

Malignancy risk among children and adults with atopic dermatitis in a population-based cohort

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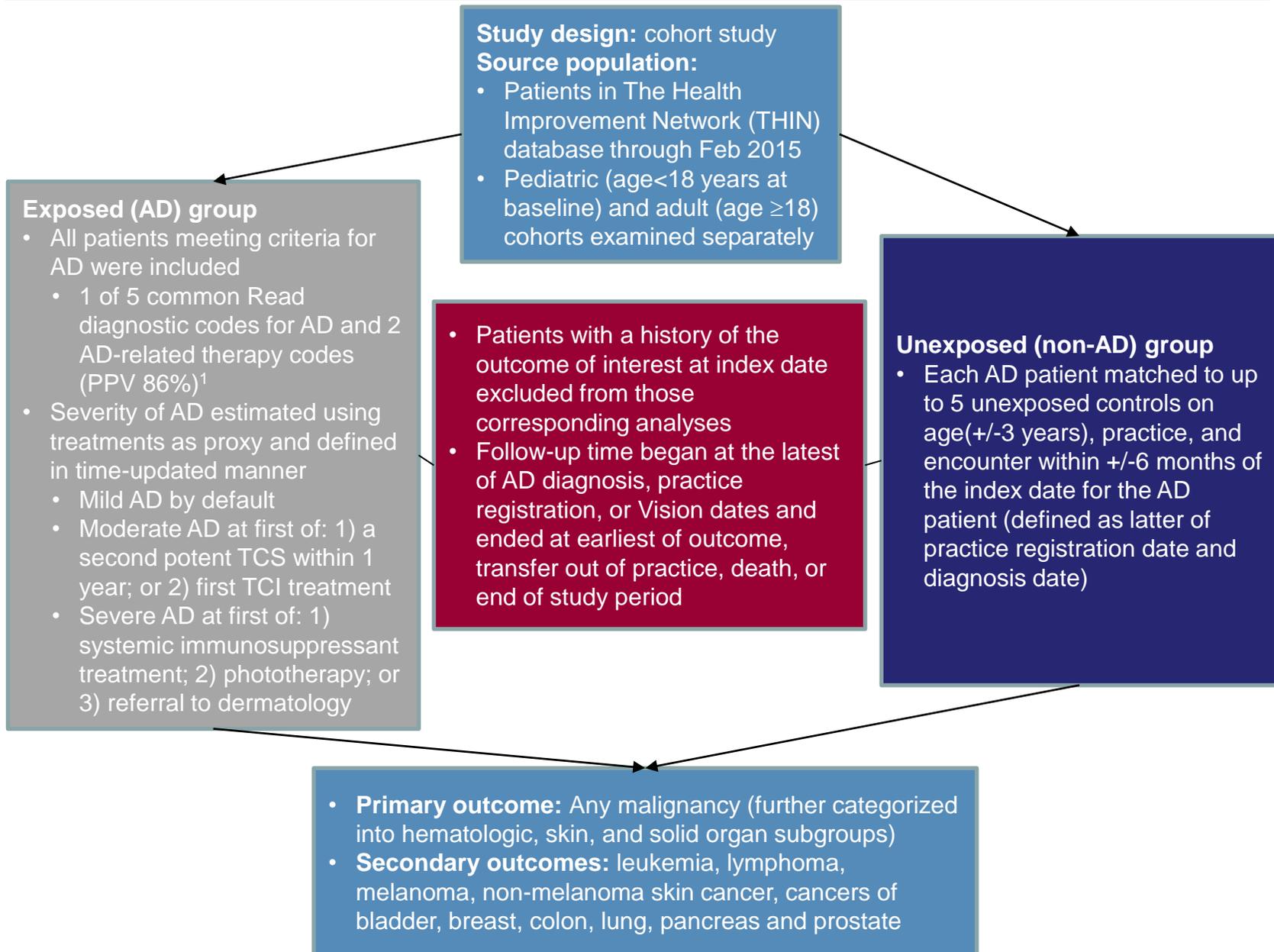
INTRODUCTION

