Radon and lung cancer, iodine and thyroid cancer afteer the Fukushima-Daiichi accident

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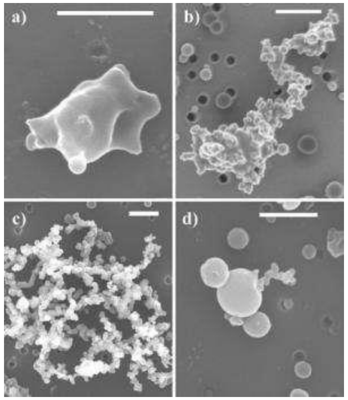
Health effects of radon and in combination with other stressors

Radon decay	Half-life
^{222}Rn	3.8 d
↓ α	
^{218}Po	3 min
↓ **α**	
^{214}Pb	27 min
↓	
^{214}Bi	20 min
↓	
^{214}Po	160 µs
↓ **α**	
^{210}Pb	22 y

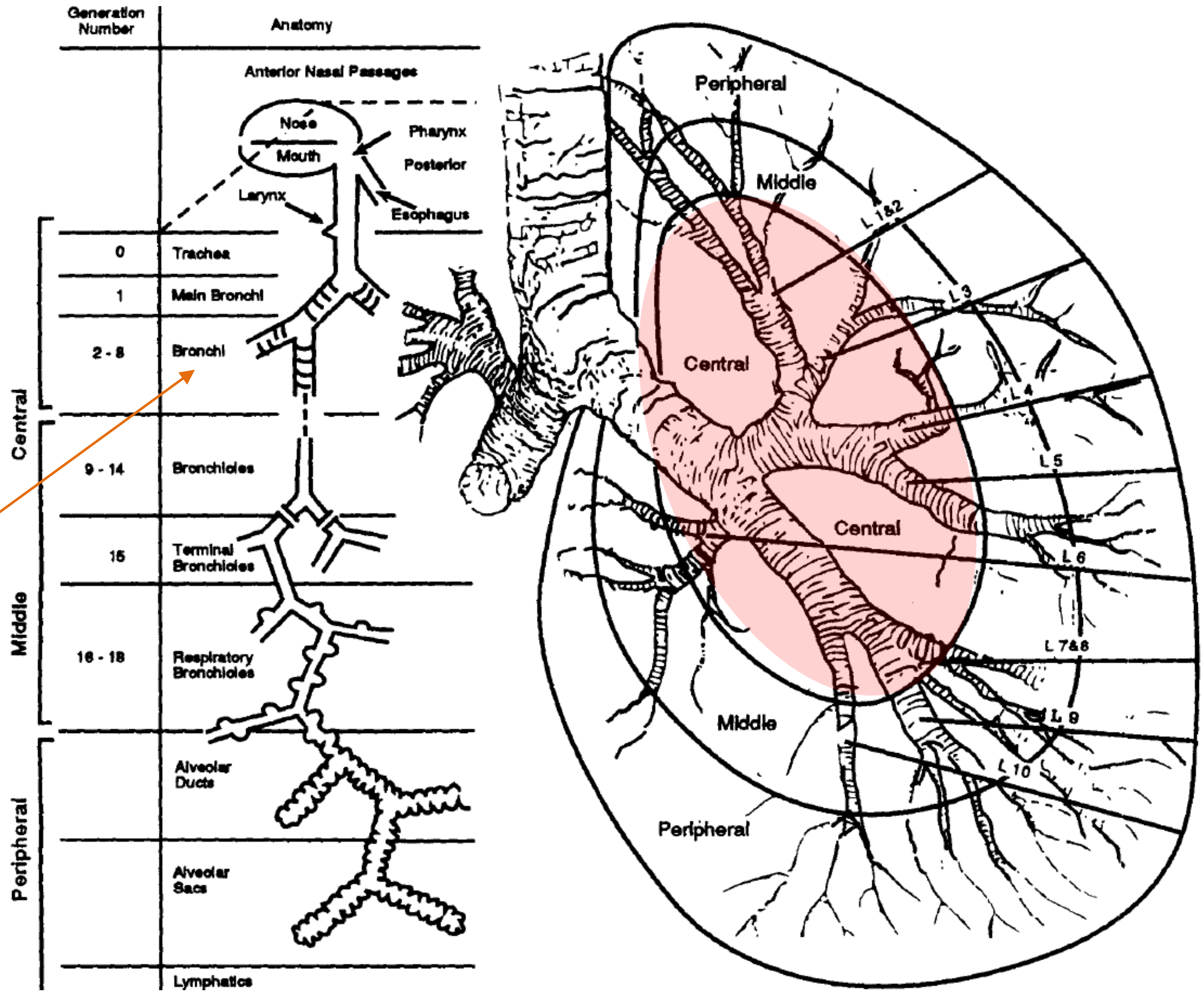
Major contributors to lung dose from solid radon progeny



The lung anatomy

Semi-diagrammatic architecture of bronchial tree showing division of the lungs into three anatomical zones: peripheral, middle and central.

Bronchi are the airways of the central lung. No gas exchange takes place in the bronchi.



Source: G. Saccomanno et al. A Comparison between the Localization of Lung Tumors in Uranium Miners and in Nonminers from 1947 to 1991. Cancer 1996.

Types of lung cancer

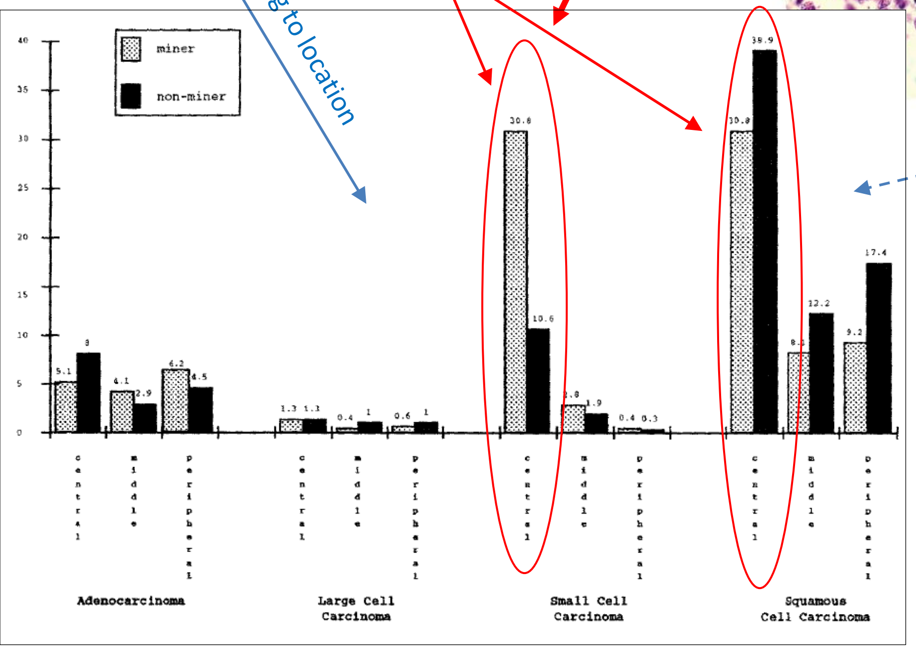
Distribution of cancers in 1991

	Miners	Nonminers
Adenocarcioma	15%	15%
Large cell	2%	3%
Small cell	34%	13%
Squamous cell	48%	68%

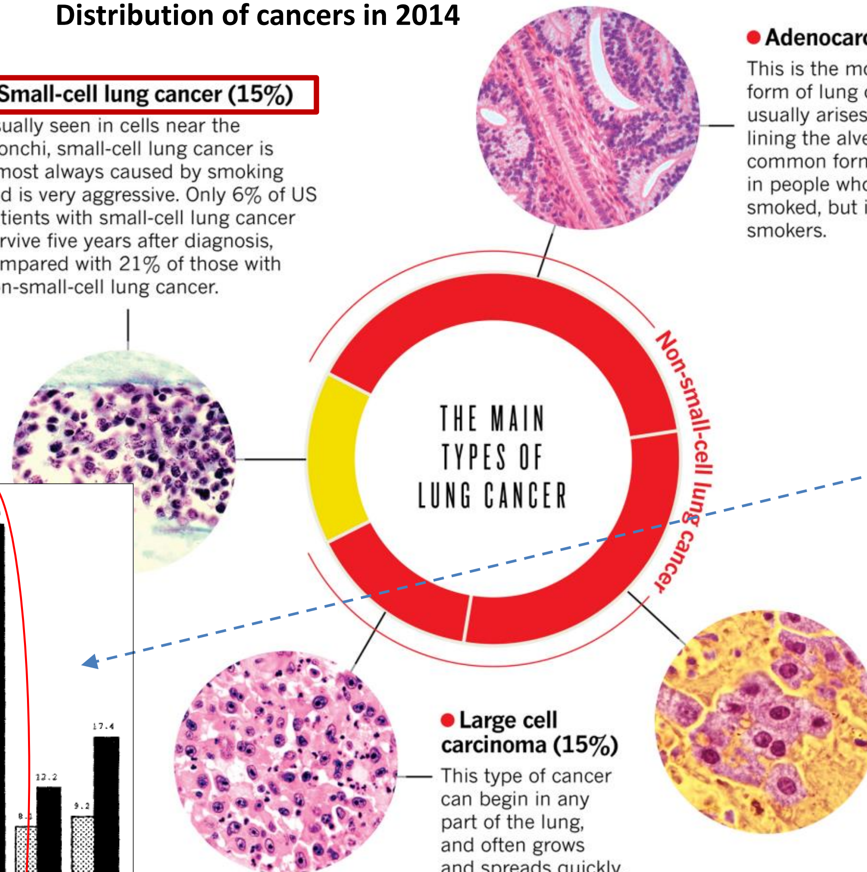
58% of miners are smokers
35% of nonminers are smokers

Split according to location

Location in the lung: central



Distribution of cancers in 2014



Small-cell lung cancer (15%)
Usually seen in cells near the bronchi, small-cell lung cancer is almost always caused by smoking and is very aggressive. Only 6% of US patients with small-cell lung cancer survive five years after diagnosis, compared with 21% of those with non-small-cell lung cancer.

Adenocarcinoma (40%)
This is the most prevalent form of lung cancer and usually arises in the cells lining the alveoli. It is a common form of lung cancer in people who have never smoked, but is also seen in smokers.

Squamous cell carcinoma (30%)
These tumours appear in the flat cells that line the inside of the airways, usually near the bronchi. This form of the disease is usually caused by smoking and is more common in men than women. The tumours tend to grow slowly.

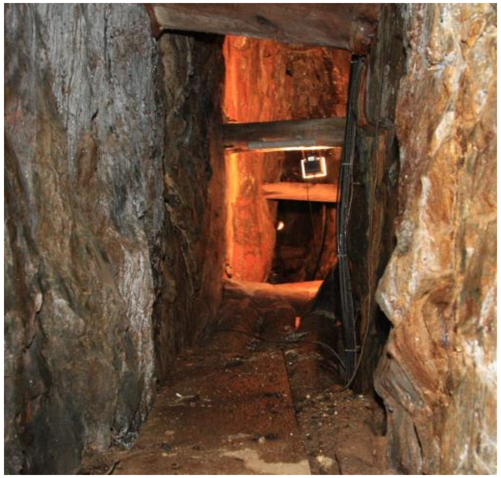
Large cell carcinoma (15%)
This type of cancer can begin in any part of the lung, and often grows and spreads quickly.

