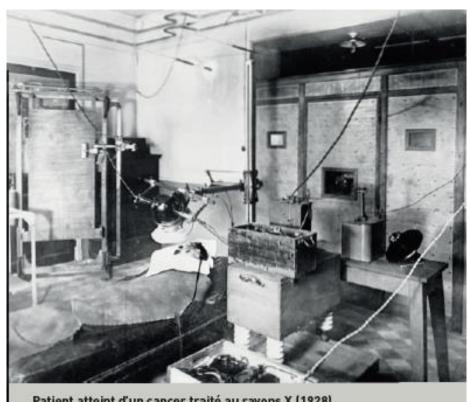
Cancers radio-induits

F. Jamar

Cours RPR 2002, 23 avril 2019

• Tout commence par un paradoxe!



Patient atteint d'un cancer traité au rayons X (1928)

Cancers radio-induits

- Est-ce que ça existe?
- · OUI!
 - Cancers secondaires en radiothérapie
 - Cancers secondaires après thérapie métabolique
 - Exposition de travailleurs
 - Survivants des grandes catastrophes nucléaires, p.ex. HN, Chernobyl, essais nucléaires
 - Imagerie médicale (d'aujourd'hui)?

Cancers radio-induits

- Est-ce que ça existe?
- OUI! Exemples historiques
 - Cancers de la peau chez les radiologues, techniciens RX,... (+leucémies?)
 - Exposition de travailleurs dans les mines d'uranium (poumon)
 - Ostéosarcomes chez les peintres de cadrans de montres (radium)
 - Tumeurs hépatiques après Thorotrast
- Ces exemples sont anecdotiques car aucune forme de dosimétrie solide n'est disponible

Cancers radio-induits: exemples historiques



Figure 10.2. Hand of a dentist who for 35 years held x-ray films in place in patients' mouths. The thumb has been partially amputated. Damaged skin on the fingers has been replaced by grafts. The lesion on the finger is a skin cancer subsequently removed. (Courtesy of Dr. Victor Bond, Brookhaven National Laboratory.)

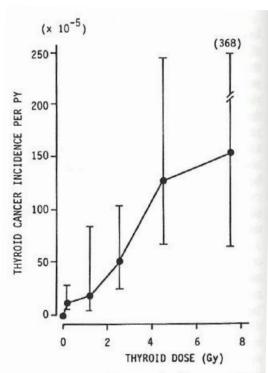
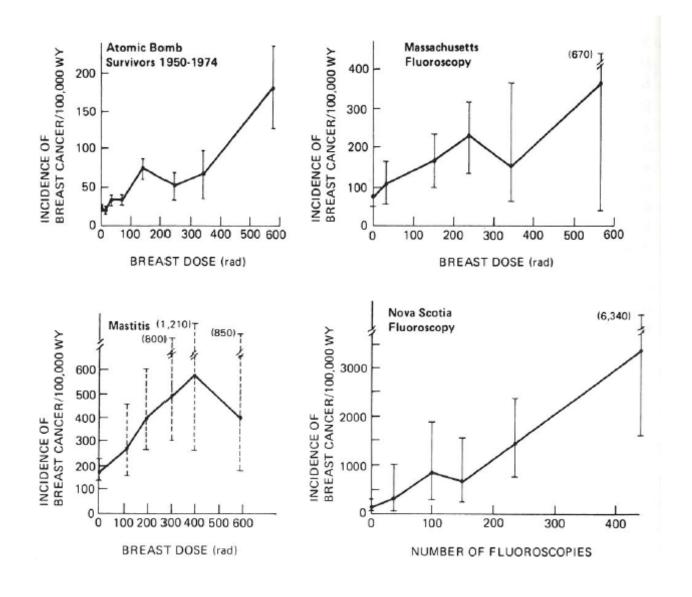
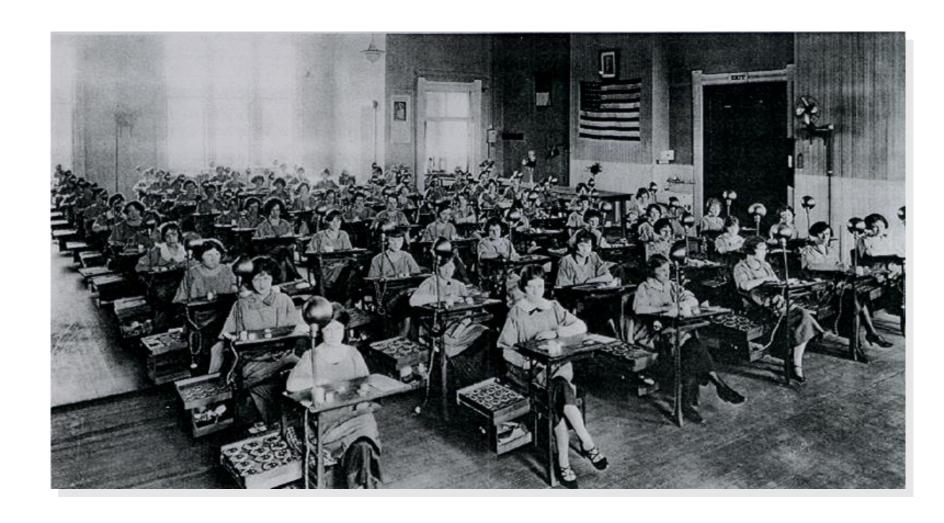


Figure 10.4. Thyroid cancer incidence per person-year (PY) as a function of the radiation dose in the thyroid. Rates adjusted for sex, ethnicity, and interval after irradiation. *Error bars* represent 90% confidence limits. (From Shore RE, Woodard E, Hildreth N, et al.: JNCI 74: 1177–1184, 1985, with permission.)

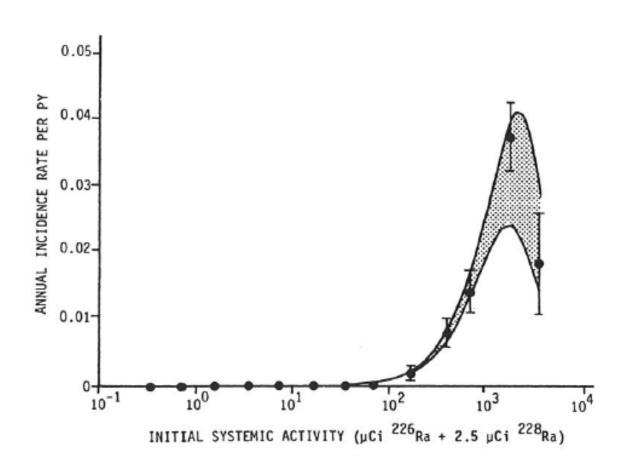
Cancers radio-induits: cancer du sein



Cancer radio-induits: radium et sarcome



Cancer radio-induits: sarcomes



Cancers radio-induits

- Est-ce que ça existe?
- OUI! Exemples plus récents
 - Survivants japonais de Hiroshima-Nagasaki
 - Radiothérapie pour SPA en UK: leucémies
 - Cancer thyroïdien après irradiation du thymus chez l'enfant (+sein)
 - Cancer salivaire, du cerveau, de la peau, leucémie après épilation pour pédiculose
 - Cancer du sein après fluoroscopie pour Tbc/scoliose
 - Cancer du sein après irradiation pour mastite du post-partum
- Dans ces cas, des données dosimétriques sont disponibles et conduisent à des modèles de risque.

