

Atopic Dermatitis and Risk of Skin Cancer

A Danish Nationwide Cohort Study (1977–2006)

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Abstract

Background: Recent data suggest a reduced risk of malignant melanoma (MM) among atopic dermatitis (AD) patients, but an increased risk of other skin cancers (including basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]).

Objective: We examined the association between AD and skin cancers in a large cohort study in Denmark from 1977 through 2006.

Methods: Our cohort consisted of 31 330 AD patients recorded in the Danish National Patient Registry, including AD patients admitted to hospitals and specialized outpatient clinics. Linkage to the Danish Cancer Registry allowed ascertainment of skin cancers. We calculated standardized incidence ratios (SIRs) and associated 95% confidence intervals (CIs) by comparing the incidence rate of skin cancers among AD patients with that among the general Danish population.

Results: The overall observed number of MM cases among AD patients was 12, with 21 expected, yielding a SIR of 0.59 (95% CI 0.30, 1.02), with the most pronounced protective effect among AD patients with more than 5 years of follow-up (SIR=0.46; 95% CI 0.19, 0.95). The corresponding SIRs for BCC and SCC were increased among AD patients (1.41 [95% CI 1.07, 1.83] and 2.48 [95% CI 1.00, 5.11], respectively).

Conclusions: Our findings support an inverse association between AD and MM, but an increased risk of BCC and SCC among AD patients.

Introduction

The atopic triad consists of hay fever, asthma, and atopic dermatitis (AD).^[1] Over the lifespan, an individual may experience one, two, or all three atopic conditions. Among Caucasians, the incidence of AD and the other atopic diseases is increasing.^[1] This parallels the increasing incidence of skin cancers, including malignant melanoma (MM) and non-melanoma skin cancers (NMSC).^[2]

To date, few studies have evaluated the association between AD and skin cancers. One Swedish study of 6280 AD patients referred to five dermatology outpatient clinics in south-eastern Sweden during 1986–2004 found an inverse non-significant association between AD and MM (i.e. a standardized incidence ratio [SIR] of 0.49; 95% CI 0.27, 1.35).^[3] Another Swedish study, including 15 666 AD inpatients identified in the Swedish National Inpatient Registry (SNIR) during 1965–99, also

found an inverse non-significant association between AD and MM (SIR=0.6; 95% CI 0.3, 1.2).^[4] A Danish study of 6275 AD inpatients identified in the Danish National Patient Registry (DNPR) during 1977–96, including 2030 adults, found no observed cases of MM, although 2.4 were expected. The data were not further analyzed.^[5]

A third Swedish study, which used the SNIR to identify 140 425 patients hospitalized with asthma during 1965–2004, found a significantly reduced risk of MM (SIR=0.39; 95% CI 0.14, 0.85) among asthma patients hospitalized in the 1970s. There was no trend associated with the number of hospitalizations.^[6] Thus, asthma may contribute to the reduced risk for MM among AD patients, which the other studies did not take into account. Furthermore, early studies evaluating the association between AD and MM were restricted to patients hospitalized for AD (except for the Synnerstad et al.^[3] study). Such patients constitute a small fraction of the population of

AD patients, because most are treated in specialized outpatient clinics and by general practitioners. At the same time, the early studies consistently showed a positive association between AD and NMSC, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).^[4,5]

The association between AD and skin cancers is important in order to advance our understanding of both the clinical course of AD and the mechanism underlying skin cancer development. We therefore examined the association between AD and skin cancers in a large cohort study in Denmark from 1977 through 2006. The cohort included patients hospitalized with AD and patients attending specialized outpatient clinics. As well, the study took into account the effect of concurrent asthma and the body-site location of the skin cancers.

Materials and Methods

We conducted this nationwide, hospital population-based cohort study in Denmark, which has approximately 5.3 million inhabitants. The entire population receives tax-supported healthcare from the Danish National Health Service, with free access to hospital care. The unique ten-digit civil registration number (CPR number) assigned to all Danish citizens, which incorporates date of birth and gender,^[7] allows linkage among national healthcare databases.

