Environmental Factors and Hepatocellular Carcinoma

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Etiology of Hepatocellular Carcinoma

Great talks on known risk factors

- *HBV Screening and Treatment for HCC Prevention*
- *Risk of HCC in NASH*
- *STOP-HCC: HCV Prevention*

- Strong evidence for HBV, HCV and fatty liver disease
- Large racial/ethnic disparity
- Etiologic role of environmental factors is less clear in the U.S.

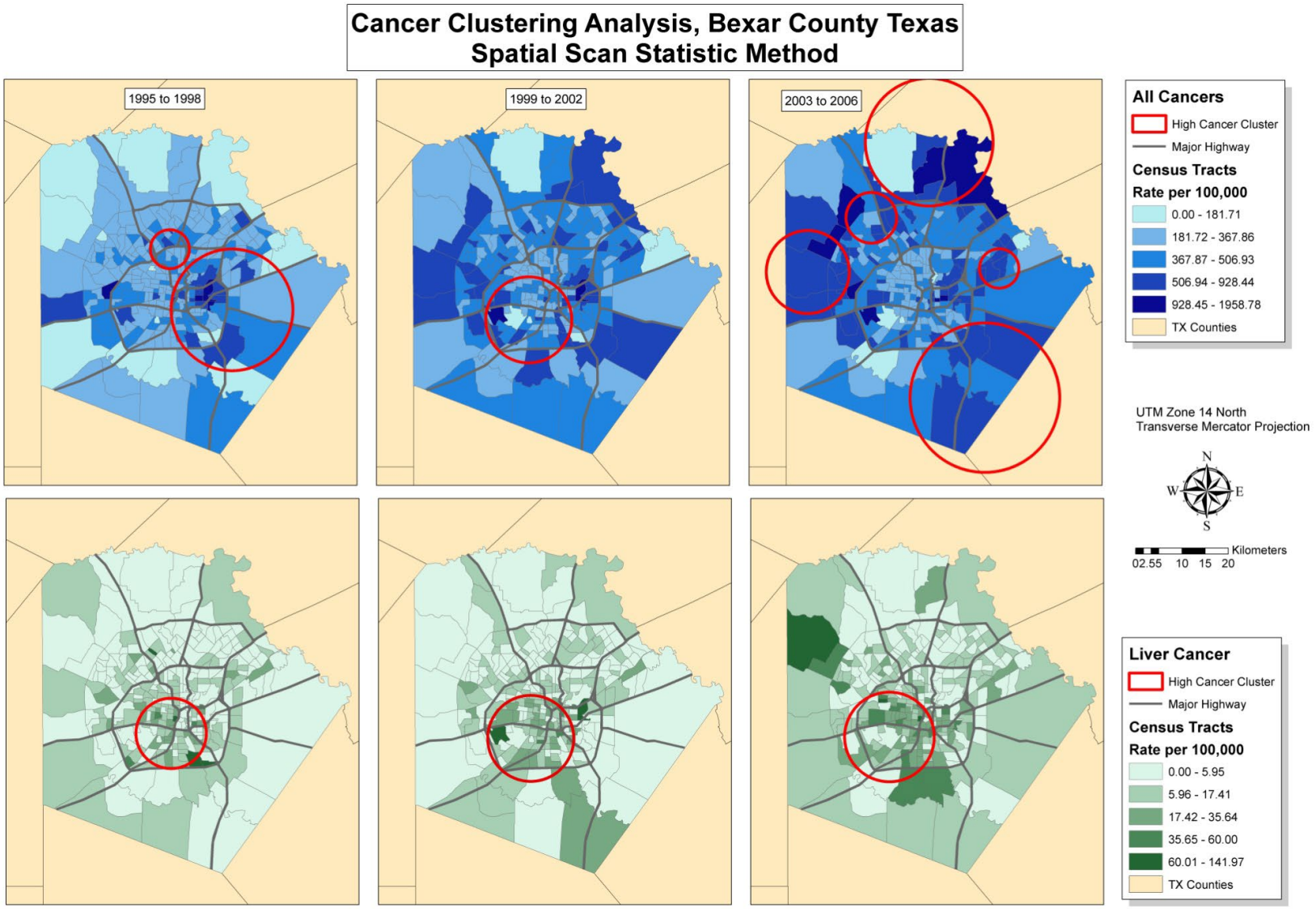
Agents Known/Suspected to Induce HCC in Humans