Sources: The Nature Outlook on lung cancer, supported by Cancer Research UK and Boehringer Ingelheim, 2014.
G. Saccomanno et al. A Comparison between the Localization of Lung Tumors in Uranium Miners and in Nonminers from 1947 to 1991. Cancer 1996.

Radon concentration and exposure levels

MINES

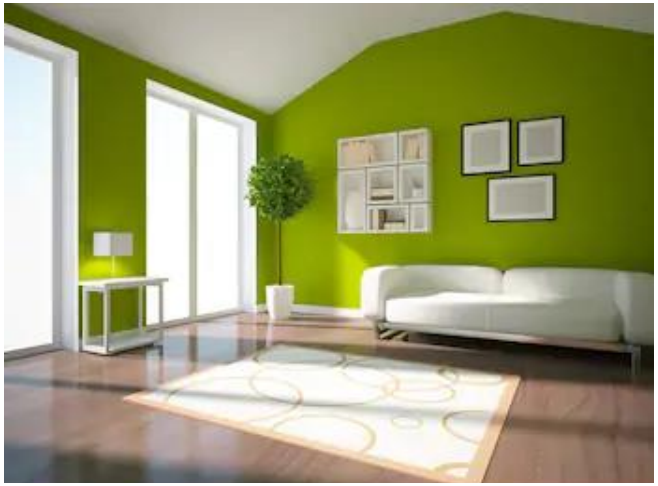
Radon exposure
Working level month (WLM)



170h per month
High breathing rate (1.25 m^3 per h)
Equilibrium factor F = 0.2 (forced ventilation)

HOMES

Radon concentration
$Bq{\cdot}m^{-3}$



500h per month (7000h per year)
Low breathing rate (0.78 m^3 per h)
Equilibrium factor F = 0.4 (natural ventilation)

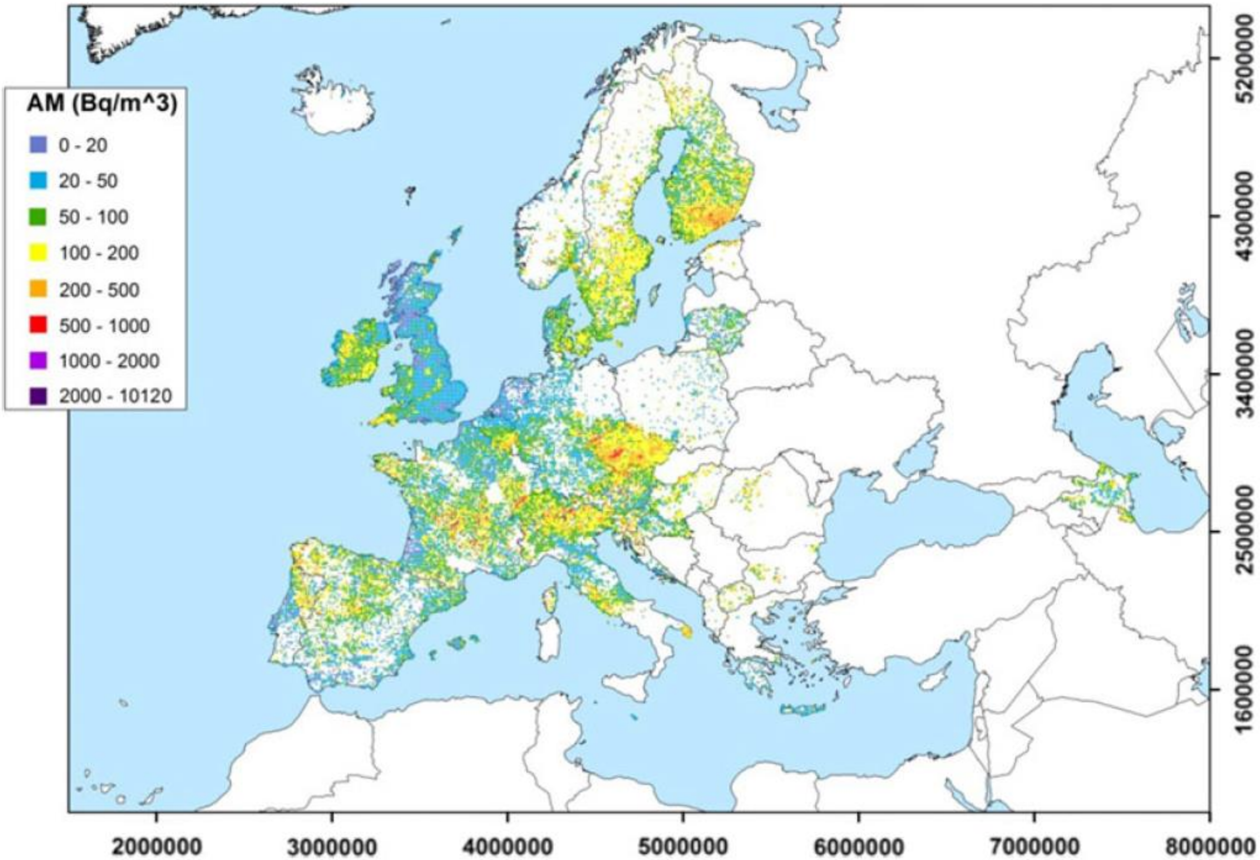
F: measure of the degree of radioactive equilibrium between radon and its short-lived radioactive decay products

1 WLM corresponds to ca 1 year at home with a radon concentration of 230 $Bq{\cdot}m^{-3}$
Living in a house for 1 year with 100 $Bq{\cdot}m^{-3}$ corresponds to lung cancer risk from 0.4 WLM

Radon concentration in European houses

Arithmetic means over 10 km × 10 km cells of long-term radon concentration in ground-floor rooms of 30 European countries. Latest update, November 2015. (The cell mean is neither an estimate of the population exposure, nor of the risk.)

Source: Hoffman et al., Radiat Prot Dosim 2016; 175: 186-93

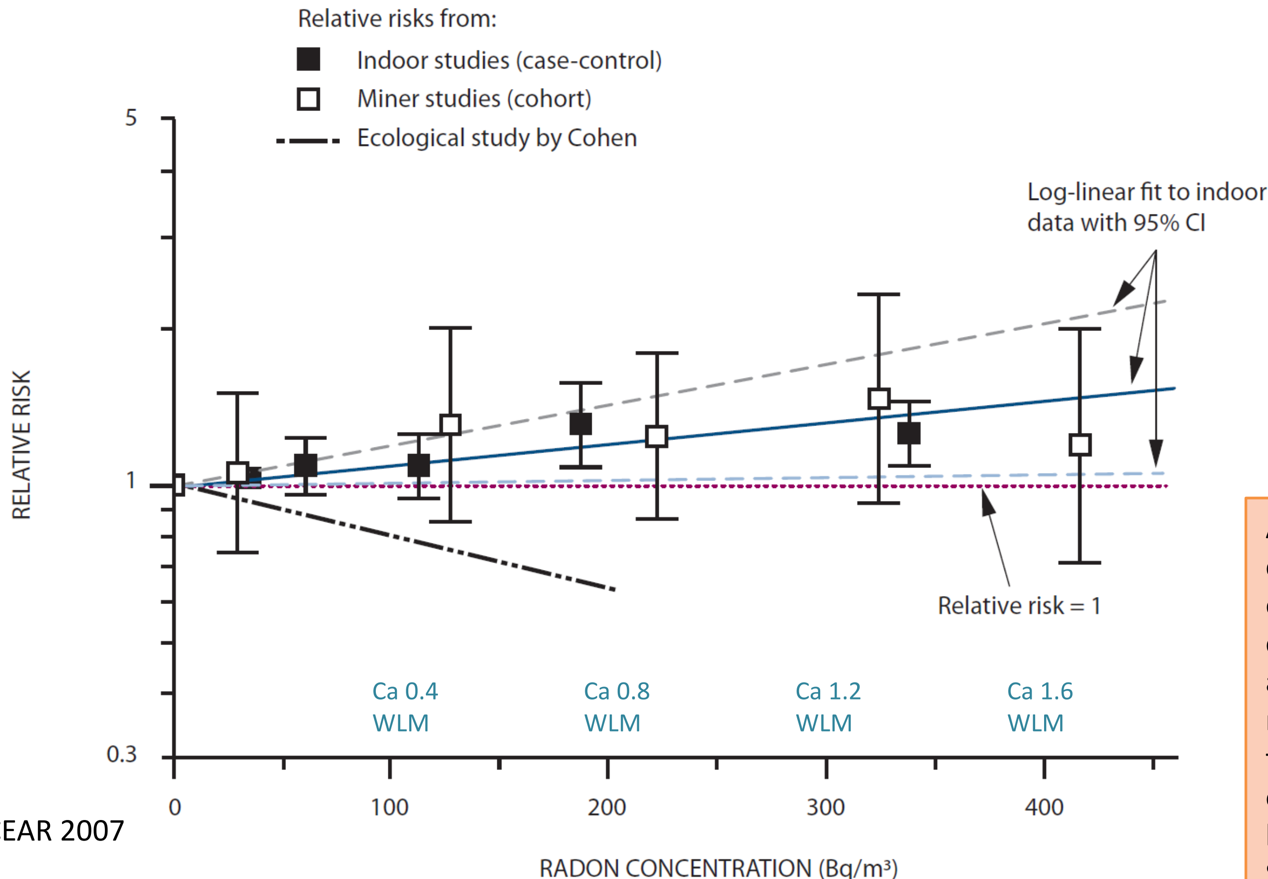


High radon concentrations are found in hard-rock uranium mines

- Intensive uranium mining from 1945-50
- Protection measures introduced from mid-1950s
- First epidemiological studies launched in the 1960s
- Radon classified as a lung carcinogen in 1988
- First studies of indoor radon launched in the 1990s
- Most uranium mines are now closed in Europe

Lung cancer risk from exposure to low radon concentrations

Risk estimates of lung cancer from exposure to radon. Summary relative risks from meta-analysis of eight indoor radon studies and from the pooled analysis of underground miner studies, together with the estimated linear relative risk from the correlation study by Cohen.