Study Population

We used the DNPR to identify all patients diagnosed with AD between 1 January 1977 and 31 December 2006. The DNPR contains information on all patient contacts with non-psychiatric hospitals in Denmark, and includes the CPR number, admitting hospital department, surgical procedures, dates of admission and discharge, discharge diagnoses and, since 1995, outpatient specialist and emergency room visits. Diagnoses in the DNPR were coded using the *International Classification of Diseases* (ICD)-8 system through 1993, and the ICD-10 system thereafter.^[8] We used the ICD-8 and ICD-10 codes listed in Appendix 1 to identify patients with a first-time inpatient stay and/or outpatient clinic visit for AD. Any patients undergoing organ transplantation (using the codes presented in Appendix 1) were censored on the surgery date, because organ transplantation is a risk factor for NMSC.^[9] We categorized inpatients as of their index hospitalization date according to the presence or absence of diagnoses other than AD. We took this approach because several chronic medical conditions may be more common among inpatients than outpatients (i.e. a chronic medical condition may deter-

mine that a patient needs to be treated in hospital), and in an earlier study we found that chronic medical conditions increased the risk of skin cancers.^[10] The ICD-8 and ICD-10 codes for the chronic medical conditions of interest are listed in Appendix 1 (covering both inpatient stay and outpatient clinic visits).

Data on Skin Cancer

We used the Danish Cancer Registry (DCR) to retrieve information on the incidence of skin cancers among AD patients. The DCR has collected information on primary cases of cancer on a nationwide basis since 1943 and its data have been shown to be 95% complete, with a specificity of 98%.^[11] The DCR files include information on cancer type, site, and morphology, as well as cancer history. Since 1978, the DCR has coded tumors according to ICD-10 and the third version of the *International Classification of Diseases for Oncology* (ICD-O-3), which includes a four-digit code for tumor morphology. Throughout the study period, the ICD-10 codes were generated by uniform conversion of the two ICD-O-3 codes (topography and morphology) for each cancer case. For MM, we used ICD-10 codes C43.x and for NMSC we used ICD-10 codes C44.x. For BCC we included only cancers with the ICD-O-3 morphology codes 80903, 80913, 80923, 80933, 80943, and 80953. For SCC we included only cancers with the ICD-O-3 codes 80513, 80523, 80703, 80713, 80743, 80753, and 80763.

Statistical Analyses

Patients were followed from the first AD diagnosis recorded in the DNPR to the date of the first primary skin cancer diagnosis, death, emigration, organ transplantation, or the end of the study (31 December 2006), whichever occurred first. The number of skin cancers observed among AD patients was compared with the number of skin cancers expected in the general Danish population. The expected number of skin cancers was computed by multiplying gender-specific cancer rates (in 5-year age groups during 5-year calendar periods) by the corresponding person-years of AD patients. The SIR, the ratio of the observed to the expected number of cancers, and 95% CI were computed using Byars approximation.^[12]

We examined the overall risk of skin cancers among patients with AD, and did a stratified analysis by age groups (0–17, 18–49, 50+ years) and gender. In addition, we stratified analyses by anatomic site of the cancers (i.e. head and neck and other sites) to evaluate the effect of topically applied immunosuppressive treatments and artificial UV light treatments versus the effect of

natural UV light exposure, particularly for NMSC risk. We further stratified our analyses according to person-time from the first AD diagnosis until a skin cancer diagnosis (<12 months, 1–4 years, and 5+ years) to examine whether AD duration affected skin cancer risk. To see whether AD disease severity affected skin cancer risk, we stratified our analyses according to AD inpatient person-time and AD outpatient clinic visit person-time, since a hospitalization for AD may indicate greater disease severity. We used the following algorithm for AD inpatient versus outpatient clinic visit person-time: patients with a first outpatient clinic contact for AD contributed time-at-risk in the outpatient group until a first hospitalization with AD, while patients with a first hospitalization for AD contributed time-at-risk in the inpatient group until the end of follow-up, regardless of a later outpatient clinic visit. We disaggregated our analyses according to time period of diagnosis (1977 through 1994 vs 1995 through 2006) to examine whether inclusion of outpatient clinic visits in the DNPR influenced our results. To evaluate the possibility of greater detection of skin cancers among AD patients due to increased medical surveillance,^[13] and further to ensure that AD preceded the diagnosis of skin cancer, we also conducted analyses excluding skin cancers diagnosed at least 1 year after the date of primary AD diagnosis (leading to exclusion of 1584 AD patients with less than 1 year of follow-up).