Good evidence	Limited evidence
Hepatitis B virus	Androgenic steroids
Hepatitis C virus	Arsenic & inorganic arsenic compounds
Aflatoxin B_1	Betel quid without tobacco
Alcohol	Polychlorinated biphenyls
Cigarette smoke	Trichloroethylene
Oral contraceptives	x- and γ-radiation
Plutonium and thorium-232	
Vinyl chloride (liver angiosarcoma)	

Santella RM Wu H-C: *J Clin Transl Hepatol*. 2013 1(2): 138–143

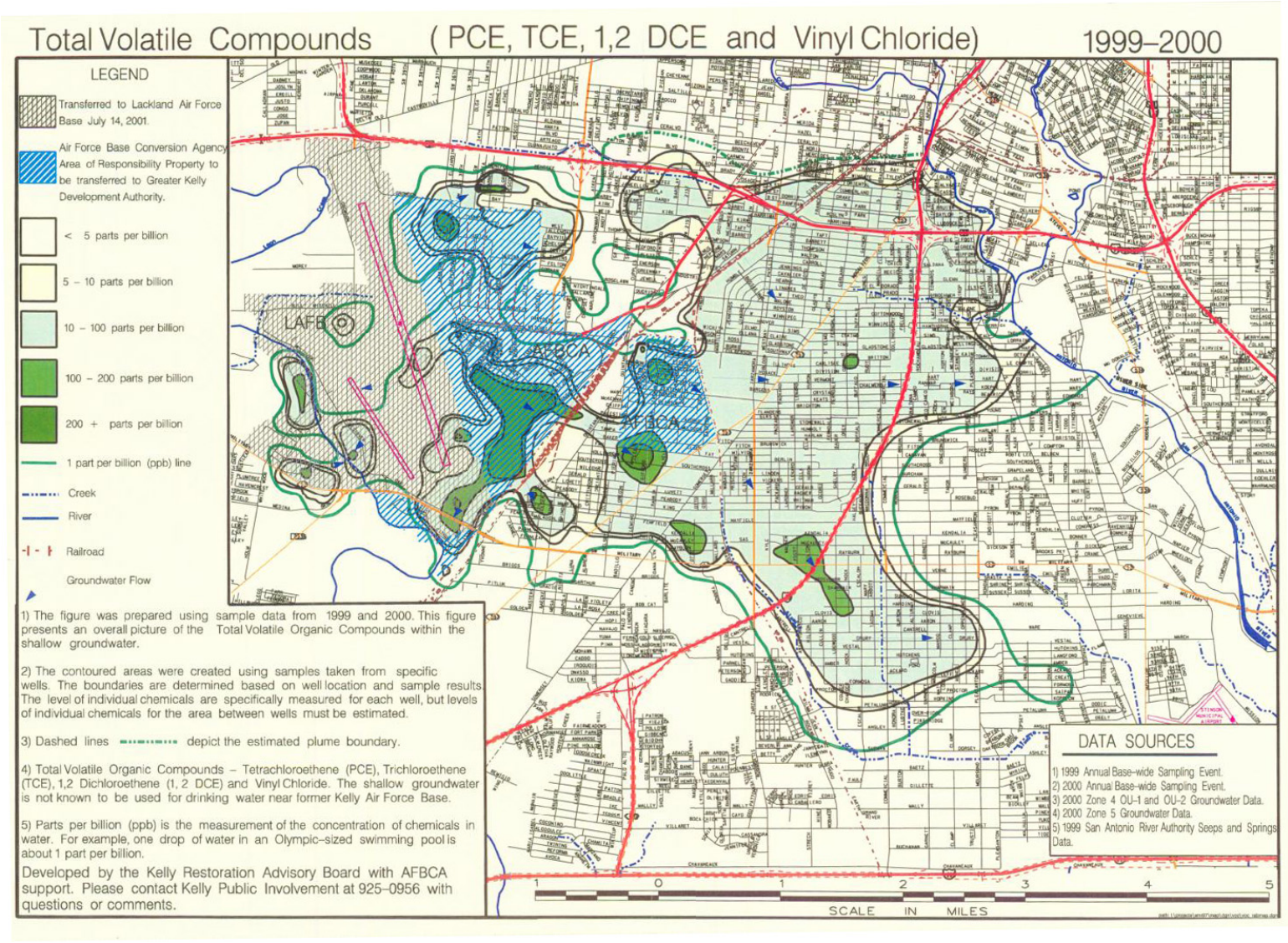
Protests At Kelly Air Force Base

Spatial Cluster Analysis: Spatial Scan

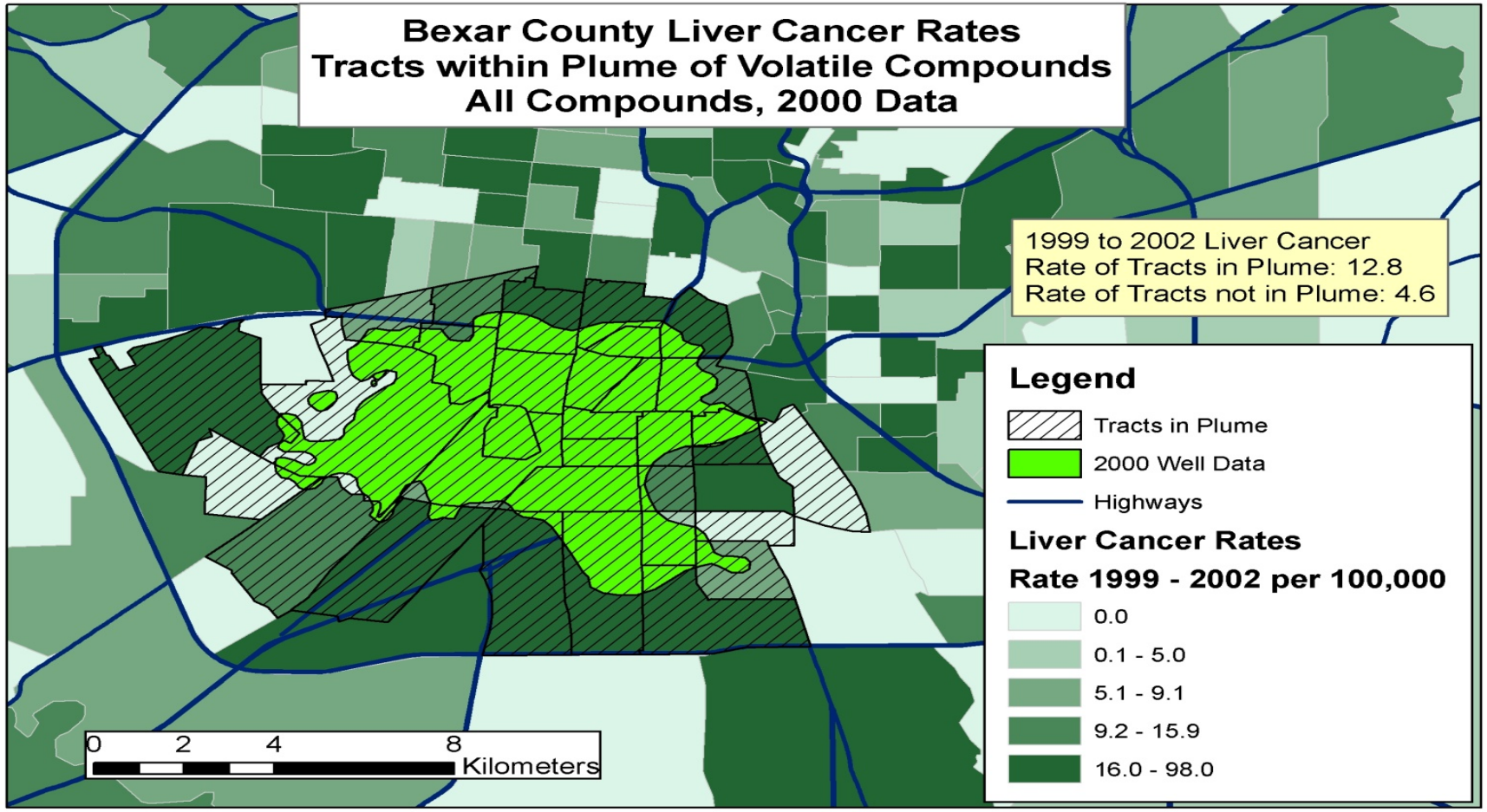


U.S. Air Force Environmental Analysis

1999–2000 Total Volatile Compounds (PCE, TCE, 1,2 DCE and Vinyl Chloride) plume map