Cancers radio-induits

* EFFETS DETERMINISTES

- Sévérité augmente avec la dose
- Existence d'un seuil (100 voire 500 mGy)
- (latence généralement courte)

EFFETS STOCHASTIQUES

- Sévérité indépendante de la dose
- Pas de seuil
- (latence généralement longue)

Cancers radio-induits = stochastique



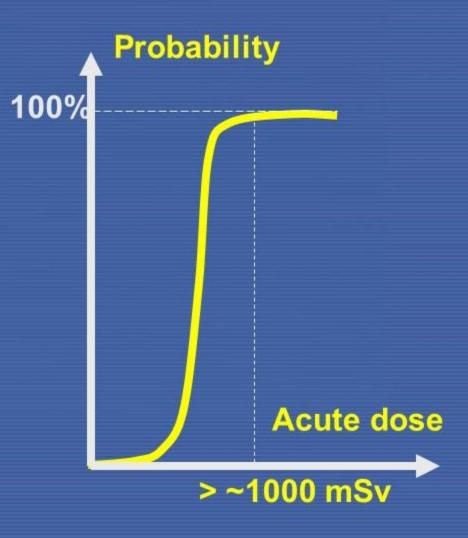


Sunburn Melanoma

deterministic stochastic

Deterministic Health Effects

- A radiation effect for which generally a threshold level of dose exists above which the severity of the effect is greater for a higher dose
 - many cells die or have function altered
 - occurs when the dose is above given threshold (characteristic for the given effect)
 - severity increases with the dose

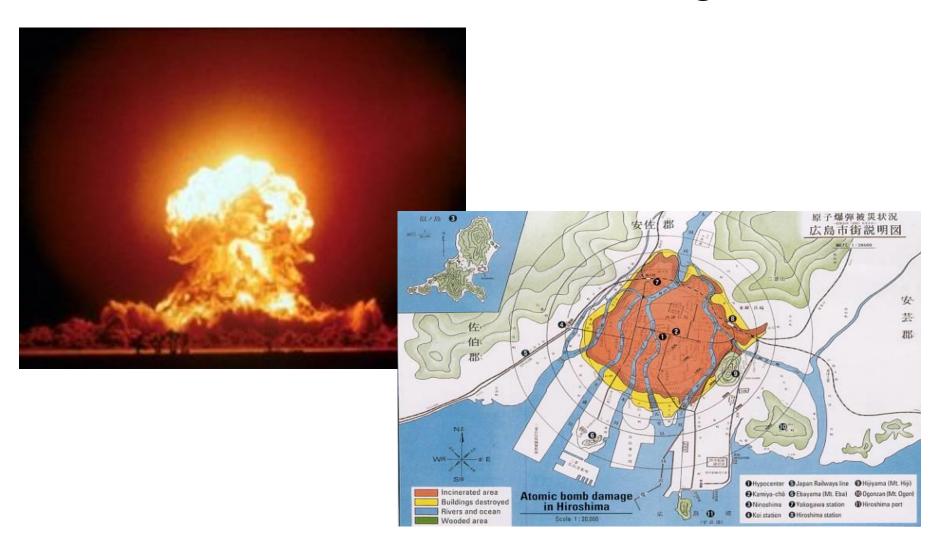




Stochastic Health Effects

- A radiation-induced health effect, occurring without a threshold level of dose:
 - probability is proportional to the dose
 - severity is independent of the dose
- Stochastic health effects:
 - Radiation-induced cancers
 - Hereditary effects
- Late appearance (years)
- Latency period:
 - Several years for cancer
 - Hundreds of years for hereditary effects





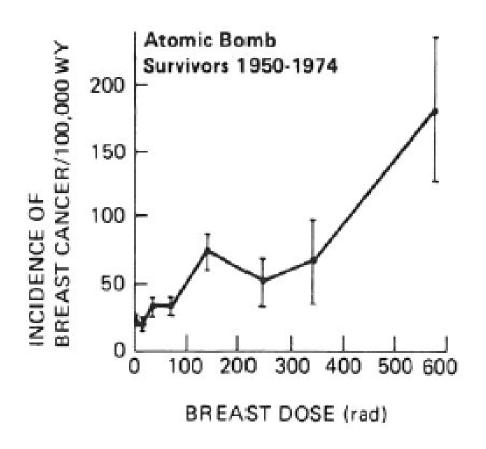
- Life Span Study, (LSS) Cohort
- Source primaire d'information:
 - 86,500 individus:
 - Des deux sexes
 - · De tous les âges
 - Données dosimétriques sur une gamme de doses étendue
 - Dose moyenne 0.27 Sv
 - ~ 6,000 individus exposés à des doses > 0.1 Sv
 - ~ 700 individuals exposés à des doses > 1 Sv

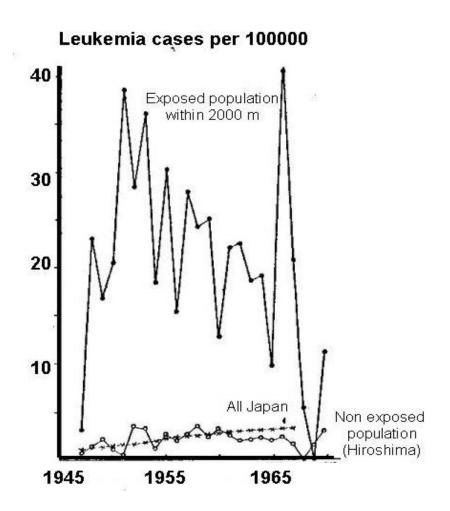
- Life Span Study, (LSS) Cohort
- 47 ans de suivi (1950-1997)
- Observés: 9,335 cas fatals de cancer solide
- Attendus: ~8,895 cas fatals de cancer solide

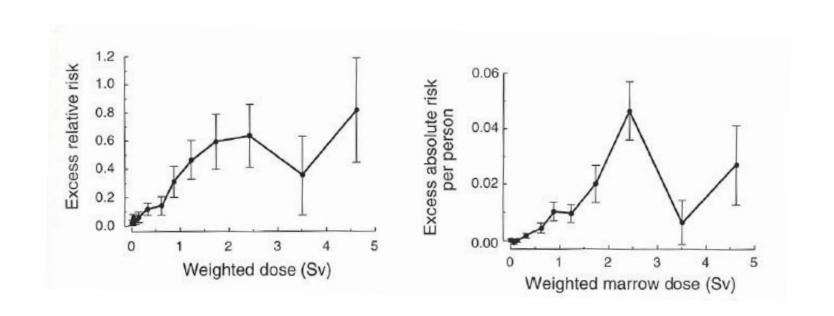
DONC: ~440 cancers (5%) attribuables aux radiations ionisantes

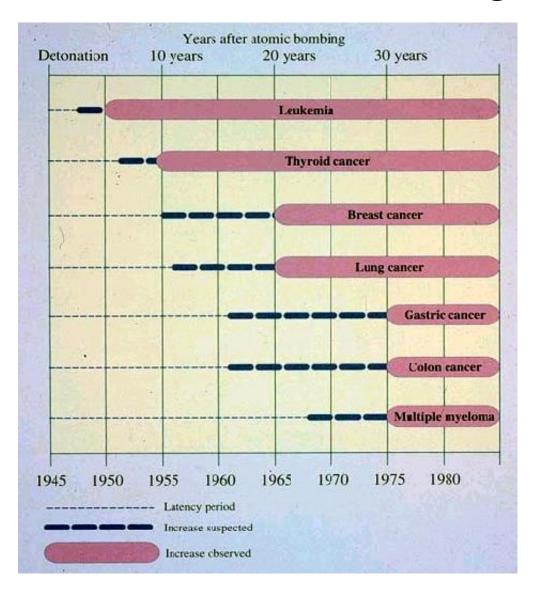
- Résumé du risque épidémiologique de cancer induit
- Risque de mortalité par cancer solide

