Radon: DNA damage, and Lung Cancer

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April 4, 2019

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Disclosures

- No disclosures relevant to this talk.

- *Slide Acknowledgments: Peter Shields, MD*

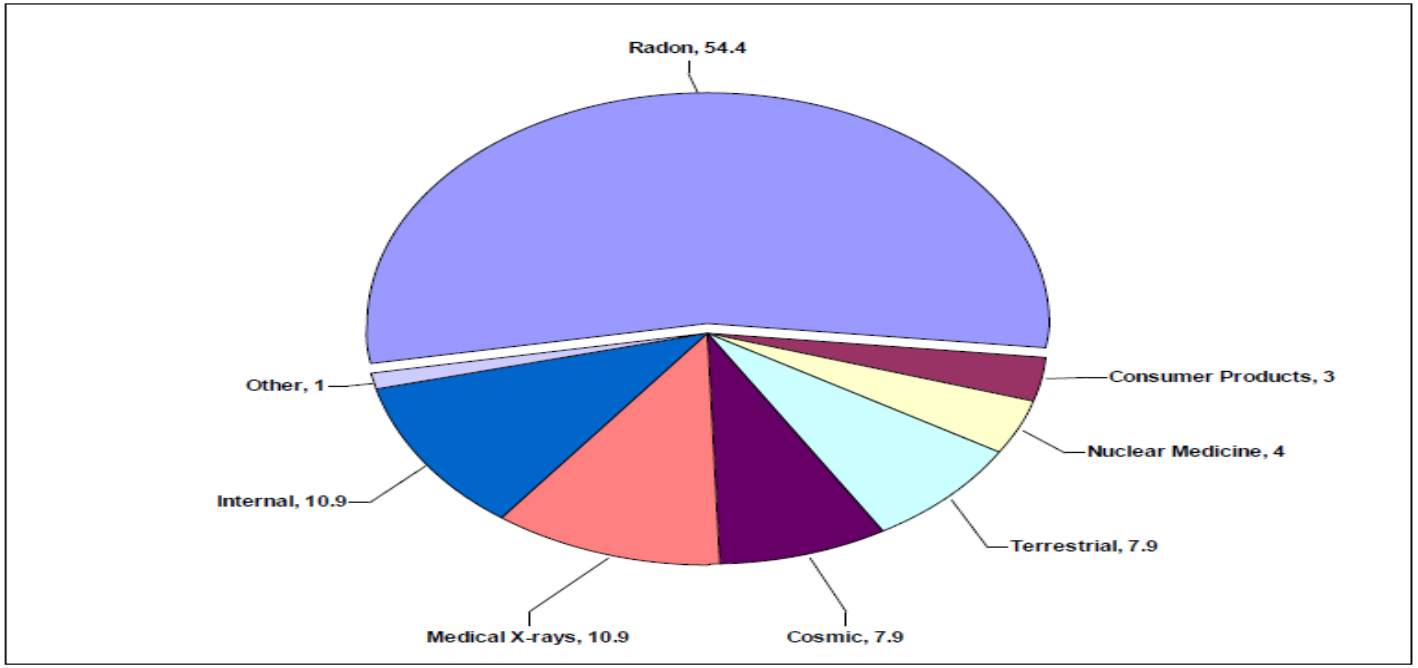
Outline

- Overview: What is radon?
- How does cancer develop?
- How does radon cause lung cancer?
- Studies of lung cancer risk
- What authoritative agencies say…
- Wrap up!

Overview: What is Radon?

- Radon is a radioactive gas that is naturally-occurring derived from uranium decay in the soil/rock; it percolates up from ground and becomes trapped indoors
  - Colorless, odorless and tasteless
  - When radon undergoes radioactive decay, the radon daughter particles are not gases and attached to particles that are deposited in the lung causing DNA damage to normal cells
  - Radon daughters eventually decay to lead (stable)
- A major known cause of lung cancer, second to smoking
  - #1 cause of lung cancer in non-smokers
  - Only inhalation is a risk
  - Does not penetrate the skin
  - Smoking and radon interact to increase risk further (synergistic)
- EPA estimates between 18,000 and 22,000 lung cancer deaths related to radon every year in the U.S.

Sources of Background Radiation for the U.S. Population



- About 80% of all radiation is from natural sources
- About 20% of all radiation from man-made sources, especially medical diagnostic procedures
- The average person receives a higher dose of radiation from the radon levels in their home than from their combined exposure to all other radiation sources

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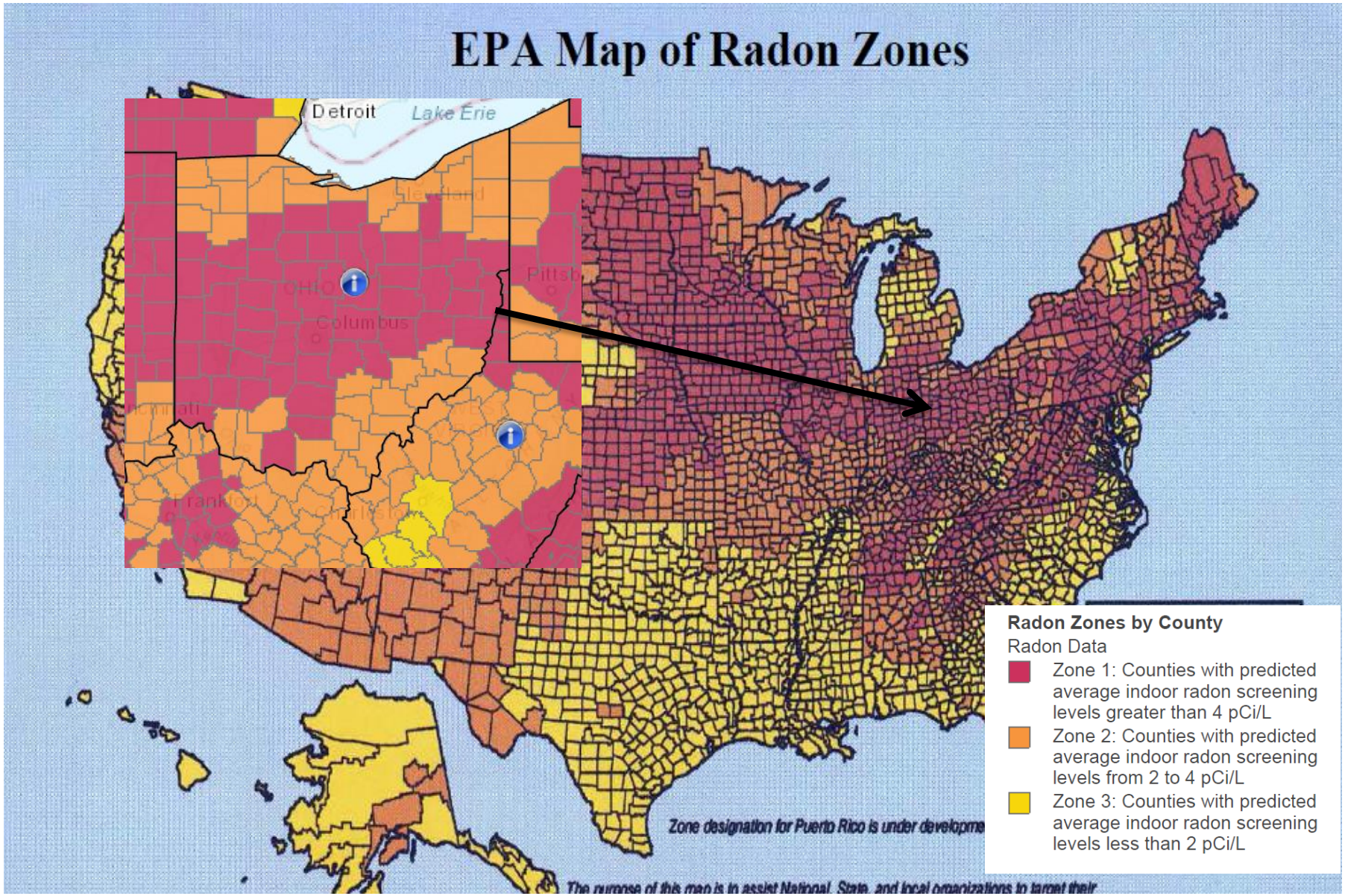
Effective radon (Rn - 222) Content of Soils