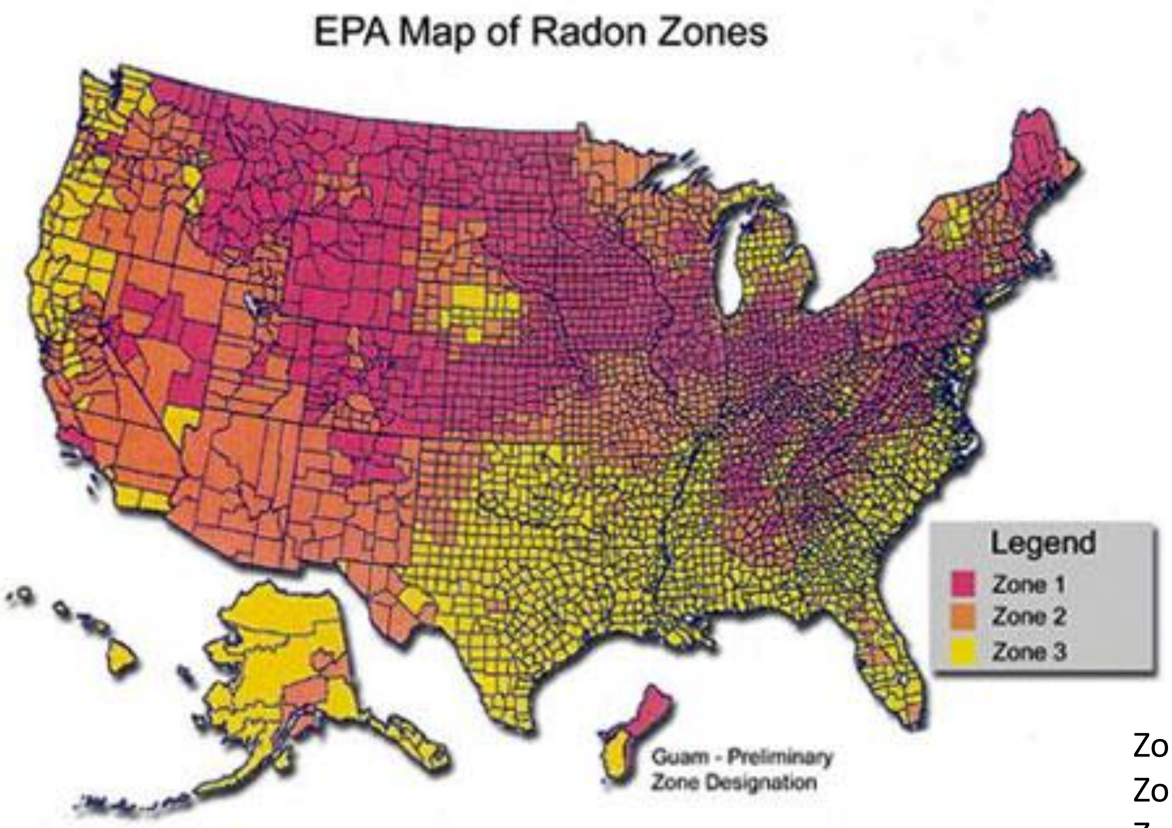


Source: UNSCEAR 2007

Although comparisons are complex, the cumulated excess absolute risk of lung cancer attributable to radon and its progeny estimated for residential exposures appears to be consistent with that obtained from miners at low levels of exposure.
Source: ICRP 115

The ecological study of Cohen

Average residential radon concentration in USA counties



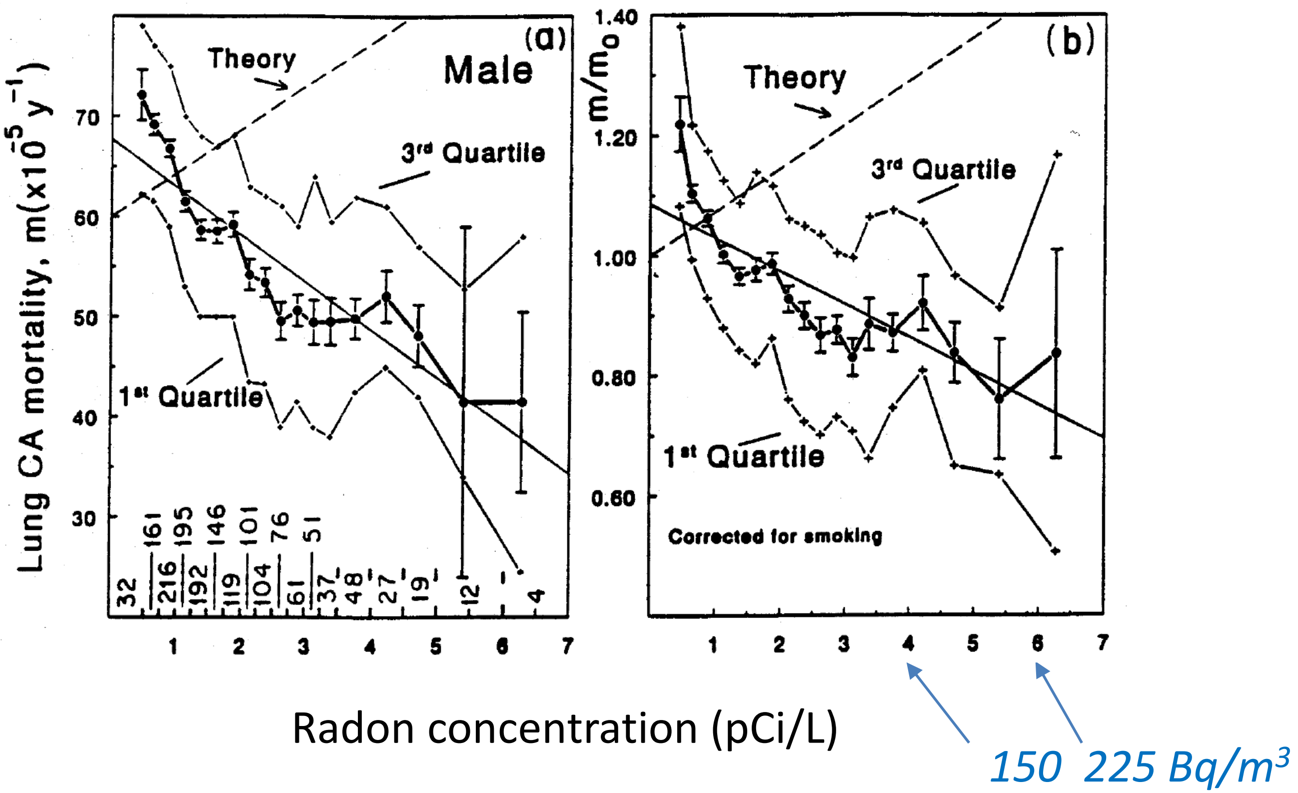
Zone 1: > 150 Bq/m^3
Zone 2: 75-150 $B1/m^3$
Zone 3: < 75 Bq/m^3

What did Cohen do? He ran an ecological study, where he correlated lung cancer mortality per county with the average residential radon concentration.

The ecological study of Cohen

B. Cohen, 68: 157-173, 1995

Lung cancer mortality rates vs. mean radon level for 1601 US counties. Data points shown are avarage of ordinates for all counties withing the range of radon concentrations shown on the vasline of figure a. The number of counties within that range is also shown there. Error bars are standard deviations of the mean and the first and third quartiles of the distributions are also shown.



The problem with the Cohen study: the ecological fallacy

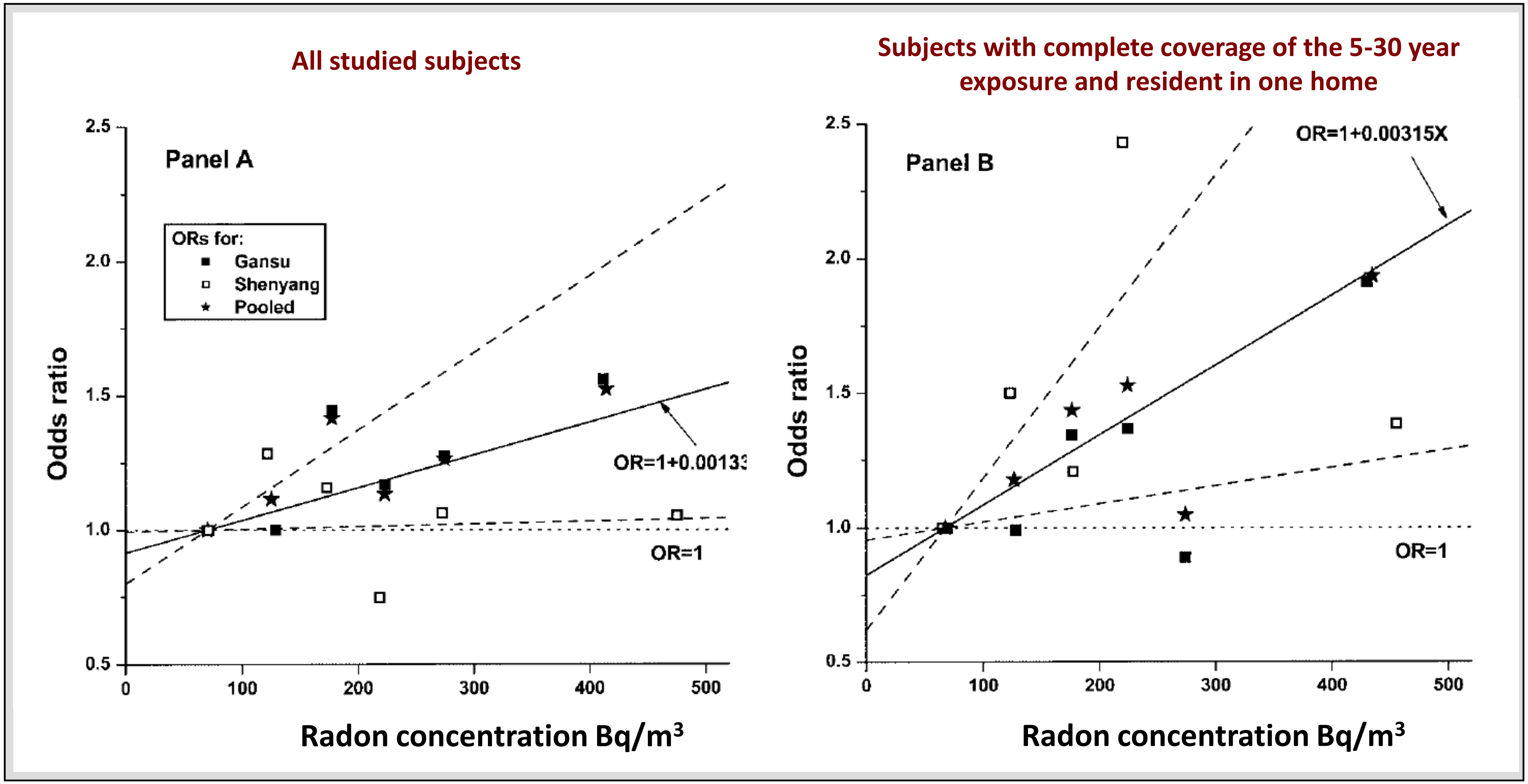
J.H. Lubin, J. Radiol. Prot. 22: 141–148, 2002: no valid inference for the radon and lung cancer association for individuals is possible on the basis of the relationship of county lung cancer rates. Cohen's results provide no information on risk to individuals, and do not necessarily contradict the 20 or more analytic studies which support an increasing association between radon and lung cancer.

Ecological fallacy: failure in reasoning that arises when an inference is made about an individual based on aggregate data for a group. In ecological studies (observational studies of relationships between risk-modifying factors and health or other outcomes in populations), the aggregation of data results in the loss or concealment of certain details of information. Statistically, a correlation tends to be larger when an association is assessed at the group level than when it is assessed at the individual level.

A prominent example: an ecological study showed that death rates from breast cancer were significantly increased in countries where fat consumption was high when compared with countries where fat consumption was low. This is an association for aggregate data in which the unit of observation is country.