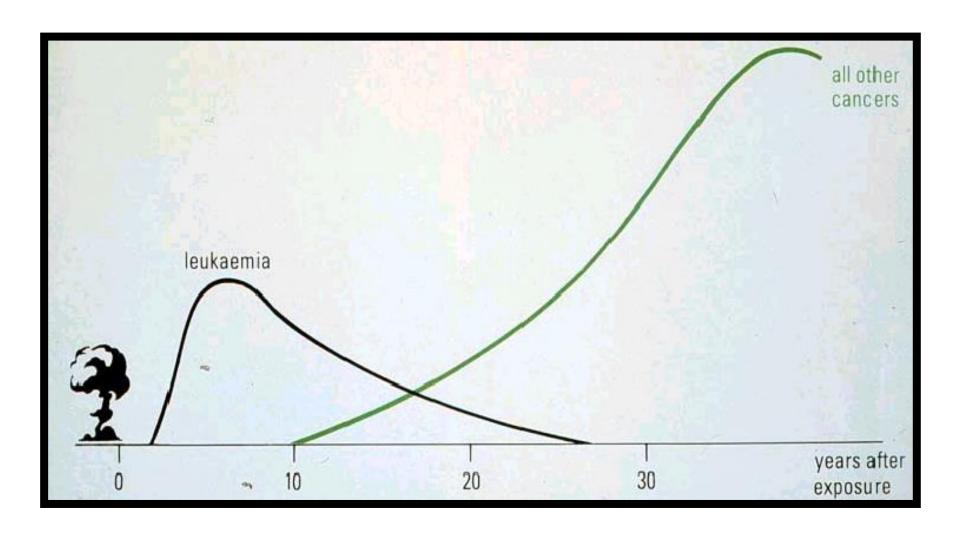
~0.005% per mSv

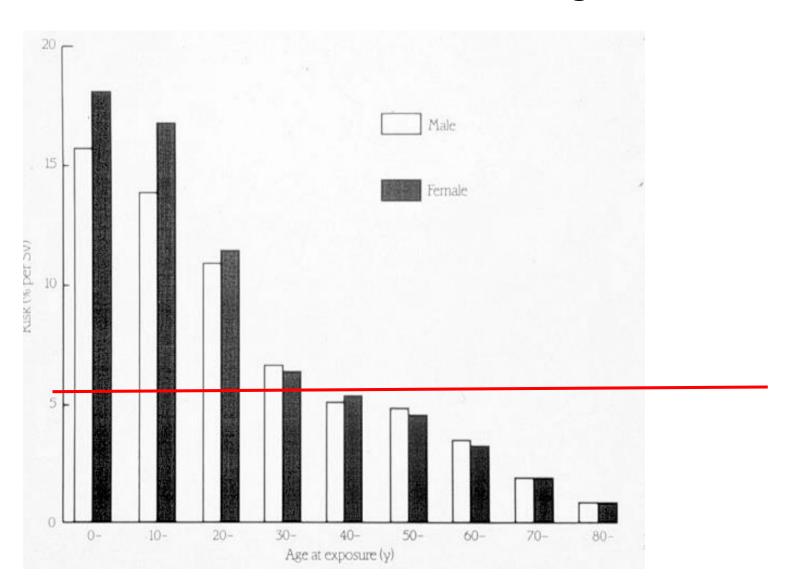












Cancers radio-induits: Chernobyl

"Liquidators"

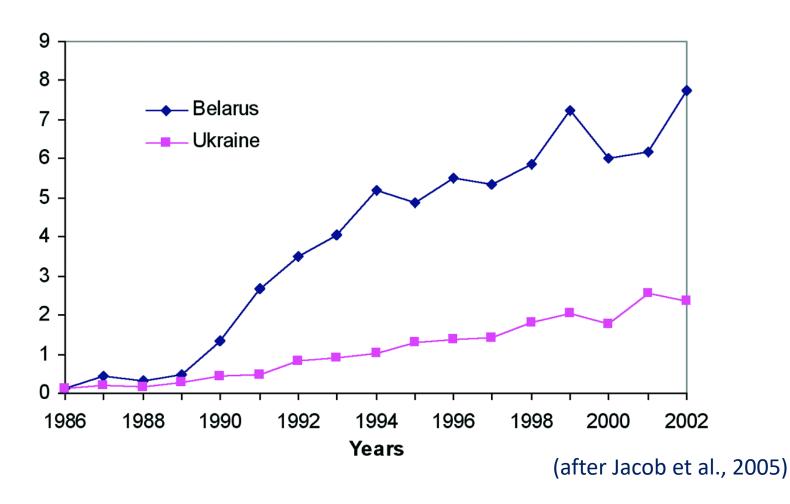
- Doublement du risque de leucémie chez les travailleurs avec des doses >150 mGy
- Discrète augmentation de la mortalité par cancer solide (~5%) et les maladies cardiovasculaires
- · Augmentation de la fréquence de la cataracte
- Les doses enregistrées dans les registres sont en moyenne de 100 mGy avec des valeurs jusque 500 mGy

Public

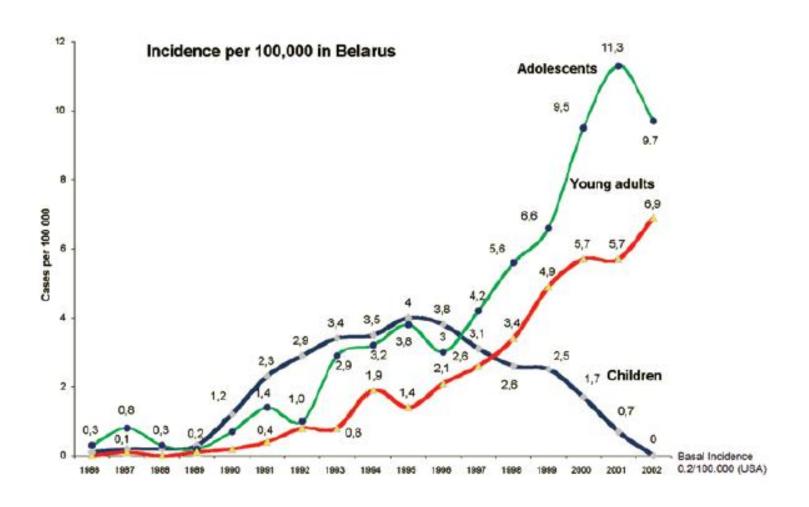
- Pas d'augmentation du risque de leucémie
- Pas d'augmentation des cancers solides à l'exception de celui de la thyroïde (enfants et adolescents)
- Les doses efficaces entre 1986-2005 vont de quelques mSv à quelques centaines de mSv avec une moyenne de 10 20 mSv

Cancers radio-induits: thyroïde

Incidence Rate of Thyroid Cancer per 100,000 Children and Adolescents as of 1986 1800 additional thyroid cancers in children



