The Role of Companion Animals as Sentinels for Predicting Environmental Exposure Effects on Aging and Cancer Susceptibility in Humans

December 1-3, 2021

The National Academies of SCIENCES ENGINEERING MEDICINE

The domestic dog as a sentinel species for environmental influence associated with cancer – ongoing studies.

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Dept. of Molecular Biomedical Sciences, College of Vet. Medicine, NCSU

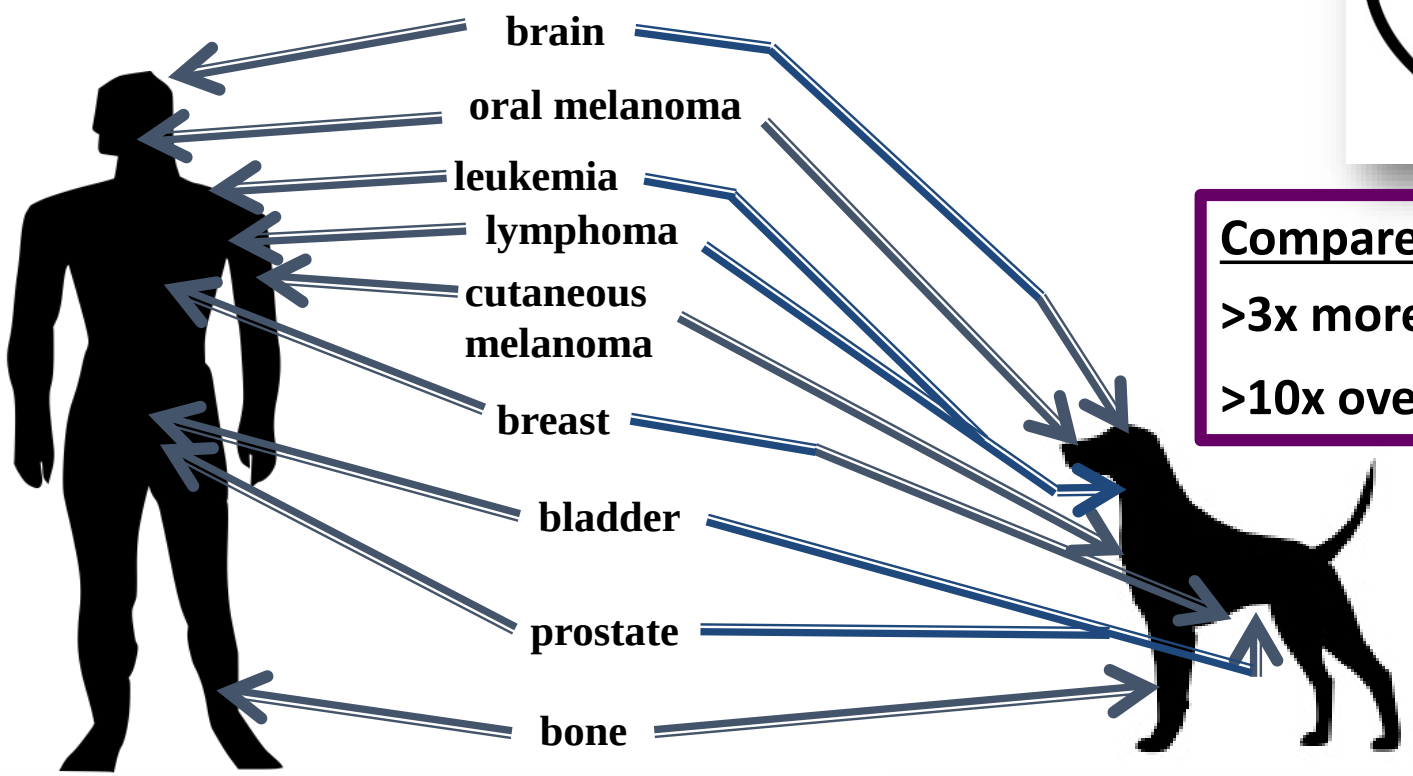
Comparative Medicine Institute, NCSU

Center for Human Health and the Environment, NCSU

Duke Cancer Institute

UNC Lineberger Comprehensive Cancer Centre

One Medicine



Compared to people, dogs have

>3x more cancer cases diagnosed/year

>10x overall cancer incidence

~1.8 million diagnoses each year
(~442 cases/100,000 population)*

~6 million diagnoses each year
(~6,600 dogs/100,000 population)

One Pathogenesis

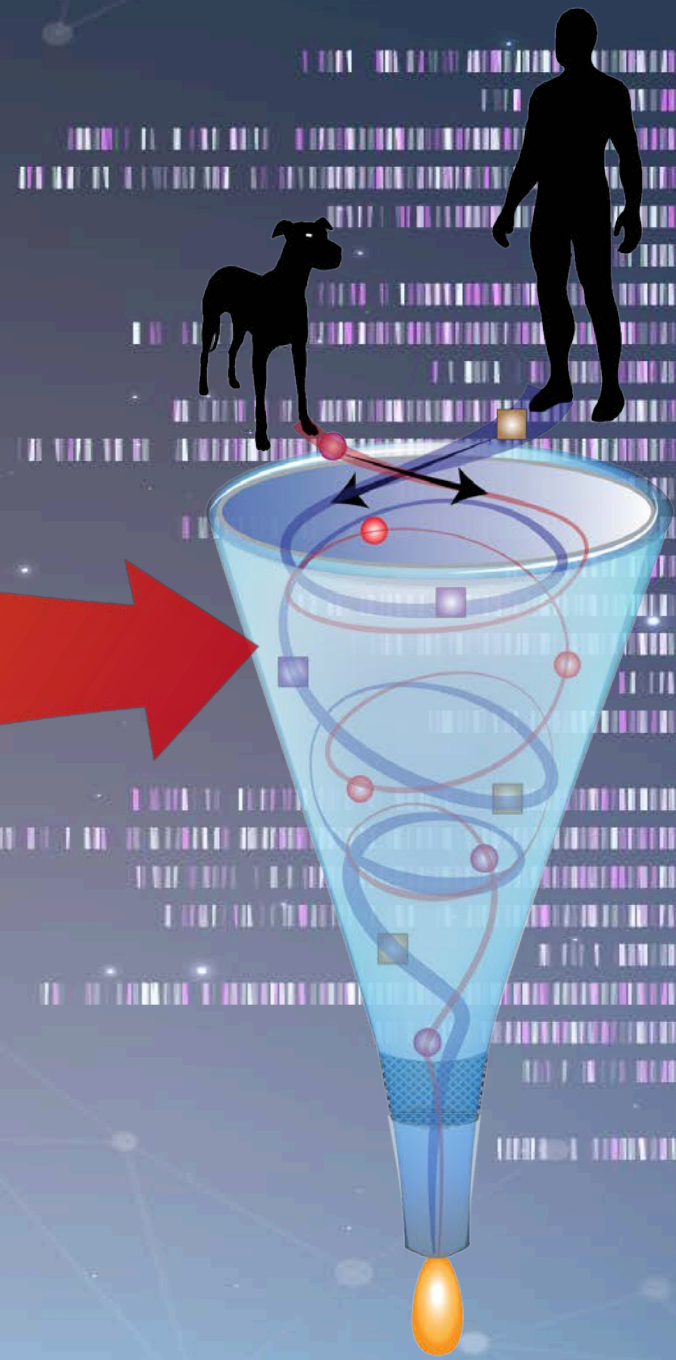
* www.cancer.gov

Updated from: Schiffman and Breen, 2015 Phil Trans B Vol 370: 19th July 2015


fixed normal tissue
snap frozen normal tissue
serum
whole blood
60M vet visits each year
6M cancer diagnoses
CLINICAL DATA
GEOSPATIAL DATA
fixed tumor tissue
plasma
snap frozen tumor tissue
FFPE specimen
urine sample

