CANCER RISK IN PATIENTS WITH ATOPIC DERMATITIS: A SYSTEMATIC REVIEW

Lily Wang, MD(C)
CSIM Annual Meeting 2018
October 11, 2018
DISCLOSURE

• Relevant relationships with commercial entities
  – None

• Potential for conflicts of interest within this presentation
  – None

• Steps taken to review and mitigate potential bias
  – None
Atopic dermatitis (AD), also known as atopic eczema
- Intense itching and recurrent lesions
- Immune dysregulation

Treated with immunosuppressive medications

The immune system is critical in preventing oncogenesis

Dysregulation and suppression of the immune system may cause AD to be associated with risk of cancer

Boguniewicz, M and Leung D YM. (2011)
AVAILABLE LITERATURE

Higher prevalence

• Keratinocyte carcinoma (KC)
  – a.k.a. non-melanoma skin cancer
• Leukemia
• Lymphoma
• Pancreatic cancer
• Esophageal cancer

No association

• Keratinocyte carcinoma (KC)
• Leukemia
• Pancreatic cancer
• Hepatic cancer

Jain et al. (1991)
Schuz et al. (2003)
Spector et al. (2004)
OBJECTIVE

• To determine the risk of non-cutaneous and cutaneous cancers in patients with AD compared to the general population (i.e. without AD).
METHODS

• **Design:** Cochrane Handbook for Systematic Reviews of Interventions

• **Reporting:** “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” guidelines

• **Registration:** PROSPERO CRD42018092929
Search: Strategy and Terms

**Databases**
- MEDLINE, EMBASE, Cochrane Registrar for randomized controlled trials
  - Through March 29, 2018

**Search Terms**
- **Intervention:** exp Dermatitis, Atopic/ OR (atopic adj1 (dermatit* or neurodermatit*)).tw. OR eczema.tw. OR disseminated neurodermatit*.tw.
- **Outcomes:** neoplas*.tw. OR exp Neoplasms/ OR tumo*.tw. OR cancer*.tw. OR malignanc*.tw.
- **Design:** observational (cohort (CO) and case control (CC)) study design
Eligibility Criteria

Inclusion

• Atopic dermatitis hx
• Control group comparator (general population or patients without AD)
• Cancer outcome
• Cohort or Case-control study in Humans
• Original data
  • All ages and cancer types

Exclusion

• No adequate intervention
• No viable outcome data
• Intervventional studies
• Non-human studies
Data Extraction

- 2 independent reviewers
- Trial characteristics:
  - Authors
  - Publication year
  - Study design
  - Cohort name
  - Study period
  - Sample size
  - Patient characteristics (age, sex, race)
- Follow-up time
- Adjusting covariates
- Cancer type
- Country of study
- Identification of AD and cancer
- Data source
- Endpoints
Risk of Bias

- Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool
  - Modified for observational studies
  - “Low risk”, “moderate risk”, “serious risk”, and “critical risk” of bias under each domain

- Domains:
  - Bias due to confounding
  - Bias in selection of participants into the study
  - Bias in classification of interventions
  - Bias due to deviations from intended interventions
  - Bias due to missing data
  - Bias in measurement of outcomes
  - Bias in selection of the reported result
Statistical Analysis

• **Software**: Review Manager version 5.3
  (Cochrane Library software, Oxford, UK)

  5

• Generic inverse variance method: Pairwise random effects meta-analysis

• **Heterogeneity analysis**:
  – Significance by Cochran’s Q; $P < 0.10$
  – Quantification with $I^2$ statistic
    • Substantial: >50%
Overall certainty and strength of the evidence

Grading of Recommendations Assessment, Development and Evaluation for quality of evidence (GRADE)

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>

**Downgrade**

- Study limitation (risk of bias)
- Inconsistency (unexplained heterogeneity)
- Indirectness (low generalizability)
- Imprecision (small sample size, wide CI)
- Publication bias

RESULTS

6,773 articles identified initially
1,523 MEDLINE (through 29 March 2018)
5,250 EMBASE (through 29 March 2018)

6,674 reports excluded based on title and/or abstract
1,439 Duplicates
3,665 No atopic dermatitis diagnosis
464 Unsuitable cancer outcome
440 Commentaries
272 Case studies
205 Reviews
80 Conference abstracts
21 Non-observational studies
88 Other

27 reports identified by manual search of references

126 reports reviewed in full

69 reports excluded
18 Conference abstracts
13 No atopic dermatitis diagnosis
12 Unsuitable cancer outcome
1 Commentary
10 Non-observational study
16 Other

57 observational studies included in the meta-analysis
9 cohorts, 48 case controls
Table of Characteristics