Finally, because AD and asthma often occur together, in additional analyses we excluded AD patients with an asthma diagnosis before or at the time of the index hospitalization for AD ($n=7008$), and censored AD patients on the date of a later occurrence of asthma recorded in the DNPR (asthma ICD codes are presented in Appendix 1).

We used SAS[®] software (SAS Institute Inc., Cary, NC, USA) to analyze the data. The study was approved by the Danish Data Protection Agency.

Results

Skin Cancer Risk Following Diagnosis of Atopic Dermatitis (AD)

A total of 31 330 AD patients (50% male) were followed for 360 628 person-years (median length of follow-up=9.5 years; range: 0–30 years). Figure 1 shows the prevalence of AD in our dynamic cohort during the entire follow-up period. The median age at first AD diagnosis was 6 years (range: 0–96 years).

The observed number of MM among AD patients was 12, with 21 expected, yielding a SIR of 0.59 (95% CI 0.30, 1.02). The reduced risk was only evident for tumors located on anatomic

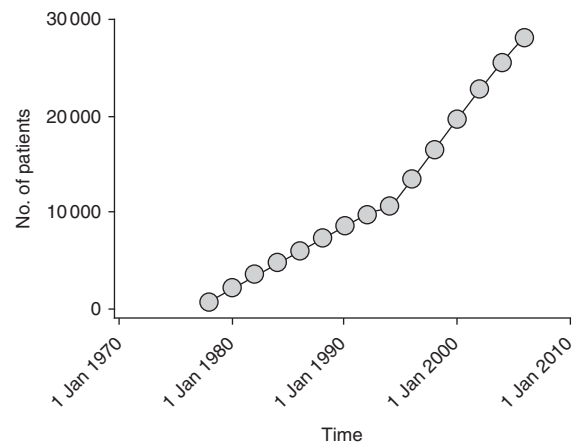


Fig. 1. The prevalence of atopic dermatitis (AD) in Denmark at a given point of time. The steep increase at 1 January 1995 represents the time at which outpatient visits were also included in the Danish National Patient Registry.

sites other than the head and neck (SIR=0.52; 95% CI 0.25, 0.96). The risk was slightly reduced with increased length of follow-up time. The reduced risk was most pronounced for patients hospitalized for AD (SIR for MM among AD inpatients=0.49; 95% CI 0.19, 1.00 vs a SIR for MM among AD outpatient clinic visits only=0.82; 95% CI 0.27, 1.92) [table I]. The MMs mainly occurred among AD patients diagnosed at 18–49 years of age, whereas no specific gender difference was found (table II).

The observed number of BCC cases among AD patients was 57, with 40 cases expected, yielding an SIR of 1.41 (95% CI 1.07, 1.83). The observed number of SCC cases among AD patients was seven, with three cases expected, yielding an SIR of 2.48 (95% CI 1.00, 5.11). All SCCs among AD patients were located on body sites other than the head and neck (SIR=5.02; 95% CI 2.0, 10.3). The association was most pronounced among AD patients diagnosed with SCC within 1 year of follow-up. Accordingly, the SCC estimates changed slightly after exclusion of SCC cases diagnosed at least 1 year after the date of AD diagnosis. All SCCs were diagnosed among AD patients hospitalized for the disease (SIR=3.80; 95% CI 1.52, 7.83). The presence of a chronic medical condition at the time of the index contact among inpatients did not influence the results (table I). The BCCs and SCCs mainly occurred among AD patients diagnosed above 50 years of age, whereas we found no specific gender difference (table II).

We found a small difference in SIR for MM, BCC, and SCC by time period of AD diagnosis (1977–94 vs 1995–2006). The most pronounced effect on risk occurred from 1977 to 1994, before outpatient visits began to be included in the DNPR (data not shown).

