Potential risks of «low» radiation doses for the patients and the public

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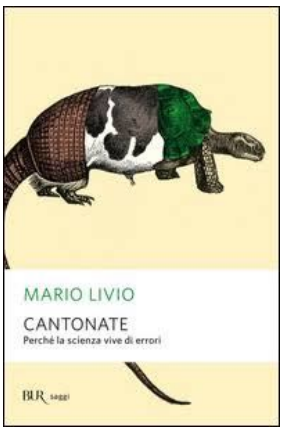
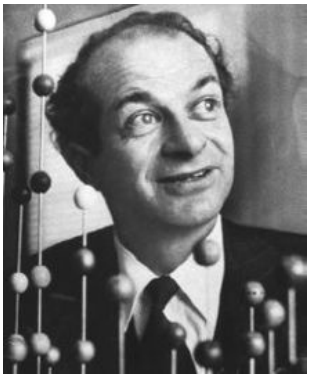
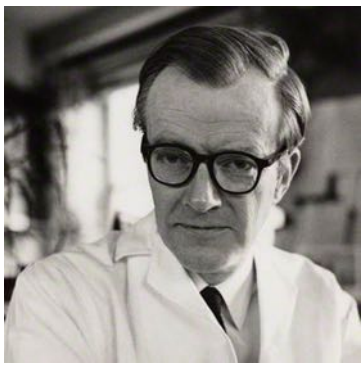
Associazione Italiana di Radioterapia Oncologica



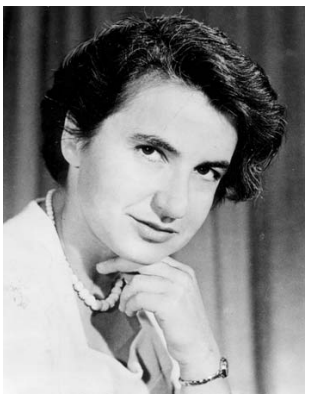


Linus Pauling



Maurice Wilkins

James Dewey Watson Francis Crick

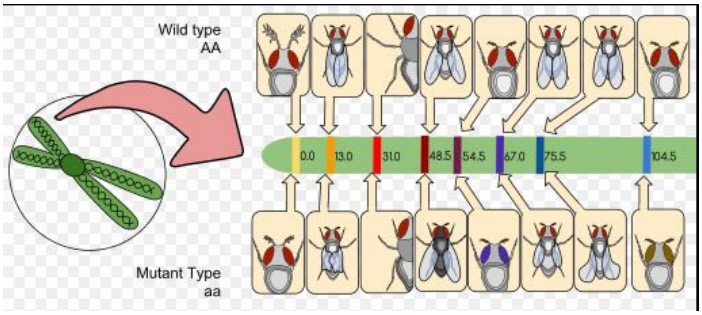


Rosalind Elsie Franklin

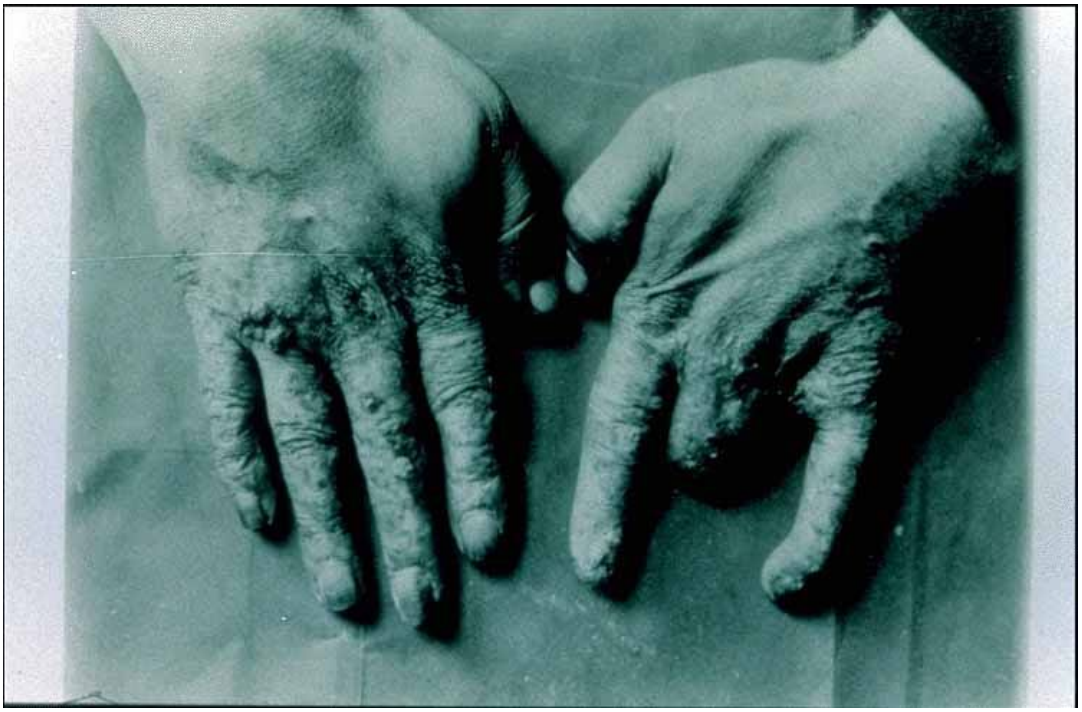
Hermann J. Muller (1890-1967), Nobel Prize in 1946 for Medicine

He was at Columbia where he spent time in T.H. Morgan's Drosophila laboratory. Muller joined other students in stealing small milk bottles from apartment steps to house the flies.

In 1927, Muller realized his research showing that X-rays could induce mutations.



Muller's discovery created a media sensation after he delivered a paper entitled **"The Problem of Genetic Modification"** at the Fifth International Congress of Genetics in Berlin; it would make him one of the better known public intellectuals of the early 20th century…. ***In the following years, he began publicizing the likely dangers of radiation exposure in humans .***



The Nobel Prize in Physiology or Medicine 1946
Hermann J. Muller

In his **Nobel Prize Lecture** **of December 12, 1946**, Hermann J. Muller **argued that the dose–response for radiation-induced germ cell mutations was linear and that there was "no escape from the conclusion that there is no threshold"**.

However, assessment of **correspondence between Muller and Curt Stern one month prior** to his Nobel Prize Lecture reveals that Muller knew the results and implications of a recently completed study at the University of Rochester under the direction of Stern, which **directly contradicted his Nobel Prize Lecture**.

This finding is of historical importance since **Muller's Nobel Lecture gained considerable international attention and is a turning point in the acceptance of the linearity model in risk assessment for germ cell mutations and carcinogens**.

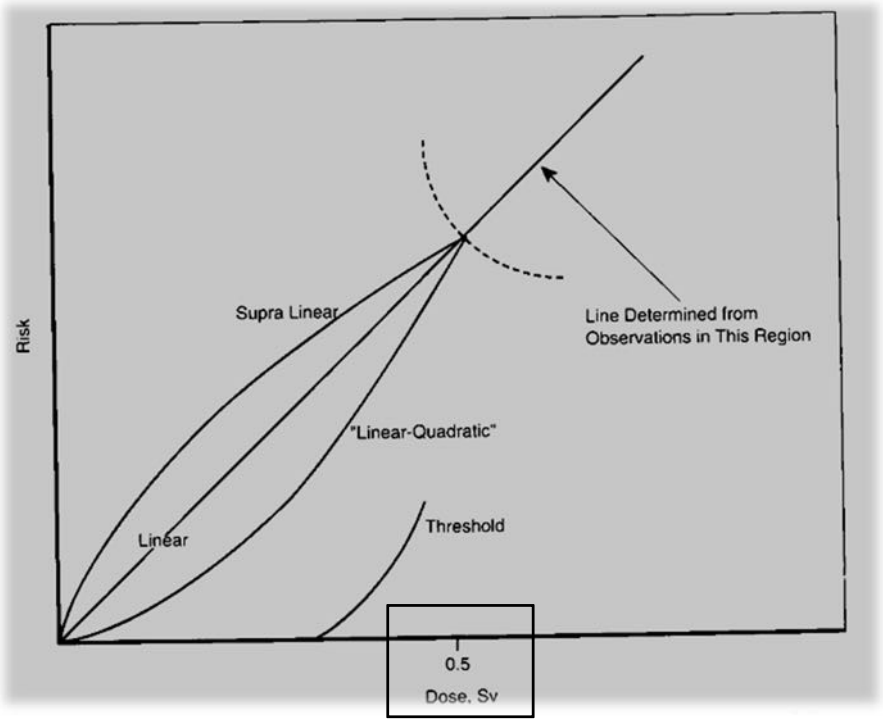
Edward J.Calabrese, Arch Toxicol (2011) 85:1495–1498

A treshold at about 50 cGy……?

- ✓ Spencer and Stern (1948): in the **25-50 cGy range** , «control mutations may equal or exceed in number those produced by radiation..»;
- ✓ Uphoff and Stern (1949) compared the frequency of mutations in exposed (**50 cGy**) and non-exposed Drosophila and observed a significant increase in non-exposed individuals ranging from 0.077 to 0.1 along with an increasing dose rate;
- ✓ Caspari and Stern (1948) data with the lower dose rate showed a smaller nonsignificant difference in mutation frequency (0.035).

These data were largely ignored by the scientific debate on low doses…

The shape matters…. For «low» doses



The Nobel Prize, in the wake of the atomic bombings of Hiroshima and Nagasaki, focused public attention on the dangers of radiation. **In 1952, nuclear fallout became a public issue; more and more evidence had been leaking out about radiation sickness and death caused by nuclear testing**, and Muller pursued an array of political activities to defuse the threat of nuclear war.