Comprehensive genomic analysis of cancer specimens

Comparison of canine and human data to identify shared features



LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

'Putting our heads together': insights into genomic conservation between human and canine intracranial tumors

Rachael Thomas · Shannon E. Duke · Huixia J. Wang · Tessa E. Breen · Robert J. Higgins · Keith E. Linder · Peter Ellis · Cordelia F. Langford · Peter J. Dickinson · Natasha J. Olby · Matthew Breen

Canine urothelial carcinoma: genomically aberrant and comparatively relevant

S. G. Shapiro · S. Raghunath · C. Williams · A. A. Motsinger-Reif · J. M. Cullen · T. Liu · D. Albertson · M. Ruvolo · A. Bergstrom Lucas · J. Jin · D. W. Knapp · J. D. Schiffman · M. Breen

Received: 10 January 2015 /Revised: 7 February 2015 /Accepted: 10 February 2015

THE ROYAL SOCIETY PUBLISHING

Comparative oncology: what dogs and other species can teach us about humans with cancer

Joshua D. Schiffman[1] and Matthew Breen[2]

Phil. Trans. R. Soc. B **370**: 20140231

Genome-wide assessment of recurrent genomic imbalances in canine leukemia identifies evolutionarily conserved regions for subtype differentiation

Sarah C. Roode · Daniel Rotroff · Anne C. Avery · Steven E. Suter · Dorothee Bienzle · Joshua D. Schiffman · Alison Motsinger-Reif · Matthew Breen

Received: 19 March 2015 /Revised: 2 May 2015 /Accepted: 5 May 2015

Cancer Genetics

Comparative approach

Evolutionarily conserved cytogenetic changes in hematological malignancies of dogs and humans – man and his best friend share more than companionship

Matthew Breen[1,2]* & Jaime F. Modiano[3,4]

Chromosome Research (2008) 16:145–154

Comparative cytogenetic characterization of primary canine melanocytic lesions using array CGH and fluorescence in situ hybridization

Kelsey Poorman · Luke Borst · Scott Moroff · Siddharth Roy · Philippe Labelle · Alison Motsinger-Reif · Matthew Breen

Received: 26 August 2014 /Revised: 7 October 2014 /Accepted: 14 October 2014

Detection of BRAF Mutation in Urine DNA as a Molecular Diagnostic for Canine Urothelial and Prostatic Carcinoma

Hiroyuki Mochizuki, Susan G. Shapiro, Matthew Breen

Published: December 9, 2015 • DOI: 10.1371/journal.pone.0144170

A genome-wide approach to comparative oncology: high-resolution oligonucleotide aCGH of canine and human osteosarcoma pinpoints shared microaberrations

Andrea Y. Angstadt [a], Venugopal Thayanithy [b], Subbaya Subramanian [b,c], Jaime F. Modiano [c,d], Matthew Breen [a,e,f,*]

PLOS COMPUTATIONAL BIOLOGY

Transcriptomic profiling in canines and humans reveals cancer specific gene modules and biological mechanisms common to both species

Gregory J. Tawa, John Braisted, David Gerhold, Gurmit Grewal, Christina Mazcko, Matthew Breen, Gurusingham Sittampalam, Amy K. LeBlanc

BMC Cancer

Molecular cytogenetic characterization of canine histiocytic sarcoma: A spontaneous model for human histiocytic cancer identifies deletion of tumor suppressor genes and highlights influence of genetic background on tumor behavior

BMC Cancer 2011, 11:201

Benoit Hedan[1], Rachael Thomas[1,2], Alison Motsinger-Reif[2,3,4], Jerome Abadie[5], Catherine André[6], John Cullen[7] and Matthew Breen[1,2,8*]

GENES CHROMOSOMES & CANCER

PLOS ONE

BRAF Mutations in Canine Cancers

Hiroyuki Mochizuki[1], Katherine Kennedy[1], Susan G. Shapiro[1], Matthew Breen[1,2,3,4]*

PLOS ONE | DOI:10.1371/journal.pone.0129534 June 8, 2015

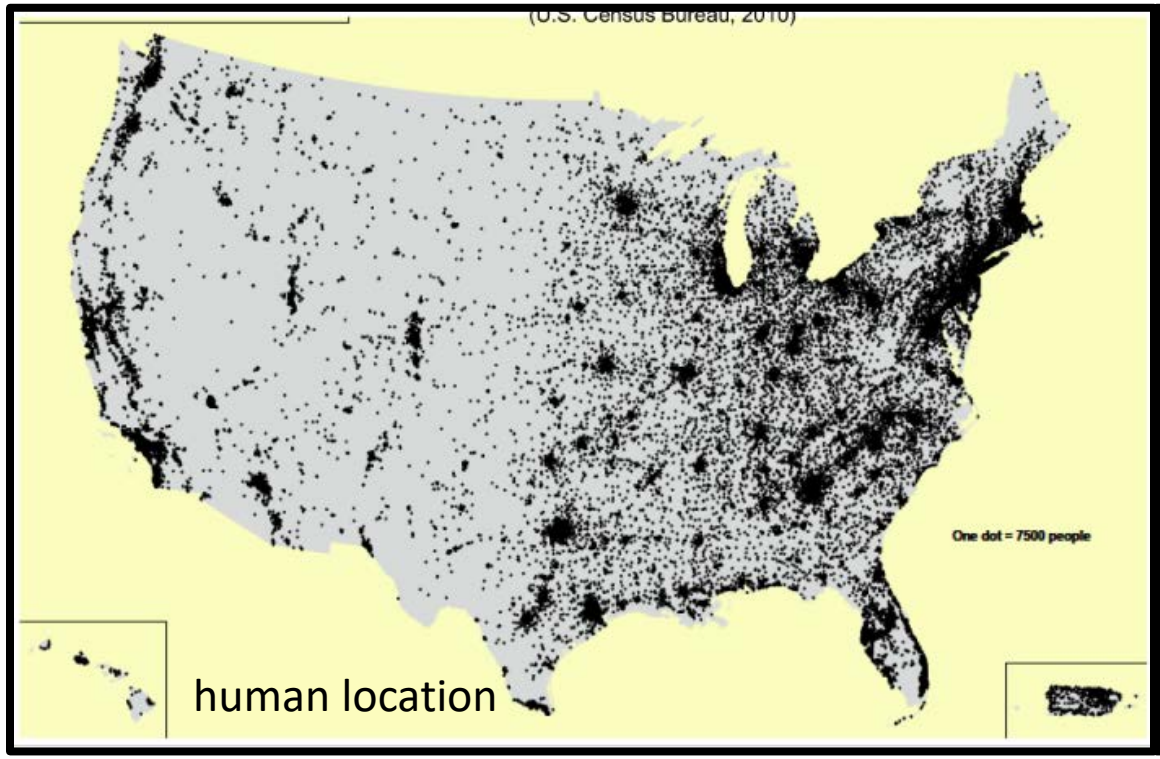
Genes Chromosomes Cancer. 2011 Nov;50(11):859-74. doi: 10.1002/gcc.20908. Epub 2011 Aug 11.