Lung cancer and residential radon in Gansu and Shenyang summary of two case control studies

J.H. Lubin et al. International J. Cancer 109:132-137, 2004

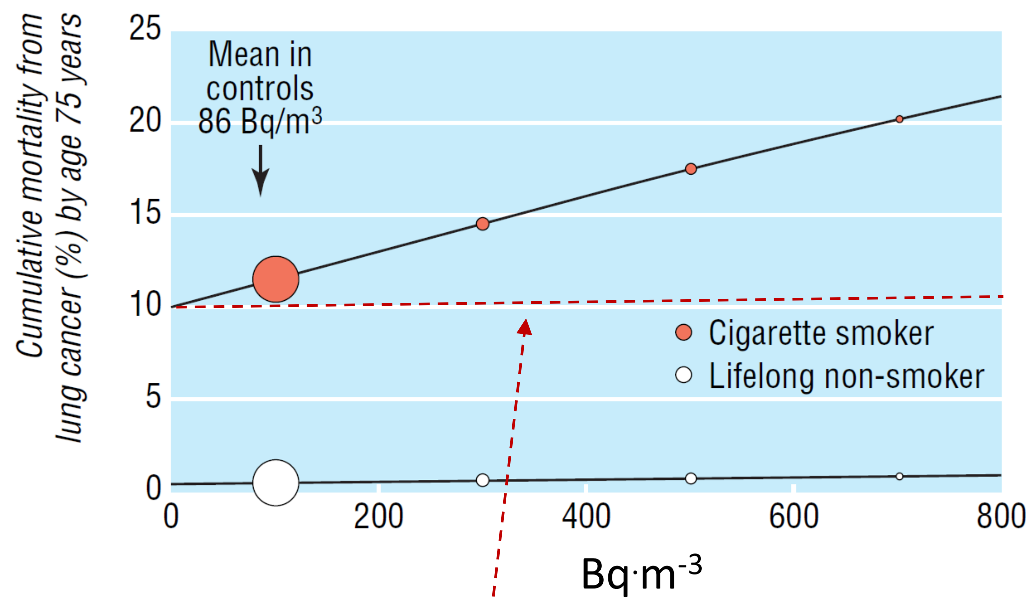


Lung cancer risk from exposure to domestic radon in smokers and non-smokers in Europe

For the overall population (smoking status stratified) the risk of lung cancer increases by about 16% per 100 $Bq{\cdot}m^{-3}$ radon (RR = 1.16, 1.05-1.31 95% CI).

Cumulative absolute risks of lung cancer by age 75 years

$Bq{\cdot}m^{-3}$	non smokers	smokers
0	0.41%	10.1%
100	0.47%	16.0%
400	0.67%	21.6%



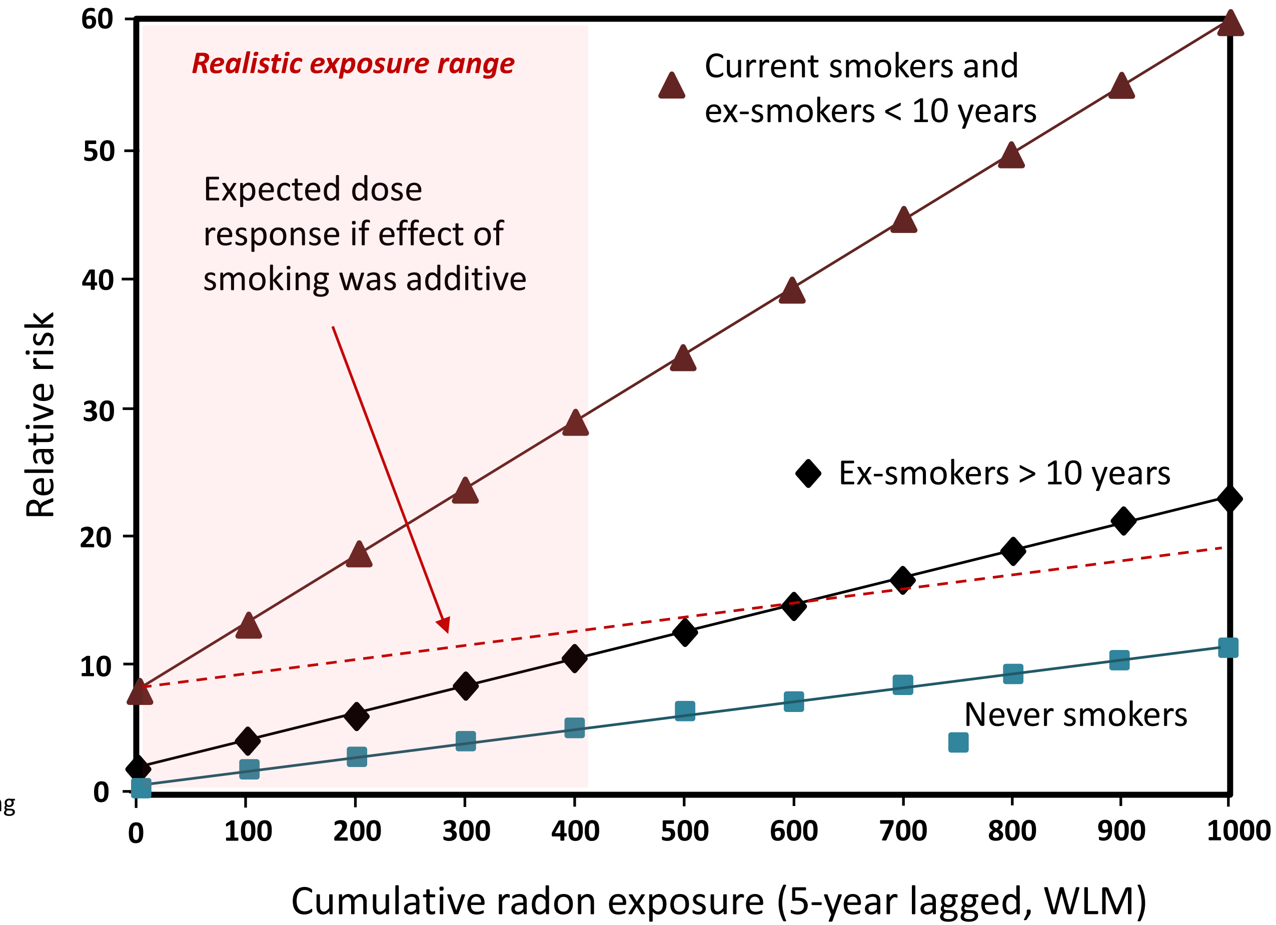
Expected dose response if effect of smoking was additive

Source: Darby et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2004.

Lung cancer risk from exposure to underground radon for smokers and non-smokers

European joint nested analysis of miners with smoking information

Data from the Czech, French and German cohorts
- 1236 lung cancer cases
- 2678 controls



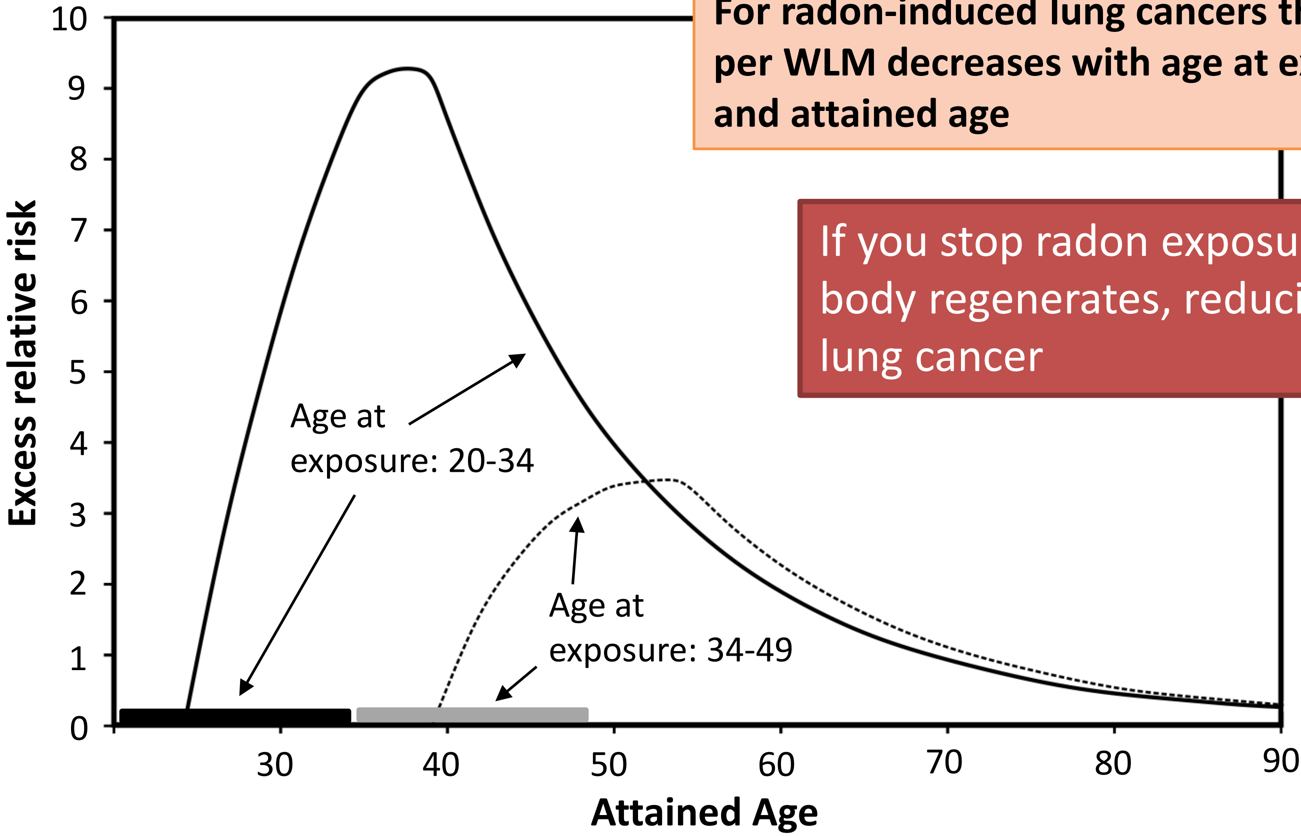
Sources:
K. Leuraud et al. Radon, Smoking and Lung Cancer Risk: Results of a Joint Analysis of Three European Case-Control Studies Among Uranium Miners. Rad. Res. 2011.
D. Laurier, Adelaide 2019.

Age dependency on lung cancer risk from exposure to underground radon

Relative risk of lung cancer death in miners associated with a cumulated exposure of 90 WLM (6 WLM per year during 15 years) received at age 20–34 (solid line and black box) or age 34–49 (dashed line and grey box). Lag period: 5 years.

For radon-induced lung cancers the ERR per WLM decreases with age at exposure and attained age

If you stop radon exposure – your body regenerates, reducing the risk of lung cancer



Source: L. Tomasek et al. RADIATION RESEARCH 169, 125–137 (2008)

Risk of smoking-induced lung cancer declines after cessation of smoking

Article

Tobacco smoking and somatic mutations in human bronchial epithelium

nature

https://doi.org/10.1038/s41586-020-1961-1

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Kenichi Yoshida[1,7], Kate H. C. Gowers[2,7], Henry Lee-Six[1], Deepak P. Chandrasekharan[2], Tim Coorens[1], Elizabeth F. Maughan[2], Kathryn Beal[1], Andrew Menzies[1], Fraser R. Millar[2], Elizabeth Anderson[1], Sarah E. Clarke[2], Adam Pennycuick[2], Ricky M. Thakrar[2,3], Colin R. Butler[2,3], Nobuyuki Kakiuchi[4], Tomonori Hirano[4], Robert E. Hynds[2,5], Michael R. Stratton[1], Iñigo Martincorena[1], Sam M. Janes[2,3,8*] & Peter J. Campbell[1,6,8*]

"Tobacco smoking increases mutational burden, cell-to-cell heterogeneity and driver mutations, but quitting promotes replenishment of the bronchial epithelium from mitotically quiescent cells that have avoided tobacco mutagenesis".