Table I. Skin cancer risk following a hospitalization and outpatient clinic visit for atopic dermatitis (AD) in Denmark, 1977–2006

Characteristic	No. of patients with AD	Malignant melanoma			Basal cell carcinoma			Squamous cell carcinoma		
		observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)
Total	31 330	12	21	0.59 (0.30, 1.02)	57	40	1.41 (1.07, 1.83)	7	3	2.48 (1.00, 5.11)
Body-site location										
Head and neck	NS	2	1	1.47 (0.18, 5.30)	29	17	1.70 (1.14, 2.44)	0	2	NA
Other sites	NS	10	19	0.52 (0.25, 0.96)	28	23	1.20 (0.80, 1.70)	7	1	5.02 (2.00, 10.3)
Follow-up time (years)										
<1	1584	1	1	0.91 (0.02, 5.05)	3	3	1.07 (0.22, 3.13)	2	0.3	8.02 (0.97, 29.00)
1–4	6481	4	4	0.94 (0.26, 2.40)	17	10	1.68 (0.98, 2.69)	1	1	1.18 (0.03, 6.56)
5+	23 265	7	15	0.46 (0.19, 0.95)	37	28	1.34 (0.95, 1.85)	4	2	2.32 (0.63, 5.95)
Hospital contact type										
Outpatient clinic visit	16 254	5	6	0.82 (0.27, 1.92)	16	13	1.22 (0.70, 1.98)	0	1	NA
Inpatient stay	16 220	7	14	0.49 (0.19, 1.00)	41	27	1.50 (1.08, 2.04)	7	2	3.80 (1.52, 7.83)
Chronic medical conditions among inpatients										
Absent	14 962	6	13	0.45 (0.17, 0.99)	35	24	1.46 (1.02, 2.04)	6	1	4.07 (1.49, 8.88)
Present	1258	1	1	0.87 (0.02, 4.84)	6	3	1.78 (0.65, 3.87)	1	1	2.72 (0.07, 15.00)

NA = not applicable; NS = not stated; SIR = standardized incidence ratio.

Skin Cancer Risk Following a Diagnosis of AD without Asthma

A total of 24 322 AD patients (48% male) were followed for 248 618 person-years (median length of follow-up = 8 years; range: 0–30 years). The median age at AD diagnosis was 5 years (range: 0–96 years).

The observed number of MMs among AD patients was 6, with 15 expected, yielding an SIR of 0.41 (95% CI 0.15, 0.89) [table III]. The reduced risk was only evident for MM located on body sites other than the head and neck (SIR = 0.36; 95% CI 0.12, 0.85), versus a SIR of 1.02 (95% CI 0.03, 5.67) for MM on the head and neck. The most pronounced protective effect of AD on MM risk was observed among AD patients with more than 5 years of follow-up (SIR = 0.19; 95% CI 0.02, 0.70). For SCC risk, a slightly weaker effect was found among AD patients without asthma (SIR = 1.38; 95% CI 0.28, 4.02) [table III] compared with a SIR of 2.48 (95% CI 1.00, 5.11) among AD patients with asthma (table I).

Discussion

Our study, based on the largest cohort of AD patients to date (n = 31 330), suggests that AD patients are at reduced risk for developing MM. The effect cannot be explained by a hospital diagnosis of asthma or calendar time. It also cannot be explained by diagnostic bias, since we found an inverse effect. At the same time, we found that AD is a positive risk factor for NMSC. While this finding may be due to diagnostic bias, because the association with SCC was only evident among AD patients diagnosed with SCC within the first year of follow-up, it does parallel those of other studies.^[4,5]

Our findings for MM also agree with previous studies.^[3–5] The immune system is activated in AD patients.^[14,15] One mechanism by which AD could decrease the risk of MM may stem from the altered immune-mediated inflammatory process underlying AD. AD is characterized by a specific immune-mediated inflammatory process with an initial T helper-2 cell response, followed by a T helper-1 cell response.^[16] Of interest, the cytokine release (i.e. interleukin [IL]-1 α , IL-6, and tumor necrosis factor- α) associated with the immune-mediated inflammatory process underlying AD has been found to inhibit melanocyte proliferation and nevus formation.^[17,18] A previous study found a lower total body count of melanocyte nevi among Swedish AD patients compared with healthy controls.^[19] Since the total number of melanocyte nevi is the strongest known risk factor for MM development,^[20–22] this may also explain the lower risk of MM among AD patients. Still, AD patients receive carcinogenic UV phototherapy