"Those fears were given greater intensity and perhaps greater legitimacy by the fallout controversy of the late 1950s and early 1960s. ***The fallout debate called sustained attention to the risks of exposure to low-level radiation for the general population more than any previous treatment of the subject****. It made radiation safety a bitterly contested political issue for the first time and it fueled already growing public apprehension of exposure."*

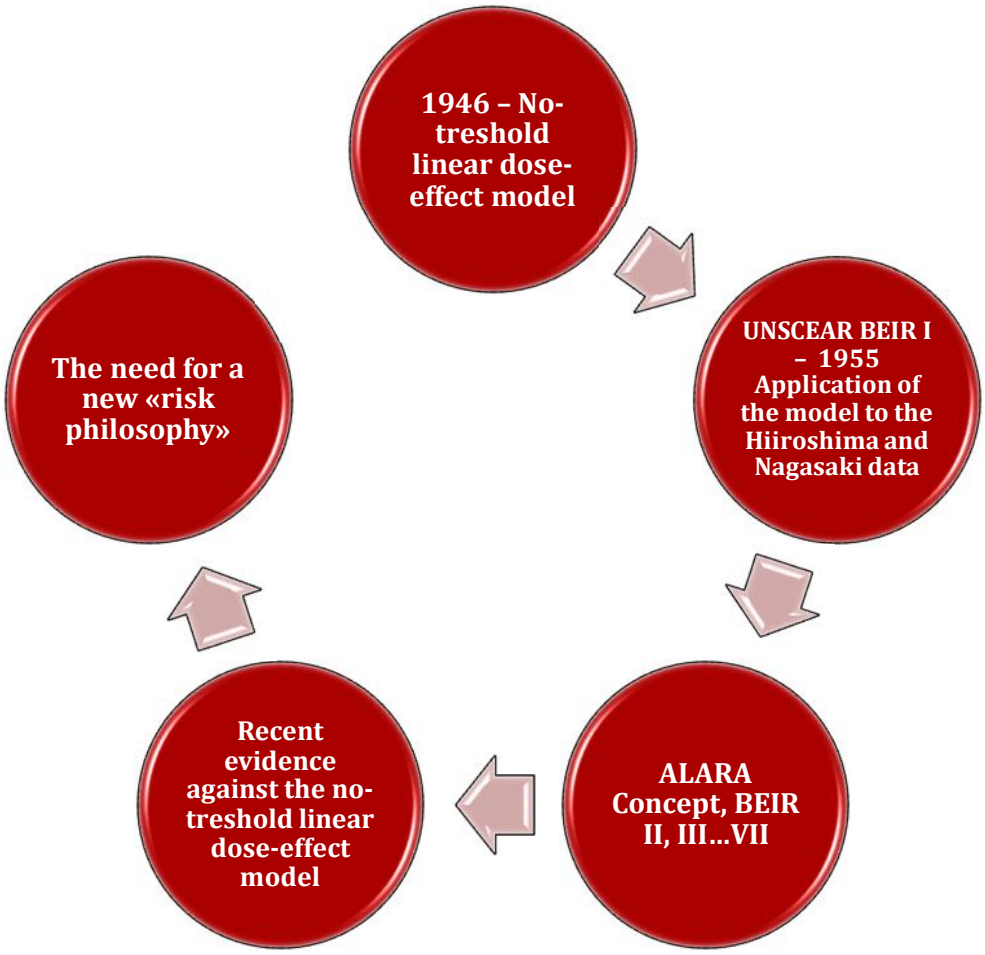
J. Samuel Walker - Permissible Dose: History of Radiation Protection in the Twentieth Century, University of California Press, Nov 2000.

SCIENTISTS TERM RADIATION A PERIL TO FUTURE OF MAN

Even Small Dose Can Prove Harmful to Descendants of Victim, Report States

A SAFETY LIMIT IS URGED

From front page of June 13, 1956 New York Times. Right column headline.



Low doses, very serious effects?

Second Tumors…..

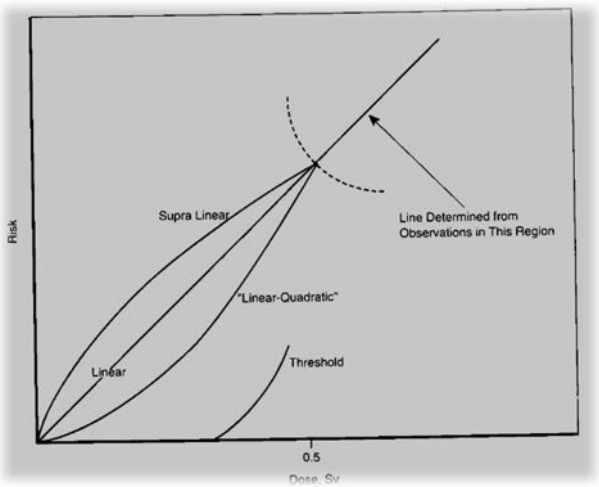
Inherited genetic effects…

Second tumors after radiation exposure have been the subject of a vast amount of scientific contributions…

Yet, the issue is largely an unresolved one … and it is charged with a strong "emotional" content.

The consequences of under- or overestimating this problem may be equally dangerous and costly.

One of the most interesting issues is the relation of low radiation dose to carcinogenesis. However, most of the data we have are related to relatively high doses, even if the concerns of the public are focused on exposure to relatively low doses.



Second tumors

Definition: The occurrence of two primary malignancies in the same individual

"Second" tumors can develop after or at the same time of the first one and for this reason we can classificate them into:

Metachronous **Synchronous**

The metachronous tumors

A metachronous tumor is usually defined as a second neoplasm:

- with histology different from that the first tumor or
- having the same hystology of the first tumor but arised after a time interval of more than 2 years
- with a different anatomic localization

Second cancers may have several causes

- ✓ They may represent a chance occurrence (in which case the two cancers developed as a result of unrelated factors)
- ✓ They may be linked to carcinogenic influences in common with the "first" tumor
- ✓ They may result from host susceptibily factors such as a genetic predisposition or immunodeficiency
- ✓ They may represent an effect of the treatment of the first tumor

Examples of factors acting as cancer initiators and/or promoters

Alkylating agents	Acute myelocytic leukemia, bladder ca
Epstein-Barr virus	Burkitt' s lymphoma, nasal T cell lymph.
Estrogens	Cancer of the endometrium, breast, liver
Ethyl alcohol	Cancer of the liver, esophagus, head and neck
HIV virus	Non Hodgkin's Lymphoma, Kaposi's sarcoma, squamous cell carcinomas
Phenacetin	Cancer of the renal pelvis and bladder
Polycyclic hydrocarbons	Cancer of the lung, skin
Papilloma virus	Uterine cervix cancer, oropharyngeal ca.
Tobacco	Cancer of the upper aerodigestive tract, bladder

The genetic predisposition

Cancer is a genetic disease because of alterations in DNA that result in unrestrained cellular proliferation. While virtually all cancer is genetic, most cancer is not inherited.

Nevertheless, certain individuals with cancer have inherited a germline mutation that predisposes them to cancer (but even in that situation additional somatic mutations are often required for a tumor to develop).

General classes of cancer genes

- ✓ Protooncogenes and oncogenes: genes that promote normal cell growth
- ✓ Tumor suppressors: genes that normally restrain cell growth
- ✓ DNA repair genes: genes that protect the integrity of genome from DNA polymerase errors and environmental influences that can damage DNA

Examples of inherited cancers with the involved tumor suppressor gene (TSG)

SYNDROME	T.S.G.	CHROMOSOME LOCATION	TUMORS
Basal cell nevus	**PTC**	9q22.3	Basal cell cancer, jaw cist, medfulloblastoma
Familial breast/ovarian cancer	**BRCA1**	17q21	Breast, ovaria, colon, prostate cancer
Familial breast cancer	**BRCA2**	13q12-13	Breast cancer, male breast cancer
Familial melanoma	**P16**	9p21	Melanoma, pancreatic cancer
Familial polyposis coli	**APC**	5q21	Intestinal polyposis, colorectal cancer
Familial retinoblastoma	**RB**	13q24	Retinoblastoma, osteosarcoma
Familial Wilms tumor	**WT1**	11p13	Wilms'tumor, aniridia, genitourinary abnormalities mental retardation
Hereditary multiple exostoses	**EXT1**	11p11-13	Exostoses, chondrosarcoma
Li-Fraumeni	**P53**	17q13	Sarcomas, breast cancer
Neurofibromatosis I	**NF1**	17q11.2	Neurofibroma, neurofibrosarcoma, brain tumor
Neurofibromatosis II	**NF2**	22q12	Acoustic neuroma, meningioma
Tuberous sclerosis	**TSC2**	16p13.3	Angiofibroma, renal angiomyolipoma
Von Hippel Lindau	**VHL**	3p25-26	Renal cell cancer, pheochromocytoma, retinal angioma, hemangioblastoma

Chemotherapy induced second primary tumors

The carcinogenic potential of chemotherapy was recognized much later than that of ionizing radiation, because chemotherapeutic agents were not introduced in cancer treatment until the late 1940s and modern multiagent combination chemotherapy, which is now known to have the strongest carcinogenic potential, was not used until the 1960s.

One of the malignancies associated with chemotherapy (CHT) is acute myeloid leukemia. There are at least two different types of CHT related leukemia

Classic alkylating agents induced AML

AML related to topoisomerase II inhibitors

Both these leukemia forms are almost unresponsive to treatment and there are no prevention strategies

More than 50% of leukemias following CHT present initially as myelodysplasia (MDS), whereas *de novo* AML is preceded by MDS much less frequently.

In summary, CHT-induced leukemias are partially distinguishable from those "spontaneously" occurring.

Chemotherapeutic agents may also induce solid tumors,such as lung, bladder, breast cancer or non-Hodgkin lymphomas.

The susceptibility to chemotherapeutic drugs can be favoured by factors such as:

- Polymorphism in drug metabolizing genes (including cytochrome P-450 enzyme, glutathione S-transferases etc.)
- Interindividual differences in repair of DNA damage
- Germ line mutations in tumor suppressor genes
- Administration of concomitant medications
- Interpatients variation in renal and hepatic function
- Interindividual differences in drug absorbtion, distribution, metabolism and excretion

Radiation induced second primary tumors

Ionizing radiations may also have a carcinogenic potential.

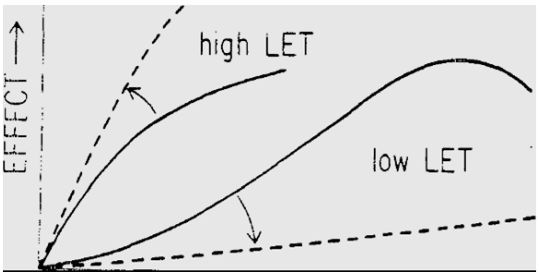
Most knowledge about radiation effects in humans has derived from epidemiologic studies of the atomic bomb survivors in Japan, occupationally irradiated workers and patients treated with radiation for malignant and nonmalignant diseases

Several features characterize radiation-induced cancers:

It is not possible to distinguish the tumors possibly caused by radiation, morphologically, from "naturally" occurring cancers.

The risk might vary according to the tissue type. The thyroid gland and breast seem to be at risk for cancer induction at relatively lower doses of radiation.