- *This process seems also valid for radon.*
- *It does <u>not seem valid</u> for gamma radiation, perhaps due to the high penetration power and lack of cells that have avoided mutagenesis.*

The effect of radioactive iodine on the incidence of thyroid cancer after the Fukushima nuclear accident

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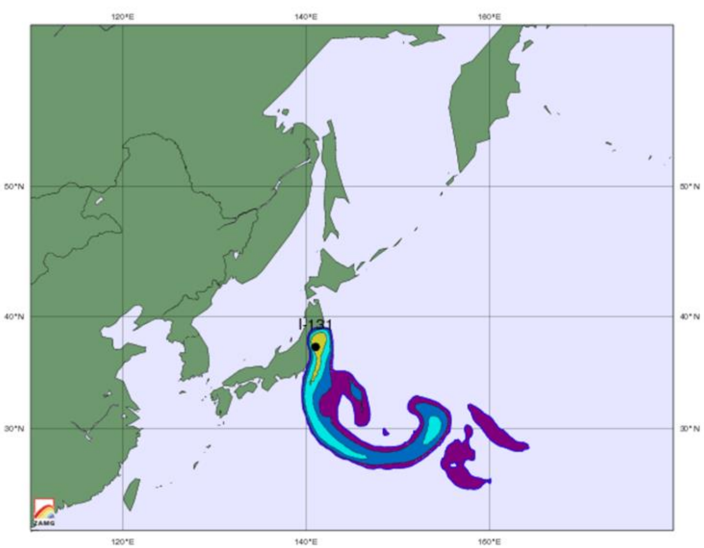
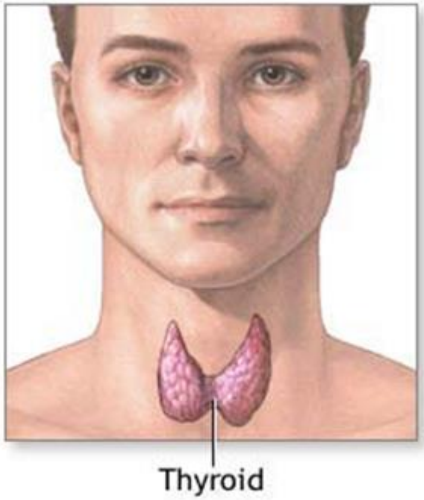
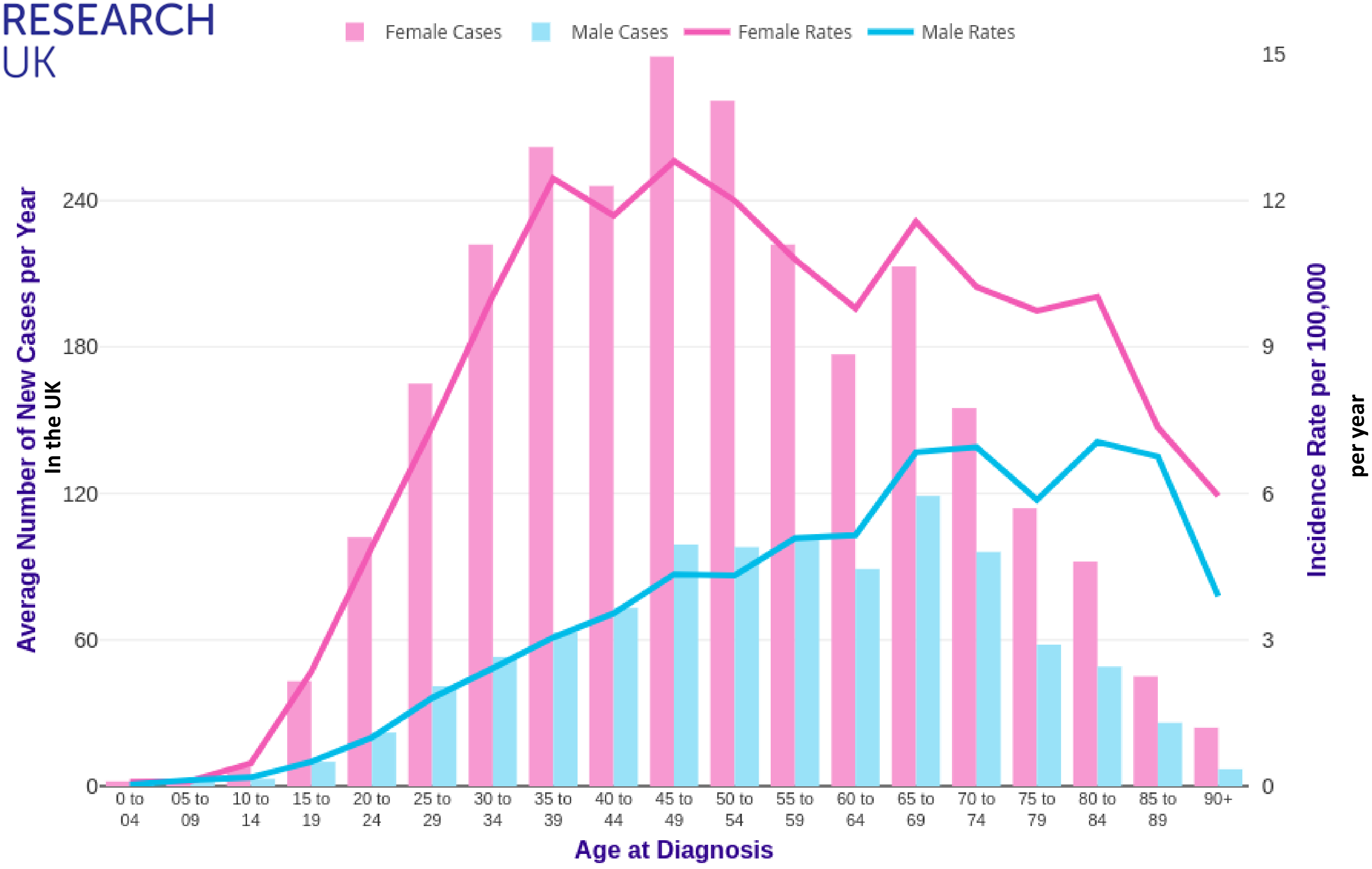
11 March 2011
Fukushima Daiichi accident



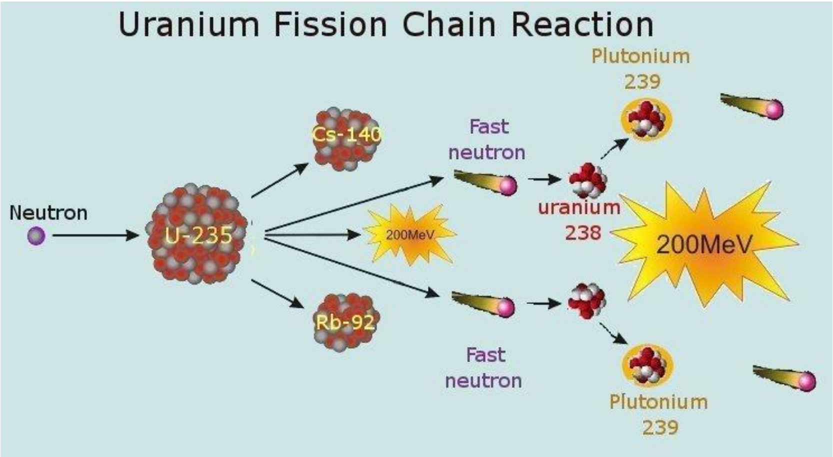


Incidence of thyroid cancer as a function of age and sex

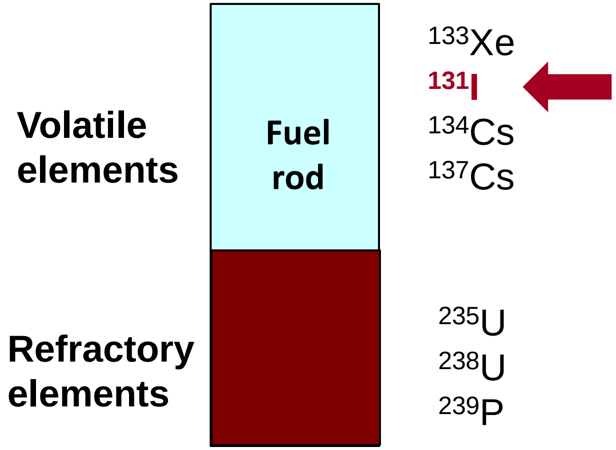
CANCER RESEARCH UK



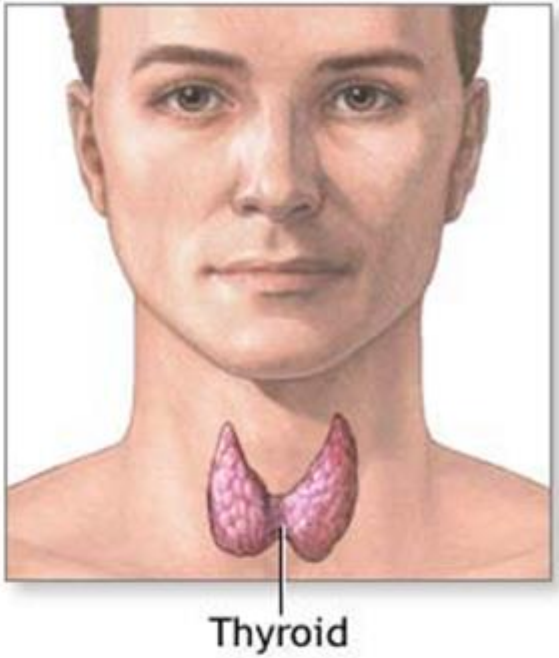
Why is radioactive iodine released in a nucler accident?



In case of a reactor core meltdown, volatile elements will be released from fuel rods



^{131}I can accumulate in the thyroid gland



- The thyroid gland uses iodine to synthetize the hormone thyroxine.
- ^{131}I is taken up by the thyroid gland in people who suffer from iodine deficiency.
- ^{131}I uptake in children increases the risk of thyroid cancer in a dose-dependent manner.