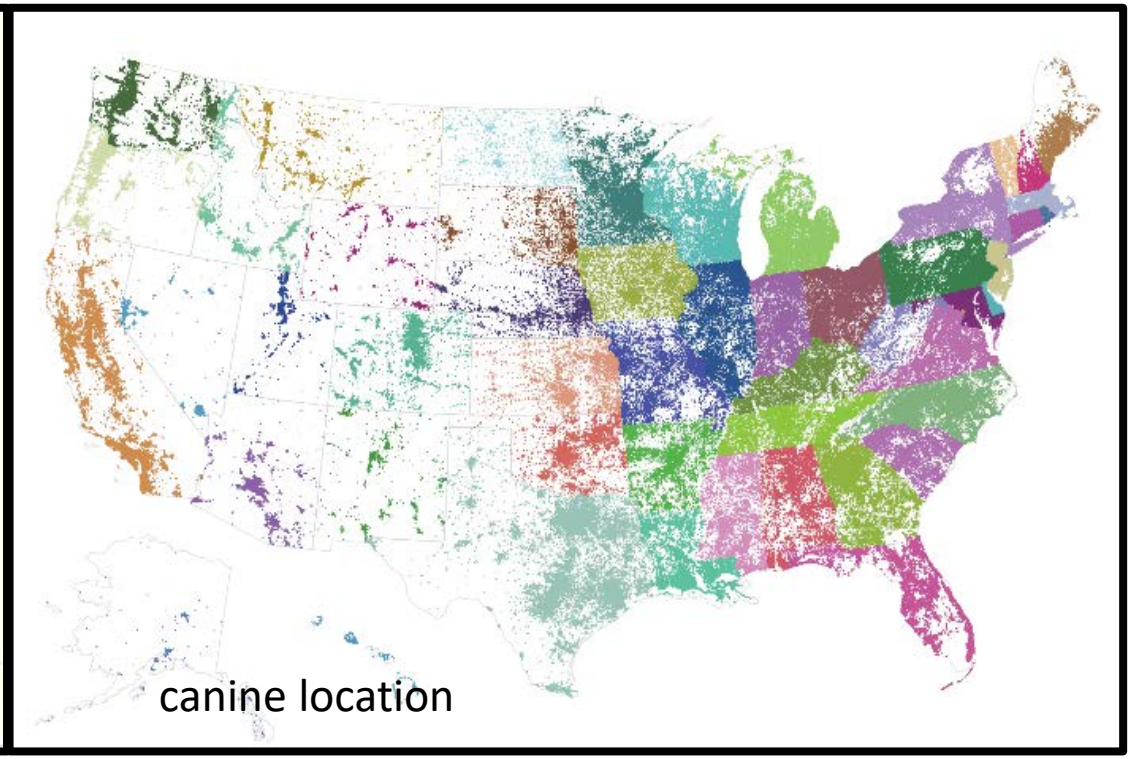
Characterization of canine osteosarcoma by array comparative genomic hybridization and RT-qPCR: signatures of genomic imbalance in canine osteosarcoma parallel the human counterpart.

Angstadt AY[1], Motsinger-Reif A, Thomas R, Kisseberth WC, Guillermo Couto C, Duval DL, Nielsen DM, Modiano JF, Breen M.

BREEN LAB @ NCSU

Environmental influences on cancer





Our dogs live where we live

77-78 years

10-12 years*

Info accessible:

Age

Sex

Pedigree (purebred)

Diet, Health records

Exposures

*** breed/size dependent. <20lbs ~ 11 yrs . Over 90lbs ~8 yrs**

A nationwide collaboration of stakeholders of animal health

Integrating the skills and resources of scientists, veterinary professionals, and dog owners








Collaboration with dog owners, breeders, veterinarians

Academic-community based collaborations

GOALS:

Work with our nationwide network, providing opportunities for them and their dogs to participate in studies designed to :

1. **monitor changes in incidence of cancer in pet dogs to highlight geographical regions of potential health concerns in the human population –** considering differences in latency of exposure
2. **participate in clinical studies that include exposure assessment –** humans and dogs in the same household with either or both diagnosed with a project focused cancer

NC STATE THINK AND DO THE EXTRAORDINARY

Duke UNIVERSITY

Heather Stapleton PhD
Ronie-Richele Garcia-Johnson Distinguished Professor
Nicholas school of the Environment
Duke University

Catherine Wise PhD
Postdoctoral Associate
Nicholas school of the Environment
Duke University

Brant Inman MD MS
Cary N. Robertson Professor of Surgery
Urologic Oncology
Duke Cancer Institute

THE V FOUNDATION for Cancer Research

DUKE CANCER INSTITUTE &
NCSU COLLEGE OF VETERNARY MEDICINE

Consortium for Canine Comparative Oncology

Duke | NICHOLAS SCHOOL OF THE ENVIRONMENT

Duke Cancer Institute

Matthew Breen (genetics), Shelly Vaden (veterinary internist), Catherine Wise (PhD student), Claire Wiley (clinician investigator), Patty Secoura (internal medicine), Eli Cohen (veterinary radiologist), Michael Mastromauro (veterinary oncologist), Tonya Harris (internal medicine)
inset: Gabi Seiler (veterinary radiologist), Nate Nelson (veterinary radiologist), Joanne Intile (veterinary oncologist)