For many types of neoplasm the incidence reaches a maximum at some intermediate dose of radiation and decreases as the dose is increased further. The **dose effect curve** generally rises more steeply with high-LET radiation than with low-LET, especially at low dose rates (the reduction in radiation dose-response at high doses is consistent with a cell killing effect)



——— high dose rate
- - - - - low dose rate

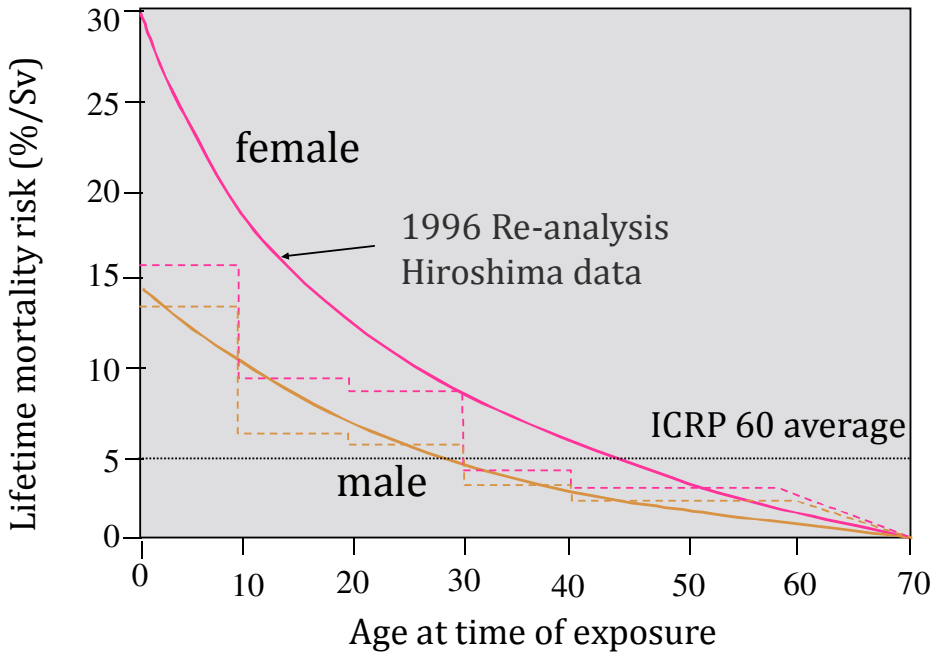
Latent periods for the production of radiation-related tumors vary according to the type of tumor

For example, the risk of leukemia in survivors of the atomic bomb has been higher in the first years after exposure and this has been followed by a gradual decline to baseline levels.

For solid tumors, an increase in the relative risk of second malignant neoplasm has been observed mainly after many years after exposure, remaining then constant over time.

Age is a very relevant factor in determining a radiation risk. In children, second cancer would be more likely to occur in tissue undergoing rapid proliferation such as thyroid tissue. On the contrary, aging itself is related with an increased frequency of the most common tumor types.

Age versus Cancer Mortality Risk



Cahan's criteria, used to define a radiation-induced sarcoma in 1948, are considered also nowadays a standard for demonstration of any alleged radiation-induced malignancy (Perez et al., Eds, Principle and Practice of Radiation Oncology, 5° Ed., Philadelphia, 2008):

- A radiation induced malignancy must have arisen in an irradiated field

- A sufficient latent period, preferibly longer than 4 years, must have elapsed between the initial irradiation and the alleged induced malignancy

- The treated tumor must have been biopsied. The alleged induced tumor must have been biopsied. The two tumors must be of different histology

- The tissue in which the alleged induced tumor arose must have been normal prior to radiation exposure

Epidemiological studies mainly devoted to cohorts exposed:

- ✓ after nuclear power plants accidents
- ✓ or in survivors of atomic bombing
- ✓ or in professionally exposed workers

Two main research fields have been explored

Patients treated with radiotherapy

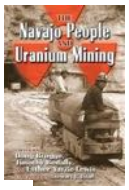
History of Epidemiologic studies:

1950 Radiologists (1900-30)

1950 Radium dial painters (1910-30)

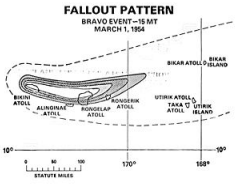
1950 Medical exposures for non malignant illnesses, diagnostic exposures (1920-40)

1950 Hiroshima-Nagasaki survivors (1945)



1960 Miners (uranium) (1940-95)

1970 Population exposed to fallout from atmospheric nuclear weapons(1950-60)



1970 Nuclear workers (1950-)

1980 Population exposed to natural background radiation

1990 Population exposed to releases fromt the Chernobyl accident

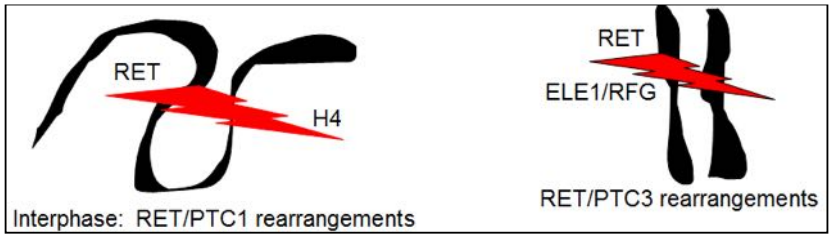
From a WEB contribution of Margot Tirmarche, Head of Laboratory of Epidemiology IRSN -FRANCE

The case of Chernobyl and thyroid cancer: in the Gomel *oblast* (an heavily contaminated area, close to the nuclear plant), incidence rose from 0.1 to 10/100.000 among the exposed children.

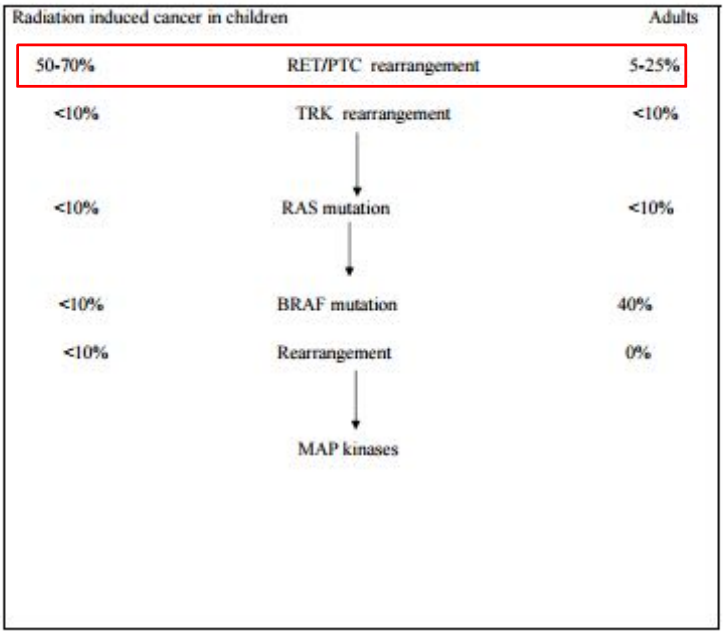
Fagin JA, Nikiforov YE (2006) Radiation-induced thyroid cancer: Lessons from Chernobyl. In: Mazzaferri EL, Harmer C, Mallick UK, Kendall-Taylor P (eds). Practical Management of Thyroid Cancer: A Multidisciplinary Approach. *Springer*, 321–326.

"The RET/PTC oncogene is the genetic hallmark of radiation-induced thyroid cancer."

Genetic analysis of papillary cancers in children exposed to radiation following Chernobyl implicated the *RET* oncogene in the pathogenesis of these tumors

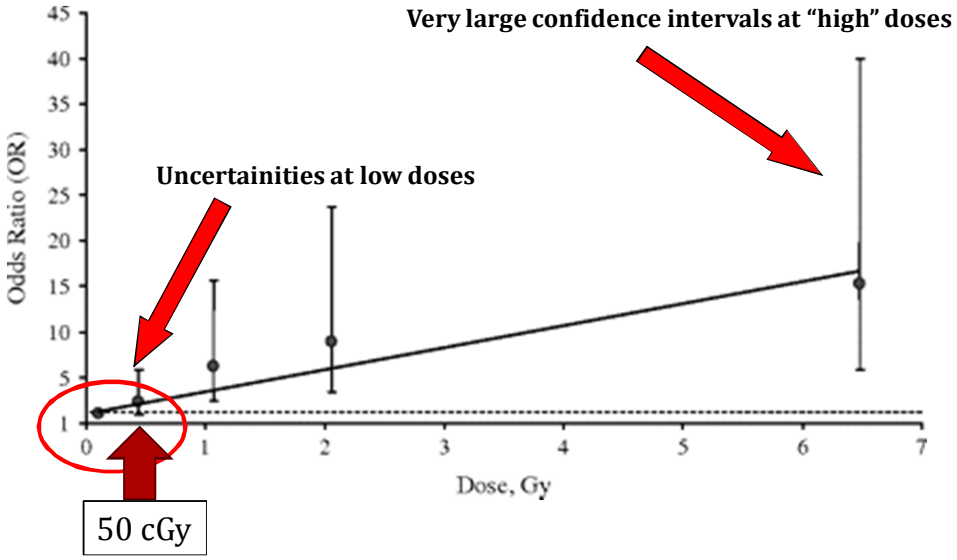


Genetics of Papillary Thyroid Cancer Initiation: Implications for Therapy, Genetics of Papillary Thyroid Cancer Initiation: Implications for Therapy,James A Fagin, Trans Am Clin Climatol Assoc. 2005; 116: 259–271.