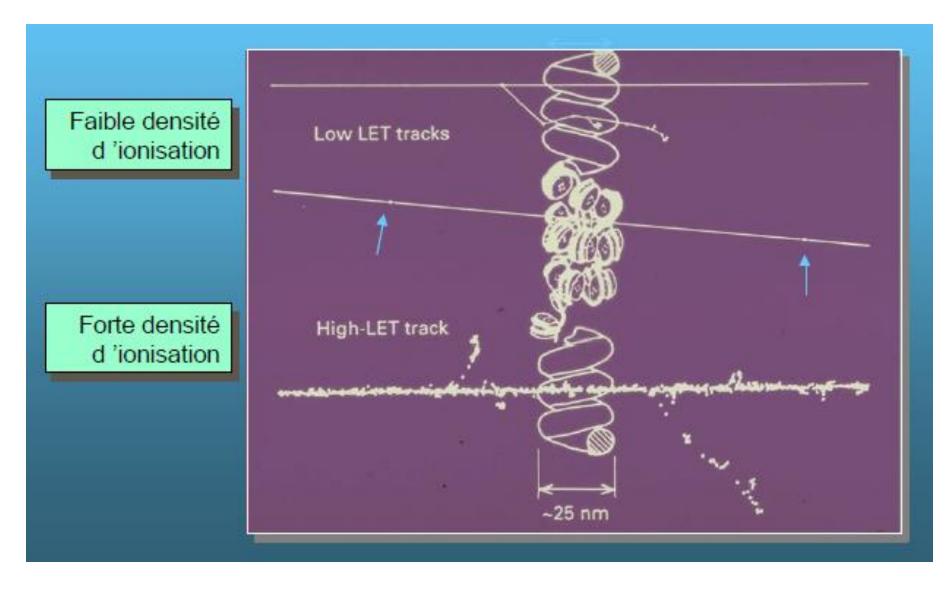
Cancers radio-induits: Chernobyl - thyroïde

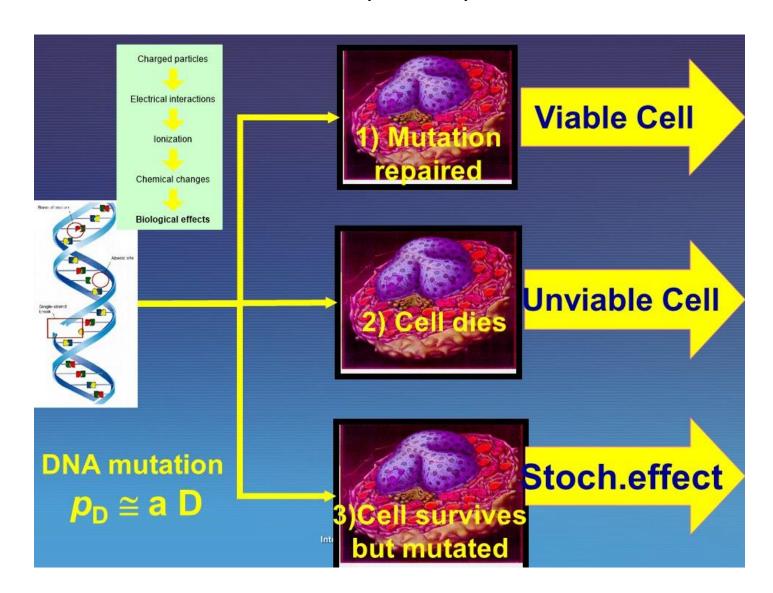


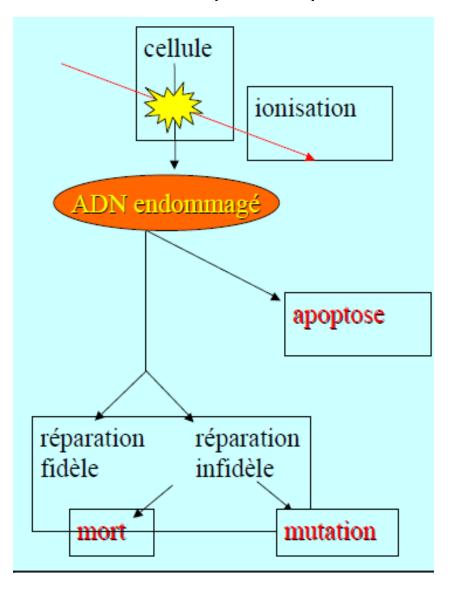
Cancers radio-induits: numbers and facts

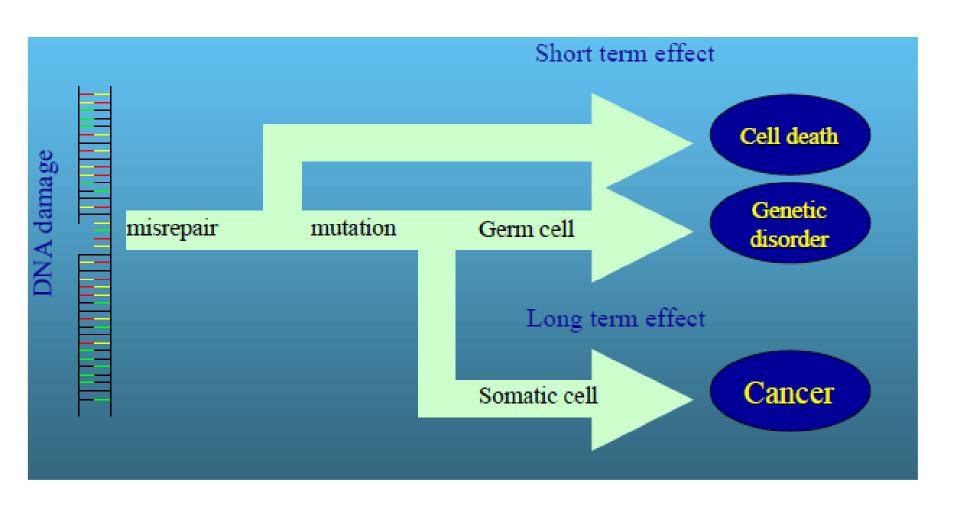
Comparison of mortality rates for human carcinogenesis (UNSCEAR 1977) at high doses and dose rates

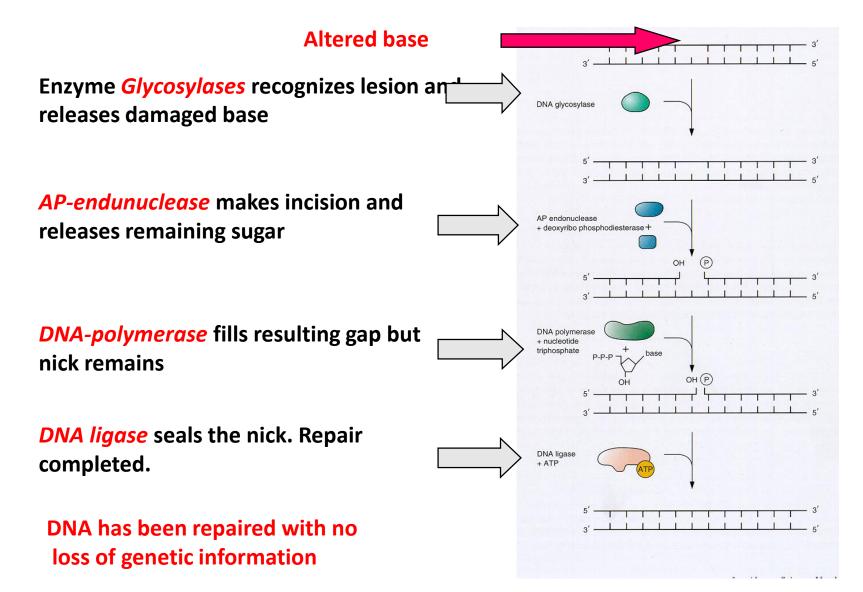
Cancer Type	Data Source	Risk Coefficient (Mortality/person-Sv)
Leukaemia	Hiroshima and Nagasaki	30 x 10 ⁻⁴
	Ankylosing spondylitis	11 to 25 x 10 ⁻⁴
	Pelvic irradiation	17 x 10 ⁻⁴
	(not in utero examinations)	
Thyroid cancer	Hiroshima and Nagasaki	0.5 to 2 x 10 ⁻⁴
	Marshali Islanders	6 x 10 ⁻⁴
	Radiotherapy of children	1 to 5 x 10 ⁻⁴
Lung cancer	Hiroshima and Nagasaki	10 to 25 x 10 ⁻⁴
	Uranium mining	40 to 180 x 10 ⁻⁴
Breast cancer	Hiroshima and Nagasaki	13 x 10 ⁻⁴
	Multiple fluoroscopy	110 x 10 ⁴
	Radiotherapy	210 x 10 ⁻⁴
Bone cancer	Radiotherapy	3 to 5 x 10 ⁻⁴
	Treatment with ²²⁴ Ra	20 to 25 x 10 ⁻⁴