NC STATE Veterinary Medicine

UTRACT
Urothelial Carcinoma Translational Research and Clinical Trials

Duke | NICHOLAS SCHOOL OF THE ENVIRONMENT

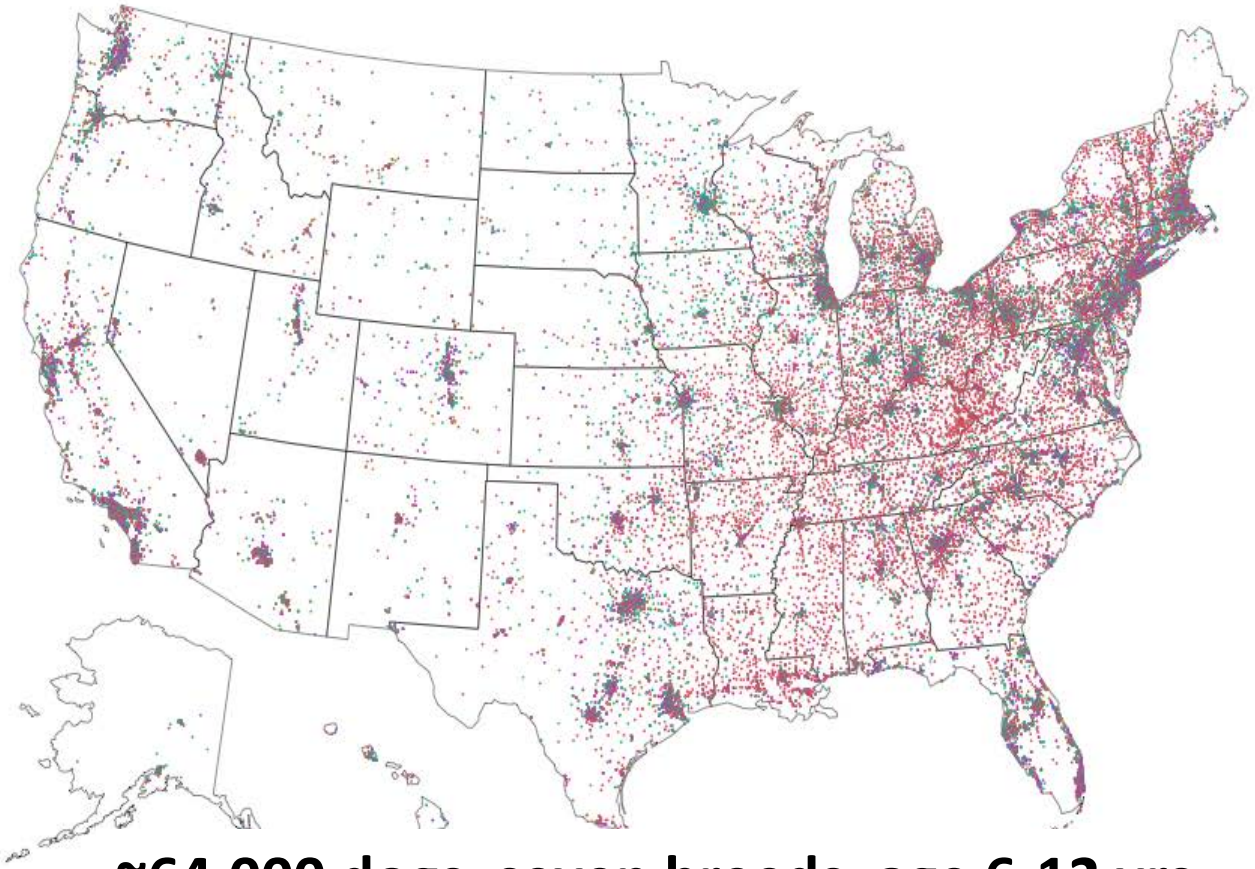
Environmental associations with canine bladder cancer

Community Engagement

Beagle

Shetland Sheepdog

West Highland White Terrier



~64,000 dogs, seven breeds, age 6-12 yrs

engaged owners of ~900 dogs within 72 hrs (now over 2,000)

identify relatives for controls

Scottish Terrier

Russell Terrier

Parson Russell Terrier

American Eskimo Dog

Use of silicone bands with dogs to investigate health impacts on humans from shared exposures

Environ Sci Technol. 2020 June 16; 54(12): 7409–7419.

Comparative Exposure Assessment Using Silicone Passive Samplers Indicates That Domestic Dogs Are Sentinels To Support Human Health Research

Catherine F Wise [1 2], Stephanie C Hammel [3], Nicholas Herkert [3], Jun Ma [4 5], Alison Motsinger-Reif [6], Heather M Stapleton [3 7], Matthew Breen [1 2 7 8 9]

Silicone monitoring devices. (a) Wristband for human (b) Dog tag affixed to dog collar.

NATIONAL GEOGRAPHIC

Domestic dogs have similar physical characteristics and diseases as humans, particularly cancers.
PHOTOGRAPH BY ROBIN SIEGEL, NAT GEO IMAGE COLLECTION

Dogs can be 'early-warning systems' for toxic chemical exposure at home

BY CARRIE ARNOLD

PUBLISHED JUNE 10, 2020

Dogs and people carry remarkably similar amounts of common household chemicals in their bodies, a possible boon for human health.

Environmental Factor
Your Online Source for NIEHS News
JULY 2020

NIH National Institute of Environmental Health Sciences

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Canine companions shed light on chemicals and disease

Previous Article | Next Article

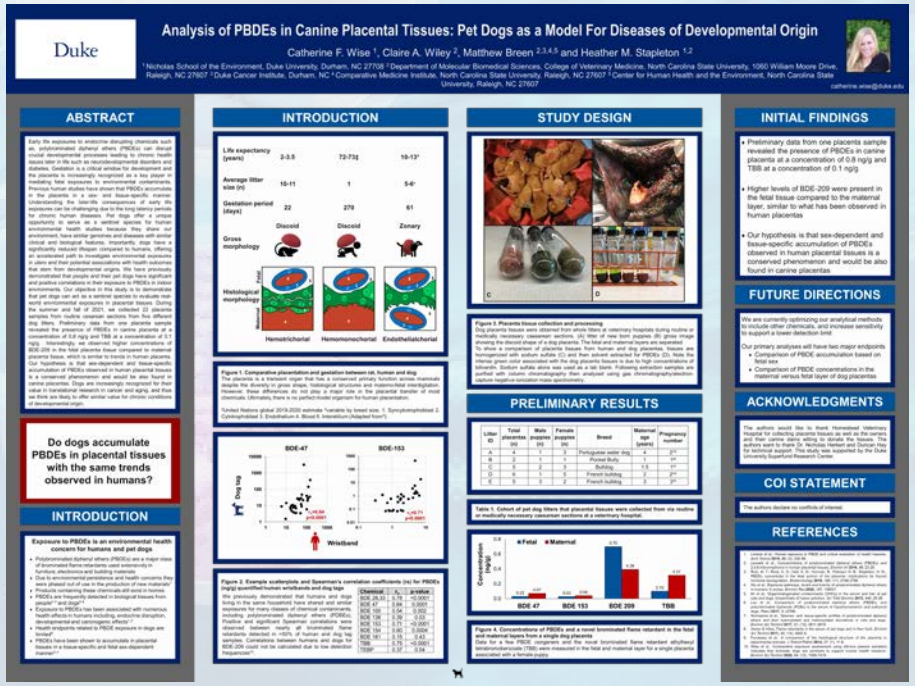
NIEHS grantees study pet dogs to better understand how human exposure to everyday chemicals may lead to cancer and other conditions.