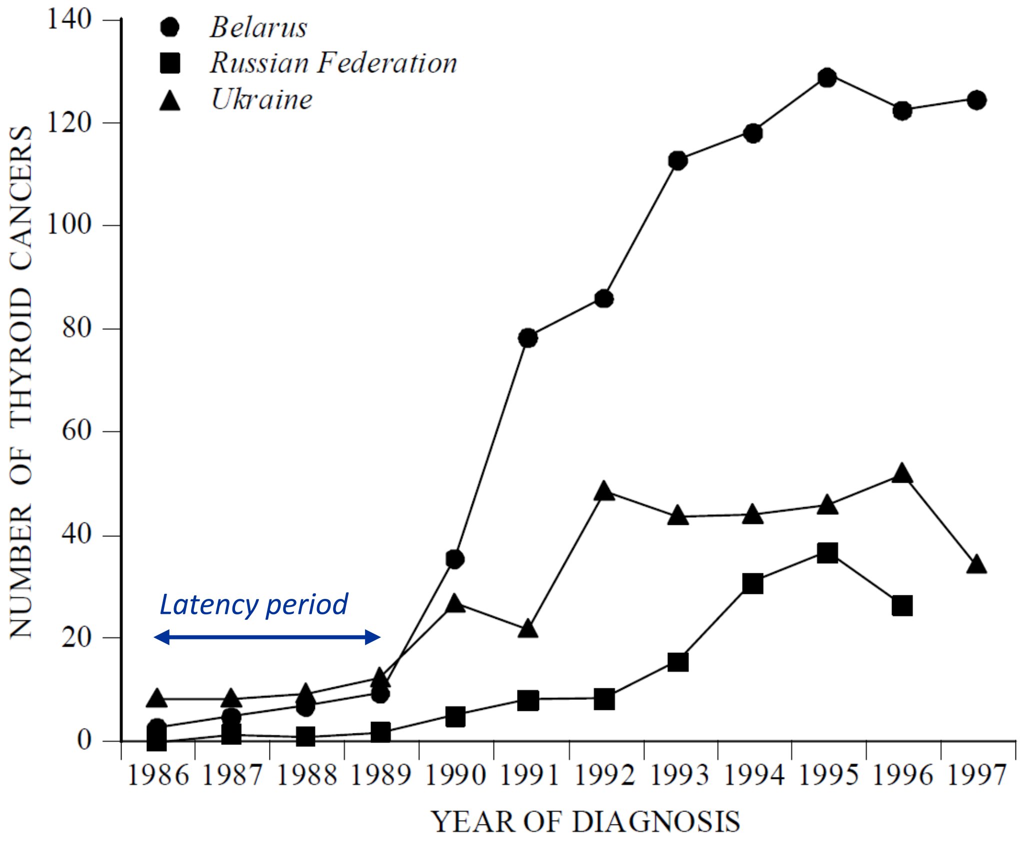
A lot of ^{131}I was released after the Chernobyl accident on 26 April 1987

^{131}I activity released:
1760 PBq = 1.76 x 10^{18} Bq

- 1 Bq: 1 radioactive decay per second
- ^{131}I has a half-life of ca 8 days and disintegrates into Xe emitting beta radiation
- After ca 10 half-times (80 days) all ^{131}I has decayed

Incidence of thyroid cancer after the Chernobyl accident

Number of thyroid cancers in children exposed before the age of 14 years as a result of the Chernobyl accident



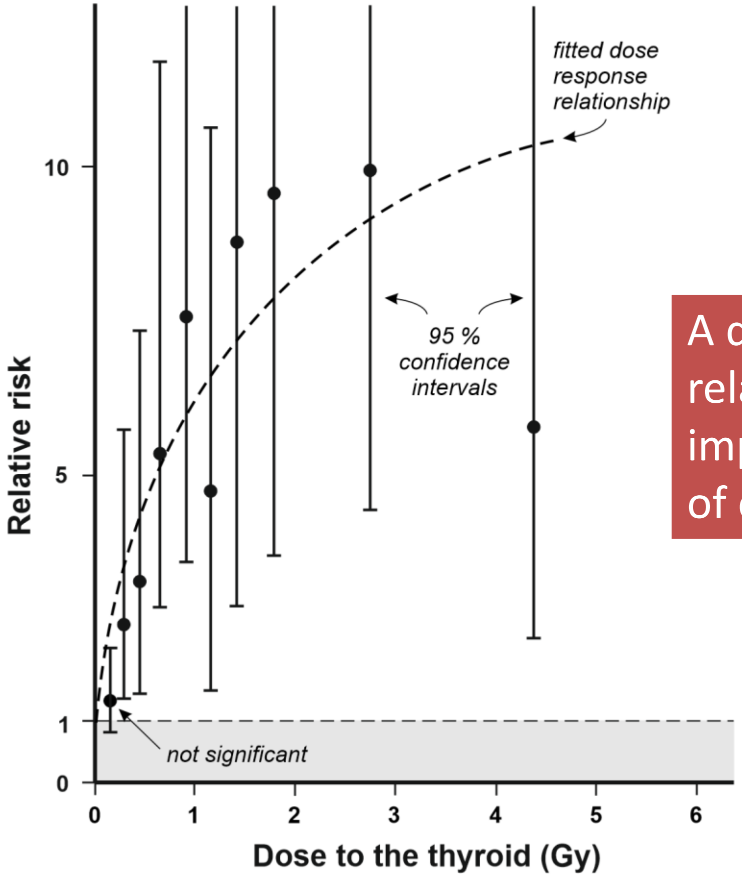
UNSCEAR 2000 Report Annex J: Exposures and effects of the Chernobyl accident

Doses to the thyroid gland and thyroid cancer dose response among the population of Russia, Ukraine and Belarus exposed to ^{131}I

Dosimetric measurements were carried out on a large scale

E. Cardis et al. Risk of Thyroid Cancer After Exposure to ^{131}I in Childhood. J Natl Cancer Inst 97:724 – 32, 2005

Dose response for risk of thyroid cancer could be established thanks to measurements



A dose response relationship is an important indicator of causality

Relative risk

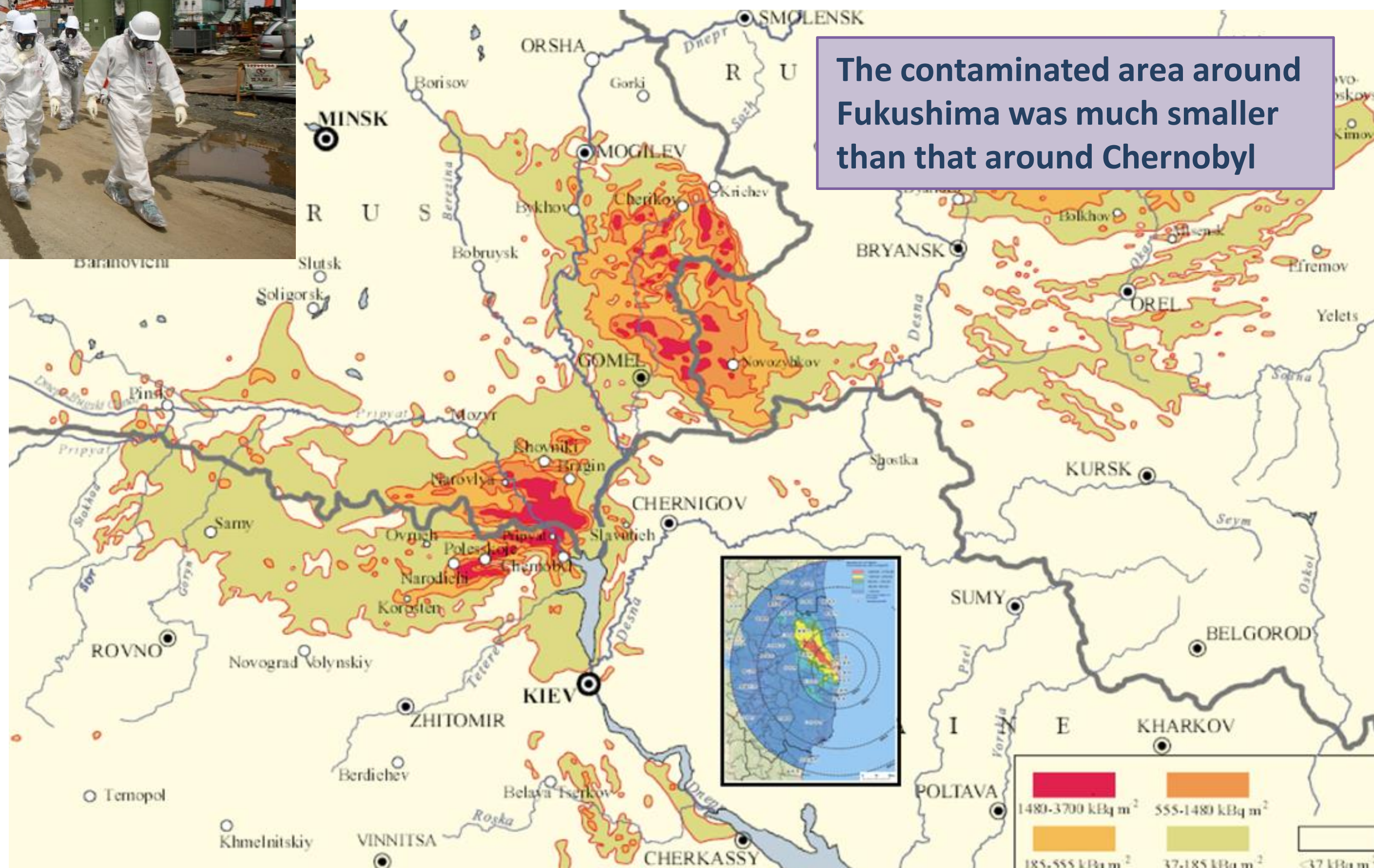
$$\frac{\text{Cases in exposed group}}{\text{Cases in control group}} \pm 95\%\ \text{CI}$$

^{131}I was also released after the Fukushima Daiichi accident on 11 March 2011

^{131}I activity released:

124 PBq = 1.24×10^{17} Bq

- This is 7% of the activity released by Chernobyl



The contaminated area around Fukushima was much smaller than that around Chernobyl

Sources: UNSCEAR 2000 J (Chernobyl), WHO 2012 (Fukushima)

Experts predicted that the thyroid cancer incidence attributable to the ^{131}I uptake would be very low

2013

World Health Organization

"The values presented in the report should be regarded as inferences of the magnitude of the health risks, rather than as precise predictions"

Doses to the thyroids were not measured because the Japanese government did not want to spread fear…

Estimated thyroid doses for children and infants were calculated based on the contamination of land with Cs-137
High contaminated area: ca 5-100 mGy
Middle contaminated area: ca 3-5 mGy
Low contaminated area: < ca 3 mGy

The population of the whole Fukushima prefecture is ca 2 million. Thyroid cancers attributed to ^{131}I will not be detectable.

But people were scared…

To calm people, the Fukushima government started the Fukushima Health Management Survey in late 2011

The survey started in late 2011 and is conducted by the Fukushima Medical University.

Its primary purpose is monitoring the long-term health of residents, promoting their future wellbeing and determining whether long-term low-dose radiation exposure has health effects.