Soils	***Range of Emanation Coefficient***	
Crushed rocks	0.005 – 0.40	
Soil	0.03 – 0.55	
Soil	0.22 – 0.32	13 % to 20 % of dry weight
Sand	0.06 – 0.18	
Sandy loam	0.10 – 0.36	
Silty loam	0.18 – 0.40	
Heavy loam	0.17 – 0.23	
Clay	0.18 – 0.40	
Soil	0.09 – 0.10	Dried at 105°C for 24 h
Uranium ore	0.06 – 26	Saturated with water
Crushed Uranium ore	0.055 – 0.55	Saturated with water
Tailings from Uranium plant	0.067 – 0.072	Dried at 110° C
Source: Nazaroff et al., 1988		

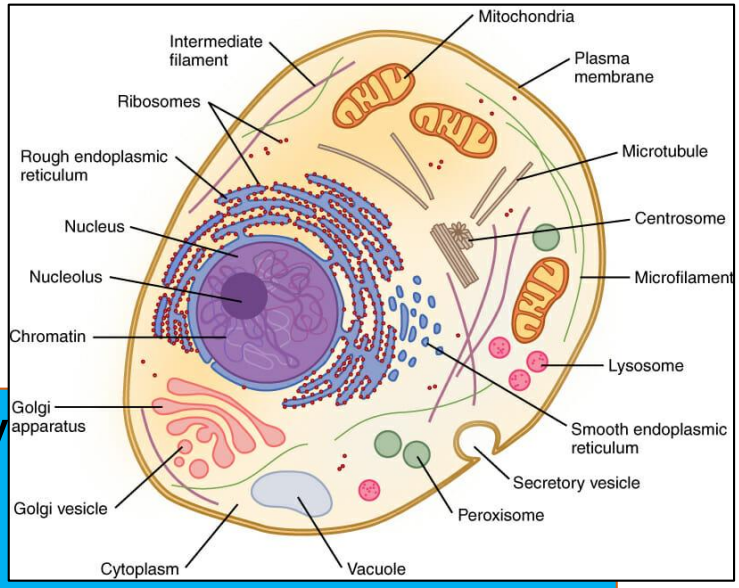


High levels of radon in all 88 counties in Ohio
Radon zones at www.epa.gov

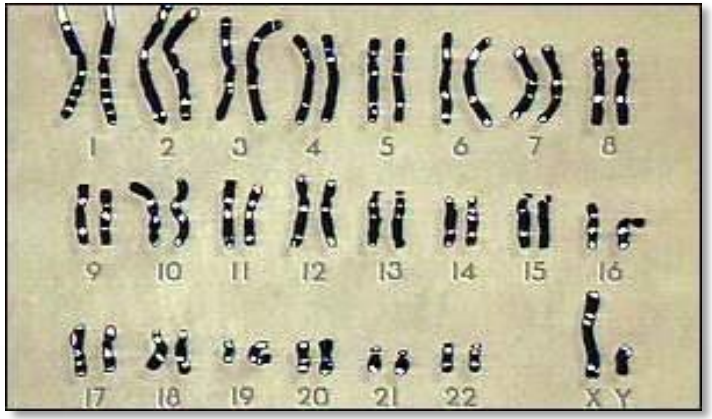
Cancer is a disease where the cells in an organ of our body become sick and grow uncontrollably.

- Our bodies are made up of different organs
- Each organ has a different function
- Each organ is made up of cells
- Some cancer-causing chemicals can cause cancer in some cells and organs but not all cells and organs
- Our cells and organs know how to fight the effects of those chemicals that may cause cancer

What Controls the Function of Cells?



- Our cells are controlled by are housed in the nucleus
- Each cell has a specific function, for example making insulin or digesting foods



Multistage Carcinogenesis

Radon

Mistakes of normal cell processes

Carcinogens made inside the body

Carcinogens from outside the body

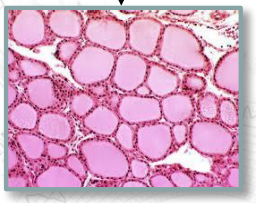
Gene Damage

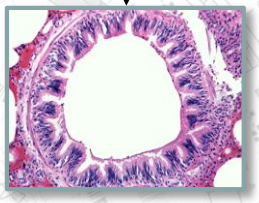
Failure to repair DNA or undergo cell death

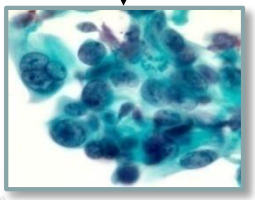
Cancer develops through accumulated genetic events

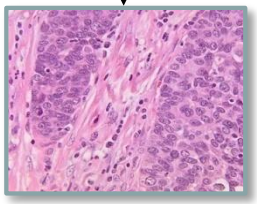
Genetic damage

Normal Cells → Initiated Cells → Preneoplastic Lesion → Malignant Clone → Clinical cancer









DNA Damage

Repair pathway	NHEJ	HR	alt-NHEJ/ MMEJ	SSA	ICL repair	SSB repair	BER	TLS	NER	MMR
Source of DNA damage	IR, radiomimetics, Topo II inhibitors	X-linking agents, replication inhibitors, antimetabolites, Topo I inhibitors			X-linking agents	IR, ROS, radiomimetics Topo I inhibitors H_2O_2, alkylating agents	Alkylating agents	UV, alkylating agents	Alkylating agents, X-linkers	DNA Pol proofreading errors
Damage sensors	Ku70/Ku80	MRN	PARP	MRN	FA core complex (FANCA, B, C, E, F, G, L and M)	PARP	DNA glycosylases, APE1	PCNA	XPC DDB2 CSA	MSH2, MSH3, MSH6, MLH1, PMS2
Signaling/ mediator proteins	DNAPK	ATM, ATR, MK2, CtIP, BRCA1/BARD1, BRCA2, PALB2, RPA		CtIP	FANCD1 [BRCA2] D2, I J [BRIP1] N [PALB2] O [RAD51C] P [SLX4]			RAD6 RAD18	XPA, XPF RPA	
Effector proteins	XRCC4 XLF LIG4 APLF Artemis PAXX WRN	RAD51 MUS81/EME1 SLX1/SLX4 RTEL1 BLM TOPOIII POLQ PARI RECQL5 FANCJ, BLM	XRCC1 LIG3, LIG1 CtIP POLQ	RAD52, others?	Shared with HR, TLS, and NER	XRCC1 PNKP POLβ FEN1, TDP1 Aprataxin, LIG1, LIG3A	As for SSB repair	REV1, POLH POLI, POLK	XPG ERCC1 POLE POLD1 LIG1, LIG3	EXO1 POLD LIG1