Mapped Exposure to Groundwater Contamination Near Kelly AFB to Census Tracts



Median liver and total cancer incidence rates in aggregated census tracts

(Aggregates of affected census tracts were formed based on presence of total volatile compounds assessed in 1999–2000)

Incident Case Time Period	Census Tract Plume Exposure Status	Median Liver Cancer Incidence Rate*		Median Total Cancer Incidence Rate*	
1999–2002	In Plume	12.8[1]	2.8×	375.8[3]	0.9×
1999–2002	Not In Plume	4.6		401.9	
2003–2006	In Plume	20.1[2]	2.6×	358.1[4]	0.9×
2003–2006	Not In Plume	7.8		420.1	

*Rates are age, race and sex standardized to 2000 Bexar county population, and expressed as number of cases per 100,000 population. [1]p=0.0003 (Wilcoxon rank sum test); [2]p<0.0001 (Wilcoxon rank sum test); [3]p=0.0137 (Wilcoxon rank sum test); [4]p=0.0012 (Wilcoxon rank sum test)

Environmental Determinants of Hepatocellular Carcinoma in South Texas

**Cancer Prevention and Research Institute of Texas (CPRIT): RP120462,
Individual Investigator Research Award**

Brad Pollock, PI, UTHSCSA

Clinical Gastroenterology and Hepatology 2017;15:1311–1312

Case-Control Study

- Incident HCC cases
  - No prior systematic treatment (chemo or radiation)
- Eligibility:
  - No concurrent cancers or cancer history within the past 5 years
  - ≥18 years old
  - Resident of Texas counties of Bexar, Comal, Kendall, Guadalupe, Wilson, Atascosa, Medina, or Bandera counties

Subject Recruitment

- Cases:
  - University Hospital (Transplant, Interventional Radiology Clinics), the Cancer Therapy and Research Center (CTRC), and UTHSCSA clinics, San Antonio, TX.
- Controls:
  - Healthy consented subjects screened for NCI-2012-02452

    Community organization events, physician groups, and public media outlets
  - Randomly selected representative sample from the general population

    Residential parcels from the Counties' Tax Appraisal Districts

Laboratory Assays

- HBV and HCV serologies/antigens
- Hepatic function panel
- Chem-20 panel
- Hemoglobin A1c
- Serum AFB_1, AFM_1 and **AFB_1-lysine adduct** assays
- Urinary AFM_1

Study Questionnaire

- In-person, trained interviewer administered questionnaire (~45 minutes)

- Survey domains:
  - Sociodemographic characteristics
  - Lifestyle factors
  - Dietary exposure
  - Medical history / comorbidities
  - Family health history
  - Occupational/environmental history
  - Food consumption over 12 months

Where possible, items were derived from previously validated instruments; e.g., Texas Neural Tube Defect (NTD) Study Questionnaire, CDC Behavioral Risk Factor Surveillance System (BRFSS), NHANES, and the Canadian Community Health Survey.