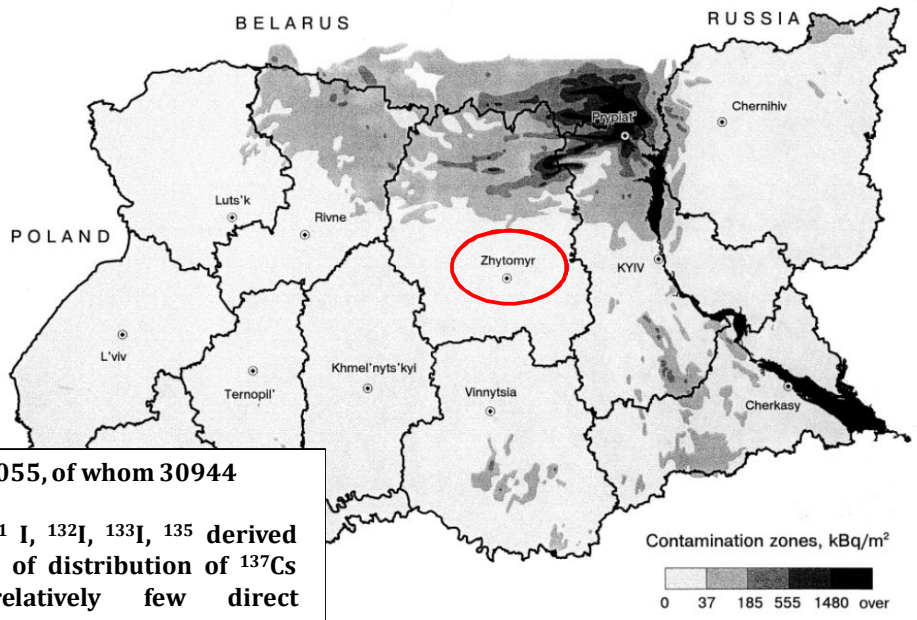
Curr Genomics. 2011 Dec; 12(8): 597–608.

PROBLEMS :



Odds ratios (ORs) and 95 confidence intervals (CI) of thyroid cancer by thyroid dose category among 13.127 subjects exposed to radiation from the Chernobyl accident in Ukraine*

Radiat Environ Biophys (1998) 36: 261–273 © Springer-Verlag 1998
G. M. Goulko · N. I. Chepurny · P. Jacob · I. A. Kairo
I. A. Likhtarev · G. Pröhl · B. G. Sobolev
Thyroid dose and thyroid cancer incidence after the Chernobyl accident:
assessments for the Zhytomyr region (Ukraine)



(for Cesium)

CAUSES:

Inhabitants : 50.055, of whom 30944 < 18 yrs old;
Exposition to ^{131}I, ^{132}I, ^{133}I, ^{135} derived from the maps of distribution of ^{137}Cs and from relatively few direct measurements
Number of thyroid cancers in individuals aged 0-18 at the time of incident: 36 up to 1995

A LOT OF FORMULAS TO COMPENSATE FOR THE PAUCITY OF DATA .....

$$D(\text{age}) = K \cdot a \exp(-b \cdot \text{age})$$

With:

D (age) – mean thyroid dose for a given age (Gy),
K – scaling parameter characterizing the thyroid dose (Gy),
a – parameter giving (together with K) the thyroid dose at age 0 (dimensionless),
b – parameter describing the age dependence of the thyroid dose (year–1)

To approximate the parameters K and a, the sums of different functions of the three parameters (^{137}Cs deposition, direction and distance from Chernobyl) were analysed, and the best correlation was obtained for the following purely empirical expressions:

$$\ln(K) = f0 + f1\,Cs + f2\,r^{-1} + f3\,j$$
$$\ln(a) = f0 + f1\,Cs + f2\,r + f3\,j$$

With:

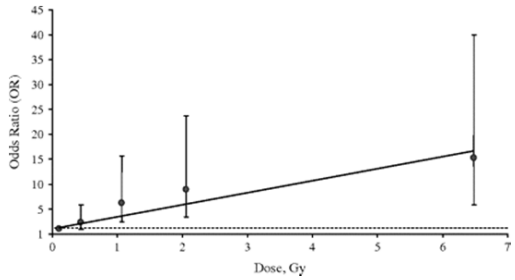
Cs – ^{137}Cs deposition (kBq ·m–2),
r – distance from Chernobyl to the settlement (km),
j – angle in radians between the direction from Chernobyl to the east and between the direction from Chernobyl to the settlement (positive direction is taken from the east to the north).

Therefore:

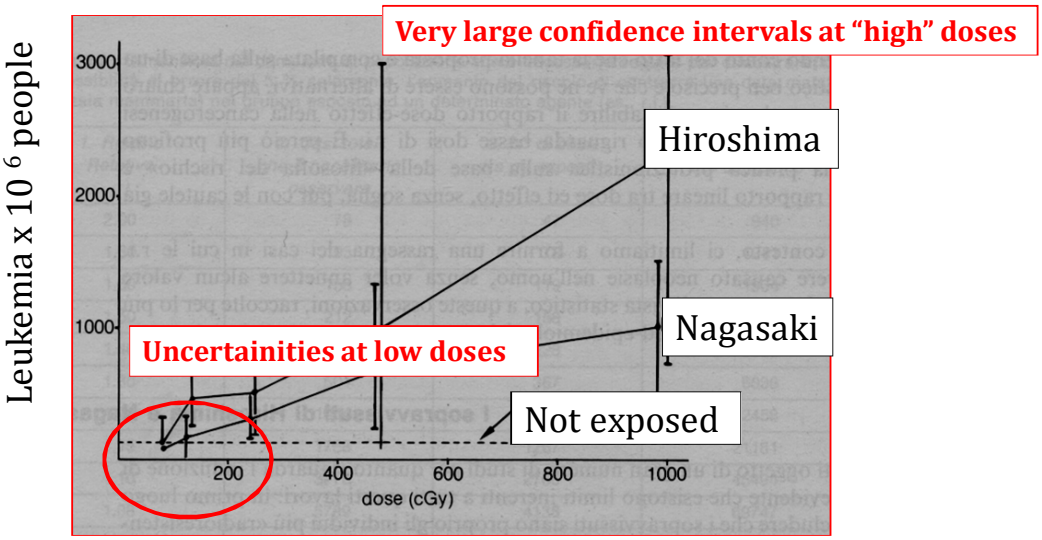
1. Very large population exposed to low doses with very few second tumors occurring and very weak statistical power to be sure of the resulting conclusions ….

2. Very small number of second tumors in the very small population exposed to high doses, and again very large CI for the resulting conclusions …

3, Everything complicated by the inaccuracies of dose calculations…



Problems with **leukemia incidence** estimates in **atomic bomb survivors** are **not very different** from those encountered with the Chernobyl childrens and thyroid cancer incidence…



Observed / Expected ratios for leukemia in survivors after Hiroshima and Nagasaki bombing according to the dose estimate (single exposure, whole body)

(Estimates based on DS86 dose evaluations)

	10 / 19	20 / 49	50 / 99	100 / 199	200/ 299	300/ 399	400 +
N. at risk	5210	6375	3042	1578	412	130	155
Obs.	11	23	24	24	15	2	4
Exp.	15	19	9	4	1	0,5	0,5
O/E	0,7	1,2	2,6	6	15	4	8

Few cancers
(Less than expected)

Few people

SOLID TUMORS

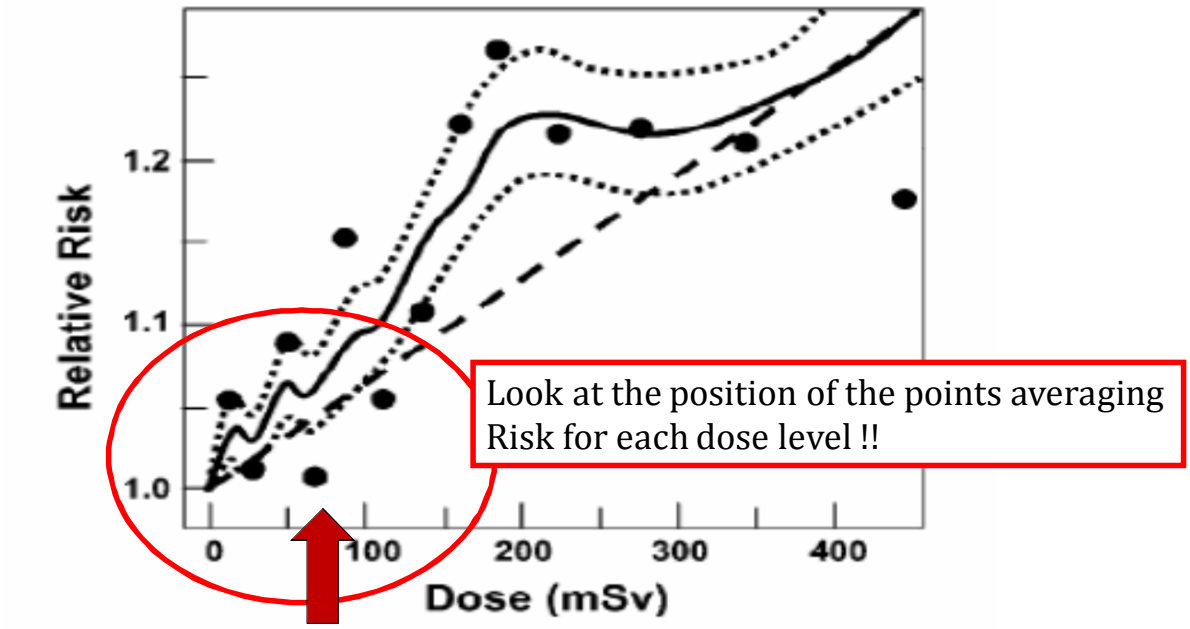


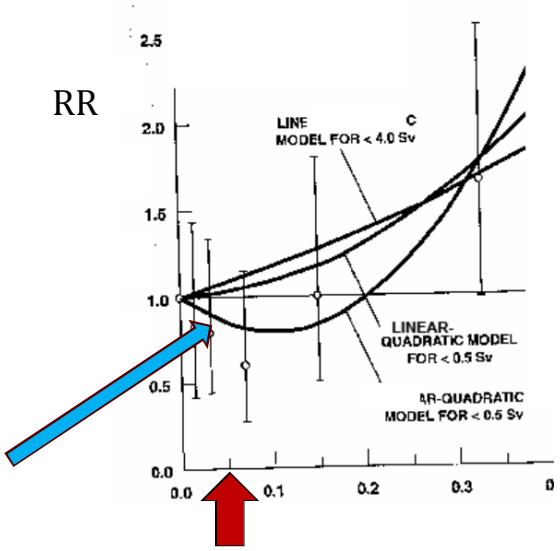
Fig. 4. Estimated risks (relative to an unexposed individual) of solid cancer in atomic bomb survivors exposed to low radiation doses (12). Data points are placed at the mean of each dose category. The solid curve represents a weighted moving average of the points shown (dotted curves: ±1 SE), and the dashed straight line is a linear risk estimate computed from all the data in the dose range from 0 to 2,000 mSv. Age-specific cancer rates from 1958 to 1994 are used, averaged over follow-up and gender.

