Cancer in Agricultural Populations

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Background: Agriculture and Cancer

- Although farming is declining worldwide, it remains an important industry
- Farmers healthier than general population
  - Lower incidence:
    - Lung, bladder, colon
  - Higher incidence:
    - Leukemia, multiple myeloma, NHL
    - Lip
    - Stomach
    - Skin
    - Brain
    - Prostate cancers

*Blair and Beane Freeman, J Agromedicine, 2009*
Background: Agriculture and Cancer

- Numerous exposures
  - Pesticides
  - Animals
  - Diesel engine exhaust
  - Biologically active dusts
  - Zoonotic microbes
  - Fuels, oils, and solvents

- Low rates of tobacco and alcohol use
- High rates of physical activity
The Agricultural Health Study

- Designed to study a wide range of health effects of agricultural exposures in farmers and their families

- Prospective cohort of 52,000 licensed pesticide applicators and 32,000 farm spouses
  - 1993-97

- Completed questionnaires on medical history, pesticide use, and current farming

- 84% of licensed applicators enrolled
Agricultural Health Study

- Two agricultural states:
Agricultural Health Study

- Regular linkage to state cancer registries
  - Population-based
- National mortality registry
- 17+ years of follow-up (median age=65 years)
- >10,000 incident cancers
- Able to control statistically for use of other pesticides and other exposures
Pesticides: A Worldwide Exposure

- 2.4 billion kg pesticide active ingredients applied worldwide in 2007
- 500 million kg of pesticide active ingredients used in 1993 in the USA
  - 890 different active ingredients
- World-wide over 1 billion people occupationally exposed to pesticides
Pesticide Application Methods: Field Crops
Pesticide Application Methods: Animals
Pesticide Application Methods: Orchards
Pesticide Application Methods: Field Crops
Mixing pesticides
Selected Pesticide Findings: Farmers

Organophosphate Insecticides

Organochlorine Insecticides
Lindane, DDT

Chloroacetilinide Herbicides
Metolachlor
Acetochlor
Organophosphate Insecticides

- Introduced in the 1970s
- Widespread use on crops and animals, agricultural and residential use (historically)
- Acetylcholinesterase inhibition
Diazinon and NHL

Relative Risks and 95% CI

Alavanja...Beane Freeman, PLoS One 2014

Adjusted for age, state, race, herbicide use
Diazinon and Lung Cancer

Relative Risks and 95% CI

- Lung Cancer
- Adenocarcinoma
- Squamous cell carcinoma
- Small Cell carcinoma

Adjusted for age, state, alcohol, smoking, family history of cancer, education

Jones...Beane Freeman, Occup Environ Med, 2015
Organochlorine Insecticides

- Introduced in the 1940s
- Persistent
- Most banned in US in 1970s
  - Lindane still used until 2006
- Many still used in around the world for vector control
Lindane and NHL

Relative Risks and 95% CI Adjusted for age, state, race, herbicide use

Alavanja...Beane Freeman, PLoS One, 2014
DDT and NHL

Relative Risks and 95% CI

Adjusted for age, state, race, herbicide use

Alavanja...Beane Freeman, PLoS One, 2014
Recent IARC Evaluations of Pesticides

- These results played an important role in recent IARC monograph evaluations
  - Lindane—Group 1 (NHL)
  - DDT—Group 2A (NHL)
  - Diazinon—Group 2A (NHL and lung cancer)
Organophosphate Insecticides and Aggressive Prostate Cancer

<table>
<thead>
<tr>
<th>Organophosphate Insecticide</th>
<th>Q4 vs. Non-exposed RR 95 % CI</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpyrifos</td>
<td>1.01 (0.80, 1.28)</td>
<td>0.84</td>
</tr>
<tr>
<td>Diazinon</td>
<td>1.31 (0.87, 1.96)</td>
<td>0.27</td>
</tr>
<tr>
<td>Fonofos</td>
<td>1.63 (1.22, 2.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malathion</td>
<td>1.43 (1.08, 1.88)</td>
<td>0.04</td>
</tr>
<tr>
<td>Parathion</td>
<td>0.98 (0.53, 1.79)</td>
<td>0.97</td>
</tr>
<tr>
<td>Phorate</td>
<td>1.36 (0.96, 1.93)</td>
<td>0.10</td>
</tr>
<tr>
<td>Terbufos</td>
<td>1.29 (1.02, 1.64)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