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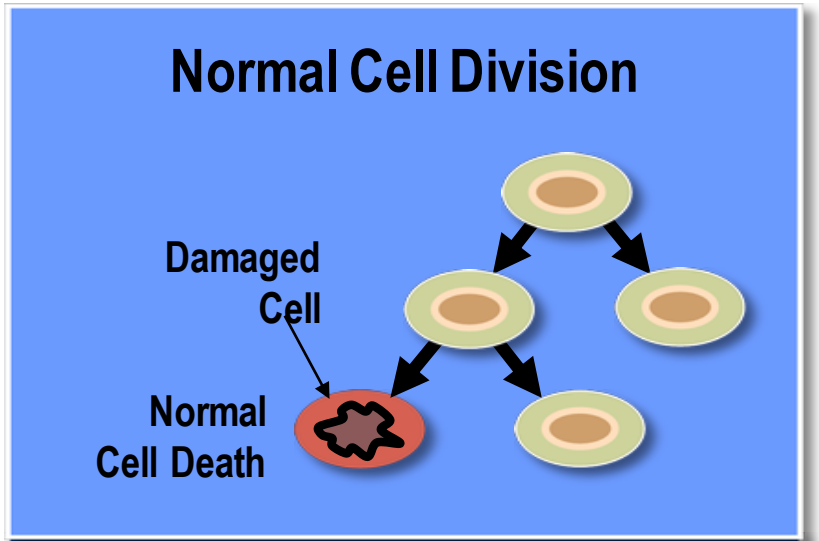
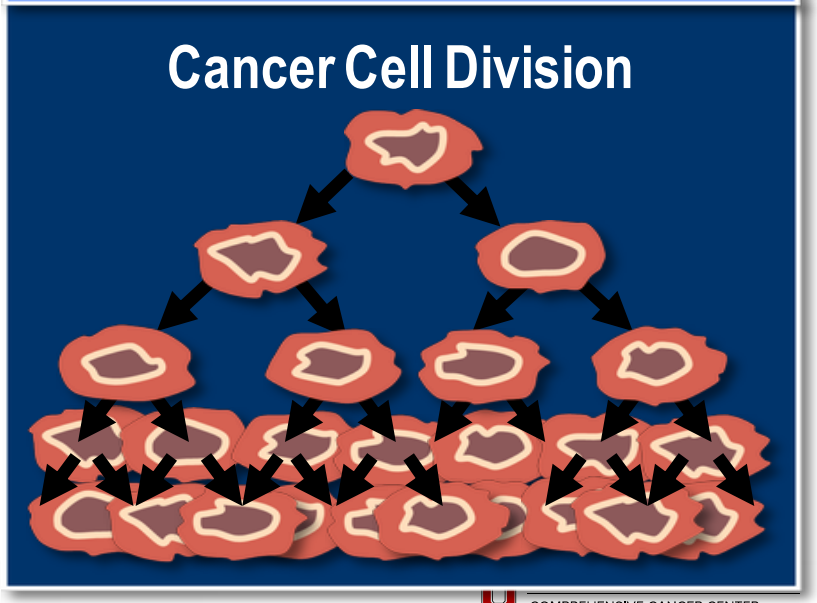
Brown et al., Cancer Discovery 2016

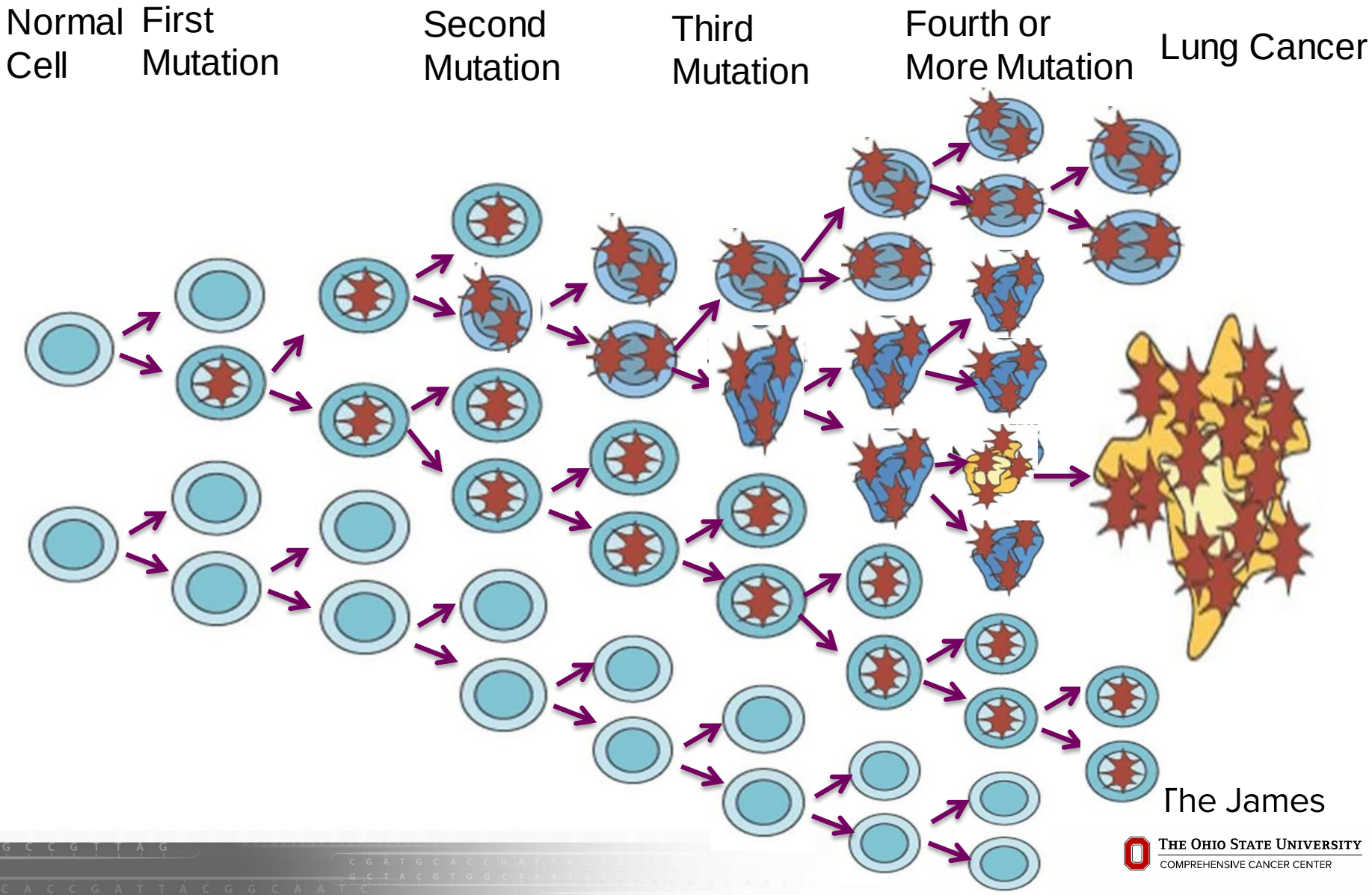
What Happens When a Cell Becomes Cancerous?

- Normal cells grow, divide and die of old age
- Cancer cells grow uncontrollably and push away normal cells in our organs
- There is no place for the good cells to work, or for the organs to function
- The cells living around the cancer cell makes proteins that promote the growth of the cancer
- The cancer cells may even help destroy the normal cells or make them non-functional (e.g. invasion, muscle-wasting)