Brenner, 2003

This implies a RR of radiation induced cancer of a little more than 1 (~ 1.02) , in the Hiroshima and Nagasaki conditions after bombing (i.e., not only external radiation, single fraction and "whole body", but varying amounts of internal contamination –difficult to calculate- starving, traumatic and heat effects, infections, all *possibly* contributing directly or indirectly to the cancer incidence).

And, again, a confidence interval and modelling problems do exist…

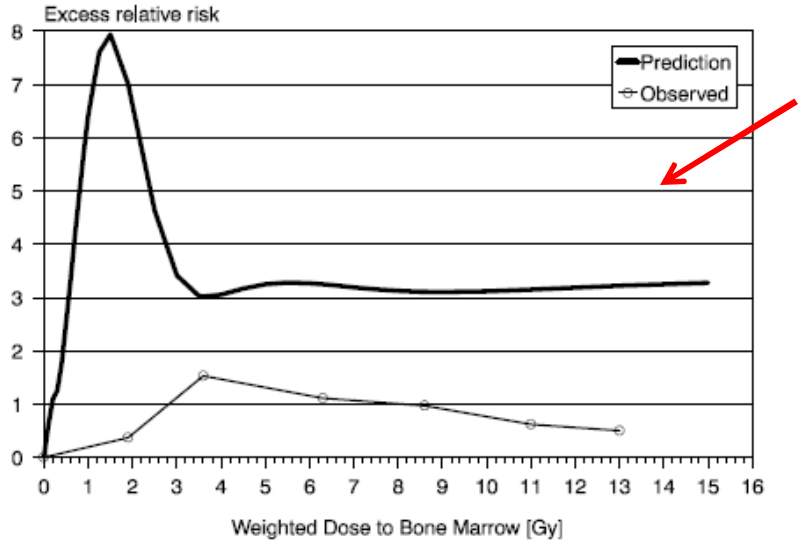
RR



Hormesis?

Sv

Shimizu, 1992

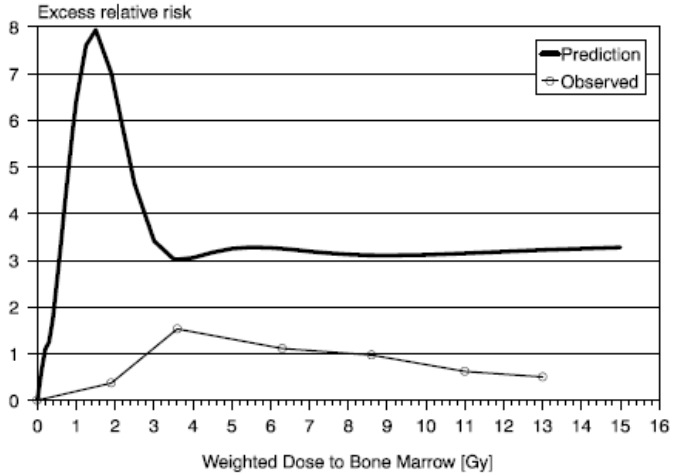


AL , Excess relative risk)

H. Kuni, Marburg
Dose-Response Relationship of Low and High LET Radiation
Marburg 2008: 2nd revised edition of a paper, originally presented at the International Workshop 'Radiation Exposures by
Nuclear Facilities, Evidence of the Impact on Health', University of Portsmouth, GB, 1996, In: Schmitz-Feuerhake, I., Schmidt, M. (Ed.): Radiation Exposures by Nuclear Facilities, Evidence of the Impact on Health, Proceedings International Workshop, University of Portsmouth, GB, 1996, Thomas Dersee, Strahlentelex, Berlin, 1998, p. 20-34.

Organ	Attributable Risk %	Excess Relative Risk / Gy	Absolute Excess / 10^4 PY-Gy
Leukaemia	50	4.37	2.7
Breast	32	1.6	6.7
Thyroid	26	1.2	1.6
Skin	24	1.0	0.84
Lung	19	1.0	4.4
Ovary	18	1.0	1.1
Urinary Bladder	16	1.0	1.2
Colon	14	0.72	1.8
Liver	11	0.49	1.6
Stomach	6.5	0.32	4.8

"About ten per cent of the diseases were **ATL, adult T-cell leukaemia, an infectious disease, endemic in Nagasaki**, without a significant dose response. The dose response of the other entities is strongly modulated by diagnosis, sex, age at exposure, city and time to onset."



In conclusion, **epidemiologic studies** have important flaws related to dosimetric and other uncertainities.

The generally accepted assumption is that a tumorigenic and leukemogenic potential of radiation exist, but is difficult to measure and more evident for doses in the intermediate range (between 100 and 500 cGy).

Epidemiologic studies are unable to clarify the shape of the dose effect curve for low doses (< 10-50 cGy), with the result that regulatory authorities and advisory groups adopted a very cautious aptitude for low-level exposures. **This might have unwanted and possibly dangerous effects by increasing the costs of medical procedures** involving the use of ionizing radiations.

"Our data on time trends cannot separate likely positive effects of human abandonment of the Chernobyl exclusion zone from a potential negative effect of radiation (though we could detect no such negative effect in our test of Hypothesis 1).

Nevertheless, they represent unique evidence of wildlife's resilience in the face of chronic radiation stress.

None of our three hypotheses postulating radiation damage to large mammal populations at Chernobyl were supported by the empirical evidence.

The results from these unique data will help society balance the negative impacts to wildlife from chronic radiation exposures against how "the removal of humans alleviates one of the more persistent and ever growing stresses experienced by natural ecosystems"

Current Biology 25, R811–R826, October 5, 2015

Correspondence

Long-term census data reveal abundant wildlife populations at Chernobyl

T.G. Deryabina[1], S.V. Kuchmel[1], L.L. Nagorskaya[2], T.G. Hinton[3], J.C. Beasley[4], A. Lerebours[5], and J.T. Smith[5,*]

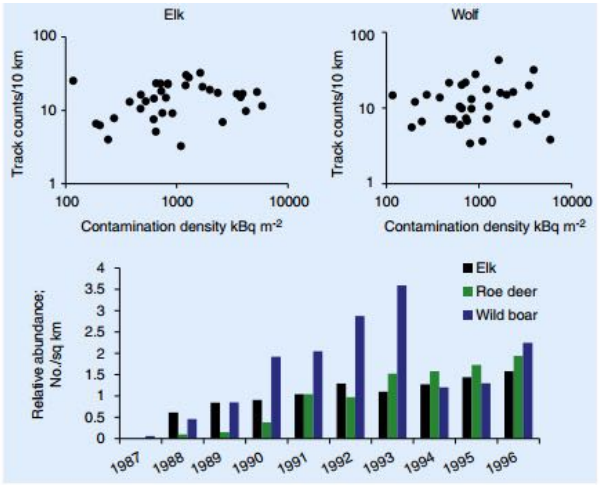


Figure 1. Animal abundances in the Chernobyl exclusion zone.
(Top) Mean number of track counts per 10 km (in 2008–2010) for elk and wolf plotted against mean ^{137}Cs contamination density of each route. Analysis using linear mixed models including habitat variables found no evidence of correlation between mammal density and contamination density. See Supplemental Information for other species studied. (Bottom) Change in relative abundance of three species in the 10 years after the Chernobyl accident.

Cancer Causes Control (2015) 26:1517–1518
DOI 10.1007/s10552-015-0638-9

LETTER TO THE EDITOR

The assumption of radon-induced cancer risk

Krzysztof W. Fornalski[1,2] · Rod Adams[3] · Wade Allison[4] · Leslie E. Corrice[5] · Jerry M. Cuttler[6] · Chris Davey[7] · Ludwik Dobrzyński[8] · Vincent J. Esposito[9] · Ludwig E. Feinendegen[10] · Leo S. Gomez[11] · Patricia Lewis[12] · Jeffrey Mahn[13] · Mark L. Miller[13] · Charles W. Pennington[14] · Bill Sacks[15] · Shizuyo Sutou[16] · James S. Welsh[17]

The paper by Axelsson et al. states that "residential exposure to radon is considered to be the second cause of lung cancer after smoking." The authors cite the publications of many well-known radon experts, especially the analysis of 13 European case–control studies by Darby et al.

They underscore their basic argument that in Sweden, there is a 16 % increase in the risk of radon induced lung cancer per 100 Bq/m3. However, there appear to be logical mistakes in their reasoning, which are presented below….

The final and general conclusion of this letter is that excess risk of lung cancer due to low concentrations of radon has been neither empirically detected nor theoretically demonstrated, while the opposite has, in fact, been supported by voluminous evidence. The putative increase in lung cancer risk due to low concentrations of radon is not a real effect; it is an assumption only.

Evacuation-related deaths now more than quake/tsunami toll in Fukushima Prefecture
Dec 18, 2013 Ida Torres National 2 Comments

Evacuation-related deaths now more than quake/tsunami toll in Fukushima Prefecture The number of deaths related to the prolonged evacuation of residents in Fukushima has already exceeded the total of those directly caused by the Great East Japan Earthquake and tsunami of 2011 in the prefecture. **As of November 30, there are already 1,605 deaths associated with the evacuation, two more than the 1,603 on record for the 2011 natural disasters.**

http://www.world-nuclear.org/info/Safety-and-Security/Safety-of-Plants/Fukushima-Accident/

A partial answer to these questions might come from the study of the incidence of second tumors in hospital series of patients treated with radiotherapy. This approach presents some advantages in comparison with the "epidemiologic" studies like the ones previously discussed.