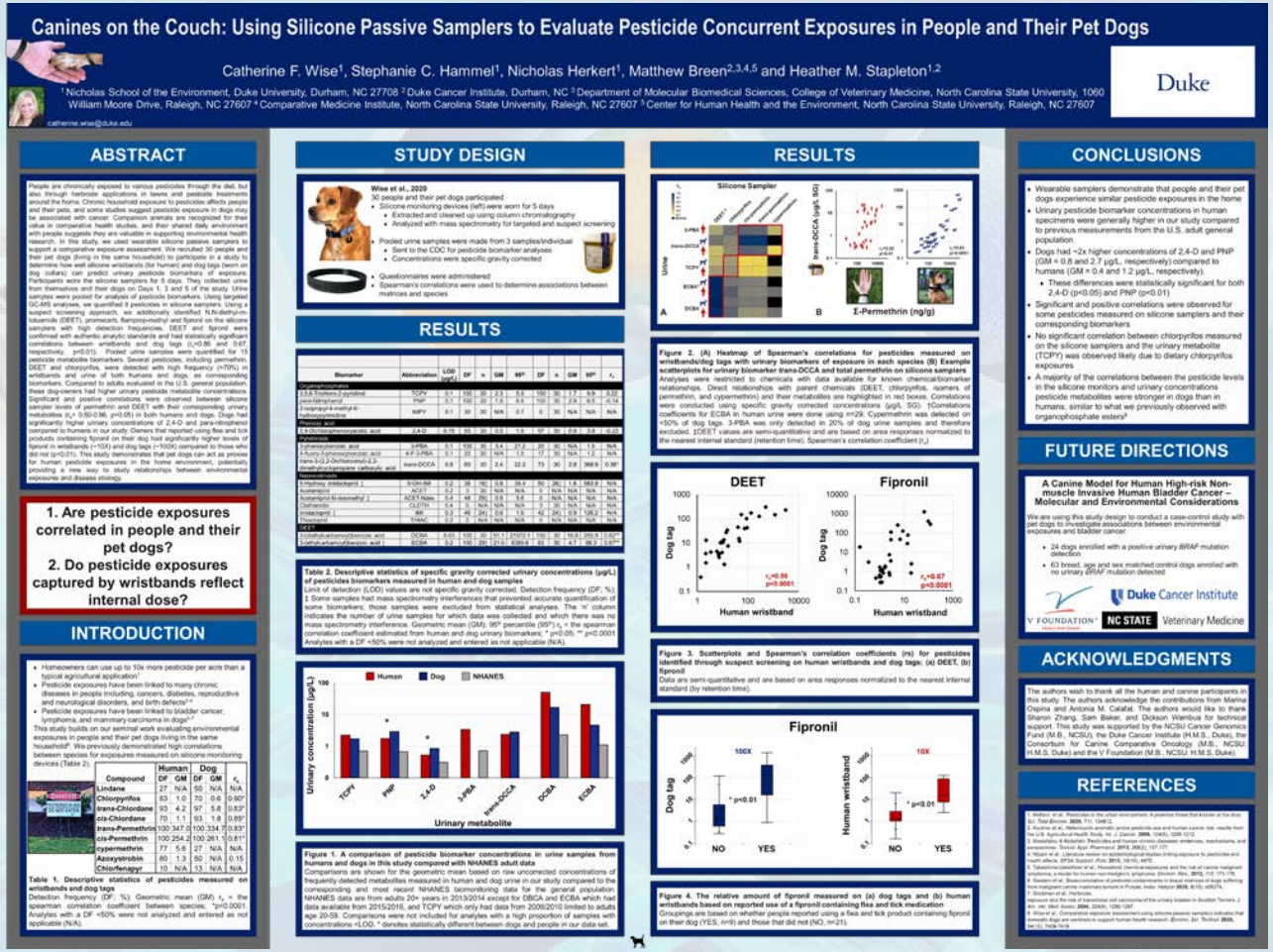
Dr. Heather Stapleton will review tomorrow & please view posters from Dr. Catherine Wise