When Cells Do Not Divide Correctly, Mutant Cells Are Created



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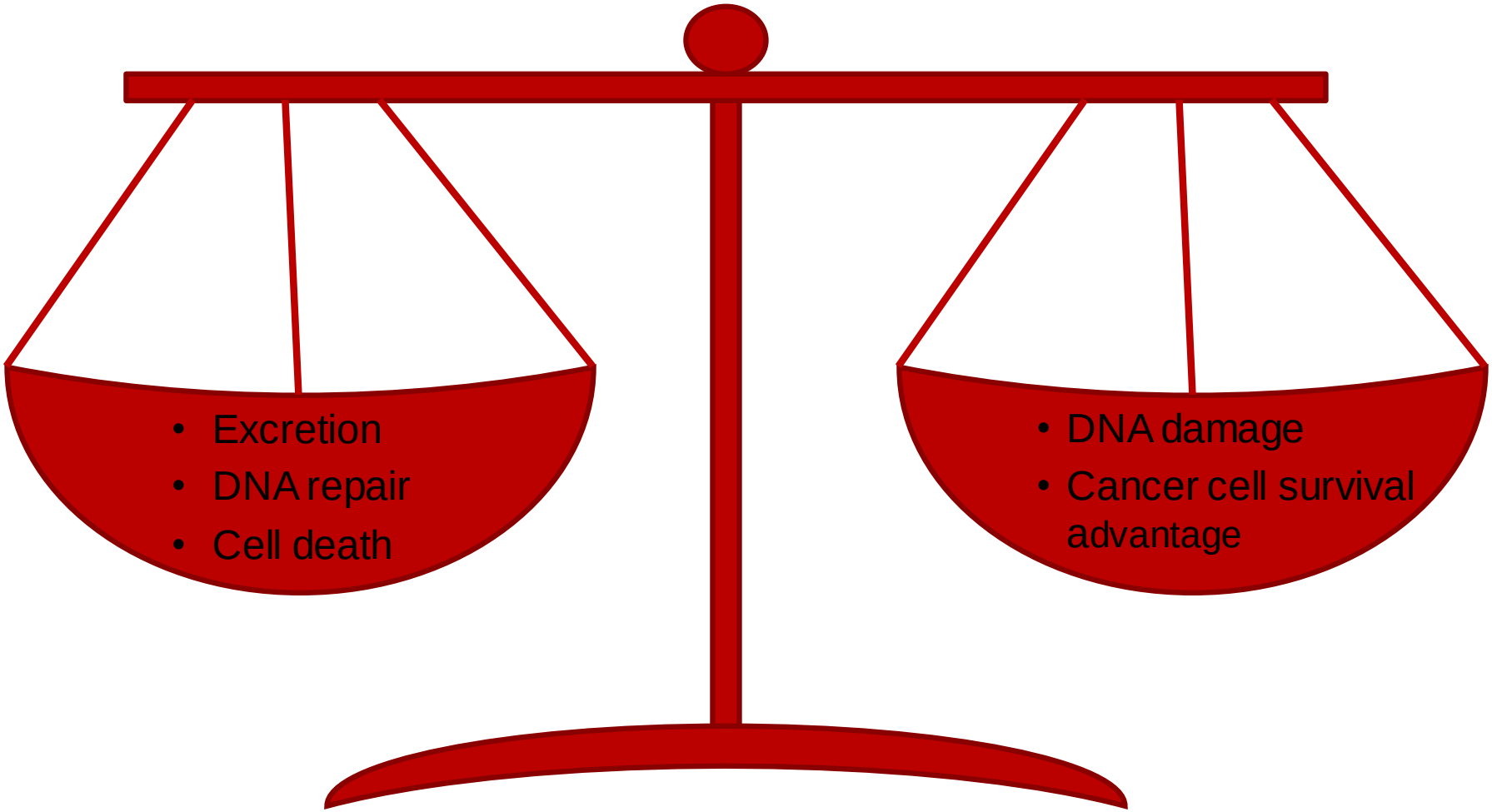
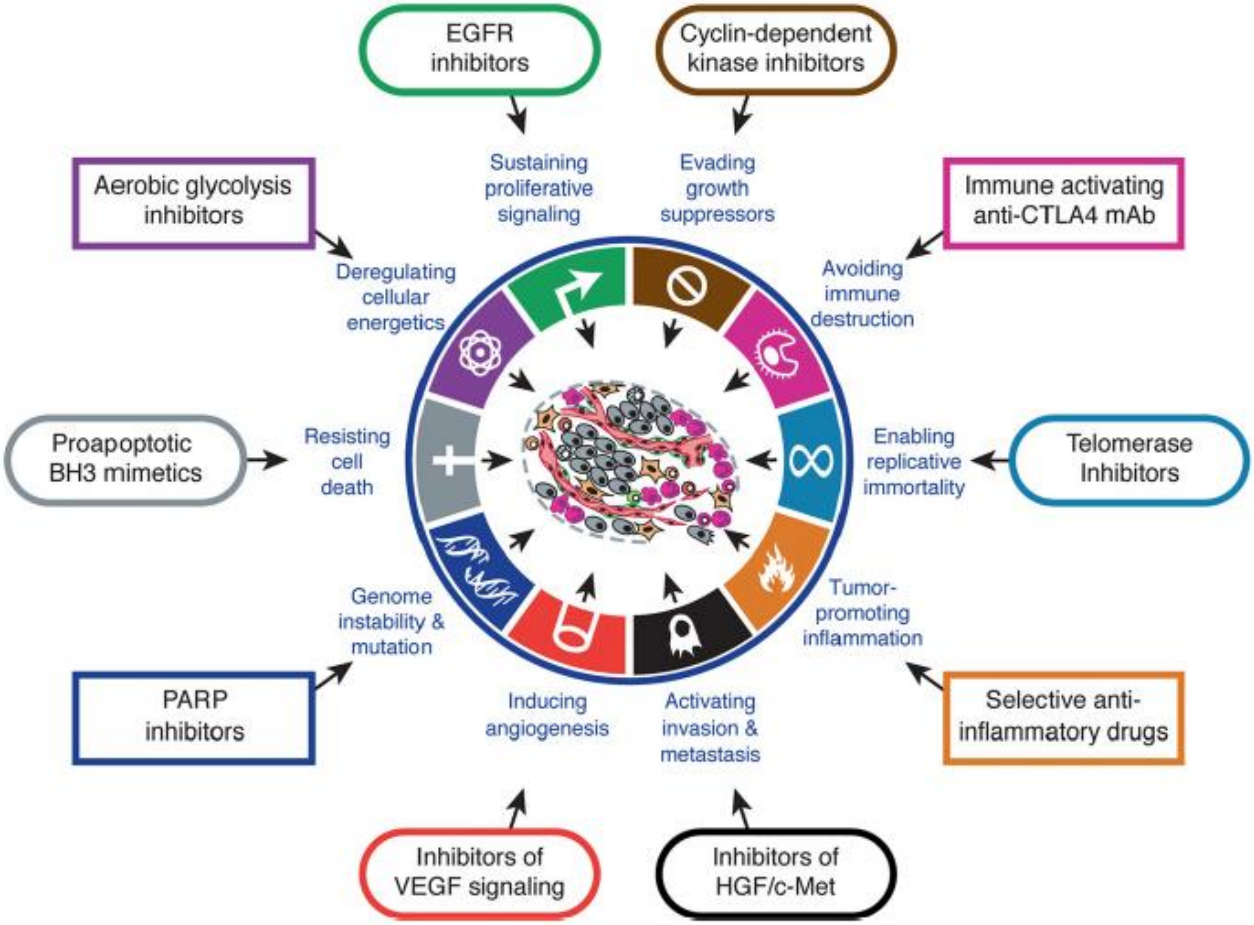
Cancer happens when there is an imbalance between protection and harm in our cells



Hallmarks of Cancer



Hanahan D and Weinberg RA, Cell, 2011

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How Does Radiation from Radon Cause Cancer?

- Dose-response
  - How much radon is in your home/workplace in the areas where you occupy
  - The amount of time you spend in your home/workplace
  - Smoking adds to the risk and there is a synergy (higher risk than if just adding the 2 risks of smoking and radon together)
- EPA action levels
  - 4.0 picocuries per liter (pCi/L) of air is a minimum level recommended to take some action to reduce potential exposures
  - Hitting action levels do not mean guarantee to get lung cancer
- WHO action levels
  - Lower than EPA: 2.7 pCi/L (100 Bq/m^3)

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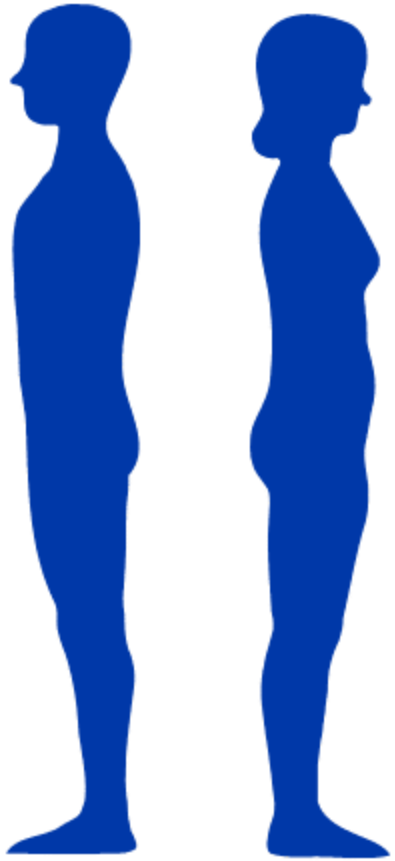
Estimated Cancer Deaths in the US in 2018

Males 323,630		Females 286,010	
Lung & bronchus	26%	25%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	8%	8%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	6%	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	4%	4%	Leukemia
Urinary bladder	4%	3%	Liver & intrahepatic bile duct
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
Kidney & renal pelvis	3%	3%	Brain & other nervous system
All other sites	24%	24%	All other sites



Lung Cancer is the #1 Cancer killer for both men and women in the U.S. (and worldwide)!