- Atopic dermatitis (AD) is a chronic disease with ~20% lifetime prevalence
- AD has been associated with immunologic dysfunction which may influence the risk of cancer development
 - AD may increase cancer risk due to chronic inflammation or immunologic defects inherent to AD and/or its treatment
 - Conversely, increased immune surveillance due to overactive immune state in AD may also protect against cancer
- Epidemiologic studies have yielded inconsistent findings across different cancer subtypes and study designs

OBJECTIVE

- To examine the risk of malignancy—including common hematologic, skin, and solid organ malignancies—in a population-based cohort of both children and adults with AD

METHODS



METHODS

- Incidence rates calculated for each outcome
- Cox proportional hazards regression models comparing AD vs. non-AD groups
- Adjusted for covariates: age, sex, socioeconomic status (all ages); also body mass index, smoking status, alcohol intake (adults only)
- Additional sensitivity analyses
 - Exclusion of patients receiving systemic immunosuppressive medications for AD
 - Exclusion of patients with asthma or allergic rhinitis
 - Restricted to patients seen at least yearly during follow-up
 - Restricted to patients with at least 5 years of follow-up
 - Restricted to patients followed for at least 1 year prior to cohort entry

RESULTS

Baseline cohort characteristics

Characteristic, N (%)	Control	Mild AD	Moderate AD	Severe AD
Pediatric cohort	N=1809029	N=381678	N=22433	N=5320
Age, median (IQR), y	4 (2, 9)	4 (1, 8)	9 (4, 14)	5 (1, 10)
Sex				
Female	872279 (48.22)	184682 (48.39)	11054 (49.28)	2335 (43.89)
Male	936750 (51.78)	196996 (51.61)	11379 (50.72)	2985 (56.11)
Townsend deprivation index				
1-Lowest	424409 (24.71)	89820 (24.89)	4768 (22.55)	1251 (25.00)
2-Low	340677 (19.84)	71979 (19.95)	4106 (19.42)	1069 (21.37)
3-Moderate	355559 (20.70)	75261 (20.86)	4551 (21.52)	1033 (20.65)
4-High	339336 (19.76)	70649 (19.58)	4316 (20.41)	900 (17.99)
5-Highest	257540 (14.99)	53113 (14.72)	3407 (16.11)	750 (14.99)
Missing/Unknown	91508 (5.06)	20856 (5.46)	1285 (5.73)	317 (5.96)
Person-time, median (IQR), y	4.99 (2.0, 9.4)	5.22 (2.1, 9.7)	6.02 (2.6, 10.2)	6.89 (2.7, 12.6)
Adult cohort	N=2678888	N=410867	N=196101	N=18115
Age, median (IQR), y	47 (32, 64)	45 (30, 63)	50 (34, 68)	47 (32, 63)
Sex				
Female	1445589 (53.96)	256071 (62.32)	109404 (55.79)	10736 (59.27)
Male	1233299 (46.04)	154796 (37.68)	86697 (44.21)	7379 (40.73)
Body mass index, kg/m ²				
Underweight (<18)	72655 (2.71)	11504 (2.80)	4150 (2.12)	525 (2.90)
Normal (18.5-24.9)	911449 (34.02)	152480 (37.11)	66015 (33.66)	6972 (38.49)
Overweight (25-29.9)	707292 (26.40)	109693 (26.70)	56021 (28.57)	4799 (26.49)
Obese (30-34.9)	285567 (10.66)	44998 (10.95)	24088 (12.28)	1900 (10.49)
Severely Obese (35-39.9)	94373 (3.52)	15720 (3.83)	8486 (4.33)	653 (3.60)
Morbidly Obese (>40)	44721 (1.67)	8341 (2.03)	4525 (2.31)	343 (1.89)
Missing/Unknown	562831 (21.01)	68131 (16.58)	32816 (16.73)	2923 (16.14)
Smoking status				
Never	1293811 (48.30)	206577 (50.28)	89588 (45.68)	8653 (47.77)
Current	576463 (21.52)	84855 (20.65)	44195 (22.54)	3914 (21.61)
Former	548828 (20.49)	92290 (22.46)	48636 (24.80)	4182 (23.09)
Missing/Unknown	259786 (9.70)	27145 (6.61)	13682 (6.98)	1366 (7.54)
Drinking status				
Never	300614 (11.22)	51208 (12.46)	24278 (12.38)	2338 (12.91)
Current	1655958 (61.82)	262008 (63.77)	125921 (64.21)	11525 (63.62)
Former	114596 (4.28)	19708 (4.80)	10187 (5.19)	965 (5.33)
Missing/Unknown	607720 (22.69)	77943 (18.97)	35715 (18.21)	3287 (18.15)
Townsend deprivation index				
1-Lowest	677724 (26.39)	102924 (26.20)	46708 (24.99)	4685 (27.26)
2-Low	564890 (22.00)	84924 (21.61)	40579 (21.71)	3821 (22.23)
3-Moderate	534554 (20.82)	81331 (20.70)	39255 (21.00)	3566 (20.75)
4-High	468773 (18.25)	73004 (18.58)	35452 (18.97)	3038 (17.67)
5-Highest	322027 (12.54)	50711 (12.91)	24936 (13.34)	2079 (12.09)
Missing/Unknown	110920 (4.14)	17973 (4.37)	9171 (4.68)	926 (5.11)
Person-time, median (IQR), y	4.96 (2.09, 9.18)	4.94 (2.05, 9.24)	5.20 (2.204, 9.44)	5.41 (2.14, 10.44)