Results

Accrual

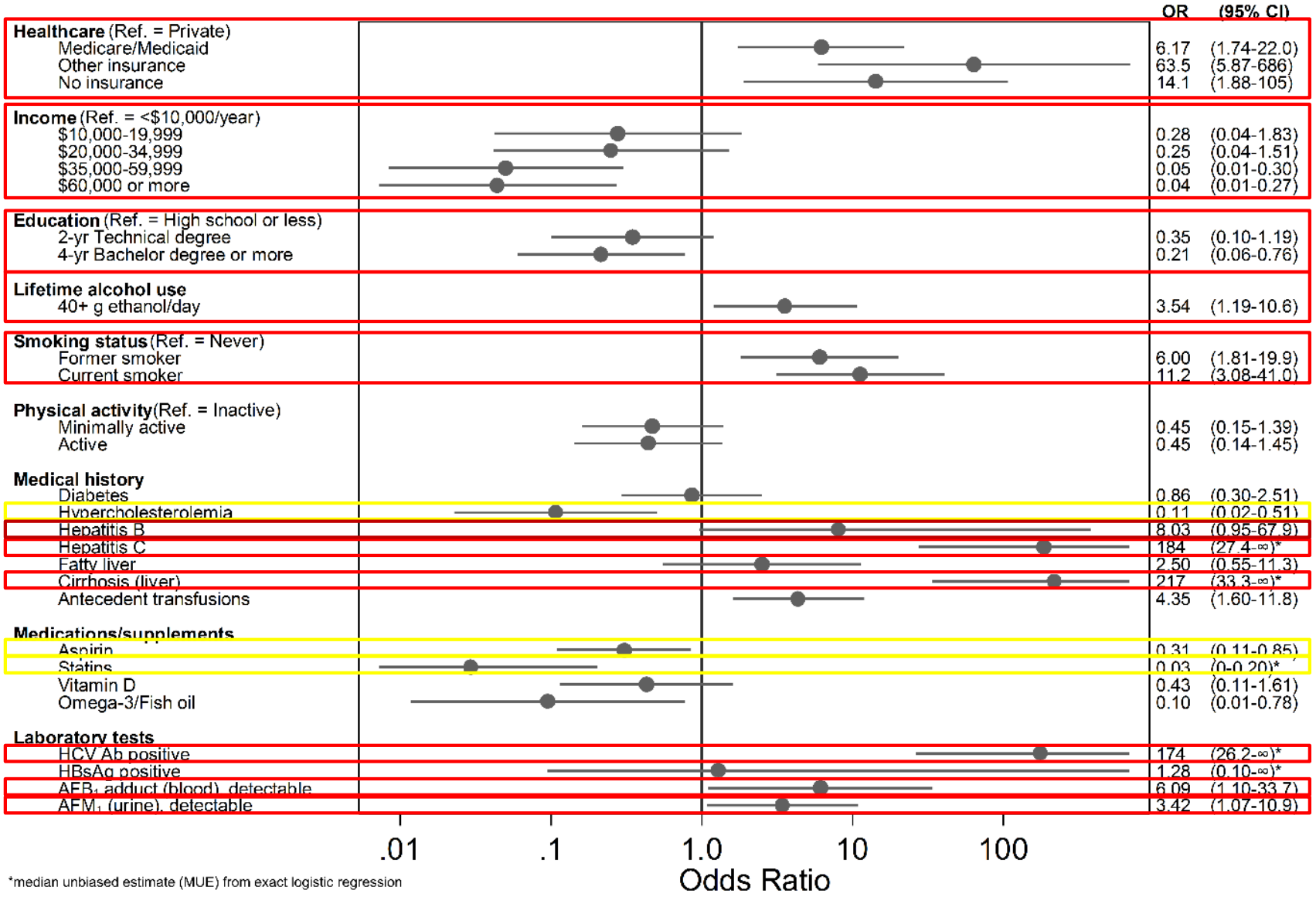
51 cases and 104 controls

- 42 pairs *post hoc* matched by:
  - Sex
  - Ethnicity (Hispanic, Non-Hispanic)*
  - Age (18–57 years, ≥58 years)

*67% of the study population self-identified as Hispanic

Association Between Risk Factors and HCC:

Adjusted Odds Ratio (95% Confidence Interval)