Lung Cancer Risk Factors

1. First-hand smoking (about 140,000 new cases per year in the U.S.)
2. Radon (about 21,000 new cases per year)
3. Second-hand smoking (about 3,000 new cases per year)
4. Other types of radiation (cancer radiotherapy, atomic bomb, CT scans)
5. Asbestos
6. Some metals in the workplace
7. Diesel Exhaust
8. Air pollution

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The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

50-Year Trends in Smoking-Related Mortality in the United States

Michael J. Thun, M.D., Brian D. Carter, M.P.H., Diane Feskanich, Sc.D., Neal D. Freedman, Ph.D., M.P.H., Ross Prentice, Ph.D., Alan D. Lopez, Ph.D., Patricia Hartge, Sc.D., and Susan M. Gapstur, Ph.D., M.P.H.

Table 2. Age-Adjusted and Multivariable-Adjusted Relative Risks of Death from Smoking-Related Diseases among Women 55 Years of Age or Older in the Three Study Cohorts, According to Smoking Status.*

Variable	Never Smoked			Current Smoker			Former Smoker†		
	CPS I Cohort (1959–1965)	CPS II Cohort (1982–1988)	Contemporary Cohort (2000–2010)	CPS I Cohort (1959–1965)	CPS II Cohort (1982–1988)	Contemporary Cohort (2000–2010)	CPS I Cohort (1959–1965)	CPS II Cohort (1982–1988)	Contemporary Cohort (2000–2010)
Death from lung cancer									
No. of deaths	179	334	513	79	1084	1485	8	381	2787
Rate per 100,000	17.70	27.74‡	21.77‡	30.19	291.86‡	505.79‡	46.50	97.77	128.84‡
Age-adjusted RR	1.00	1.00	1.00	2.74	12.62	26.18	1.30	3.77	6.66
95% CI				2.07–3.62	11.13–14.31	23.65–28.98	0.64–2.65	3.25–4.38	6.06–7.31
Multivariable-adjusted RR§	1.00	1.00	1.00	2.73	12.65	25.66	1.30	3.85	6.70
95% CI				2.07–3.61	1.15–14.34	23.17–28.40	0.64–2.64	3.32–4.47	6.09–7.36

Time lag from smoking fits multi-stage carcinogenesis model

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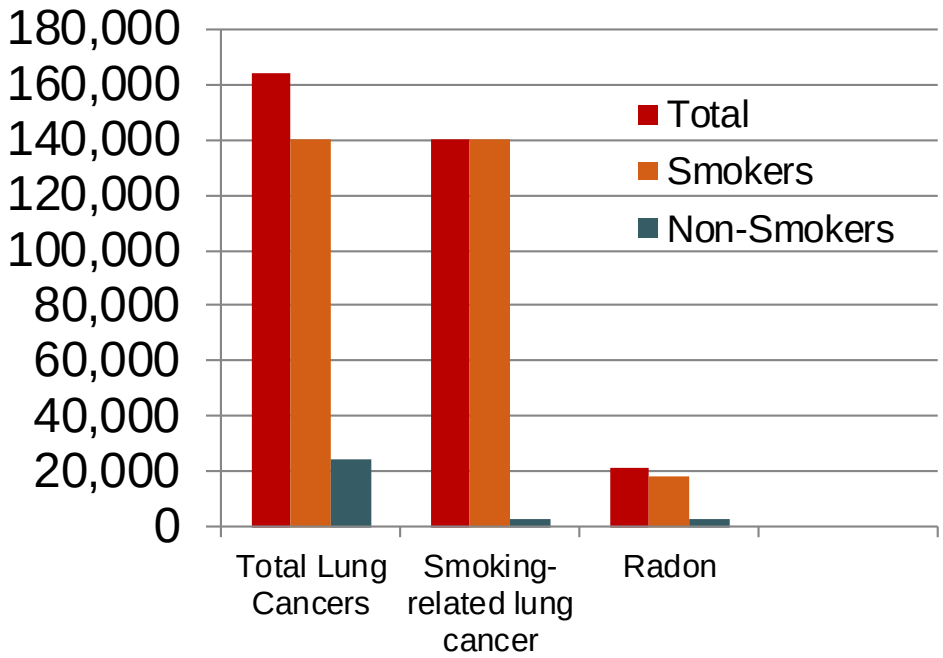
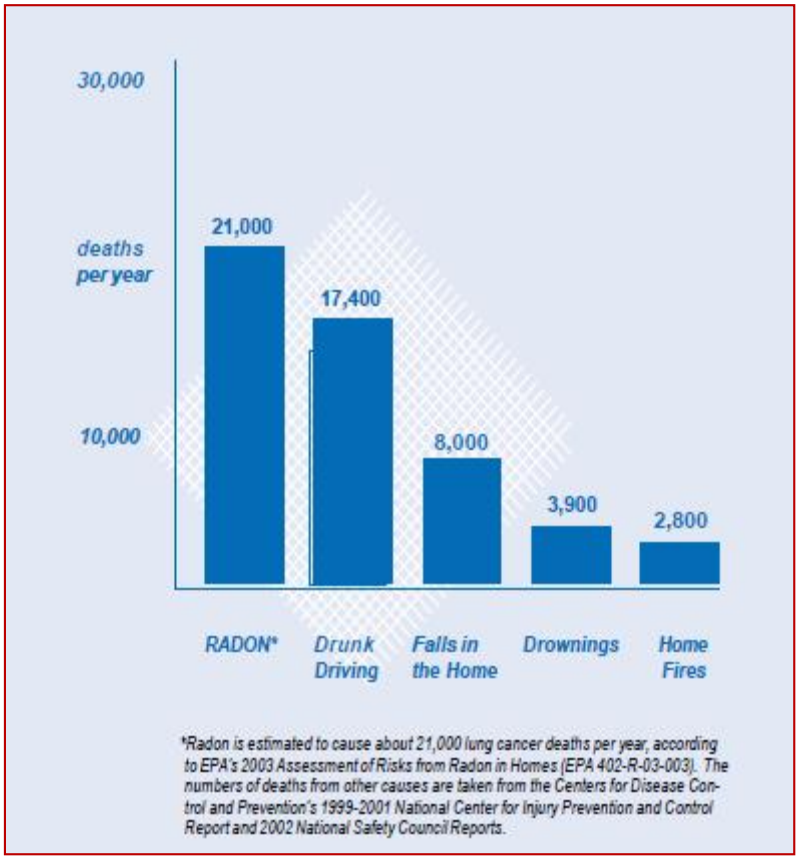
Lung Cancer Rates And Causes





	Total	Smokers	Non-Smokers
Total Lung Cancers	164,000	140,000	24,000
Smoking-related lung cancer	140,000	140,000	3,000
Radon	21,000	18,000	3,000

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What EPA Says About Non-Smokers And Radon Risk

RADON RISK IF YOU'VE NEVER SMOKED

Radon Level	If 1,000 people who never smoked were exposed to this level over a lifetime*...	The risk of cancer from radon exposure compares to**...	WHAT TO DO:
20 pCi/L	About 36 people could get lung cancer	35 times the risk of drowning	Fix your home
10 pCi/L	About 18 people could get lung cancer	20 times the risk of dying in a home fire	Fix your home
8 pCi/L	About 15 people could get lung cancer	4 times the risk of dying in a fall	Fix your home
4 pCi/L	About 7 people could get lung cancer	The risk of dying in a car crash	Fix your home
2 pCi/L	About 4 people could get lung cancer	The risk of dying from poison	Consider fixing between 2 and 4 pCi/L
1.3 pCi/L	About 2 people could get lung cancer	(Average indoor radon level)	(Reducing radon levels below 2 pCi/L is difficult)
0.4 pCi/L		(Average outdoor radon level)	

Note: If you are a former smoker, your risk may be higher.
*Lifetime risk of lung cancer deaths from *EPA Assessment of Risks from Radon in Homes* (EPA 402-R-03-003).
**Comparison data calculated using the Centers for Disease Control and Prevention's 1999-2001 National Center for Injury Prevention and Control Reports.