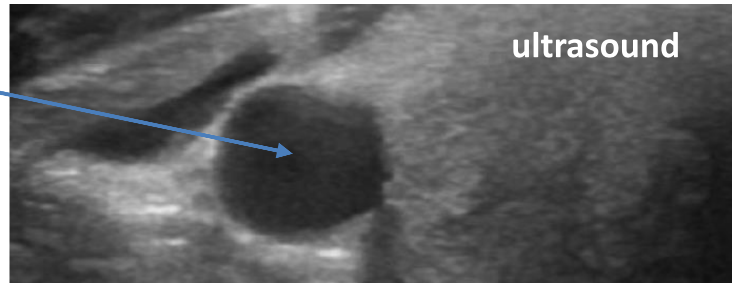
The survey includes a thyroid ultrasound screening examination (residents between 0 and 18 years).
The chronology:

- 2011-2013 base line measurements
- Thereafter every 2 years until age 20
- Thereafter every 5 years

Thyroid screening has never been conducted in Japan before so no reference results existed

The screening for thyroid cancer in the Fukushima prefecture – diagnostic criteria

cyst



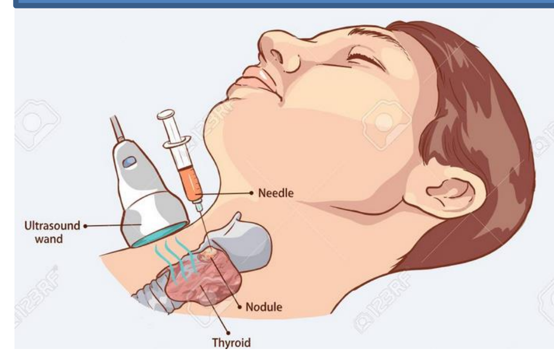
Category	Diagnosis
A1	no nodules or cysts
A2	nodules smaller than 5.0 mm and/or cysts smaller than 20 mm
B	nodules larger than 5.1 mm and/or cysts larger than 20.1 mm
C	large or suspicious thyroid tumour/lymph node

Normal thyroid ← A1

Thyroid abnormalities that may lead to cancer development ← A2, B

Indication of existing cancer ← C

Fine needle aspiration



C → Fine needle aspiration cytology (FNAC)

Positive FNAC → Surgical treatment

S. Suzuki. Childhood and Adolescent Thyroid Cancer in Fukushima after the Fukushima Daiichi Nuclear Power Plant Accident: 5 Years On. Clinical Oncology 28:263-271, 2016.

Let us take a break and talk about early cancer diagnosis and treatment success

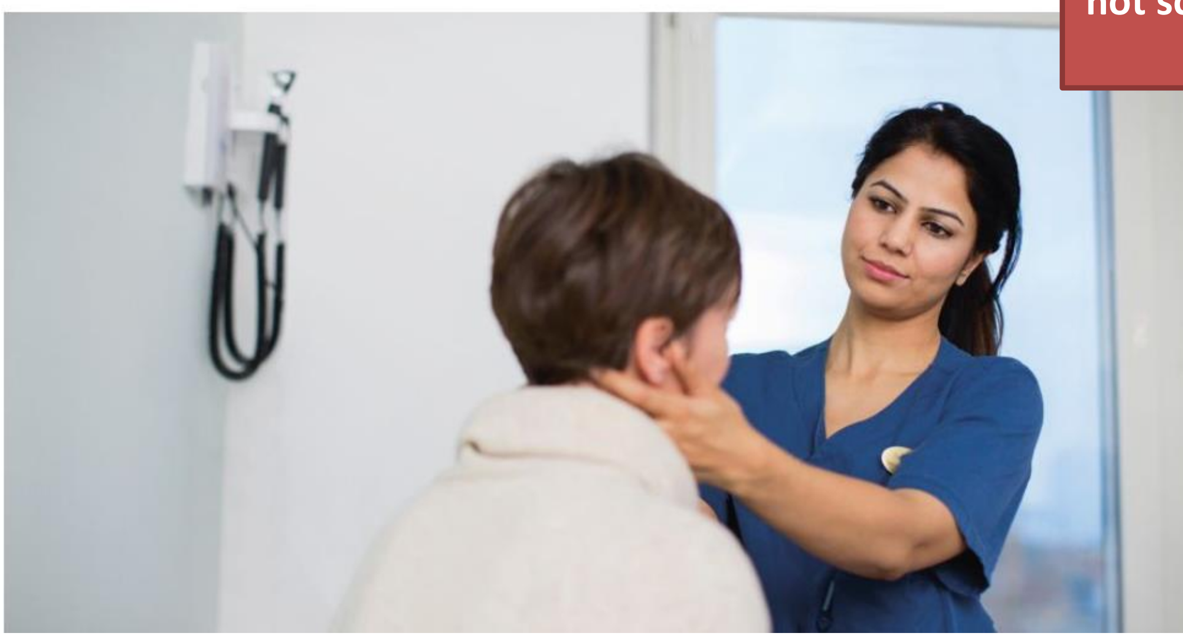
CANCERFONDEN

Tidig upptäckt räddar liv

8 oktober 2020

Överlevnaden ökar dramatiskt vid många cancerformer om symtomen upptäcks tidigt. Men trots att över 70 procent av cancerdiagnoserna upptäcks på vårdcentralen har forskning och utbildning låg prioritet i primärvården.

If early diagnosis is so important – why not screen the population for early stage cancer?



Early diagnosis and screening

Early diagnosis of cancer

Early diagnosis refers to investigation at first signs of disease.

Screening

Screening refers to the use of simple tests across a healthy population to identify those individuals who have a disease, but do not yet have symptoms.

World Health Organization
REGIONAL OFFICE FOR Europe

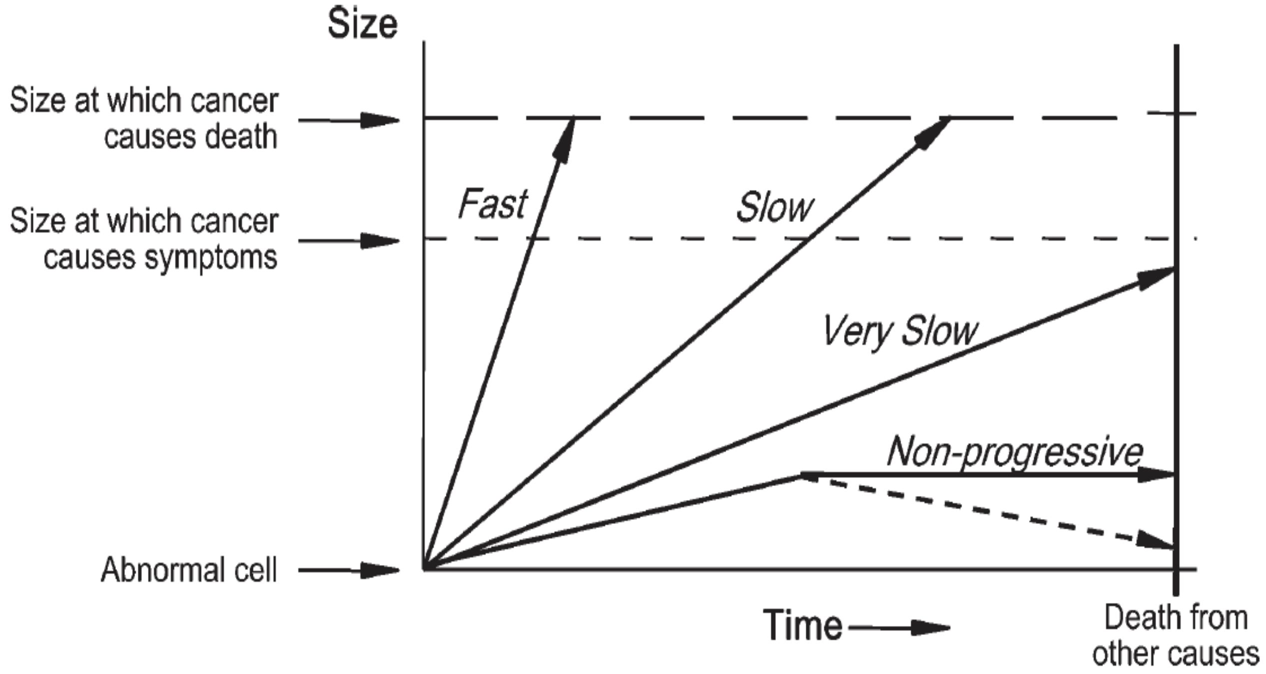
WHO does not recommend general screening programs
Why not?

Overdiagnosis: when finding cancer can do more harm than good

A major problem with screening is that it can lead to overdiagnosis

and unnecessary treatment that injures the patient.

Heterogeneity of cancer progression. Some cancer may never become manifest

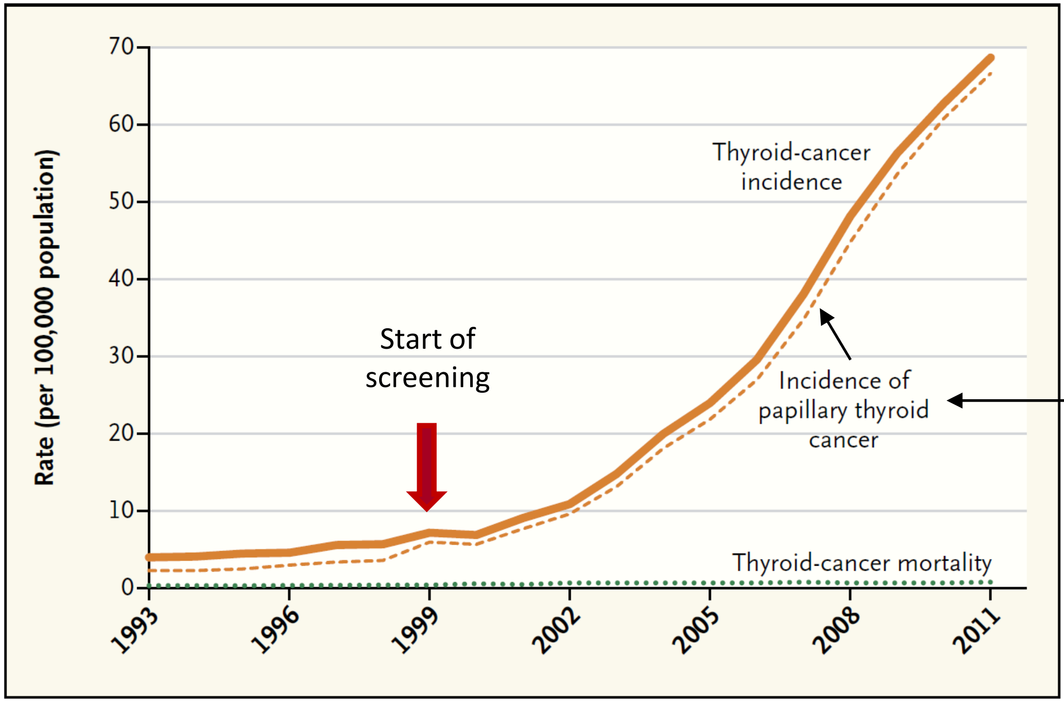


Source: H.G. Welch et al. Overdiagnosis in Cancer. JNCI 102(9), 2010.

The national screening program in South Korea: cancer incidence and mortality

In 1999, the Korean government initiated a national screening program for cancer and other common diseases. This program provides screening for breast, cervical, colon, gastric, hepatic and thyroid cancer.

Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011



The most common type

By 2014 thyroid cancer was the most common cancer diagnosed in South Korea leading to a surge of surgery.

Source: H.S. Ahn et al. Korea's Thyroid-Cancer "Epidemic" — Screening and Overdiagnosis. N Eng J Med 371, 2014.

The screening for thyroid cancer in the Fukushima prefecture: the 2011-2013 baseline results

Baseline screening carried out in **ca 300 000** youths

Category	Baseline investigation
A1	51%
A2	48%
B	1%
C	< 1%
FNAC positive	113

Normal thyroid ← A1

Thyroid abnormalities that may lead to cancer development ← A2, B

Indication of existing cancer ← C

FNAC positive → **386 cancer cases per 1 million = prevalence**

Prevalence: number of people ill at a given moment

Incidence: number of new disease cases per time (e.g. year)

The screening for thyroid cancer in the Fukushima prefecture – the 2011-2014 baseline results and interpretation by Tsuda et al.