1. Patients may have been followed in hospital Centers assuring long term *follow up* of the patients treated (= more information)

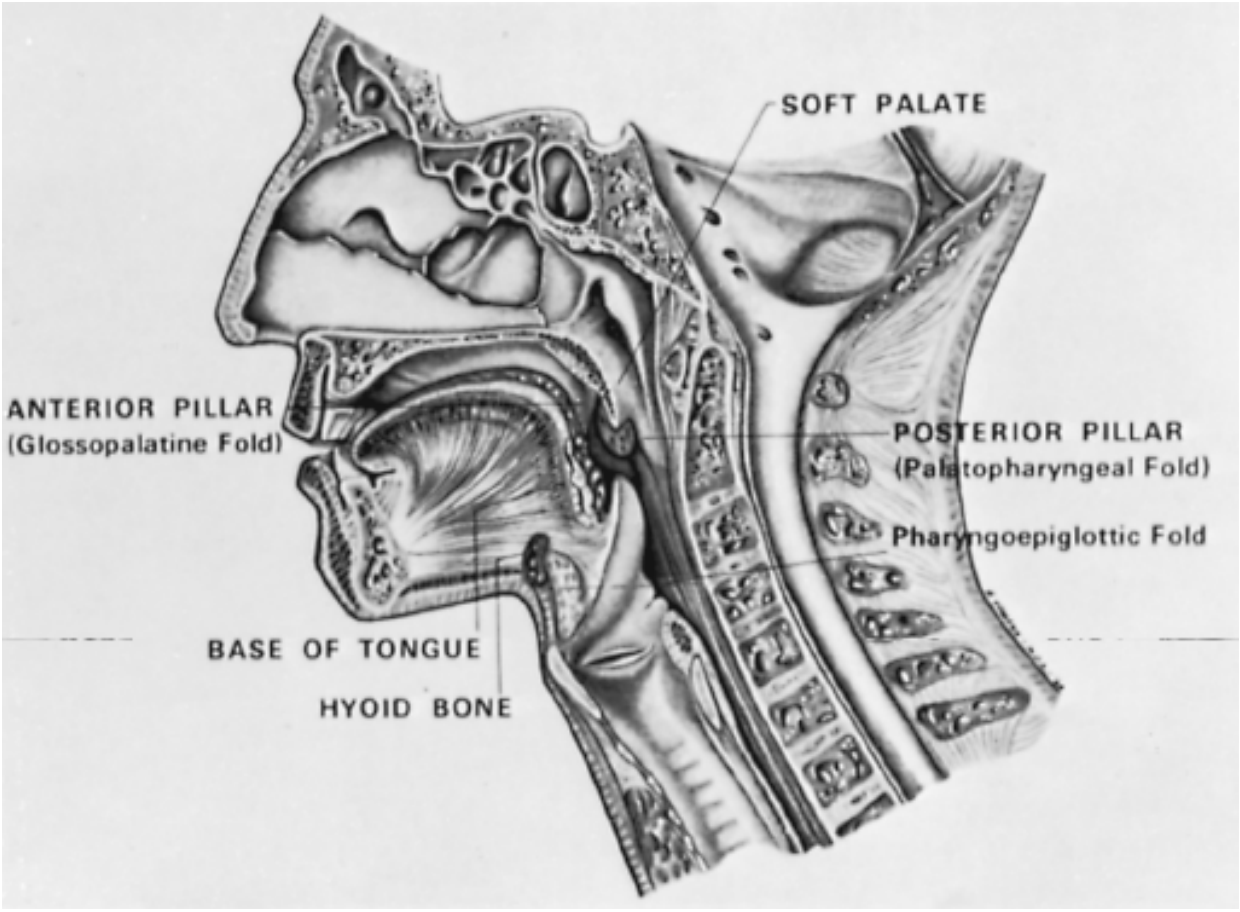
2. Competing risk factors for cancer occurrence are usually better known

3. Quality of dosimetric data is usually better

4. Incidence data might be compared with those of the general population, drawn from the Tumor Registries (if present)

"Second" and "first" tumors sharing the same risk factors *versus* radiation induced "second" tumors

The case of head and neck cancer



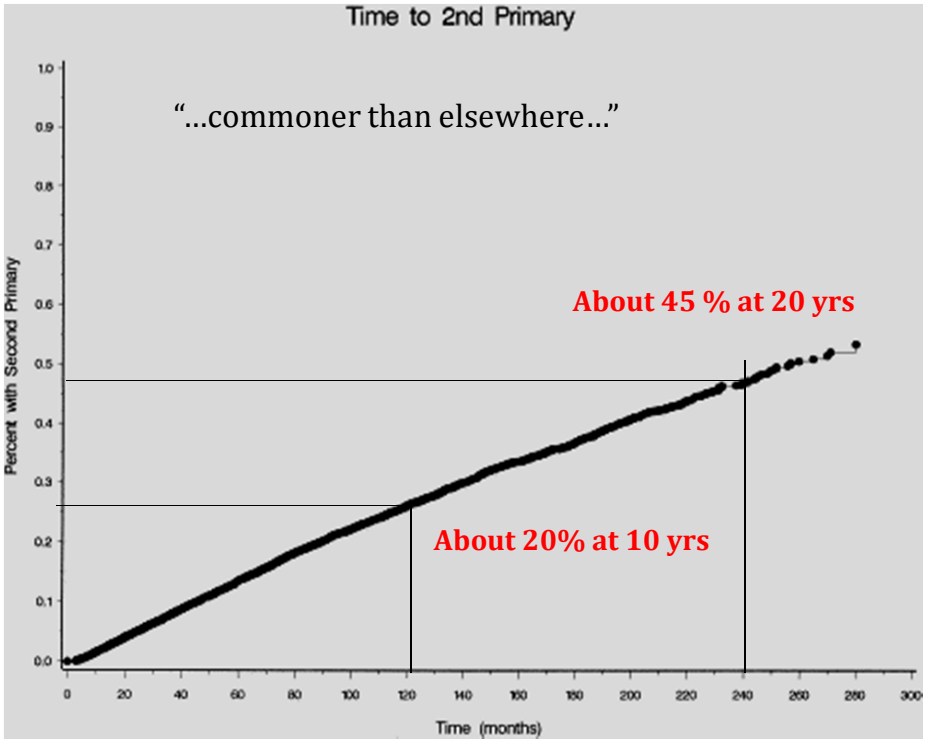
bmj.com BMJ. 1991 January 26; 302(6770): 193–194.

Second malignant tumours in head and neck cancer. *G R Ogden*

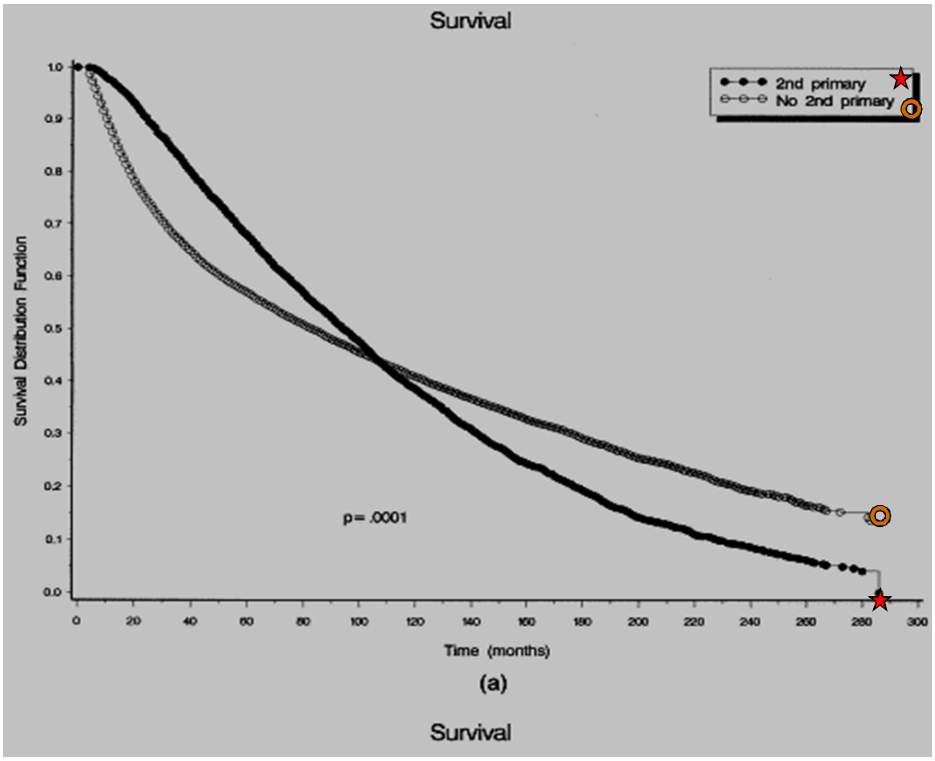
1. Second malignant tumours in head and neck cancer commoner than elsewhere

2. Among patients with head and neck cancer more are alleged to die from second tumours than from their original disease.

Little is known about the influence of the treatment of the first primary tumour on the development of a second.



Cumulative probability of second primaries in 20,074 patients with a diagnosis of primary invasive cancer of the larynx identified from the SEER database 1973–1996; *Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 2, pp. 427–435, 2003*



Second primaries kill …. long survivors

Radical radiotherapy for early glottic cancer: Results in a series of 1087 patients from two Italian radiation oncology centers. I. The case of T1N0 disease.

Enrico Cellai, M.D. , Paolo Frata, M.D. , Stefano M. Magrini, M.D. ·Fabiola Paiar, M.D. , Raffaella Barca, M.D. , Simona Fondelli, M.D. , Caterina Polli, M.D. , Lorenzo Livi, M.D. , Bartolomea Bonetti, M.D. , Elisabetta Vitali, M.D. , Agostina De Stefani, M.D., Michela Buglione, M.D. , Gianpaolo Biti, M.D.

Department of Radiation Oncology, Florence University Hospital, Florence, Italy, A.O. Careggi, Florence, Italy
Department of Radiation Oncology, Brescia University Hospital, Istituto del Radio "O. Alberti," Brescia, Italy

	3 years ± SE	5 years ± SE	10 years ± SE
Overall survival	86% ± 1	77% ± 1.5	57% ± 2
Local control	86% ± 1	84% ± 1	83% ± 1
Disease-specific survival	96% ± 1	95% ± 1	93% ± 1
Second primary cancer	**4.6% ± .1**	**8.4% ± 1**	**13% ± 1**
At risk (no. cases)	671	519	266

IJROBP, 63: 1378-86, 2005

Relative risks for second primaries at specific sites after laryngeal cancer as compared with the general population (20,074 patients with a diagnosis of primary invasive cancer of the larynx identified from the SEER database 1973–1996).