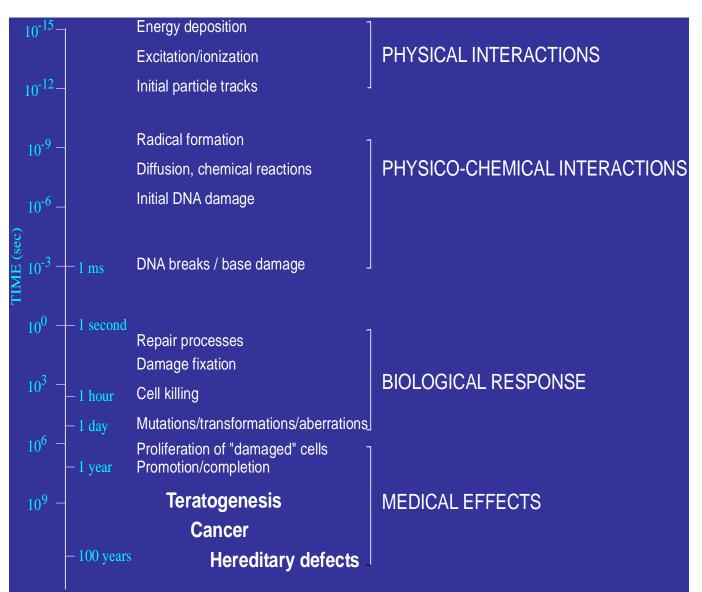




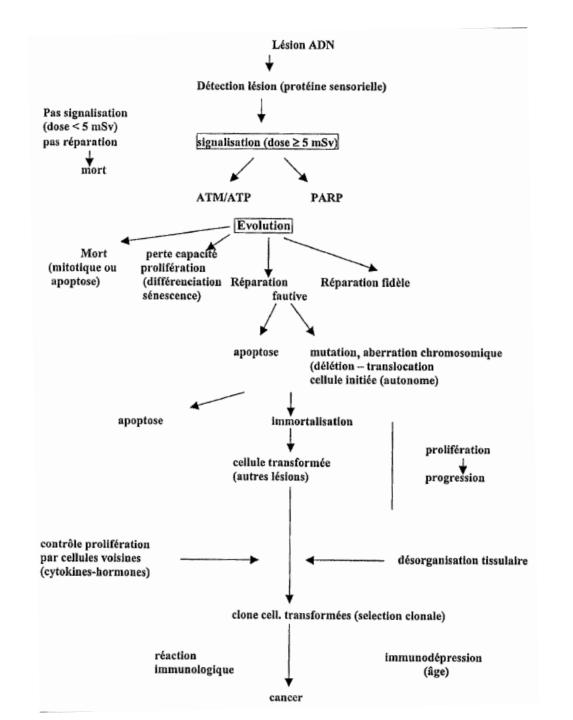








- Différentes étapes tout n'est pas lié uniquement à une mutation
- 999 cellules / 1000 mutées se réparent
- 999 cellules mutées / 1000 meurent (ceci n'est pas un problème...)
- Beaucoup de cellules avec mutation(s) sont viables
- Il faut donc d'autres étapes:
 - Initiation: mutation d'un gène qui affecte la prolifération (proto-oncogène ou gène suppresseur)
 - Promotion: multiples facteurs: hormones, alcool, toxiques (dont chimio), inflammation → nouvelles mutations
 - Progression: prolifération non contrôlée → nouvelles mutations



- Multiples facteurs favorisants/modulateurs
 - Age
 - Sexe
 - Toxicité combinée (ex. radon et tabac)
 - Effet du débit de dose
 - Transfert linéique d'énergie
 - Effet du fractionnement (aigu vs protracted vs chronique)
 - Type de tissu
 - Phase du cycle cellulaire
 - Index mitotique naturel: ex. leucémie

Cancers radio-induits: effets sur la radiosensibilité

Physical

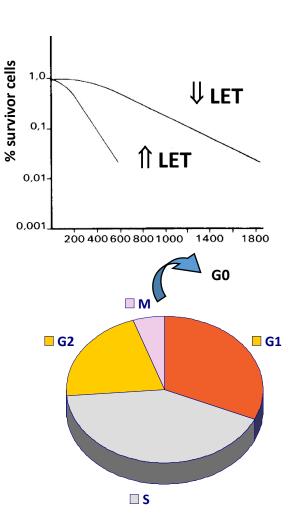
- LET (linear energy transfer): ↑ RS
- Dose rate: ↑ RS
- Temperature ↑ RS

Chemical

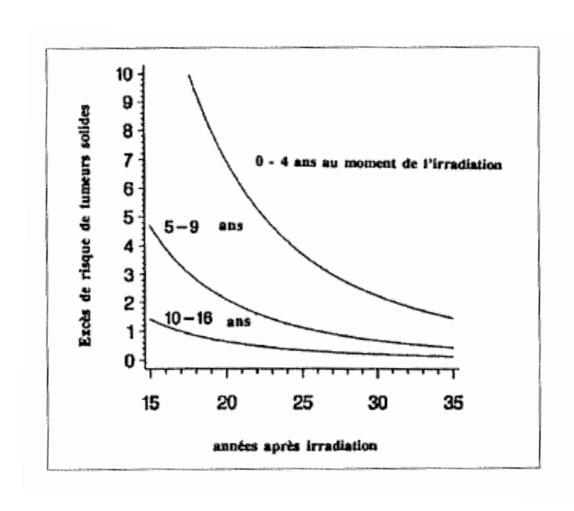
- Increase RS: OXYGEN, cytotoxic drugs.
- Decrease RS: SULFURE (cys, cysteamine...)