9 cohorts in 1,304,736 people
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Cohort Name</th>
<th>Design of Cohort</th>
<th>Mean Age (Range)</th>
<th>Inclusion Period</th>
<th>Exposure Variable</th>
<th>Cohort Size (n)</th>
<th>Cancer (n)</th>
<th>AD (n)</th>
<th>Cancer diagnosis</th>
<th>Assessment of Exposure</th>
<th>Follow Up (years)</th>
<th>Adjustment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arana et al. 2010</td>
<td>UK</td>
<td>The Health Improvement Network (THIN) database</td>
<td>Populatio n based</td>
<td>Female 38.9, Male 38.1</td>
<td>1 January 1992 to 23 March 2006</td>
<td>Atopic dermatitis</td>
<td>4 518 131</td>
<td>129 972</td>
<td>66 258</td>
<td>EMR database</td>
<td>EMR database</td>
<td>6.78</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Dyer et al. 2010</td>
<td>USA</td>
<td>VATTC Trial</td>
<td>Non-populatio n based</td>
<td>72 (&lt;60), &lt;80</td>
<td>January 1, 1965, and December 31, 1999</td>
<td>Eczema</td>
<td>1131</td>
<td>49,764</td>
<td>52</td>
<td>Dermatologist examination every 6 months and biopsy of suspicious lesions,</td>
<td>Eczema self reported diagnosis</td>
<td>3.6</td>
<td>None</td>
</tr>
<tr>
<td>Hagstromer et al. 2005</td>
<td>Sweden</td>
<td></td>
<td>Non-populatio n based (Hospital based)</td>
<td>15.7</td>
<td>Atopic dermatitis</td>
<td>15 666</td>
<td>331</td>
<td>15 666</td>
<td>National cancer register.</td>
<td>Inpatient hospital register.</td>
<td>15.4</td>
<td>Age, sex and time period</td>
<td></td>
</tr>
<tr>
<td>Hwang et al. 2012</td>
<td>Taiwan</td>
<td>Taiwan National Health Insurance Research Database cohort</td>
<td>Populati on based</td>
<td>23.4</td>
<td>1996 - 2008</td>
<td>Atopic dermatitis</td>
<td>1,000,000</td>
<td>319</td>
<td>34,263</td>
<td>National insurance research database</td>
<td>National insurance research database</td>
<td>5.27</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Jensen et al. 2012</td>
<td>Denmark</td>
<td>Danish Nationwide Cohort Study</td>
<td>Populati on based</td>
<td>1977-2006</td>
<td>Atopic dermatitis</td>
<td>31330</td>
<td>76</td>
<td>31330</td>
<td>National cancer registry</td>
<td>National patient registry</td>
<td>9.5</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Juan et al. 2016</td>
<td>Taiwan</td>
<td>Taiwan National Health Insurance Research Database Cohort</td>
<td>Populati on based</td>
<td>N/A (40+)</td>
<td>2000 to 2010 for diagnosis of eczema, December 31, 2011 for diagnosis of cancer</td>
<td>Eczema</td>
<td>131157</td>
<td>1629 (in AD), 1014 (no AD)</td>
<td>43,719</td>
<td>Registry for Catastrophic Illness Patient Database</td>
<td>Diagnosis made by dermatologist</td>
<td>8.53</td>
<td>Age, sex and comorbid diseases (asthma, chronic obstructive pulmonary disease, alcoholic liver damage, and diabetes)</td>
</tr>
<tr>
<td>First author, year</td>
<td>Country</td>
<td>Cohort Name</td>
<td>Design of Cohort</td>
<td>Mean Age (Range)</td>
<td>Inclusion Period</td>
<td>Exposure Variable</td>
<td>Cohort Size (n)</td>
<td>Cancer (n)</td>
<td>AD (n)</td>
<td>Cancer diagnosis</td>
<td>Assessment of Exposure</td>
<td>Follow Up (years)</td>
<td>Adjustment Factors</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
<td>-------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td>------------</td>
<td>--------</td>
<td>-----------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Arana et al. 2010</td>
<td>UK</td>
<td>The Health Improvement Network (THIN) database</td>
<td>Population based</td>
<td>Female 38.9, Male 38.1</td>
<td>1 January 1992 to 23 March 2006</td>
<td>Atopic dermatitis</td>
<td>4 518 131</td>
<td>129 972</td>
<td>66 258</td>
<td>EMR database</td>
<td>EMR database</td>
<td>6.78</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Dyer et al. 2010</td>
<td>USA</td>
<td>VATTC Trial</td>
<td>Non-population</td>
<td>72 (&lt;60), &lt;80</td>
<td>Eczema</td>
<td>1131</td>
<td>49,764</td>
<td>52</td>
<td>Dermatologist examination every 6</td>
<td>Eczema self reported</td>
<td>3.6</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