NC STATE THINK AND DO THE EXTRAORDINARY

Duke UNIVERSITY

CDC

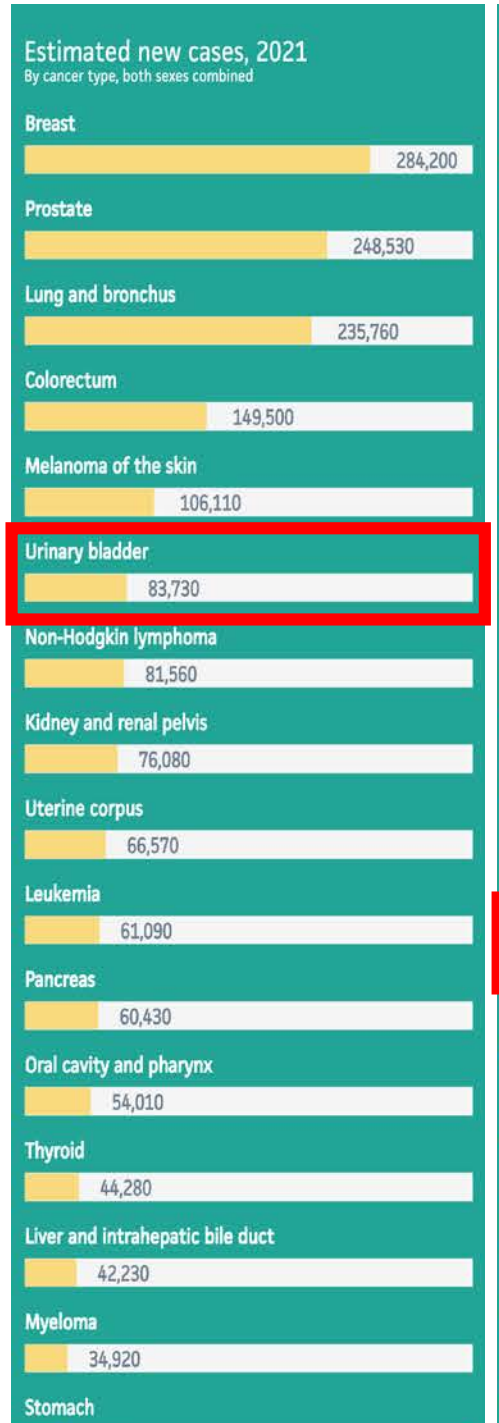


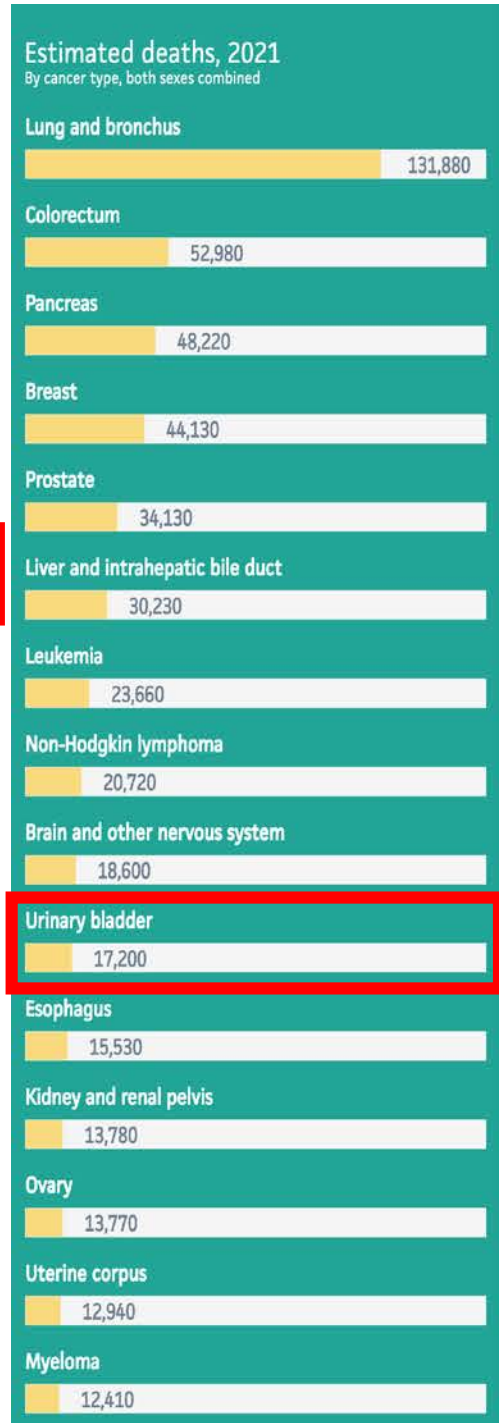


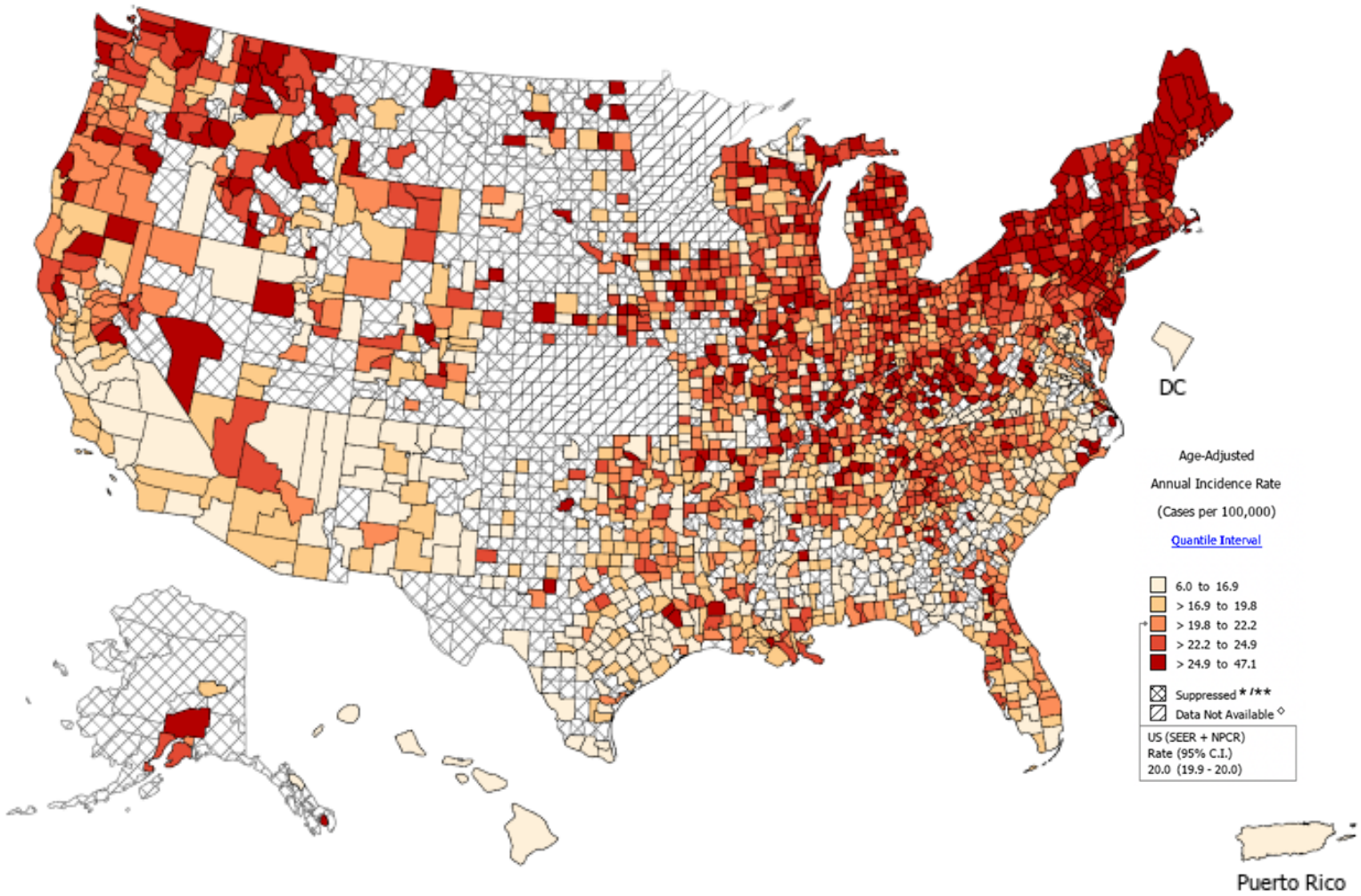
POSTERS

Catherine Wise PhD
Postdoctoral Associate
Nicholas school of the Environment
Duke University