First study to show association with aggressive prostate cancer

*Koutros, Beane Freeman et al., American Journal of Epidemiology, 2014*
## Association between pesticides and prostate cancer among men with risk allele identified in genome-wide association studies

<table>
<thead>
<tr>
<th>Gene/Region</th>
<th>Pesticide</th>
<th>Non-exposed</th>
<th>Low exposed OR (95% CI)</th>
<th>High exposed OR (95% CI)</th>
<th>P-int</th>
</tr>
</thead>
<tbody>
<tr>
<td>8q24, rs4242382</td>
<td>FONOFOS</td>
<td>REF</td>
<td>1.2 (0.7, 2.2)</td>
<td>2.9 (1.5, 5.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>8q24, rs1447295</td>
<td>FONOFOS</td>
<td>REF</td>
<td>1.1 (0.6, 2.0)</td>
<td>2.8 (1.4, 5.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>8q24, Region 3</td>
<td>TERBUFOS</td>
<td>REF</td>
<td>1.5 (0.9, 2.5)</td>
<td>1.8 (1.0, 2.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>EHBP1</td>
<td>MALATHION</td>
<td>REF</td>
<td>2.2 (0.9, 5.1)</td>
<td>3.4 (1.4, 8.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>PDLIM5</td>
<td>TERBUFOS</td>
<td>REF</td>
<td>1.4 (0.9, 2.1)</td>
<td>1.6 (1.0, 2.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>17q24</td>
<td>TERBUFOS</td>
<td>REF</td>
<td>1.7 (1.0, 3.0)</td>
<td>2.1 (1.2, 3.6)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Koutros, Beane Freeman et al., Cancer Research, 2010
Koutros...Beane Freeman PLoS One, 2013
Metolachlor: Chloroacetilinide Herbicide

- Used primarily on corn
- EPA Class C, Possible Human Carcinogen
- Based primarily on liver tumors in rats

Source: USGS Pesticide Use Maps
Metolachlor and Liver Cancer

Relative Risks and 95% CI

Non-exposed  Q1  Q2  Q3  Q4

p-trend=0.03

Silver...Beane Freeman, Int J Cancer, 2015
Mixtures Can Be Important

- Important to evaluate individual active ingredients
- Pesticides often applied as mixtures of different products
- May have synergistic effects
Chloroacetilinide Herbicides: Acetochlor

- Registered for use in 1994
- Registration based on reduction in use of other herbicides including atrazine
## Acetochlor/Atrazine and Lung Cancer

<table>
<thead>
<tr>
<th></th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetochlor alone</td>
<td>1.96 (0.70-5.50)</td>
</tr>
<tr>
<td>Atrazine alone</td>
<td>1.3 (0.9-1.9)</td>
</tr>
</tbody>
</table>

Lerro... Beane Freeman, *Int J Cancer*, 2015
## Acetochlor/atrazine and Lung Cancer

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Acetochlor alone</td>
<td>1.96 (0.70-5.50)</td>
</tr>
<tr>
<td>Atrazine alone</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>Atrazine + Acetochlor</td>
<td>2.33 (1.30-4.17)</td>
</tr>
</tbody>
</table>
Cancer in Women

32,345 spouses of farmers enrolled in AHS

60% used pesticides at enrollment

Information on ever/never personal use
## Personal Diazinon Use and Cancer Among Spouses

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Exposure</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Any OP</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td></td>
<td>Diazinon</td>
<td>1.1 (0.3-1.4)</td>
</tr>
<tr>
<td>Ovary</td>
<td>Any OP</td>
<td>1.5 (0.8-2.7)</td>
</tr>
<tr>
<td></td>
<td>Diazinon</td>
<td>1.9 (1.0-3.4)</td>
</tr>
</tbody>
</table>

Controlled for age, state, smoking, alcohol, BMI, education, menopausal status, parity, OC use, and correlated pesticides.
Cancer in Women

32,345 spouses of farmers enrolled in AHS

60% used pesticides at enrollment

All are married to a farmer who applies pesticides

Potential for non-occupational exposures
Non-occupational Pesticide Exposure

- Represent high level of general population exposures

- Important to consider impact of occupational pesticide use on general population in rural areas
  - Proximity to fields/agricultural drift
  - Para-occupational (take-home)
  - Residential use

- Follow up on associations we observed in farmers
Other Agricultural Exposures
Biologically Active Dusts/Endotoxins
Agricultural Exposures and Lung Cancer