Site	obs	exp	(male/female)	O/E	95% CI
All second cancers	**3533**	**2101.8**	**(1858.7/243.1)**	**1.68**	**1.58–1.79**
Head and neck	**333**	**69.2**	**(64/5.2)**	**4.81**	**4.31–5.58**
Lung	**1372**	**385.7**	**(353.7/32)**	**3.56**	**3.34–3.79**
Esophagus	**111**	**27.8**	**(26.2/1.6)**	**3.99**	**3.29–4.83**
Prostate	**497**	**565.9**	**(565.9/NA)**	**0.88**	**0.81–0.97**
Colorectum	**331**	**308.1**	**(270.6/37.5)**	**1.07**	**0.96–1.19**
Urinary tract	**214**	**192.7**	**(181.3/11.4)**	**1.11**	**0.96–1.28**
Thyroid	**13**	**8.7**	**(6.4/2.3)**	**1.5**	**0.80–2.57**
Leukemia	**43**	**43.12**	**(37.8/5.4)**	**0.99**	**0.71–1.36**

Second primary cancers in patients with laryngeal cancer: a population-based study, Xiang Gao, M.D., Ph.D.,* Susan G. Fisher, Ph.D.,† Najeeb Mohideen, M.D.,‡ And Bahman Emami, M.D.‡, Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 2, pp. 427–435, 2003

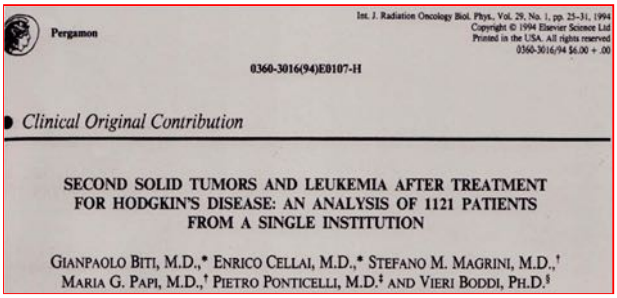
Age-adjusted relative risks (RR) for second primaries after laryngeal cancer over time: radiotherapy versus no radiotherapy

Site	≤5 years		>5 years		Entire follow-up	
	RR 95% CI	*p* value	RR 95% CI	*p* value	RR 95% CI	*p* value
All second cancers	1.09 0.98–1.20	0.100	1.11 1.00–1.23	0.055	1.10 1.02–1.18	0.012
Head and neck	1.00 0.73–1.37	0.996	1.68 1.16–2.43	0.007	1.26 0.99–1.60	0.061
Esophagus	1.63 0.86–3.08	0.134	1.26 0.70–2.27	0.434	1.43 0.93–2.19	0.105
Lung	1.20 1.02–1.41	0.025	1.16 0.97–1.37	0.100	1.18 1.05–1.33	0.006
Colorectum	0.98 0.71–1.35	0.889	0.89 0.64–1.24	0.490	0.93 0.74–1.17	0.557
Prostate	0.85 0.64–1.11	0.232	1.21 0.93–1.58	0.151	1.03 0.85–1.24	0.796
Urinary tract	1.52 0.96–2.38	0.072	0.54 0.37–0.79	0.002	0.87 0.65–1.15	0.322
Thyroid	2.12 0.46–9.68	0.332	*		2.40 0.53–10.8	0.255
Leukemia	0.71 0.30–1.70	0.442	1.80 0.66–4.92	0.254	1.10 0.57–2.11	0.779

… even if some authors claims radiotherapy might have also a (marginal) role under some circumstances…

Multiple risk factors *and*
the effect of aging:
"second" tumors as a "consequence of survival"

The case of Hodgkin's disease



Int. J. Radiation Oncology Biol. Phys., Vol. 29, No. 1, pp. 25–31, 1994

0360-3016/94 $6.00 + .00

Pergamon

0360-3016(94)E0107-H

Clinical Original Contribution

SECOND SOLID TUMORS AND LEUKEMIA AFTER TREATMENT FOR HODGKIN'S DISEASE: AN ANALYSIS OF 1121 PATIENTS FROM A SINGLE INSTITUTION

GIANPAOLO BITI, M.D.,* ENRICO CELLAI, M.D.,* STEFANO M. MAGRINI, M.D.,†
MARIA G. PAPI, M.D.,† PIETRO PONTICELLI, M.D.‡ AND VIERI BODDI, PH.D.§

THIS IS COHORT ANALYSIS WITHOUT EXTERNAL COMPARISON

Cumulative probability of having Leukemia (L) or a "Solid" Tumor (ST) has been calculated for the different clinical and therapeutic subgroups of a population of 1121 patients consecutively treated (1960-1988) for Hodgkin's disease in Florence.

Table 3. Cumulative 15-year probability (Kaplan–Meier) of developing a ST, a SST, or AL in different clinical subgroups and according to treatment at presentation (relapsed patients censored at relapse)

	No. cases	Cumul. 15 years probabil. (%) ST	SST	AL
Total	1121	10.8	8.9	1.6
Males	613	14.4	12.0	2.7
Females	508	7.3	6.1	0.6
Age				
< 20	203	1.4	—	1.4
20–40	533	7.9	7.2	0.7
41–60	292	22.9	17.0	4.6
> 60	93	25.2	25.2	—
CS				
I	161	9.3	8.7	2.3
II	582	11.7	11.3	0.3
III	309	10.0	5.4	4.2
IV	69	12.6	2.3	7.7
A	840	9.9	8.3	1.3
B	281	15.6	12.7	3.4
Laparotomy with splenectomy	578	11.8	10.3	1.7
No laparotomy	543	9.5	7.6	1.2
RT alone	745	7.8	7.6	0.2
CT alone	104	20.0	9.5	11.1
RT and CT	272	19.6	14.1	4.3
IF/M	559	7.0	6.1	0.9
STNI/TNI	458	14.6	12.4	1.4
CT				
MOPP	263	21.6	15.4	5.0
MOPP/ABVD	41	12.5	—	12.5
ABVD	25	6.7	6.7	—
Other	47	—	—	—
1–3 cycles	119	12.8	8.7	—
4–6 cycles	212	24.4	18.1	7.7
> 6 cycles	45	9.9	2.4	7.7
IF/M	393	5.1	5.1	—
STNI/TNI	352	12.0	11.6	3.4
IF/M + CT	166	14.8	11.0	4.2
STNI/TNI + CT	106	26.0	17.9	4.4
CT alone	104	19.6	9.5	11.1

Note: Abbreviations as in Table 1.

PREDICTIVE FACTORS:

- Older age at the diagnosis
- Chemotherapy
- Chemo-radiotherapy
- N° of cycles of CT
- Extent of RT volumes

Table 4. Results of multivariate analysis (Cox model) of risk factors for ST and SST occurrence (1121 patients, relapsed patients censored at relapse)

Factor	ST RR	p	SST RR	p
Age at diagnosis				
< 20	1		1	
20–40	2.7	.105	3.7	.075
40–60	6.7	.003	8.2	.006
> 60	18.4	< .001	27.9	< .001
Treatment intensity				
IF/M	1		1	
STNI/TNI	1.9	.099	1.9	.119
IF/M + CT	2.3	.117	1.5	.492
STNI/TNI + CT	5.8	.001	4.4	.013
CT	4.3	.012	3.9	.031

CLINICAL INVESTIGATION Hodgkin's Disease

THE RISK OF SECOND MALIGNANT TUMORS AND ITS CONSEQUENCES FOR THE OVERALL SURVIVAL OF HODGKIN'S DISEASE PATIENTS AND FOR THE CHOICE OF THEIR TREATMENT AT PRESENTATION: ANALYSIS OF A SERIES OF 1524 CASES CONSECUTIVELY TREATED AT THE FLORENCE UNIVERSITY HOSPITAL

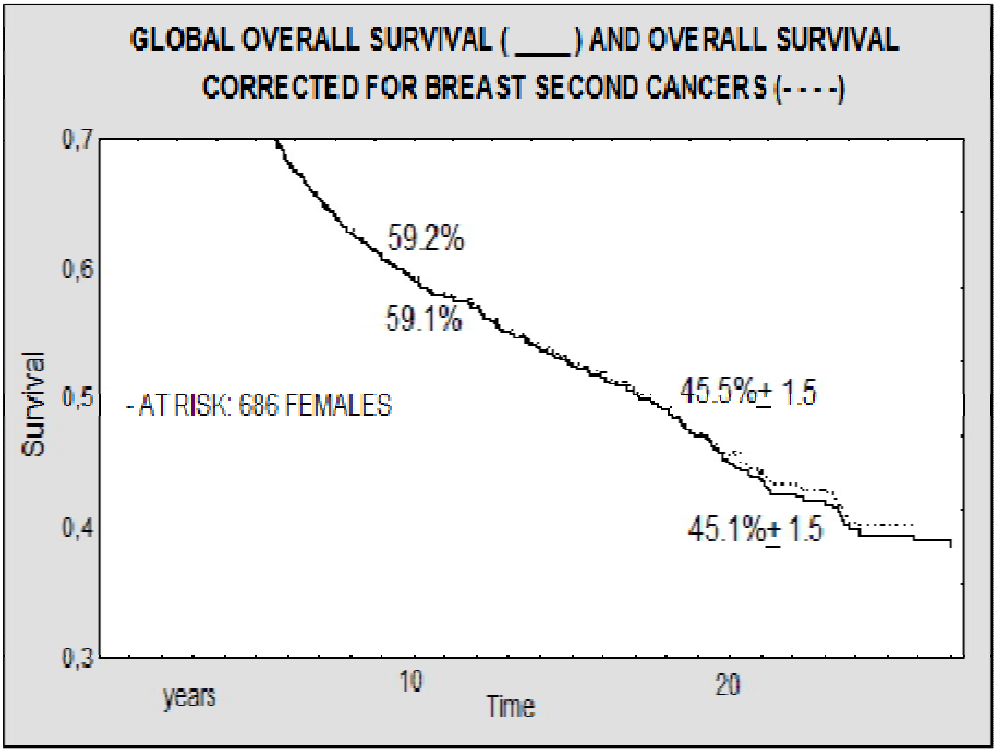
Enrico Cellai, M.D.,* Stefano M. Magrini, M.D.,† Giovanna Masala, M.D.,‡ Renato Alterini, M.D.,§ Adele Seniori Costantini, M.D.,‡ Luigi Rigacci, M.D.,§ Laura Olmastroni,‡ Maria G. Papi, M.D.,* Massimo A. Spediacci, M.D.,* Fabio Innocenti, M.D.,§ Gianpiero Bellesi, M.D.,§ Pierluigi Rossi Ferrini, M.D.,§ and Gianpaolo Biti, M.D.*

THIS IS COHORT ANALYSIS WITH EXTERNAL COMPARISON

A 14.9% 20-year probability of second malignant tumors was registered …. .
A statistically significant relationship between leukemia incidence and treatment with CHT, alone or in combination with RT.

A significant excess of breast cancers has been observed in RT-treated patients with longer follow-up; an excess of other common SST (lung, non-Hodgkin's lymphomas) is evident in pts treated with either RT, RT+CHT, or CHT.

The actuarial long-term survival of the series would have been better of about 3%, in absence of the SMT mortality possibly due to HD treatment, which is almost equally divided between patients treated with RT alone, CHT alone, and RT plus CHT."