What EPA Says About Smokers and Radon Risk

RADON RISK IF YOU SMOKE

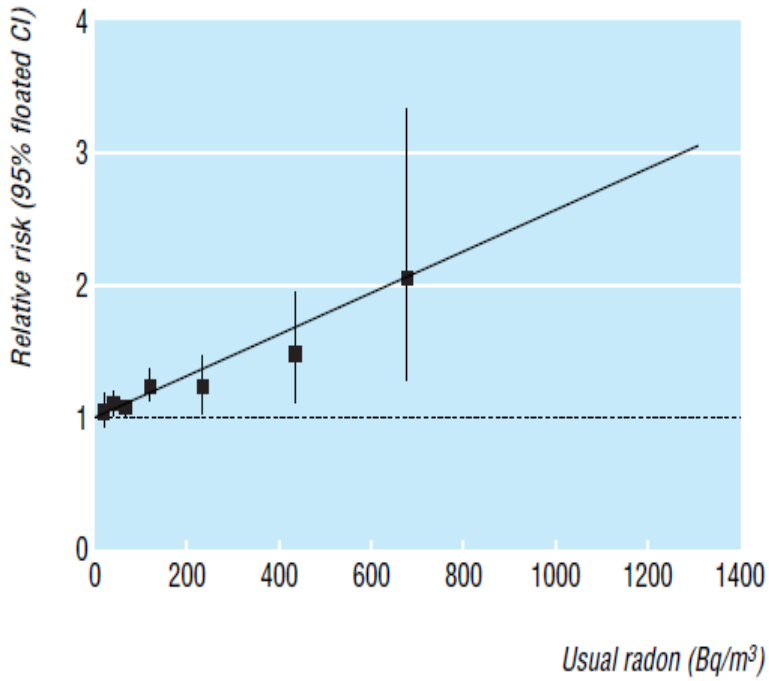
Radon Level	If 1,000 people who smoked were exposed to this level over a lifetime*…	The risk of cancer from radon exposure compares to**…	WHAT TO DO: Stop Smoking and…
20 pCi/L	About 260 people could get lung cancer	250 times the risk of drowning	Fix your home
10 pCi/L	About 150 people could get lung cancer	200 times the risk of dying in a home fire	Fix your home
8 pCi/L	About 120 people could get lung cancer	30 times the risk of dying in a fall	Fix your home
4 pCi/L	About 62 people could get lung cancer	5 times the risk of dying in a car crash	Fix your home
2 pCi/L	About 32 people could get lung cancer	6 times the risk of dying from poison	Consider fixing between 2 and 4 pCi/L
1.3 pCi/L	About 20 people could get lung cancer	(Average indoor radon level)	(Reducing radon levels below 2 pCi/L is difficult)
0.4 pCi/L		(Average outdoor radon level)	

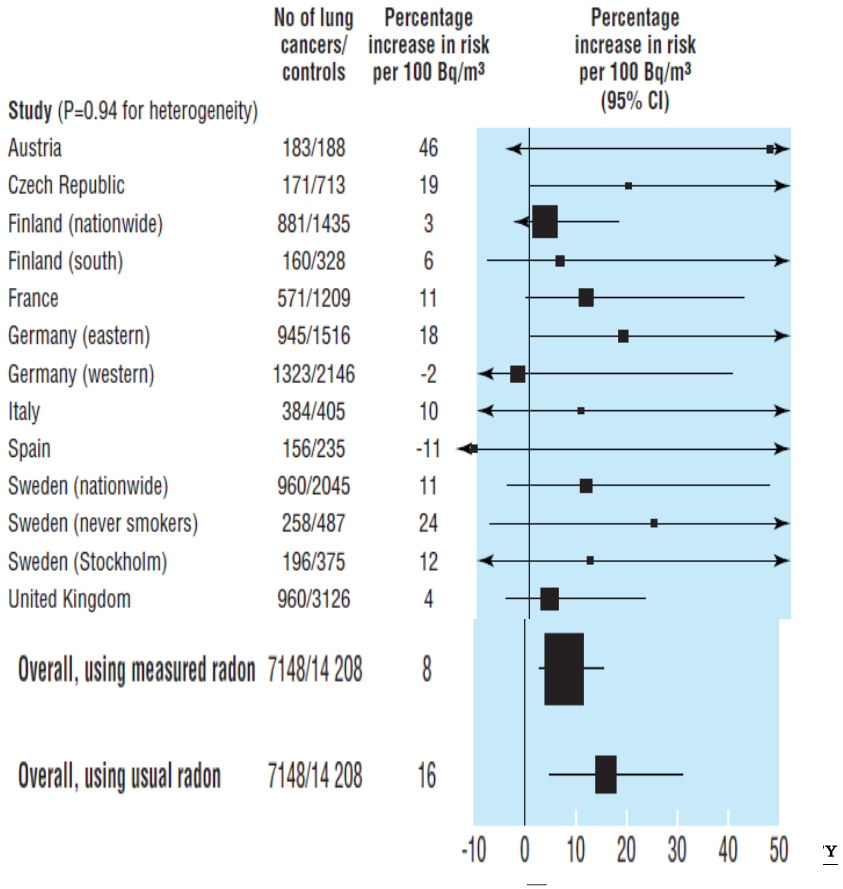
Note: If you are a former smoker, your risk may be lower.

BMJ, doi:10.1136/bmj.38308.477650.63 (published 21 December 2004)

Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies

S Darby, D Hill, A Auvinen, J M Barros-Dios, H Baysson, F Bochicchio, H Deo, R Falk, F Forastiere, M Hakama, I Heid, L Kreienbrock, M Kreuzer, F Lagarde, I Mäkeläinen, C Muirhead, W Oberaigner, G Pershagen, A Ruano-Ravina, E Ruosteenoja, A Schaffrath Rosario, M Tirmarche, L Tomášek, E Whitley, H E Wichmann, R Doll