Assessment of households with human bladder cancer

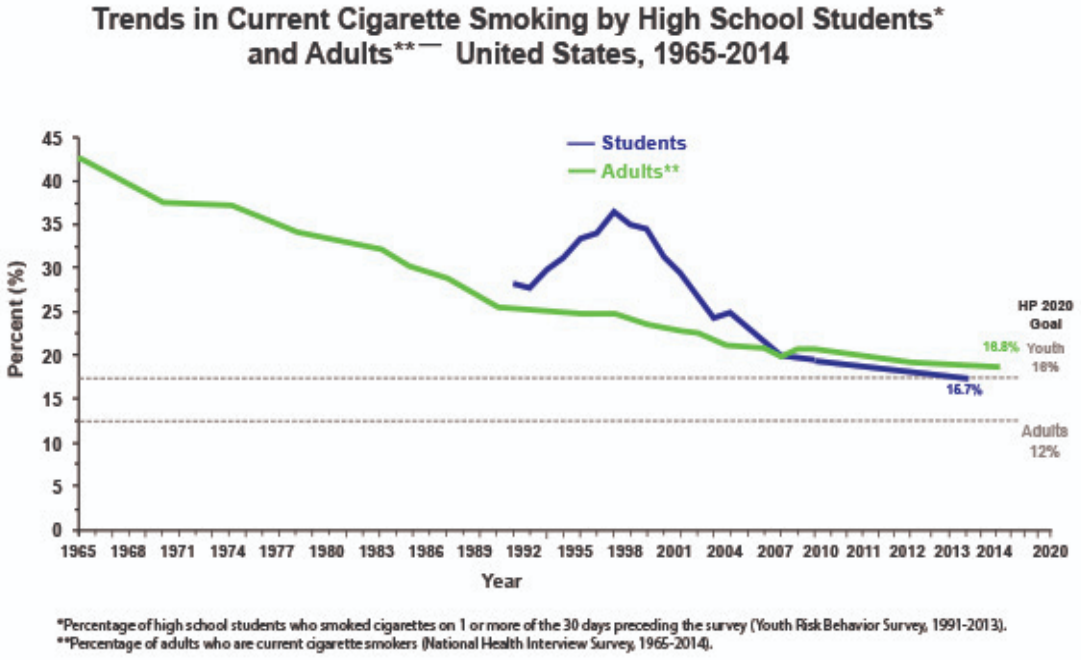


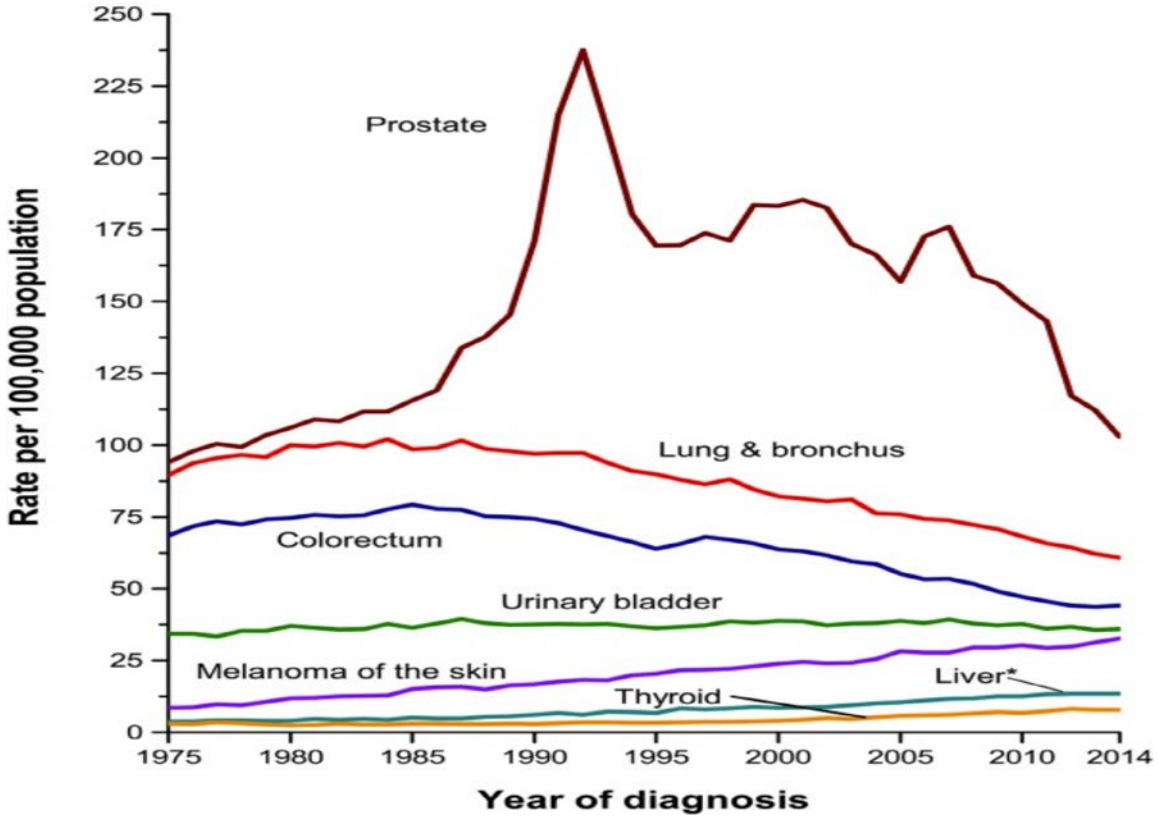




Assessment of households with bladder cancer patients

SMOKING – No 1 risk factor for bladder cancer





- Incidence of lung cancer has been decreasing over the last 30 years, likely due to decreased smoking rates.
- **BUT - bladder cancer incidence rates have remained steady over the same period at ~40/100,000.**
- **QUESTION: Is this due to an increase in non-smoking causes of bladder cancer?**
  - **E.g. workplace exposures (e.g. aromatic amines), arsenic, aristolochic acid**

2018 OH Bladder Cancer Incidence

Cleveland Clinic

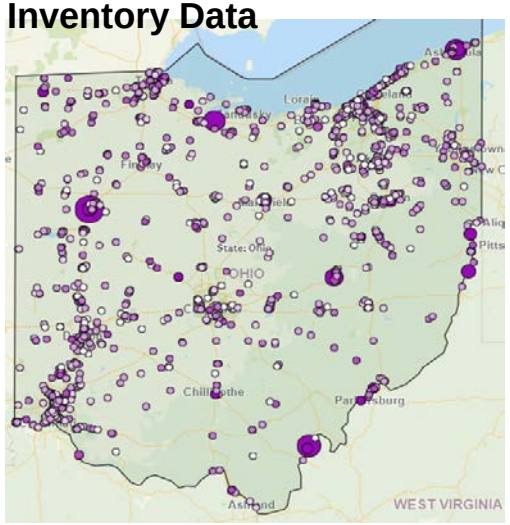
Bladder Cancer Hotspots in Ohio

Cleveland Clinic
Lerner Research Institute

Byron Lee, M.D., Ph.D.
Assistant Professor of Surgery
Section of Urologic Oncology
Department of Urology
Cleveland Clinic

Daniel Rotroff, PhD, MSPH
Department of Quantitative Health Sciences
Lerner College of Medicine
Cleveland Clinic

2019 EPA Toxic Release Inventory Data



- **GOAL: Evaluating exposures of bladder cancer patients in OH hotspots**
- **APPROACH: Assessment of dogs and humans for associated exposures (water, urine, wristband)**

Personalized Environment and Genes Study (PEGS)

Formerly the Environmental Polymorphisms Registry

- **North Carolina Based Cohort**
  - **Est. 2002**
  - **n~20,000 enrolled**
  - **n~11,000 active participants**

Dr. Janet Hall

Dr. Alison Motsinger-Reif

National Institute of Environmental Health Sciences
Your Environment. Your Health.