Documents of the NRPB: Volume 11, No. 1

Risks of Second Cancer in Therapeutically Irradiated Populations: Comparison with Cancer Risks in the Japanese Bomb Survivors and in Other Exposed Groups: Report of an Advisory Group on Ionising Radiation

«In general, for most cancer sites the relative risks for the induction of second cancers are comparable with or less than the relative risks derived from the Japanese data. In many cases the difference is not statistically significant, due at least in part to the small numbers of cases that are involved when total cancers are subdivided into individual types. For lung cancer, bone cancer, ovarian cancer and leukaemia the differences are statistically significant. At least for leukaemia, the discrepancy can be explained by cell-sterilisation effects and leukaemia subtype differences. **The fact that in general the relative risks in the second cancer studies are lower than those based on the Life Span Study (LSS) data is reassuring for the therapist in so far as the risks derived from the LSS are likely to constitute an upper bound to the risks associated with radiotherapy.** «

«Sorry Stefano I could no attend…….because of SIRM board….»

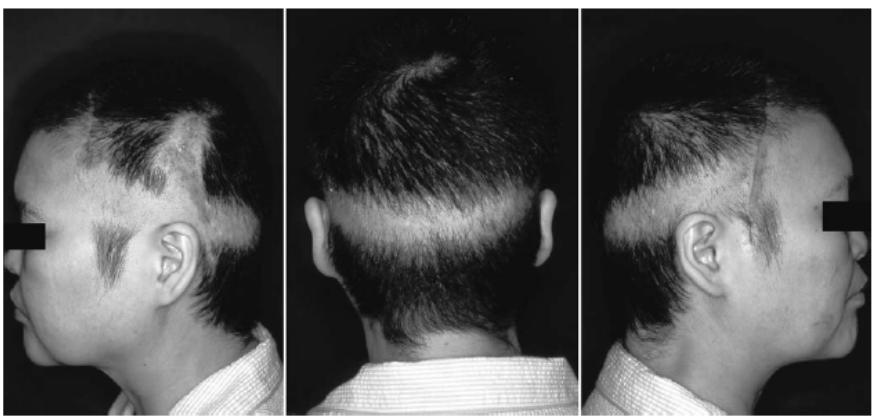
«Don't worry, for sure we have similar opinions on the subject…Send me The material you prepared…»

Eur Radiol (2005) 15:41–46
DOI 10.1007/s00330-004-2459-1

NEURO

Yoshimasa Imanishi
Atsushi Fukui
Hiroshi Niimi
Daisuke Itoh
Kyouko Nozaki
Shunsuke Nakaji
Kumiko Ishizuka
Hitoshi Tabata
Yu Furuya
Masahiko Uzura
Hideto Takahama
Suzuo Hashizume
Shiro Arima
Yasuo Nakajima

Radiation-induced temporary hair loss as a radiation damage only occurring in patients who had the combination of MDCT and DSA



Potential risks of «low radiation doses»

- Given the paucity of direct epidemiological data, the cancer risks from low-dose radiation have been assessed using models based on the linear, no-threshold theory.
- This theory holds that excess cancer risks related to low-dose radiation are directly proportional to the dose.
- This model is used to extrapolate excess cancer risk at low doses from the known risk at higher doses.
- However, some question the validity of the linear no-threshold theory and think that below a certain threshold carcinogenesis ceases to be a concern.

Potential risks of «low radiation doses»

- Despite some controversy over the excess cancer risk of low-dose radiation, the linear no-threshold theory is widely used because an alternative method for assessing the potential risks of low-dose radiation is lacking.
- In addition, it is this author's opinion that the epidemiological data directly suggest increased cancer risk in the 10 mSv to 100 mSv range, which is relevant to nuclear cardiac and many CT studies.
- A widely used figure is a 5% excess risk of death from cancer with a 1 Sv (1000 mSv) dose.

Risks Associated with Low Doses and Low Dose Rates of Ionizing Radiation: Why Linearity May Be (Almost) the Best We Can Do[1]

Radiology

Mark P. Little, DPhil
Richard Wakeford, PhD
E. Janet Tawn, PhD
Simon D. Bouffler, PhD
Amy Berrington de Gonzalez, DPhil

Conclusion

In summary, excess cancer risks observed in the Japanese atomic bomb survivors and in many medically and occupationally exposed groups exposed at low or moderate doses are generally statistically compatible. For most cancer sites, the dose response in these groups is compatible with linearity over the range observed. The available data on biologic mechanisms do not provide general support for the idea of a low-dose threshold or hormesis. This large body of evidence does not suggest, and indeed is not statistically compatible with, any very large threshold in dose or with possible hormetic effects.

radiology.rsnajnls.org • **Radiology:** Volume 251: Number 1—April 2009

- Although the estimated risks from low levels of radiation of a single CT exam are uncertain, it is prudent to minimize the dose from CT by applying common sense solutions and using other simple strategies as well as exploiting technologic innovations.

- These efforts will enable us to take advantage of all the clinical benefits of CT while minimizing the likelihood of harm to patients.

Radiation Dose: Philosophy and Responsibility

- **Justify exam**
  - Right test for right reasons
  - Move from CT to MR over long term
- **Optimize dose**
  - ALARA, Image Gently, Image Wisely
- **Audit**
  - Best standard of care
  - Reference values / guidelines
  - ACR Registry

Golding, SJ Radiology 2010; 255:683-6

Stanford Encyclopedia of Philosophy

1. **risk = an unwanted event which may or may not occur.**
An example of this usage is: "Lung cancer is one of the major risks that affect smokers."

2. **risk = the cause of an unwanted event which may or may not occur.**
An example of this usage is: "Smoking is by far the most important health risk in industrialized countries."

3. **risk = the probability of an unwanted event which may or may not occur.**
"The risk that a smoker's life is shortened by a smoking-related disease is about 50%."

4. **risk = the statistical expectation value of an unwanted event which may or may not occur.** The expectation value of a possible negative event is the product of its probability and some measure of its severity.

5. **risk = the fact that a decision is made under conditions of known probabilities** ("decision under risk" as opposed to "decision under uncertainty")

Imaging for Appendicitis: Should Radiation-induced Cancer Risks Affect Modality Selection?[1]

Radiology

Sorapop Kiatpongsan, MD, PhD
Lesley Meng, MPH
Jonathan D. Eisenberg, BA
Maurice Herring, BA
Laura L. Avery, MD
Chung Yin Kong, PhD
Pari V. Pandharipande, MD, MPH

Purpose: To compare life expectancy (LE) losses attributable to three imaging strategies for appendicitis in adults—computed tomography (CT), ultrasonography (US) followed by CT for negative or indeterminate US results, and magnetic resonance (MR) imaging—by using a decision-analytic model.

"Viewing risks through this larger lens enables an objective understanding of the impact of radiation exposure from CT in the clinical setting of appendicitis, hopefully providing quantitative evidence to guide institutional policymakers who are considering practice changes.»

Figure 1

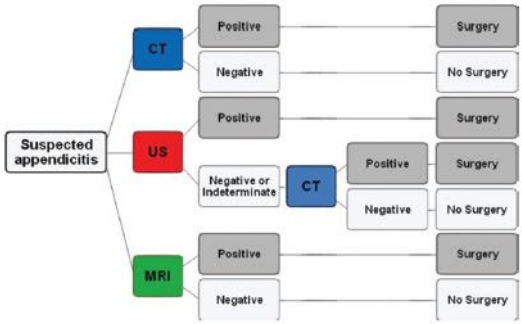


Figure 1: Flow diagram shows three imaging strategies for suspected acute appendicitis: *(a)* CT alone, *(b)* combined US and CT, and *(c)* MR imaging alone. Patients who underwent CT alone were triaged to surgery for appendectomy if they had positive results; patients with negative results did not undergo surgery. For the combined US and CT approach, patients underwent US, with triage to CT in circumstances of negative or indeterminate US results. Patients who underwent MR imaging alone were triaged to surgery for appendectomy if they had positive results; patients with negative results did not undergo surgery.

Life Expectancy Loss Associated with Each Imaging Strategy

Imaging Strategy	Total Projected Life Expectancy Loss (d)	Projected Life Expectancy Loss Attributable to Test Performance and Consequent Management (d)	Projected Life Expectancy Loss Attributable to Radiation-induced Cancers (d)
CT	8.18	6.48	1.71
CT and US	6.84	5.79	1.05
MR imaging	5.81	5.81	0.00

Radiology: Volume 273: Number 2—November 2014

Table 1 Materials and results

Case	Sex	Age	Diagnosis	Exam. period (days)	Number of CT perfusion studies		Angiography of head			Duration of temporary bandage-shaped hair loss after first examination
					Studies with 200 mA[a]	Studies with 100 mA[a]	Number of angiographies	Total fluoroscopic time (min)	Total DSA[b]-run time (s)	
1	M	70	Acute subdural hematoma	8	4		0			Negative
2	M	68	Acute subdural hematoma	9	4		0			Negative
3	M	20	Acute subdural hematoma with operation	10	4		0			Negative
4	F	53	Rupture of aneurysm with operation	15	4		2	22.4	193	From 37th day for 51 days
5	F	54	Brain contusion with hematoma	7	2	2	0			Negative
6	F	58	Putaminal hemorrhage	4[c]	2		3 (9 years ago)[c]	19.5	84	Negative
7	M	46	Acute subdural hematoma	6	2		0			Negative
8	M	28	Subarachnoid hemorrhage of unknown origin	8	2		2	34.0	386	From 23rd day for 98 days
9	M	45	Rupture of aneurysm with operation	8	2		2	16.5	205	From 22nd day for 92 days
10	M	66	Putaminal hemorrhage	16	2		0			NA[a] (transferred into other hospital at 20th day)
11	M	75	Rupture of aneurysm with operation	27	1		4	91.4	285	Negative
12	M	66	Subarachnoid hemorrhage of unknown origin	7	1		2	28.0	212	Negative
13	M	85	Subependymal hemorrhage	1	1		0			NA[a] (died at 4th day)
14	M	79	Brain contusion and hematoma	1	1		0			NA[a] (transferred into other hospital at 18th day)
15	M	54	Brain infarction	1	1		0			NA[a] (died at 6th day)
16	F	71	Chronic subdural hematoma	1	1		0			Negative
17	F	87	Occlusion of internal carotid rightartery	1	1		0			NA[a] (died at 1st day)
18	F	58	Acute subdural hematoma	1	1		0			Negative

Thank you !!