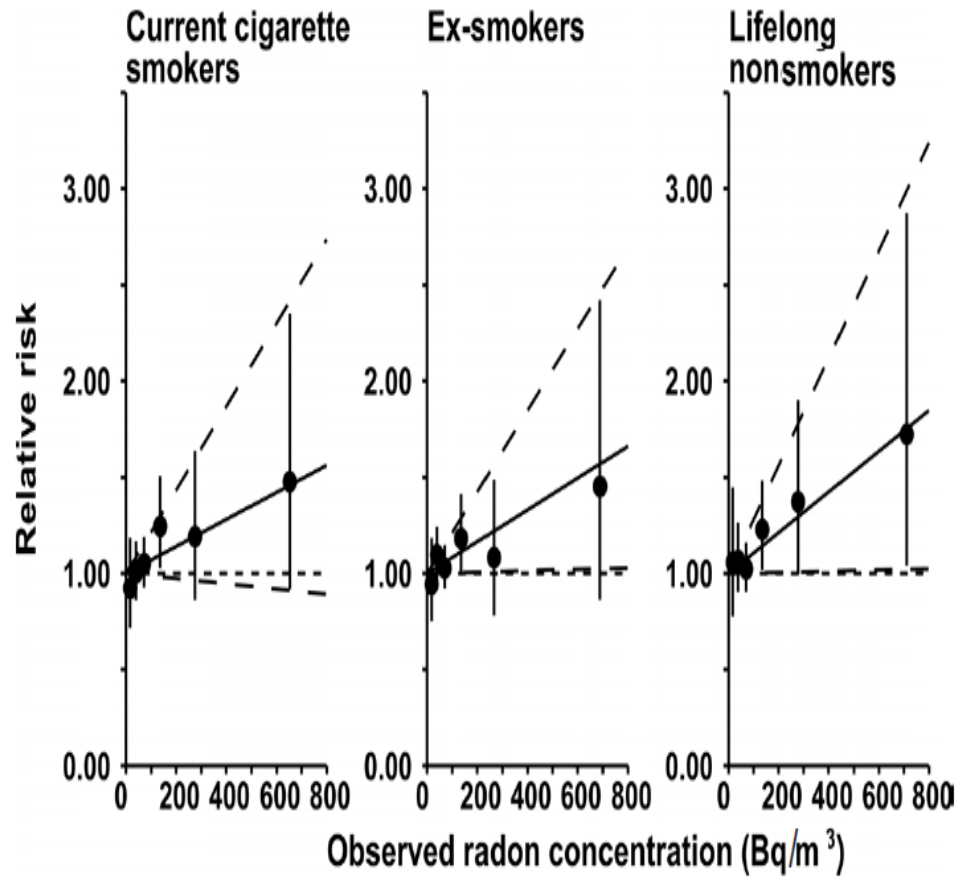


100 Bq/m^3 = 2.7 pCi/L

Scand J Work Environ Health 2006;32 suppl 1:1–84

Residential radon and lung cancer—detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14 208 persons without lung cancer from 13 epidemiologic studies in Europe

by Sarah Darby,[1] David Hill,[1] Harz Deo,[2] Anssi Auvinen,[3] Juan Miguel Barros-Dios,[4] Hélène Baysson,[5] Francesco Bochicchio,[6] Rolf Falk,[7] Sara Farchi,[8] Adolfo Figueiras,[4] Matti Hakama,[9] Iris Heid,[10] Nezahat Hunter,[11] Lothar Kreienbrock,[12] Michaela Kreuzer,[13] Frédéric Lagarde,[14] Ilona Mäkeläinen,[15] Colin Muirhead,[11] Wilhelm Oberaigner,[16] Göran Pershagen,[14] Eeva Ruosteenoja,[15] Angelika Schaffrath Rosario,[10] Margot Tirmarche,[5] Ladislav Tomášek,[17] Elise Whitley,[18] Heinz-Erich Wichmann,[10] Richard Doll[1]



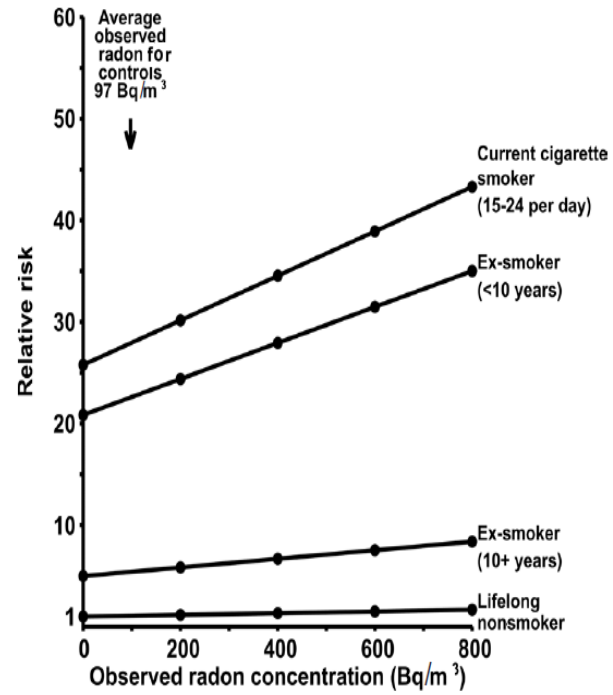


Figure 5. Risk of lung cancer relative to that of lifelong nonsmokers with no radon exposure by the observed radon concentration. See table 28 for the methodological details.

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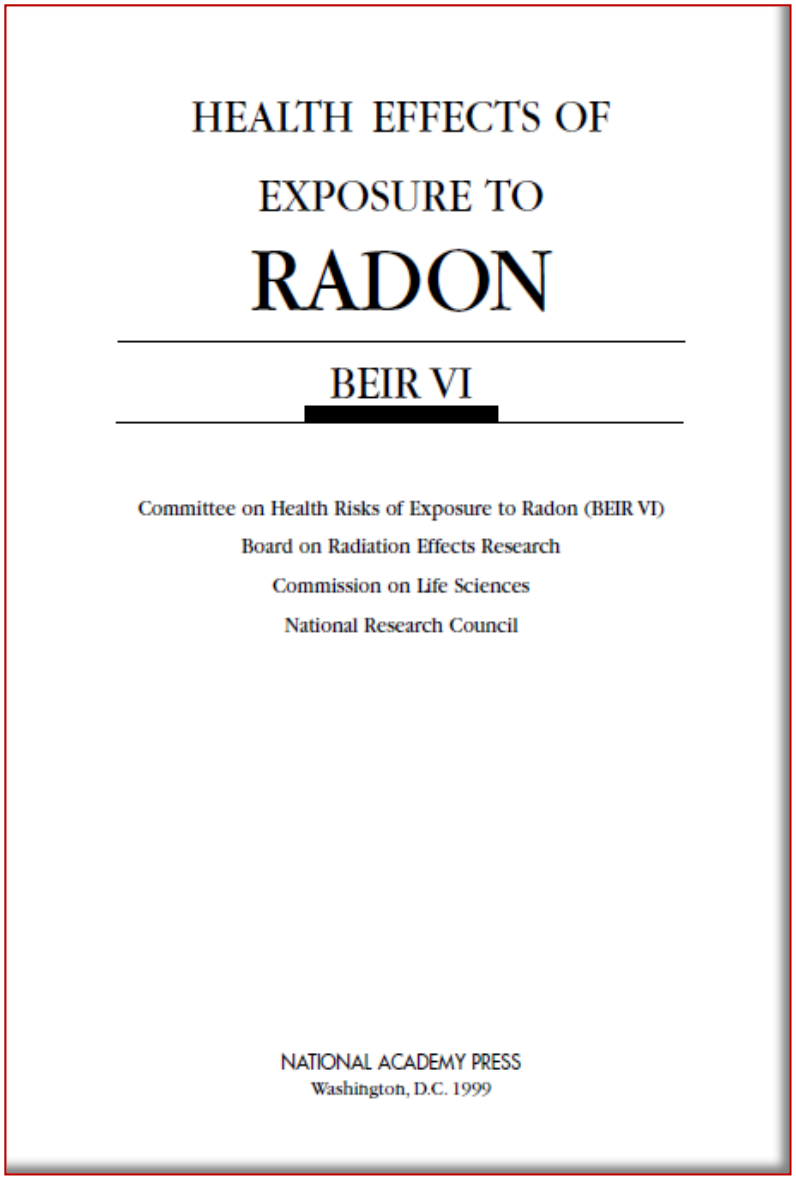


HEALTH EFFECTS OF

EXPOSURE TO

RADON

BEIR VI

Committee on Health Risks of Exposure to Radon (BEIR VI)