- 9 cohorts in 1,304,736 people
  - 5/9 (56%) studies population based
  - UK (2), Sweden (3), Taiwan (2) and Denmark (2)
  - Study period: 1886 to 2001
  - Mean age of cohorts: 15-56
  - Average follow up: 5-42 years
  - 5/9 used national cancer registry to determine endpoint
Keratinocyte carcinoma (KC)

<table>
<thead>
<tr>
<th>Type and Study</th>
<th>Population</th>
<th>Cancer</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinocyte Carcinoma</td>
<td>Arana (2010)</td>
<td>Atopic dermatitis</td>
<td>NMSC</td>
<td>187</td>
<td>26,297</td>
<td>1.45 (1.27, 1.68)</td>
</tr>
<tr>
<td></td>
<td>Hegstromer (2005)</td>
<td>Atopic dermatitis</td>
<td>NMSC</td>
<td>12</td>
<td></td>
<td>1.50 (0.83, 2.70)</td>
</tr>
<tr>
<td></td>
<td>Hwang (2012)</td>
<td>Atopic dermatitis</td>
<td>NMSC</td>
<td>7</td>
<td>9.36</td>
<td>0.75 (0.33, 1.70)</td>
</tr>
<tr>
<td></td>
<td>Jensen (2012)</td>
<td>Atopic dermatitis w/o asthma</td>
<td>BCC</td>
<td>39</td>
<td>30</td>
<td>1.29 (0.93, 1.79)</td>
</tr>
<tr>
<td></td>
<td>Jensen (2012)</td>
<td>Atopic dermatitis w/o asthma</td>
<td>SCC</td>
<td>3</td>
<td>2</td>
<td>1.38 (0.96, 5.23)</td>
</tr>
<tr>
<td></td>
<td>Cleeen (2005)</td>
<td>Atopic dermatitis w/o asthma</td>
<td>KC</td>
<td>16</td>
<td>6.6</td>
<td>2.40 (1.44, 4.01)</td>
</tr>
<tr>
<td>Subgroup (I-squared = 25.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.46 (1.20, 1.77)</td>
</tr>
<tr>
<td>Overall (I-squared = 25.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SIR 1.46 [95% CI: 1.20, 1.77]</td>
</tr>
</tbody>
</table>

Case controls OR 1.53 [95% CI: 1.08, 2.18]
### ROBINS-I: Risk of bias

<table>
<thead>
<tr>
<th>Domain</th>
<th>Study</th>
<th>Arana</th>
<th>Hagstromer</th>
<th>Hwang</th>
<th>Jensen</th>
<th>Juan</th>
<th>Montgomery</th>
<th>Olesen</th>
<th>Soderberg</th>
<th>Schwartzbaum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias due to confounding</td>
<td></td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
</tr>
<tr>
<td>Bias in selection of participants into the study</td>
<td></td>
<td>Serious risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Bias in classification of interventions</td>
<td></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Bias due to deviations from intended interventions</td>
<td></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Bias due to missing data</td>
<td></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Serious risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Serious risk</td>
<td>Low risk</td>
<td>No info</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Bias in measurement of outcomes</td>
<td></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Moderate risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Bias in selection of the reported result</td>
<td></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Moderate risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
<td>Moderate risk</td>
<td>Serious risk</td>
</tr>
</tbody>
</table>

- 3 **serious** risk of bias
- 6 **moderate** risk of bias
- Moderate or serious “bias due to confounding” (9/9)
Study Certainty

• 7 outcomes: very low evidence
• 5 outcomes: low evidence

• Recall: observational studies start with a low grade
CONCLUSION

• Significant association between AD and increased risk of
  • Keratinocyte carcinoma: CO SIR 1.46 [95% CI: 1.20, 1.77] and CC OR 1.53 [95% CI: 1.08, 2.18]
  • Female GU cancers: CO SIR 1.80 [95% CI: 1.05, 3.08]
  • Kidney cancer: CO SIR 1.86 [95% CI: 1.14, 3.04]
  • Pancreatic cancer: CO SIR 1.90 [95% CI: 1.03, 3.50]

• No cohorts concluded a reduction in cancer risk for patients with AD

LIMITATIONS
• Substantial heterogeneity
  1. No information about AD diagnosis criteria
  2. Detection bias

SIGNIFICANCE

• Provide further insight into the effect of AD on cancer risk

• Strengthen the evidence-base for guidelines on early AD management
  – Importance of regular skin examination for early detection and management of cancerous lesions

• Opportunities for further investigations
THANK YOU
ACKNOWLEDGMENTS

- Dr. An-Wen Chan
- Dr. Aaron Drucker
- Rachel Bierbrier
Article Screening

Selected studies from database and manual searches

Exclusion based on title and abstract

Full article review

Exclusion based on full review of article

Final studies included in meta-analysis
All pooled cohorts