Biological

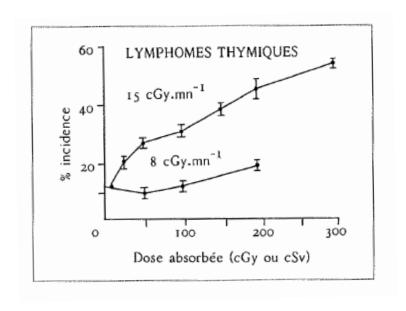
- Cycle status:
 - ↑ RS: G2, M
- Repair of damage (sub-lethal damage may be repaired e.g. fractionated dose)

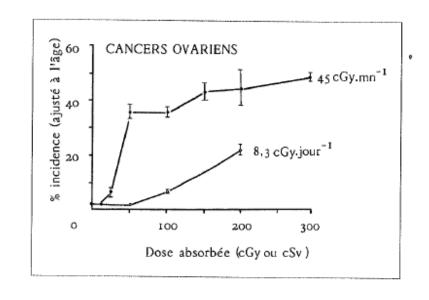


Cancers radio-induits: effet de l'âge



Cancers radio-induits: effet du débit de dose





Cancers radio-induits: différenciation cellulaire

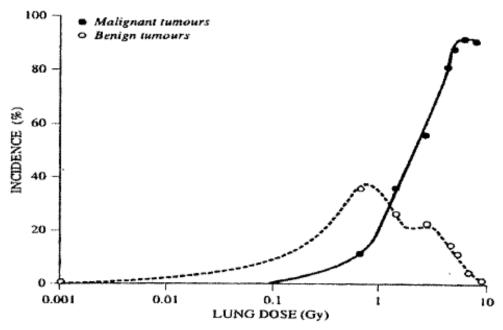


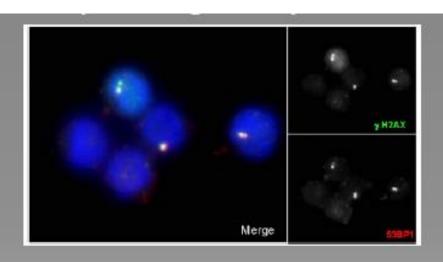
Figure 8 :
Tumeurs bénignes et malignes provoquées par inhalation d'un aérosol de ²³⁹PUO₂.
Les tumeurs bénignes sont provoquées par des doses plus faibles que les malignes, ce qui correspond vraisemblablement à un moindre nombre d'altérations de l'ADN (d'après UNSCEAR 1986).

Cancers radio-induits: effets sur la radiosensibilité

High RS	Medium RS	Low RS
Bone Marrow	Skin	Muscle
Spleen	Mesoderm	Bones
Thymus	organs (liver,	Nervous system
Lymphatic nodes	heart, lungs)	
Gonads		
Eye lens		
Lymphocytes (exception to the RS laws)		

Cancers radio-induits: marqueurs?

DNA repair foci after ¹³¹I therapy -100 mCi, 0.3 Gy to blood Lassmann et al. JNM 2010



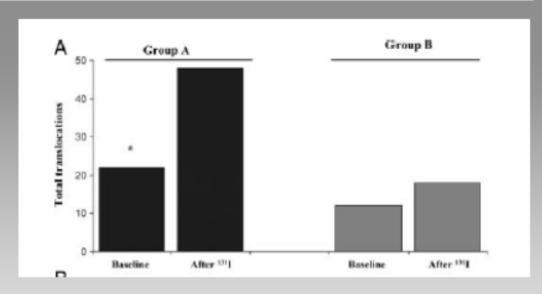
		Т	ime after radioiodi	ne administration (h)	
Variable	2	24	48	72	96	120
y-H2AX Median (mGy/h)-1 n*	0.0168 20	0.0338 13	0.0695 19	0.108	0.1413 13	0.276
S3BP1 Median (mGy/h) ⁻¹ n'	0.0180	0.0234	0.0675 19	0.1351 17	0.1096 13	0.175

"Number of patients with evaluable samples for each time point.

See "Results" section for explanation of nonevaluable patients and samples.

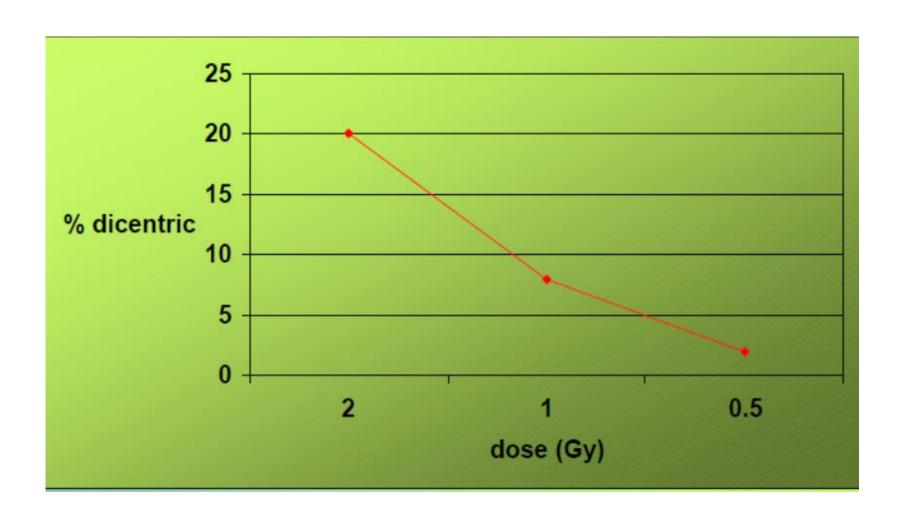
Cancers radio-induits: marqueurs?

Chromosome Translocation Frequency after Radioiodine Thyroid Remnant Ablation: A Comparison between Recombinant Human Thyrotropin Stimulation and Prolonged Levothyroxine Withdrawal



Frigo et al. JCEM 2009

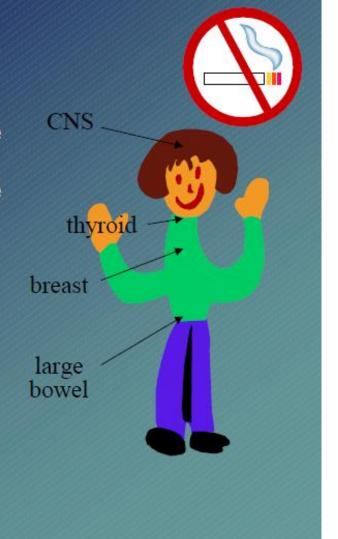
Cancers radio-induits: marqueurs?



Cancers radio-induits: second cancer (ou +) après radiothérapie

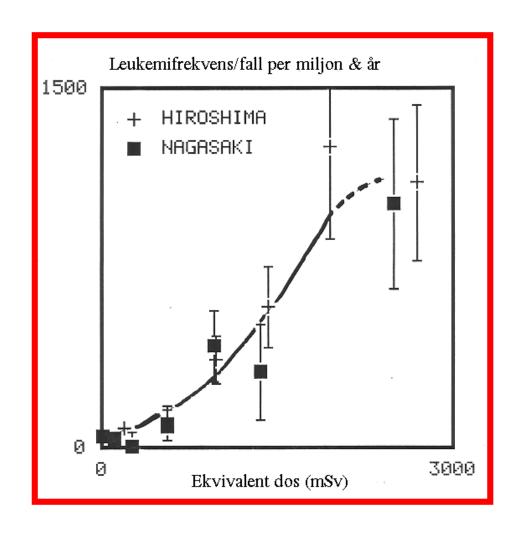
Take home message

- The younger the patient the higher the risk.
- The younger the patient the longer the latency.
- Beware genetic factors.
- Some tissues are more vulnerable.
- Leukaemia up to 10y after.
- Solid tumours from 10y on or earlier...
- Screening necessary.