Board on Radiation Effects Research

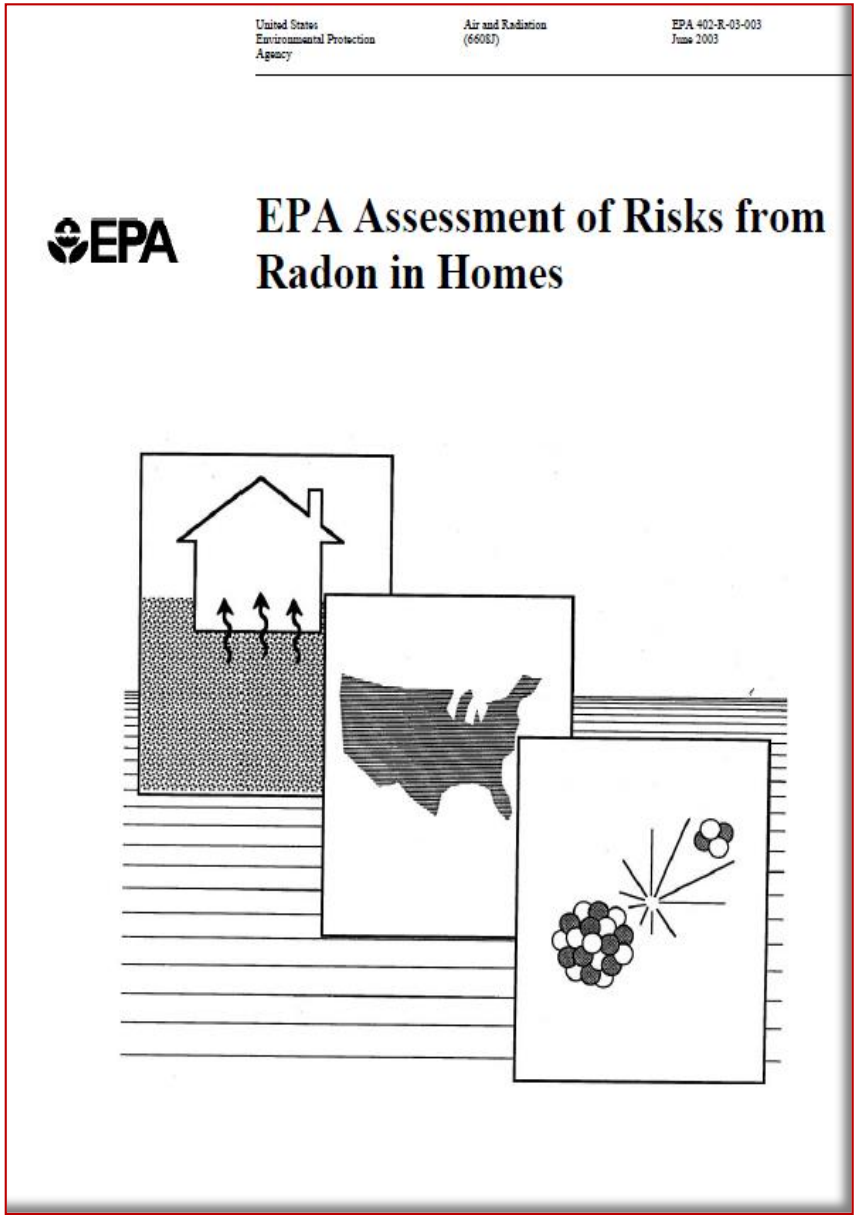
Commission on Life Sciences

National Research Council

NATIONAL ACADEMY PRESS

Washington, D.C. 1999

- Serious public health problem for lung cancer
- Second leading cause of lung cancer second to smoking
- Presented models to estimated excess number of lung cancers due to radon
  - 15,400 or 21,800 cases due to radon
  - Uncertainty – 3,000 to 33,000
  - 1 in 8 ever-smokers with lung cancer is due to radon
  - 1 in 4 never-smoker with lung cancer is due to radon
- Risk increases with chronic exposure rather than higher short term exposures
- Risk decreases with time since exposure


United States Environmental Protection Agency | Air and Radiation (6608J) | EPA 402-R-03-003 June 2003

EPA

EPA Assessment of Risks from Radon in Homes

- 21,100 (13.4%) of 157,400 lung cancer deaths in 1995 due to radon
- Recommended action level is 4 picocurie/liter by EPA
  - No threshold model
  - Would reduce deaths by 25%
  - The estimated risks from lifetime exposure at the 4 pCi/L action level are: 2.3% (all), 4.1% (smokers), and 0.73% (never smokers)
  - Radon and smoking are synergistic
  - Relative risks: never-smokers>smokers

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Radon Exposure: Using the Spectrum of Prevention Framework to Increase Healthcare Provider Awareness

Jane Worrell, MSN, RN, OCN®, Phillip Gibson, BA, MS, and Deborah "Hutch" Allen, PhD, RN, CNS, FNP-BC, AOCNP®

Level 1: Strengthening individual knowledge and skills

- Provide radon test kits and resources for mitigation at county health departments.
- Engage providers to assess exposure and encourage testing through 1:1 interactions.
- Continue to increase kit accessibility and follow-up of results.

Level 2: Promoting community education

- Promote National Radon Action Month (January) by advertisements in healthcare newsletters and signs for home testing in comprehensive cancer centers and clinics.
- Provide radon tests and resources for mitigation at community health fairs.
- Promote media coverage and encourage school nurses to identify at-risk students.

Level 3: Educating providers

- Submit manuscripts targeted at primary care providers to increase provider education (nurses association, medical society).
- Provide continuing education programs and increase provider education via conference programs, webinars, and regional meetings.

Level 4: Fostering coalitions and networks

- Introduce healthcare associations to real estate associations, construction and building industry representatives, and government agencies to promote radon awareness. These include, but are not limited to, the following: regional chapters of the Oncology Nursing Society, medical and nursing schools, National Association of Home Builders, National Association of Realtors, state health directors, and American Cancer Society.

Level 5: Changing organizational practices

- Review federal, state, and local building codes; mitigation standards; and real estate transaction policies.
- Create language for electronic health record documentation about radon exposure risks, testing, and exposure (duration, concentration).

Level 6: Influencing policy and legislation

- Consider regulating all new construction to provide radon prevention materials or radon reduction systems.

FIGURE 2. Spectrum of Prevention Framework: Identified Opportunities to Reduce Radon Exposure

- Cracks in concrete slabs, flooring, or walls
- Pores or cracks in concrete blocks
- Drain tile, if drained to open sump
- Open tops of block walls
- Some building materials (e.g., rocks)
- Cavities inside walls, such as between brick veneer and framing (particularly increased on uncapped hollow-brick foundations)
- Construction joints, such as floor-wall or mortar joints
- Exposed soil, such as in a sump
- Gas around service pipes or loose pipe fittings
- Water supply, such as wells

FIGURE 1. Modes of Radon Entry Into Homes or Buildings

Note. Based on information from Environmental Protection Agency, 2012, 2015.

What is the right Radon action level?

- A safe level of radon gas is <u>no radon gas</u>
  - Lung cancer risk increases with higher exposure
- EPA: "Any radon exposure has some risk of causing lung cancer. The lower the radon level in your home/workplace, the lower the individual's risk of lung cancer".
- The national average of outside radon levels is **0.4 pCi/L** (depending on geographic location, as high as 0.75 pCi/L)
  - National Academy of Sciences estimates outdoor radon levels cause approximately 800 of the 21,000 radon induced lung cancer deaths in the U.S. each year
- Risk of lung cancer rises **16% per 2.7 pCi/L** increase in radon exposure

What is the right Radon action level?

- Radon Act 51 passed by Congress set the natural outdoor level of radon gas (0.4 pCi/L) as the target radon level for indoor radon levels
  - Unfortunately, 2/3rds of homes exceed this level!
- EPA was tasked with setting practical guidelines and recommendations
  - Action level set at 4 pCi/L
  - This does not imply a level below 4 pCi/L is considered acceptable
- It is estimated that reduction of radon levels to below 2.0 pCi/L nationwide would likely reduce the yearly lung cancer deaths attributable to radon by <u>50%</u>
- Even with the action level of 2.0 pCi/L, the cancer risk would still be <u>hundreds of times</u> greater than the risks allowed for carcinogens in our food and water!

OSU-CCC Stance on Radon

- While no level of radon gas is completely safe, we must balance the benefits and costs to find our own "acceptable/feasible" levels
- In accordance with World Health Organization (WHO) guidelines, we recommend action at **2.7 pCi/L** to reduce radon gas in homes/workplaces
- Periodic testing is recommended as radon levels may change or increase over time
- Adjustments may be needed to test and reduce radon from buildings where individuals/families spend long periods of time
- Radon testing and removal are NOT required under State of Ohio or local municipality laws
- It is up to the individual to take action for testing!
- **Save Lives- let's get to testing!**

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Resources

- Ohio's Radon Line 1-800-523-4439
- WHO Handbook on Indoor Radon
- EPA Fix it helpline: 1-800-644-6999 (https://sosradon.org)

Thank You

To learn more about Ohio State's cancer program, please visit **cancer.osu.edu** or follow us in social media:

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