- **Environmental Exposures**
  - Health and exposure questionnaires (n~9,000)
  - Internal and external exposome questionnaires (n~3,000)
  - Geospatial exposure from residential address histories

- **Phenotypes**
  - Questionnaires (n~9,000)
  - Soon: health records from UNC and Duke

Health records for the household dogs (est >5,000)

- **Genotypes**
  - Whole genome sequencing (n~4,700)
  - Candidate genes (n~11,000)

Omics of household dogs

https://www.niehs.nih.gov/research/clinical/studies/pegs/index.cfm

Personalized Environment and Genes Study

Formerly the Environmental Polymorphisms Registry

Growing Number of Geospatial Data Layers

- Airports
- Conc Animal Feeding OP
- Cellular towers
- Drinking water
- Dry cleaners
- Hazardous waste
- Highways
- Nuclear sites
- Wastewater
- Population info
- Power lines
- PR landfills
- Railroads
- Spills
- Sanitary landfills
- Superfund sites
- Toxic release sites
- Air pollution

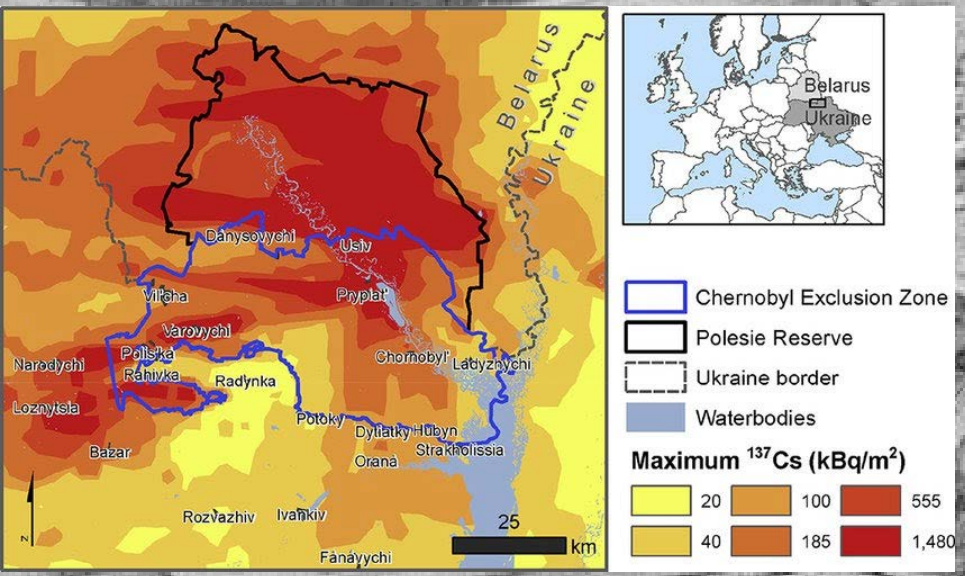
others

- **Overlay canine health data onto these exposure maps**
- **Do these exposures impact the health of the canine population BEFORE they impact the human population?**

https://www.niehs.nih.gov/research/clinical/studies/pegs/index.cfm

CHERNOBYL

1986



CHERNOBYL

2021

ChAES, Energoblok N° 1
Енергоблок №1
Чорнобильської АЕС

Chornobyl Nuclear Power Plant
Чорнобильська атомна електростанція

Elektrownia atomowa w ćarnobylu

Sarkofah 2 Chetvertoho Reaktoru Chaes
Саркофаг 2 четвертого реактору ЧАЕС

Nuclear power plant

Jaderná elektrárna Černobyl

how have these dogs survived and what has been their biological response to continuous insult by these exposures?

Google earth Nov 15th 2021

Photographs courtesy of Dr. N. Kleiman

Photo by Sam Berkhead

Dogs of Chernobyl.

A model for human health effects arising from chronic exposure to radiation, heavy metals, and other environmental toxins

NIH National Human Genome Research Institute

Elaine Ostrander PhD
Chief & NIH Distinguished Investigator
Cancer Genetics and Comparative Genomics Branch

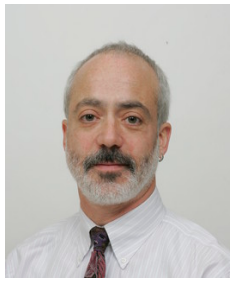
Gabriella Spatola MS
PhD student

UNIVERSITY OF South Carolina

Timothy Mousseau PhD
Professor, Biological Sciences
University of South Carolina

University of South Carolina Chernobyl Research Initiative

COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK



Norman Kleiman PhD
Assistant Professor
Environmental Health Sciences
Columbia University Medical Center

genomic analyses, population structure, mutational profiling, epigenetics, pathogens, microbiome, heavy metals

NC STATE UNIVERSITY

Megan Dillon
PhD student
Molecular Biomedical Sciences

Martha Burford-Reiskind PhD
Assistant Professor
Dept. Biological Sciences

Exposure research related to cancer is now bidirectional

and accelerating

Sharing exposures to environmental influences …

the keys to unlocking some of the puzzles may be walking right beside us

Acknowledgements

NC State University

Jaiden Bartley – student
Marth Burford-Reiskind – Population Genetics
Eli Cohen – Veterinary Radiology
Megan Dillon – PhD student
Emma Droste – Research Assistant
Lauren Hale - student
Tonya Harris – Internal Medicine
Joanne Intile - Veterinary Oncology
Michael Mastromauro – Veterinary Oncology
Nate Nelson - Veterinary Radiology
Michael Nolan – Veterinary Radiation Oncology
Carley Ruslander - student
Patty Secoura - Internal Medicine
Gabi Seiler - Veterinary Radiology
Kristina Stayer – student
Rachael Thomas – genetics/genomics
Shelly Vaden - Veterinary Internal Medicine
Claire Wiley - Veterinary Internal Medicine

Canine models of exposure

AKC: Mark Dunn, Vanessa Skou Chuck Bettini
CDC: Maria Ospina, Antonia Calafat
Duke: Heather Stapleton, Catherine Wise, Nick Herkert
NIEHS: Alison Motsinger-Reif, Janet Hall et al

Dogs of Chernobyl

Columbia University: Norman Kleiman
NHGRI: Elaine Ostrander, Gabby Spatola
University of South Carolina: Tim Mousseau

Urothelial carcinoma

Cleveland Clinic: Daniel Rotroff, Byron Lee
Duke University: Brant Inman
University of Wisconsin: Michael Wood, Jessica Pritchard

Acknowledgements

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Jaiden Bartley – student
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Emma Droste – Research Assistant
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Tonya Harris – Internal Medicine
Joanne Intile - Veterinary Onc
Michael Mastromauro
Nate Nelson - Vete
Michael Nolan – Ve
Carley Ruslander - s
Patty Secoura - Inte
Gabi Seiler - Veterina
Kristina Stayer – stud
Rachael Thomas – genetics/genomics
Shelly Vaden - Veterinary Internal Medicine
Claire Wiley - Veterinary Internal Medicine

Canine models of exposure

AKC: Mark Dunn, Vanessa Skou
CDC: Maria Ospina,
Duke: Heath
NTP

ck Bettini
Wise, Nick Herkert
et Hall et al
abby Spatola
Carolina: Tim Mousseau

1,000's of dog owners, breeders, and veterinarians that collaborate to provide samples and information

Urothelial carcinoma

Cleveland Clinic: Daniel Rotroff, Byron Lee
Duke University: Brant Inman
University of Wisconsin: Michael Wood, Jessica Pritchard

MORRIS ANIMAL FOUNDATION Est. 1948

NATIONAL INSTITUTES OF HEALTH

Duke Cancer Institute

THE V FOUNDATION for Cancer Research

NC STATE UNIVERSITY · COLLEGE OF VETERINARY MEDICINE

NC STATE UNIVERSITY College of Veterinary Medicine

Thank you for your attention

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