*median unbiased estimate (MUE) from exact logistic regression

Total Dietary Intake of 16 Foods During the Past 12 Months

Food	Cases (N=42)	Controls (N=42)	OR (95% CI)	p-value
Traditional Mexican Foods[a] (items/week), mean (sd)	7.9 (11.0)	6.8 (11.3)	1.01 (0.97-1.05)	0.653
*Corn[b] (cups/week), mean (sd)	0.9 (2.3)	0.8 (1.5)	1.02 (0.82-1.27)	0.861
*Products made with corn[c] (cups/week), mean (sd)	0.7 (0.7)	1.0 (1.1)	0.66 (0.36-1.22)	0.189
*Corn tortillas (per week), mean (sd)	6.7 (12.5)	4.5 (8.5)	1.02 (0.98-1.07)	0.348
Flour tortillas (per week), mean (sd)	9.4 (14.0)	5.3 (9.0)	1.04 (0.99-1.09)	0.117
Rice (cups/week), mean (sd)	3.1 (5.9)	2.0 (2.5)	1.07 (0.95-1.21)	0.276
Peanut butter[d] (tbs/week), mean (sd)	2.2 (3.4)	7.4 (14.0)	**0.88 (0.79-0.98)**	**0.026**
Peanuts, walnuts, seeds[e] (cups/week), mean (sd)	0.4 (0.8)	0.9 (1.3)	0.63 (0.38-1.06)	0.083
*Tortilla chips/corn chips (cups/week), mean (sd)	1.1 (1.8)	1.9 (2.5)	0.84 (0.67-1.06)	0.137
Mexican candy[f] (pcs/month), mean (sd)	1.2 (5.5)	0.8 (2.0)	1.02 (0.92-1.15)	0.675

Total Dietary Intake of 16 Foods During the Past 12 Months

(continued)

Food	Cases (N=42)	Controls (N=42)	OR (95% CI)	p-value
*Stews like pozole or menudo (cups/month), mean (sd)	1.5 (1.7)	2.0 (2.1)	0.83 (0.64-1.07)	0.144
Specialty dishes like mole (cups/month), mean (sd)	0.3 (0.9)	0.8 (1.4)	0.68 (0.45-1.03)	0.071
*Drinks made from corn/rice[g] (cups/month), mean (sd)	0.3 (1.0)	0.8 (1.8)	0.77 (0.55-1.08)	0.136
Frozen meals[h] (servings/month), mean (sd)	3.7 (6.9)	3.2 (5.7)	1.01 (0.94-1.08)	0.774
Meal replacements[i] (per month), mean (sd)	5.4 (9.9)	3.8 (12.4)	1.01 (0.97-1.05)	0.531
Other processed/boxed foods[j] (per month), mean (sd)	4.1 (5.4)	5.1 (6.5)	0.97 (0.90-1.04)	0.425

Positive Associations

- Lower socioeconomic status
- More lifetime exposure to alcohol and tobacco
- HCV antibodies* [**174.0** (26–∞)]
- Blood transfusions [**4.35** (1.60–11.84)]
- Aflatoxin markers in:
  - Blood [**6.09** (1.10–33.71)]
  - Urine [**3.42** (1.07–10.91)]
- Cirrhosis [**2.2** (33.3–∞)]

*[OR (95% C.I.)]

Inverse Associations

- Hypercholesterolemia [**0.11** (0.02–0.51)]
- Aspirin use [**0.31** (0.11–0.85)]
- Statin use [**0.03** (0–0.20)]
- Omega-3/fish oil use [**0.10** (0.01–0.78)]
- Peanut butter consumption [**0.88** (0.79–0.98)]

*[OR (95% C.I.)]

Conclusions

- **Aflatoxin** serum markers and evidence of **HCV** infection were strongly associated with increased risk
- **Lower SES**, and increased **alcohol** use and **tobacco** use were also associated with increased risk
- No evidence of direct dietary associations with corn and corn product consumption (study design and sample size limitations?)
- **Cirrhosis** is an intermediate risk factor:
  - Important to GI docs and their patients
  - Not an optimal target for population-based preventive interventions (too late)

Conclusions (continued)

- **Strengths**
  - Incident HCC cases (pre-systemic treatment)
  - In-person in-depth interviews by trained observers
  - Highly sensitive aflatoxin biomarker assessment
- **Limitations**
  - Very crude dietary assessment (12-month recall)
  - Potential selection bias:
    - Clinical convenience sample of cases (UTHSCSA referrals)
  - Relatively small sample size