RESULTS

Incidence rates of malignancy, per 10,000 person-years

Outcome	Pediatric cohort				Adult cohort			
	Non-AD	Mild AD	Moderate AD	Severe AD	Non-AD	Mild AD	Moderate AD	Severe AD
Any malignancy	1.98 (1.90-2.06)	1.90 (1.72-2.08)	2.87 (2.31-3.58)	3.43 (2.30-5.11)	103.7 (103.2-104.2)	97.4 (96.1-98.8)	119.9 (118.0-121.7)	125.3 (120.1-130.8)
Hematologic	0.75 (0.70-0.80)	0.76 (0.66-0.89)	0.93 (0.64-1.37)	1.00 (0.48-2.09)	9.15 (9.01-9.30)	8.61 (8.22-9.01)	12.03 (11.48-12.60)	14.03 (12.42-15.85)
Leukemia	0.42 (0.38-0.46)	0.40 (0.33-0.49)	0.14 (0.05-0.38)	0.14 (0.02-1.01)	2.37 (2.30-2.45)	2.14 (1.96-2.35)	2.75 (2.50-3.03)	2.21 (1.63-3.00)
Lymphoma	0.23 (0.20-0.26)	0.27 (0.21-0.35)	0.57 (0.35-0.94)	0.85 (0.38-1.90)	3.12 (3.03-3.20)	3.08 (2.86-3.33)	4.32 (4.00-4.67)	7.41 (6.27-8.76)
CTCL	0.01 (0.006-0.02)	0.01 (0.002-0.04)	0.04 (0.01-0.25)	n/a*	0.11 (0.09-0.13)	0.17 (0.12-0.24)	0.65 (0.53-0.80)	1.78 (1.26-2.50)
Hodgkin lymphoma	0.12 (0.10-0.14)	0.14 (0.10-0.20)	0.43 (0.24-0.76)	0.14 (0.02-1.01)	0.26 (0.24-0.29)	0.38 (0.31-0.47)	0.41 (0.32-0.53)	0.86 (0.53-1.41)
Skin	0.27 (0.24-0.30)	0.33 (0.26-0.41)	0.43 (0.24-0.76)	0.57 (0.21-1.52)	35.3 (35.0-35.6)	35.4 (34.6-36.2)	42.0 (40.9-43.1)	47.5 (44.4-50.8)
Melanoma	0.17 (0.14-0.19)	0.17 (0.13-0.24)	0.22 (0.10-0.48)	0.14 (0.02-1.01)	4.56 (4.46-4.67)	4.17 (3.91-4.45)	4.77 (4.43-5.14)	4.64 (3.76-5.74)
NMSC	0.11 (0.09-0.13)	0.16 (0.11-0.22)	0.22 (0.10-0.48)	0.43 (0.14-1.32)	31.7 (31.4-32.0)	32.1 (31.4-32.9)	38.4 (37.3-39.4)	43.6 (40.7-46.8)
Solid	0.97 (0.91-1.03)	0.83 (0.72-0.96)	1.58 (1.18-2.12)	1.99 (1.18-3.37)	69.4 (69.0-69.8)	63.7 (62.6-64.8)	79.1 (77.7-80.6)	81.7 (77.6-86.0)
Bladder	0.01 (0.006-0.02)	0.004 (0.001-0.03)	0.04 (0.01-0.25)	0.14 (0.02-1.01)	4.05 (3.95-4.15)	3.61 (3.37-3.88)	4.79 (4.45-5.16)	3.83 (3.03-4.83)
Breast#	0.03 (0.02-0.05)	0.05 (0.02-0.11)	0.15 (0.04-0.58)	0.31 (0.04-2.23)	23.5 (23.2-23.8)	20.1 (19.4-20.9)	23.3 (22.3-24.4)	21.9 (19.3-24.9)
Colon	0.023 (0.02-0.03)	0.004 (0.001-0.03)	0.04 (0.01-0.25)	n/a*	8.77 (8.63-8.91)	7.74 (7.37-8.12)	9.55 (9.07-10.07)	8.86 (7.60-10.32)
Lung	0.005 (0.002-0.01)	0.004 (0.001-0.03)	0.04 (0.01-0.25)	n/a*	9.12 (8.98-9.27)	7.73 (7.37-8.11)	10.41 (9.91-10.95)	12.65 (11.13-14.37)
Pancreas	0.01 (0.006-0.02)	n/a*	n/a*	n/a*	1.78 (1.72-1.85)	1.57 (1.41-1.75)	2.27 (2.04-2.53)	1.88 (1.35-2.62)
Prostate^	0.01 (0.004-0.02)	n/a*	n/a*	n/a*	23.5 (23.1-23.8)	26.9 (25.8-28.1)	29.4 (28.0-30.7)	25.3 (22.0-29.2)