Table II. Skin cancer risk following a hospitalization and outpatient clinic visit for atopic dermatitis (AD) in Denmark, 1977–2006 (stratified by age and gender)

Characteristic	No. of patients with AD	Malignant melanoma			Basal cell carcinoma			Squamous cell carcinoma		
		observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)
Total	31 330	12	21	0.59 (0.30, 1.02)	57	40	1.41 (1.07, 1.83)	7	3	2.48 (1.00, 5.11)
Age stratified (years) ^a										
0–17	22 976	5	7	0.71 (0.23, 1.66)	3	5	0.65 (0.13, 1.90)	0	0	NA
18–49	7255	7	12	0.62 (0.25, 1.27)	30	21	1.37 (0.93, 1.96)	2	1	2.36 (0.29, 8.51)
50+	1099	0	2	NA	24	14	1.71 (1.10, 2.55)	5	2	2.70 (0.87, 6.29)
Gender stratified										
Female	15 646	9	14	0.62 (0.29, 1.19)	34	24	1.38 (0.95, 1.92)	3	1	2.52 (0.52, 7.35)
Male	15 684	3	6	0.49 (0.10, 1.49)	23	16	1.46 (0.72, 2.19)	4	2	2.46 (0.67, 6.29)

^a Age at entry in the study.

NA = not applicable; SIR = standardized incidence ratio.

(mainly UVB), and exposure to UV radiation is a well established environmental risk factor for MM development.^[23] This exposure could have increased the risk for MM among AD patients and may thus mask the inverse link between AD and MM.

Since AD patients are exposed to various immuno-suppressive agents (e.g. topical and oral glucocorticoids and azathioprine) combined with carcinogenic UV phototherapy from artificial sources, this may explain the link between AD and NMSC. Glucocorticoids, in particular, are known to increase the risk of NMSC.^[24,25] Among our AD study patients, SCC occurred on body sites other than normally sun-exposed areas,^[26] indicating a causative role of topically applied immunosuppressive treatments or artificial UV phototherapy. The body site localization observed for SCCs among AD patients is consistent with that reported in the previous Danish study.^[5] It is also consistent with that observed among psoriasis patients treated with UV phototherapy and immunosuppressive agents,^[27] whose anatomic distribution of SCC differs from that observed in the general population.^[26] Thus, while cumulative natural UV exposure explains most SCCs in the general population,^[28] UV phototherapy and immunosuppressive agents may be responsible for SCC in AD patients. This theory is supported by the occurrence of SCCs only among AD patients in our study who were hospitalized for their disease. These patients likely have the most severe disease and received the highest cumulative dose of UV phototherapy and immunosuppressive treatments. Our findings contrast with those of Ming et al.^[29] who conducted a case-control study among patients admitted to a university clinic in the US, evaluating whether individuals with AD were more likely than other patients with dermatologic conditions to develop NMSC. They found no increased risk for NMSC among users of topical glucocorticoids and topical tar preparations. The study reported an odds ratio of 0.78 (95% CI 0.61, 0.98) for NMSC among AD patients compared with other dermatologic patients.^[29] However, the study did not take into account use of artificial UV phototherapy, and excluded cases and controls with a history of systemic use of immunosuppressive agents – most likely the most severe cases.

Several factors support the validity of our study's results. The uniformly organized Danish healthcare system allows a true population-based design among patients referred to Danish hospitals, avoiding selection bias due to loss of follow-up. Identification of patients was based on diagnosis codes from the DNPR. The diagnosis of AD in the DNPR has been reported to be highly accurate if AD is diagnosed in pediatric or dermatology departments,^[30] which was the case for 90% of our AD patients. As well, we included both inpatients and out-

Table III. Skin cancer risk following a hospitalization and outpatient clinic visit for atopic dermatitis (AD) in patients without asthma in Denmark, 1977–2006