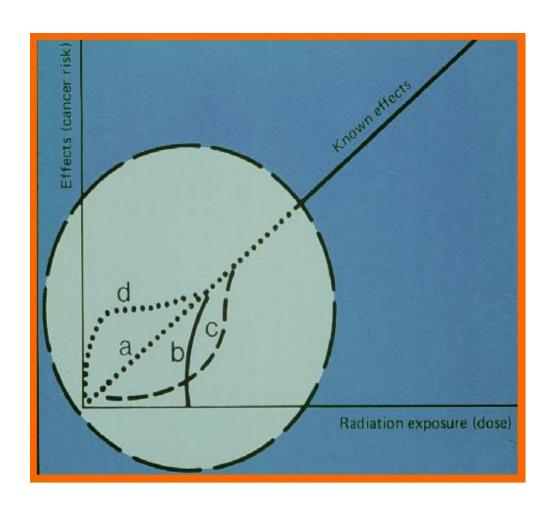




Cancers radio-induits: hautes doses

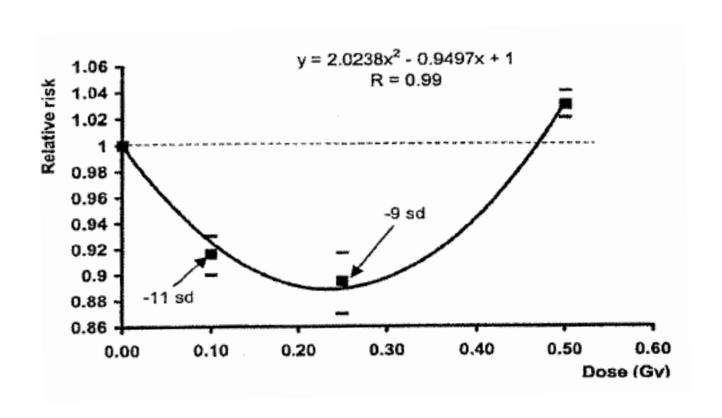


Cancers radio-induits: faibles doses?

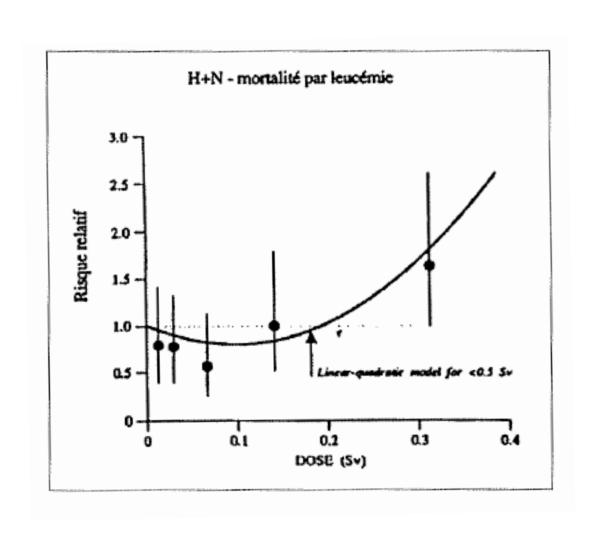


- a) Linear extrapolation
- b) Threshold dose
- c) Lower risk per dose for low doses
- d) Higher risk per dose for for low doses

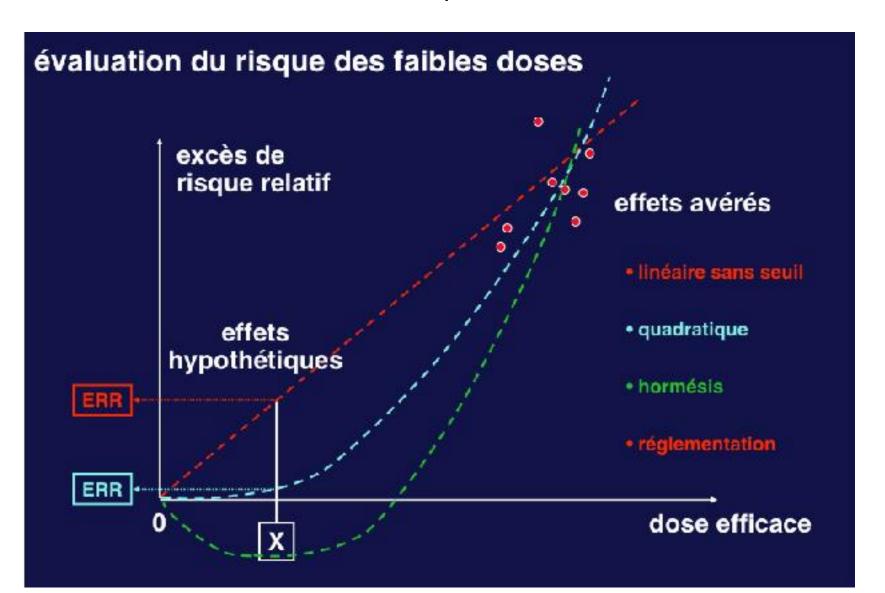
Cancers radio-induits: hormésis –souris (γ)



Cancers radio-induits: hormésis - Hiroshima

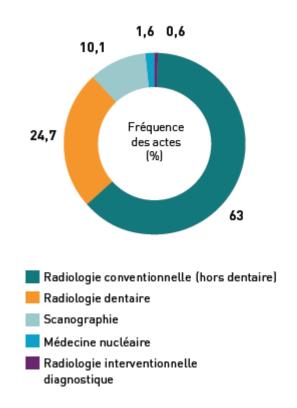


Cancers radio-induits: quel modèle choisir



Cancers radio-induits: faibles doses et imagerie

Quelle irradiation pour quel examen?



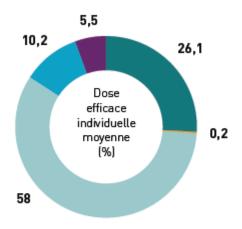
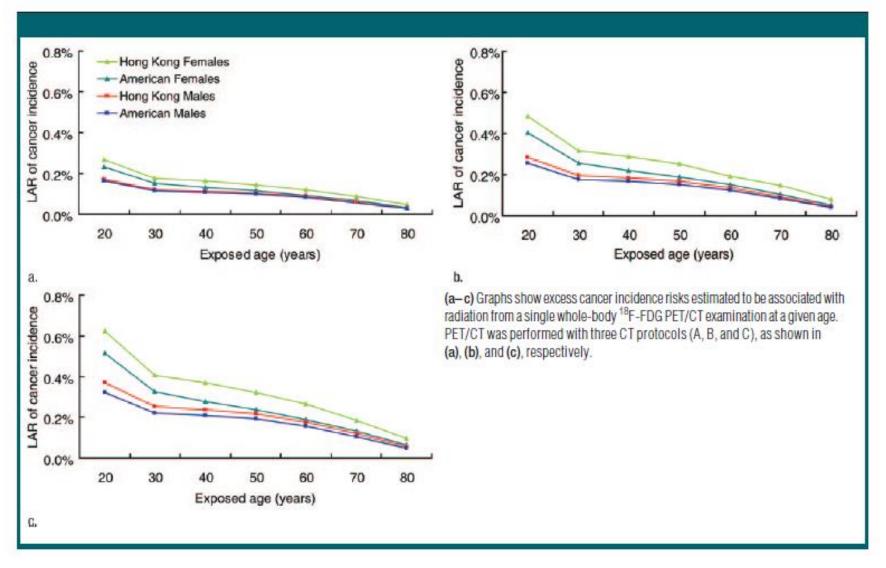


