.9	
Atherosclerosis		411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.2, 414.3, 414.4, 414.8, 414.9
Myocardial Infarction (MI)		410.01, 410.11, 410.21, 410.31 410.41, 410.50, 410.51, 410.52 410.61, 410.71, 410.81, 410.91
Cardiomyopathy (Heart Failure)		398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Stroke/TIA		430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Pulmonary Diseases	490, 491.0, 491.1, 491.8, 491.9, 492.0, 492.8, 491.20, 491.21, 491.22, 494.0, 494.1, 496, 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.81, 493.82, 493.90, 493.91, 493.92, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9	
COPD		490, 491.0, 491.1, 491.8, 491.9, 492.0, 492.8, 491.20, 491.21, 491.22, 494.0, 494.1, 496
Asthma		493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Bronchitis		491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9
Metabolic Disease	249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07, 366.41, 277.7, 571.8, 571.0, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4	
Type 2 Diabetes Mellitus (Type 2 DM)		249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07, 366.41
Insulin Resistance		277.7
Fatty Liver Disease		571.8, 571.0
Chronic Kidney Disease (CKD)		249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4

Diseases of Inflammaging	ICD-09 codes to use for analysis by group	ICD-09 codes for specific diseases
Supplemental Table 1 (cont'd): Diseases of Inflammaging and ICD-09 codes used to identify claims in SEER-Medicare		
Bone and Joint Diseases	274.00, 274.01, 274.02, 274.03, 274.10, 274.11, 274.19, 274.81, 274.82, 274.89, 274.9, 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 733.00, 733.01, 733.02, 733.03, 733.09, 721.2, 721.3, 721.41, 721.42, 721.90, 721.91, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.2, 721.0, 721.1	
Osteoarthritis		715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.2, 721.0, 721.1, 721.2, 721.3, 721.41, 721.42, 721.90, 721.91
Osteoporosis		733.00, 733.01, 733.02, 733.03, 733.09
Rheumatoid Arthritis		714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33
Gout		274.00, 274.01, 274.02, 274.03, 274.10, 274.11, 274.19, 274.81, 274.82, 274.89, 274.9
Neurologic Diseases	331.0, 332.0, 332.1, 340, 362.50, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.40, 290.41, 290.42, 290.43, 294.10, 294.11, 294.20, 294.21, 331.11, 331.19, 331.2, 331.7, 331.83, 331.6, 331.89, 331.9, 797, 335.2	
Alzheimers Disease		331.0
Parkinson's Disease		332.0, 332.1
Amyotrophic Lateral Sclerosis (ALS)		335.2
Multiple Sclerosis		40
Other Dementias		290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.40, 290.41, 290.42, 290.43, 294.10, 294.11, 294.20, 294.21, 331.11, 331.19, 331.2, 331.7, 331.83, 331.6, 331.89, 331.9, 797
Age-Related Macular Degeneration		362.50

Supplemental Methods, Table 2: ICD-O3 codes used to identify malignancies in SEER-Medicare		
Diseases of Inflamamaging	Site Codes	ICD-09 codes
Myeloid Neoplasms used to define MDS/CMML cohort		
Myelodysplastic Syndrome (MDS)	C420, C421, C424	9980, 9982, 9983, 9984, 9985, 9986, 9989, 9991, 9992
Chronic Myelomonocytic Leukemia (CMML)	C420, C421, C424	9942
Excluded Hematologic Malignancies for defining Solid Malignancy and Representative Medicare Cohorts[1]		
Myeloid Malignancies[2]	C420, C421, C424	9840, 9860, 9861, 9865, 9866, 9867, 9869, 9870, 9871, 9872, 9873, 9874, 9891, 9895, 9896, 9897, 9910, 9911, 9980, 9982, 9983, 9984, 9985, 9986, 9989, 9991, 9992, 9960, 9961, 9962, 9963, 9964, 9966, 9967, 9950, 9863, 9875, 9876, 959, 965, 966, 967, 968, 969, 970, 971, 972, 973, 981, 982
Lymphoid Malignancies		
Plasma Cell Dyscrasia		
Invasive Solid Cancers used to define solid malignancy cohort[3]		
*Lung Cancer (NSCLC and SCLC)	C340-C343, C348-C349	8000, 8001, 8003, 8004, 8005, 801x, 8020x, 803x,805x, 807x, 808x, 812x, 814x, 824x, 825x, 8002, 804x
*Prostate Cancer	C619	800x, 801x, 802x, 803x, 804x, 805x, 807x, 812x, 813x, 8140x, 8143, 8141, 8148, 820x, 821x, 826x, 831x, 848x, 850x, 851, 855x, 856x, 857x
*Breast Cancer	C500-C506, C508-C509	800x, 801x, 802x, 803x, 805x, 807x, 814x, 820x, 821x, 823, 850x, 852x, 854
*Colorectal Cancer	C210-C212, C218, C209, C170-C173, C178-C179, C180, C182-C189, C199	800x, 801x, 802x, 804x, 805x, 807x, 812x, 8140, 8141, 8143, 821x, 826x, 843x, 848x, 856x, 857x
†Uterine and Ovarian Cancer	C530-C531, C538-C539 C540-543, C48-C549, C559, C569, C570, C519	800x, 802x, 804x, 805x, 807x, 808x, 812x, 813x, 820x, 823x, 826x, 8310, 8313,, 832x, 838x, 844x, 845x, 846x, 847x, 848x, 849x, 851x, 856x, 857x, 859x, 860x, 862x, 863x, 895x, 906x, 907x, 908x
†Pancreatic Cancer	C250-C254, C257-C259	800x, 801x, 802x, 803x, 804x, 805x, 807x, 8140, 8141, 8143, 815x, 824x, 825x, 826x, 831x, 832x, 843x, 844x, 845x, 847x, 848x, 849x, 850x, 851x, 852x, 855x, 856x, 857x, 880x, 889x, 897x, 898x
†Head and Neck Cancers	C000-C006, C008-C009, C019, C020-C024, C028-C029, C030-C031, C039-C041, C048-C052, C058-C062, C068-C069, C079-C081, C088-C089, C090C091, C098-C104, C108-C109, C110 -C113, C118-C119, C129-C132, C138C139, C140, C142-C148,	800x, 801x, 802x, 803x, 804x, 805x, 807x, 805x, 807x, 808x, 8141, 8140, 8143, 819x, 820x, 825x, 826x, 831x, 843x, 844x, 850x, 855x, 848x, 856x, 857x, 894x
†Bladder Cancer	C670-C679	800x, 801x, 802x, 803x, 804x, 805x, 812x, 813x, 8140, 8141, 8143, 8230, 8231, 825x, 826x, 831x, 832x, 848x, 849x, 851x,
†Renal Cancer	C656, C669, C649	800x, 801x, 802x, 803x, 804x, 805x, 807x, 812x, 8140, 8141, 8143, 819x, 821x, 823x, 826x, 832x, 831x, 848x, 856x,
†Thyroid Cancer	C739	800x, 801x, 802x, 803x, 804x, 805x, 807x, 8122x, 813x, 8140, 8141, 8143, 819x, 821x, 823x, 825x, 826x, 829x, 831x, 832x, 833x, 834x, 835x, 844x, 845x, 848x, 856x,
†Melanoma	Any	872x, 873x, 874x, 876x, 877x

1. Non-melanomatous skin cancers were not counted as malignancies in this study
2. Myeloid Malignancies here includes all myeloid disorders except for MDS and CMML
3. Most common malignancies in persons age 65 and older are included in this list