- Lung Cancer
  - Standardized incidence ratio = 0.48 (0.44, 0.53)
- Due partially to lower smoking rates
- Endotoxins—linked to ↓ lung cancer rates
  - Components of Gram (-) cell walls
  - Found in agricultural settings, including animals and stored grain/hay

Koutros...Beane Freeman, JOEM 2010
Lenters, Basinas, Beane Freeman et al, Cancer Causes Control 2010
Animal Exposures and Lung Cancer

<table>
<thead>
<tr>
<th>Type of Animals</th>
<th># Exposed Cases</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>130</td>
<td>1.0 (0.8-1.3)</td>
</tr>
<tr>
<td>Dairy</td>
<td>17</td>
<td>1.3 (0.8-2.0)</td>
</tr>
<tr>
<td>Hogs</td>
<td>70</td>
<td>1.0 (0.8-1.3)</td>
</tr>
<tr>
<td>Sheep</td>
<td>5</td>
<td>0.7 (0.3-1.7)</td>
</tr>
<tr>
<td>Poultry</td>
<td>22</td>
<td>0.6 (0.4-0.97)</td>
</tr>
</tbody>
</table>

Number of livestock

<table>
<thead>
<tr>
<th>Number of livestock</th>
<th># Exposed Cases</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>171</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;100</td>
<td>115</td>
<td>1.1 (0.2-1.5)</td>
</tr>
<tr>
<td>100-999</td>
<td>60</td>
<td>0.9 (0.8-1.3)</td>
</tr>
<tr>
<td>1,000+</td>
<td>12</td>
<td>0.5 (0.3-0.97)</td>
</tr>
</tbody>
</table>

p-trend=0.04

Adjusted for age, state, education and smoking
Lung Carcinogens on the Farm

Diesel exhaust

IARC Group 1 lung carcinogen
Dieselized Farm Equipment Use and Lung Cancer in Farmers

Lung Cancer Overall
p-trend=0.18

Adenocarcinoma
p-trend=0.01

Relative Risks and 95% CI

Adjusted for age, state, race, education, smoking, animal exposure

Tual...Beane Freeman, In Press, Environ Hlth Perspectives
Dieselized Equipment and Adenocarcinoma by Endotoxin Exposure

No Endotoxin-related Activities

Endotoxin Activities

Relative Risks and 95% CI

p-trend=0.003

p-trend=0.3

p-interaction=0.05

Adjusted for age, state, race, education, smoking

Tual...Beane Freeman, In Press, Environ Hlth Perspectives
Early Life Exposures
Early Life Exposures: Future Cancer Risk?

- 92% of farmers
- 60% of spouses grew up on a farm
Increased risk of NHL among those who grew up on a farm

Adjusted for sex, state, race, family history, alcohol, smoking, and BMI
Allergies and NHL

- Living on a farm, particularly during childhood prevalence of allergies
- Potential immune effects
  - Th1/Th2 balance
  - Enhanced $T_{reg}$ activity
  - Increased IL-10 production
- In AHS:
  - Decreased risk of NHL with allergies at enrollment
  - HR=0.6 (0.5-0.8)

Hofmann…Beane Freeman, CEBP 2015
What’s next? Mechanistic Insights

Molecular studies evaluating mechanisms of specific pesticide disease associations

- Intermediate effect biomarkers
  - Epigenetics
  - Hormones
  - Inflammation
- Disease precursors
- Somatic mutations in tumor tissue
- Gene-environment interactions
Summary

- Specific pesticides may influence cancer risk for both farmers and those not occupationally exposed:
  - High quality human studies with information on specific chemicals/exposures necessary for public health
- Other exposures on the farm may also be important
- Non-occupational adult and early life exposures
Collaborators

**NCI**
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Ken Cantor  
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Nicole Deziel  
Melissa Friesen  
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Barry Graubard  
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**North Carolina State University**
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Peter Thorne

**Environmental Protection Agency**
Jane Hoppin  
Kent Thomas
The Agricultural Health Study works to understand how agricultural, lifestyle, and genetic factors affect the health of farming populations.

www.aghealth.nih.gov
Early Life Pesticide Exposures: Future Cancer Risk?

- Data on 38,000 children of AHS participants
- Early evaluation showed increased risk of
  - Lymphoma
  - Brain tumors

Now linking to parental exposures
Farm exposures, allergies, and risk of NHLs

- Farm childhood
- Allergies
- NHLs
Association between pesticides and prostate cancer among men with risk allele GWAS

Increased risk of prostate cancer with several organophosphate insecticides