Abbreviations: AD, atopic dermatitis; CTCL, cutaneous T-cell lymphoma; NMSC, non-melanomatous skin cancer; THIN, The Health Improvement Network
 *No events. #Breast cancers in females only. ^Prostate cancers in males only.

RESULTS

Adjusted risk of malignancy outcomes

Outcome	Adjusted hazard rate ratio (95% CI) [ref: non-AD]							
	Pediatric cohort*				Adult cohort**			
	Overall AD	Mild AD	Moderate AD	Severe AD	Overall AD	Mild AD	Moderate AD	Severe AD
Any malignancy	1.02 (0.92, 1.12)	1.01 (0.91, 1.12)	0.99 (0.79, 1.25)	1.39 (0.93, 2.08)	1.00 (0.99, 1.02)	1.03 (1.01, 1.04)	0.96 (0.95, 0.98)	1.15 (1.10, 1.20)
Hematologic	1.07 (0.91, 1.25)	1.04 (0.88, 1.23)	1.25 (0.84, 1.86)	1.39 (0.66, 2.92)	1.07 (1.03, 1.10)	1.01 (0.96, 1.06)	1.09 (1.03, 1.14)	1.44 (1.27, 1.64)
Leukemia	0.88 (0.70, 1.10)	0.93 (0.74, 1.17)	0.47 (0.17, 1.25)	0.40 (0.06, 2.81)	0.95 (0.88, 1.02)	0.97 (0.88, 1.07)	0.94 (0.85, 1.05)	0.86 (0.63, 1.18)
Lymphoma	1.41 (1.09, 1.83)	1.28 (0.96, 1.71)	1.71 (1.01, 2.90)	3.13 (1.39, 7.06)	1.18 (1.11, 1.25)	1.06 (0.98, 1.15)	1.19 (1.10, 1.30)	2.28 (1.92, 2.71)
CTCL	3.51 (0.78, 15.73)	2.85 (0.52, 15.69)	7.74 (0.83, 72.20)	n/a	4.09 (3.29, 5.07)	1.73 (1.21, 2.47)	5.60 (4.34, 7.23)	18.09 (12.43, 26.32)
Hodgkin lymphoma	1.41 (0.99, 2.00)	1.342 (0.90, 2.00)	1.77 (0.94, 3.34)	0.78 (0.11, 5.61)	1.63 (1.36, 1.97)	1.51 (1.19, 1.92)	1.60 (1.22, 2.11)	3.38 (2.02, 5.66)
Skin	1.21 (0.95, 1.53)	1.38 (1.07, 1.79)	0.68 (0.38, 1.22)	1.10 (0.41, 2.97)	1.06 (1.04, 1.08)	1.08 (1.06, 1.11)	1.00 (0.97, 1.03)	1.30 (1.21, 1.39)
Melanoma	0.99 (0.71, 1.38)	1.28 (0.91, 1.82)	0.43 (0.19, 0.98)	0.35 (0.05, 2.51)	0.96 (0.91, 1.01)	0.96 (0.89, 1.03)	0.96 (0.89, 1.04)	0.99 (0.80, 1.22)
NMSC	1.52 (1.07, 2.16)	1.55 (1.06, 2.27)	1.16 (0.50, 2.69)	2.66 (0.84, 8.45)	1.06 (1.04, 1.08)	1.10 (1.07, 1.12)	1.00 (0.97, 1.03)	1.33 (1.24, 1.43)
Solid	0.92 (0.80, 1.06)	0.90 (0.77, 1.06)	0.89 (0.65, 1.21)	1.37 (0.81, 2.33)	0.97 (0.96, 0.99)	0.99 (0.98, 1.01)	0.93 (0.92, 0.95)	1.10 (1.04, 1.16)
Bladder	1.17 (0.33, 4.19)	0.46 (0.06, 3.54)	3.25 (0.40, 26.17)	14.23 (1.81, 111.78)	0.93 (0.88, 0.98)	0.99 (0.92, 1.06)	0.88 (0.81, 0.95)	0.89 (0.70, 1.12)