Characteristic	No. of patients with AD	Malignant melanoma			Basal cell carcinoma			Squamous cell carcinoma		
		observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)
Total	24 322	6	15	0.41 (0.15, 0.89)	39	30	1.29 (0.92, 1.77)	3	2	1.38 (0.28, 4.02)
Body-site location										
Head and neck	NS	1	1	1.02 (0.03, 5.67)	20	13	1.56 (0.96, 2.41)	0	1	NA
Other sites	NS	5	14	0.36 (0.12, 0.85)	19	17	1.09 (0.66, 1.71)	3	1	2.81 (0.58, 8.2)
Follow-up time (years)										
<1	1226	1	1	1.10 (0.03, 6.11)	2	2	0.87 (0.10, 3.13)	2	0.21	9.57 (1.16, 35.00)
1–4	4849	3	4	0.87 (0.18, 2.54)	12	8	1.48 (0.76, 2.58)	1	0.7	1.46 (0.04, 8.16)
5+	18 247	2	10	0.19 (0.02, 0.70)	25	20	1.27 (0.82, 1.87)	0	1.28	0
Hospital contact type										
Outpatient clinic visit	12 602	2	5	0.40 (0.05, 1.46)	9	11	0.85 (0.39, 1.61)	0	0.8	0
Inpatient stay	12 535	4	10	0.41 (0.11, 1.05)	30	20	1.53 (1.03, 2.19)	3	1	2.15 (0.44, 6.28)
Chronic medical conditions among inpatients										
Absent	12 248	4	10	0.42 (0.11, 1.07)	27	19	1.48 (0.97, 2.15)	2	1	1.69 (0.20, 6.08)
Present	287	0	0.3	0	3	1	2.32 (0.48, 6.76)	1	0.2	4.81 (0.12, 27)

NA = not applicable; NS = not stated; SIR = standardized incidence ratio.

patients, capturing the majority of AD patients treated in specialized outpatient clinics. It must be noted, however, that we lacked outpatient clinic person-years from 1977 through 1994 (outpatient clinic visits were not included in the DNPR before 1995), which may have led to an overestimation of the overall risk association between AD and MM, BCC and SCC.

Study limitations include lack of data on AD patients' use of immunosuppressive agents and their exposure to UV radiation from both natural and artificial sources. The study also lacked data on health behaviors, such as smoking and alcohol use. However, Mills et al.^[31] found no difference in smoking habits in patients with AD and matched healthy controls. Similarly, had the majority of AD patients been alcohol abusers, we would have expected more to have a history of another chronic medical condition. Another concern is that co-occurrence of seasonal allergic rhinitis (hay fever) in AD patients may have led to uncontrolled confounding of AD on skin cancer risk. We were not able to consider concurrent seasonal allergic rhinitis among AD patients, because the completeness of this diagnosis in the DNPR is unknown. Finally, the number of patients with skin cancer was low (i.e. 76 in total), producing unstable risk estimates.

Conclusions

Our findings support an inverse association between AD and MM. Our study also found that AD patients are at increased risk of BCC and SCC.

Acknowledgments

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Appendix 1

Atopic dermatitis, asthma, organ transplantation type, and associated Nordic Classification of Surgical Procedure (NCSP) codes, and chronic medical condition *International Classification of Diseases* (ICD)-8 and ICD-10 codes

Diseases	ICD-8 and/or NCSP code	ICD-10 and/or NCSP code
Atopic dermatitis	691	L20
Organ transplantations and asthma		
Condition with heart transplantation	NCSP procedure: 32209, 32219, 32240	DZ941, or NCSP procedure: KFQA00, KFQA10, KFQA20, KFQA30, KFQA40
Condition with lung transplantation	NCSP procedure: 35609	DZ942, or NCSP procedure: KGDG03, KGDG10, KGDG13, KGDG30, KGDG96
Condition with kidney transplantation	Y9509, or NCSP procedure: 57480-57490	DZ940, or NCSP procedure: KKAS00, KKAS10; KKAS20
Condition with liver transplantation	NCSP procedure: 47270-47279	DZ944, or NCSP procedure: KJJC10, KJJC20, KJJC30, KJJC40
Asthma	493	J45
Chronic medical conditions at atopic dermatitis diagnosis date present or absent		
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0 I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic obstructive pulmonary disease	490-492, 515-518	J40-J44, J46-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes mellitus type 1 and 2	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Diabetes with end organ failure	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-8, E11.2-8
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastasis	195-198; 199	C76-C80
Acquired immunodeficiency syndrome	079.83	B21-B24

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