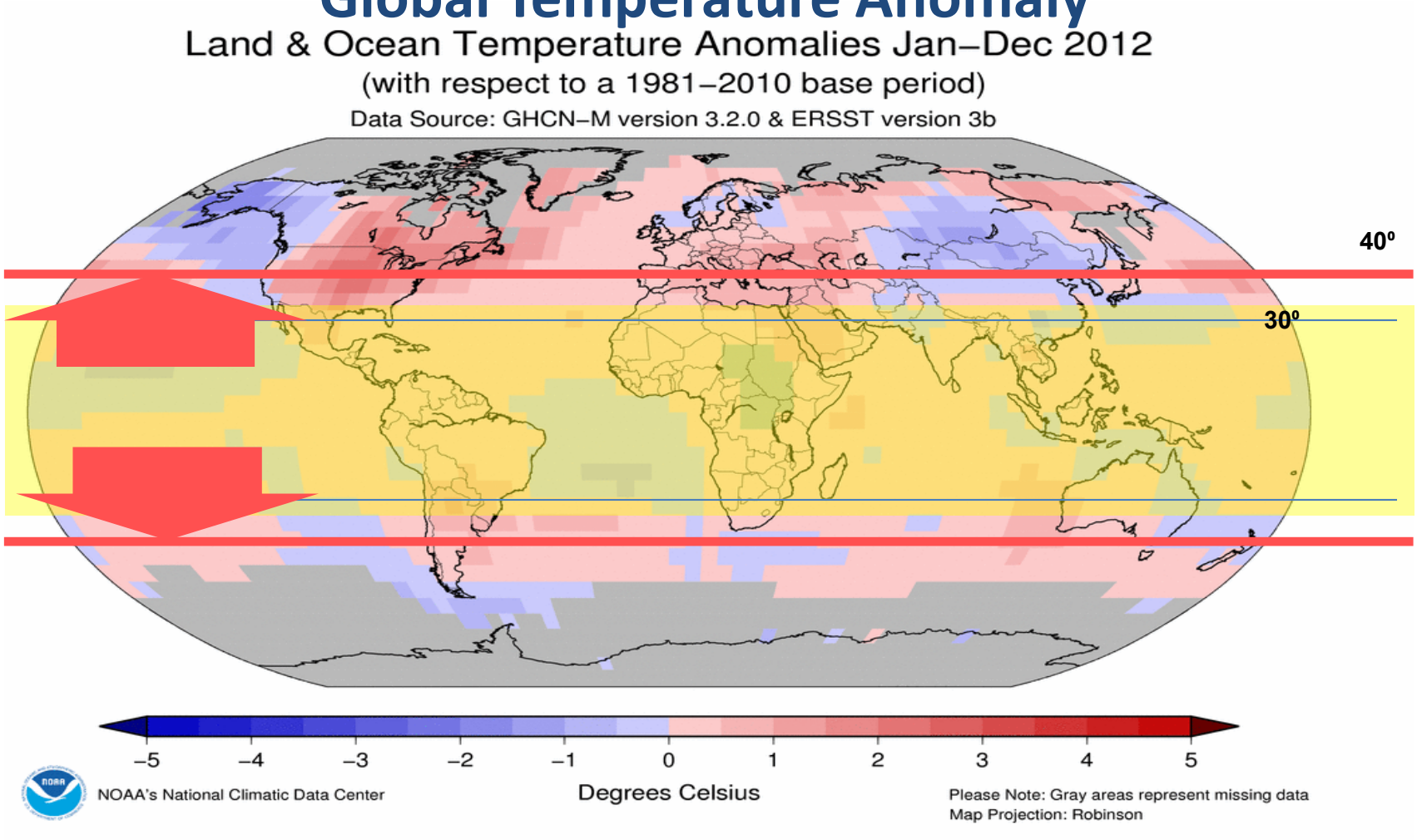
This study provided strong evidence that aflatoxin exposure is a risk factor in the U.S.

Aflatoxins

Globally, aflatoxins are probably the second most common set of HCC risk factors after chronic Hepatitis B and Hepatitis C infection

Plants like corn that are heat stressed produce more aflatoxins

Global Temperature Anomaly



Global Differences in HCC Risk Factors

- Developing countries:
  - Hepatitis B virus (HBV) infection
  - Environmental factors:
    - Dietary exposure to mycotoxins
- Developed countries:
  - Hepatitis C virus (HCV) infection
  - Obesity
  - Diabetes
  - Environmental factors
    - Excessive alcohol consumption
    - Mycotoxins?

Thank you

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