Breast [#]	0.92 (0.36, 2.37)	1.65 (0.61, 4.49)	0.21 (0.02, 1.79)	0.81 (0.09, 7.29)	0.95 (0.92, 0.98)	0.95 (0.92, 0.99)	0.94 (0.90, 0.99)	0.92 (0.80, 1.05)
Colon	0.23 (0.05, 0.995)	0.24 (0.03, 1.76)	0.27 (0.03, 2.19)	n/a	0.92 (0.88, 0.95)	0.95 (0.91, 1.004)	0.87 (0.82, 0.92)	0.96 (0.82, 1.13)
Lung	1.27 (0.25, 6.43)	1.06 (0.13, 8.88)	2.01 (0.20, 20.21)	n/a	0.91 (0.87, 0.94)	0.94 (0.89, 0.99)	0.85 (0.80, 0.89)	1.20 (1.06, 1.37)
Pancreas	n/a				0.97 (0.89, 1.05)	0.95 (0.84, 1.06)	0.99 (0.89, 1.11)	0.92 (0.65, 1.30)
Prostate [^]	n/a				0.95 (0.92, 0.98)	1.04 (0.99, 1.09)	0.86 (0.82, 0.91)	0.90 (0.77, 1.04)

- Sensitivity analyses led to mostly similar results as the primary analysis
 - Excluding those receiving systemic immunosuppressive medications, moderate/severe AD remained associated with greater lymphoma risk while severe AD no longer associated with skin cancer or solid malignancy in adults; findings unchanged in children

DISCUSSION

- Overall, we found no significant association between AD and malignancy, but results also varied by age, AD severity, specific cancer type
- Adults with severe AD had 15% greater risk of cancer overall compared to controls without AD
- Moderate/severe AD was associated with greater risk of lymphoma (71-313% greater risk in children; 19-228% greater risk in adults) compared to non-AD group
- Adults with moderate AD had slightly lower risk of solid organ malignancy, including bladder, breast, colon, lung and prostate cancers
- Potential limitations:*
 - Misclassification of AD severity (due to use of treatments as proxy and time-updated defns)
 - Ascertainment bias
 - Relatively short duration of study follow-up
 - Inability to disentangle effects of AD severity from AD treatment

CONCLUSIONS

- AD is associated with increased risk of select cancers, particularly lymphoma, and potentially lower risk of some solid malignancies
- As immunomodulatory therapies continue to emerge for AD, this heterogeneous relationship between AD and malignancy requires continued investigation