Category	Baseline investigation
A1	51%
A2	48%
B	1%
C	< 1%
FNAC positive	113

Thyroid Cancer Detection by Ultrasound Among Residents Ages 18 Years and Younger in Fukushima, Japan: 2011 to 2014

Toshihide Tsuda,[a] Akiko Tokinobu,[b] Eiji Yamamoto,[c] and Etsuji Suzuki[b]

(*Epidemiology* 2016;27: 316–322)

→ **386 cancer cases per 1 million = prevalence in the year 2013**

In overall Japan the **incidence** (number of diseased per year) of thyroid cancer in youths is ca 3 per million. Prevalence is not calculated because thyroid cancer is quickly treated.

Because radiation-induced thyroid cancer has a latency period of ca 4 years, Tsuda et al. divided 386 (**prevalence**) by 4 to calculate **incidence** and compare with overall Japan.

$$\frac{386}{4} = 96.5$$ which is ca **30 times higher than 3**

Conclusion of the Tsuda study: ^{131}I is a much stronger inducer of thyroid cancer then previously assumed. The current radiation protection assumptions are wrong.

The reactions to the Tsuda paper were strong

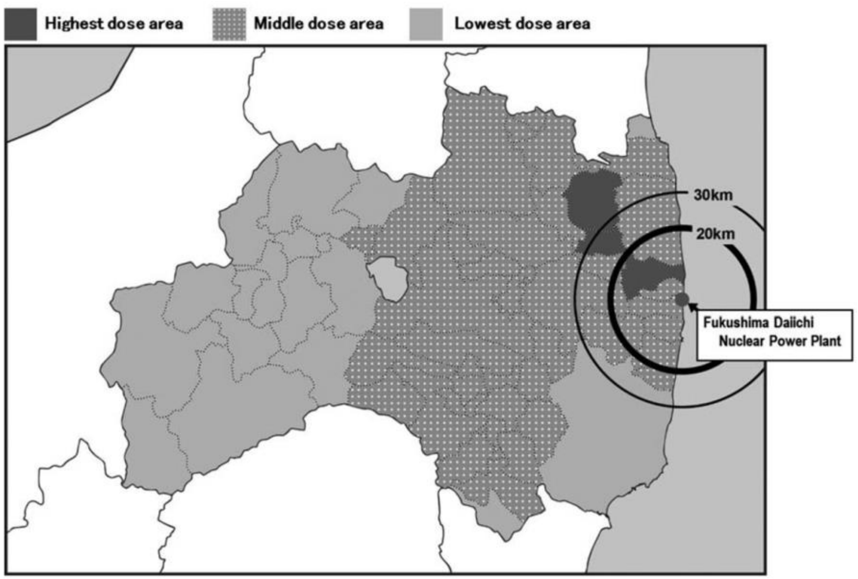
In Iwaki, a town south of the Fukushima nuclear plant, a doctor conducts a thyroid examination on 4-year-old Maria Sakamoto. Scientists are puzzled over a high number of thyroid abnormalities observed so soon after the accident. © Toru Hanai/Reuters

Mystery cancers are cropping up in children in aftermath of Fukushima

By Dennis Normile | Mar. 4, 2016 , 10:45 AM

Validation of the Tsuda conclusions
Is there a dose-response relationship for thyroid cancer?

Geographic details of the highest dose area, middle dose area, lowest dose area, and the Fukushima Daiichi Nuclear Power Plant.



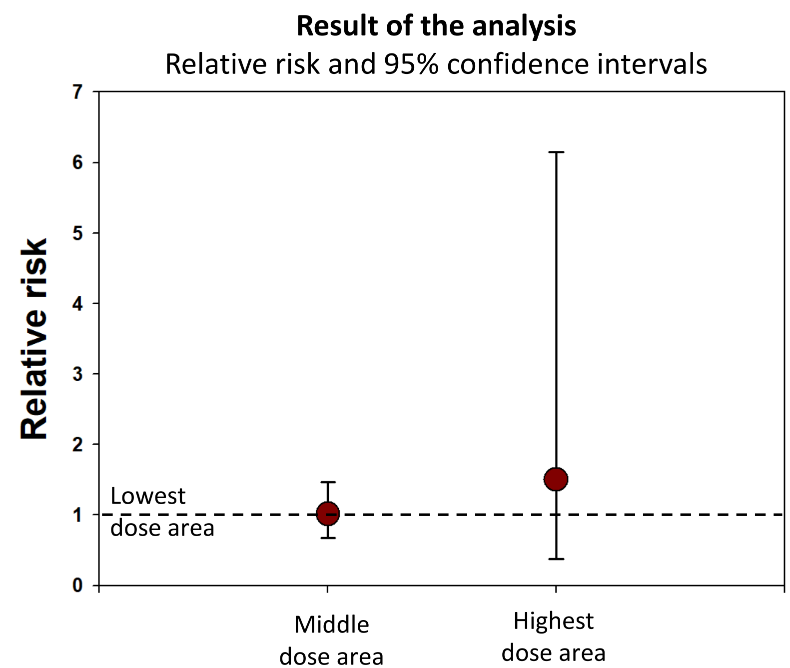
Highest. More than 1% of people received ≥5 mGy
Middle. Less than 1% of people received ≥5 mGy
Lowest. 99.9 % of people received < 1 mGy = **reference**

Comparison of childhood thyroid cancer prevalence among 3 areas based on external radiation dose after the Fukushima Daiichi nuclear power plant accident

The Fukushima health management survey

Tetsuya Ohira, MD, PhD[a,b,*], Hideto Takahashi, PhD[a], Seiji Yasumura, MD, PhD[a,c], Akira Ohtsuru, MD, PhD[a,d],

Medicine (2016) 95:35(e4472)



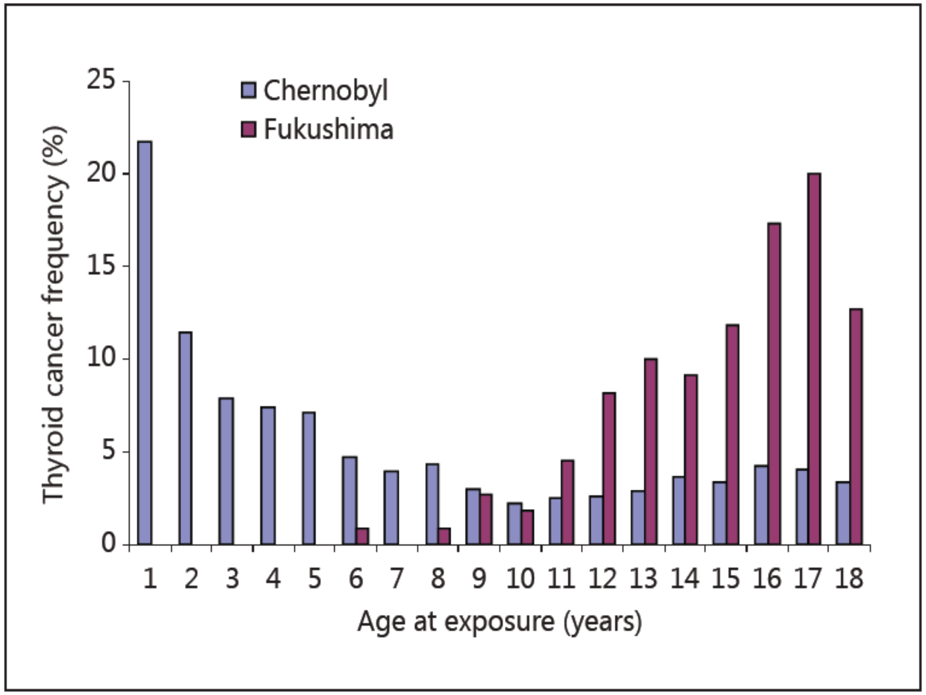
Conclusion of the Ohira study: there is no dose-response for ^{131}I-induced thyroid cancers, so the results of Tsuda et al. are due to screening.

Validation of the Tsuda conclusions: is there a negative correlation between age at exposure and thyroid cancer incidence?

Thyroid cancer frequency (percentage distribution) by age at exposure to fallout from Chernobyl and in the first 3 years after Fukushima.

Thyroid Growth and Cancer

Dillwyn Williams   Eur Thyroid J 2015;4:164–173



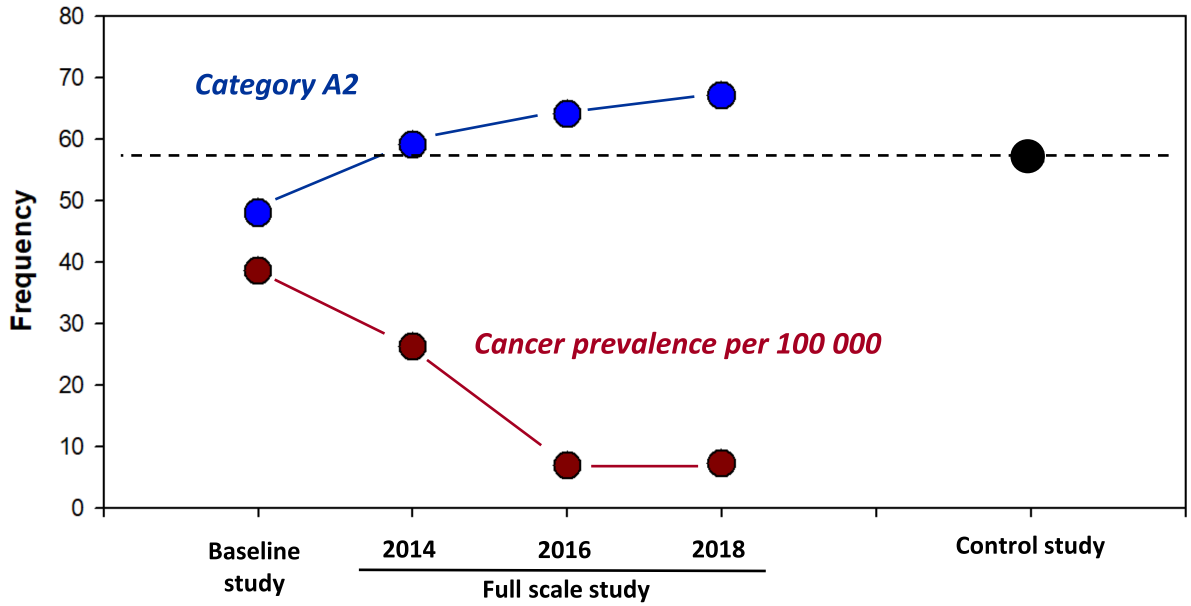
The Chernobyl age distribution shows that the risk of ^{131}I-induced cancers decreases with age at exposure. The Fukushima distribution shows that the risk increases with age at exposure.

Conclusion of the Williams study: The risk of thyroid cancer among the Fukushima youths increased with age at exposure which is to be expected for spontaneous cancers. Therefore, the results of Tsuda et al. are due to screening.

The screening for thyroid cancer in the Fukushima prefecture – the follow-up results

Category	Baseline study 2011-2013	Full scale study 2014-2015	Full scale study 2016-2017	Full scale study 2018-2019	Control study
A1	51%	40%	35%	32%	42%
A2	48%	59%	64%	67%	57%
B	1%	1%	1	1%	1%
C	< 1%	< 1%	< 1%	< 1%	< 1%
Cancer prevalence	386	262	69	71	Not carried out

Carried out in non-contaminated area in Japan



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