Figure 1 : Répartition des examens et de la dose efficace associée en fonction des modalités d'imagerie en 2007

Cancers radio-induits: faibles doses et imagerie



Cancers radio-induits: faibles doses et imagerie

Table 5																		
LARs of Cancer Incidence for U.S. and Hong Kong Populations Lifetime risk for 100 mSv																		
									Age at Ex	posure ((y)							
	()	1	0	2	0	3	0	4	0	5	0	6	0	7	0	(80
	United	Hong	United	Hong	United	Hong	United	Hong	United	Hong	United	Hong	United	Hong	United	Hong	United	Hong
Sex and Cancer Site	States	Kong	States	Kong	States	Kong	States	Kong	States	Kong	States	Kong	States	Kong	States	Kong	States	Kong
Male patients																		
Stomach	66	139	48	100	35	72	24	51	23	49	22	44	17	36	12	25	6	12
Colon	309	384	222	275	159	197	115	140	112	135	104	124	86	103	60	68	28	29
Liver	71	229	50	163	35	116	26	82	24	77	22	66	16	48	9	29	3	13
Lung	308	405	212	279	146	191	103	131	102	130	99	125	87	110	64	82	33	46
Prostate	89	39	64	28	46	20	34	14	34	14	32	14	25	12	13	8	5	4
Bladder	217	177	156	127	112	91	82	65	82	64	79	62	69	55	49	41	24	21
Other solid organ	1112	1609	498	533	309	341	196	223	170	196	139	160	97	116	56	68	23	28
Thyroid	147	125	64	54	27	23	12	9	4	8	1	7	0	4	0	3	0	0
Female patients																		
Stomach	90	203	64	146	46	104	32	74	31	69	28	59	24	46	17	25	10	8
Colon	207	165	149	117	107	83	77	59	74	54	69	48	58	38	42	22	22	8
Liver	31	243	22	173	16	122	11	87	11	76	10	60	8	41	6	19	2	6
Lung	777	831	534	567	367	389	257	267	254	258	244	244	213	220	156	167	82	95
Breast	1089	1351	662	813	399	487	235	288	131	274	65	237	29	180	11	118	4	59
Uterus	47	6	33	5	24	3	17	2	15	2	12	2	8	1	5	0	2	0
Ovary	82	57	58	40	40	28	27	20	24	16	20	12	14	8	9	5	4	2
Bladder	218	204	157	141	112	101	81	73	80	72	76	71	66	65	48	53	25	33
Other solid organ	1312	1869	513	822	317	547	203	369	177	312	145	246	107	196	67	148	29	79
Thyroid	856	736	371	319	153	133	55	54	19	44	5	33	1	22	0	12	0	2

Note.—Data are numbers of cancer cases in the lifetimes of 100 000 persons exposed to a radiation dose of 100 mSv. LARs were calculated as described in Appendix E1 (http://radiology .rsnainls.org/cgi/content/full/2511081300/DC1) and by applying the Hong Kong Cancer Statistics 2005 (15) and Hong Kong Life Table 2005 (16).

	All Solid	d Cancer	Leukemia		
Excess cases (including non-fatal cases) from	Males	Females	Males	Females	
exposure to 100 mSv	800 (400–1600)	1300 (690–2500)	100 (30–300)	70 (20–250)	
Number of cases in the absence of exposure	45,500	36,900	830	590	
Excess deaths from exposure to 100 mSv	410 (200-830)	610 (300–1200)	70 (20–220)	50 (10–190)	
Number of deaths in the absence of exposure	22,100	17,500	710	530	

Table 1. The table shows the estimated number of cancer cases and deaths expected to result in 100,000 persons (with an age distribution similar to that of the entire U.S. population) exposed to 100 mSv. The estimates are accompanied by 95% subjective confidence intervals shown in parentheses that reflect the most important uncertainty sources including statistical variation, uncertainty in adjusting risk for exposure at low doses and dose rates, and uncertainty in the method of transporting data from a Japanese to a U.S. population. For comparison, the number of expected cases and deaths in the absence of exposure is listed.

- 2Approximately 42 cancers per 100 individuals calculated from Table 12-4 in Chapter 12 of the BEIR VII report.
- 3 In special cases, such as in utero exposure, some evidence suggests excess cancers can be detected as low as 10 mSv.

Cancers radio-induits: according to BEIR V

	Annual X-rays	Males		Females		Total		
	per 1000*	Attributable risk (%)	Cases cancer per year	Attributable risk (%)	Cases cancer per year	Attributable risk (%)	Cases cancer per year	
Country								
Australia	565	1.2	204	1.5	227	1.3	431	
Canada	892	1.1	406	1-0	378	1.1	784	
Croatia	903	1.5	66	2.2	103	1.8	169	
Czech Republic	883	0.9	67	1.2	105	1.1	172	
Finland	704	0-7	20	0.7	30	0.7	50	
Germany	1254	1.3	963	1.7	1086	1.5	2049	
Japan†	1477	2.9	3724	3-8	3863	3.2	7587	
Kuwait	896	0-7	25	0-6	15	0.7	40	
Netherlands	600	0-7	100	0.7	108	0.7	208	
Norway	708	1.3	28	1.1	49	1.2	77	
Poland	641	0.5	99	0.7	192	0.6	291	
Sweden	568	1.1	91	0-8	71	0.9	162	
Switzerland	750	1.0	93	1.0	80	1.0	173	
UK	489	0.6	341	0-6	359	0.6	700	
USA	962	0.9	2573	1-0	3122	0.9	5695	

^{*}Taken from worldwide survey.¹ †Estimates assume annual frequency of CT examinations in Japan was equal to that for all health-care level 1 countries. However, number of CT scanners per million population in Japan is 3·7 times that for all health-care level 1 countries. If this number is reflected in annual frequency of CT examinations, then for Japan estimated annual number of X-rays per 1000 increases to 1573 and the attributable risk increases to 4-4%, corresponding to 9905 cases of cancer per year.

Table 6: Frequency of diagnostic X-rays per 1000 population, percentage of cumulative cancer risk to age 75 years attributable to diagnostic X-rays, and number of radiation-induced cases of cancer per year for 15 countries

Cancers radio-induits: according to BEIR V

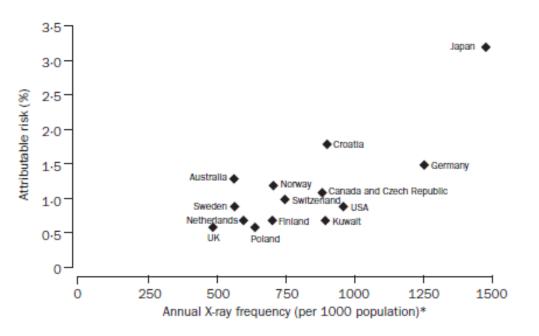


Figure 3: Risk of cancer attributable to diagnostic X-ray exposures versus annual X-ray frequency

	Cases of cancer p	radiation-ind er year*	Cases per million	
	Males	Females	Total	examinations*
X-ray type				
Abdomen	16	15	31	30
Barium meal	5	6	11	40
Barium enema	27	28	55	170
Chest	1	3	4	1
Coronary angiography	13	28	41	280
CT scan	31	39	70	60
Cerebral angiography	1	1	2	180
Hip or pelvis	28	24	52	30
Lumbar spine	23	16	39	40
Screening mammography		8	8	8
Thoracic spine	2	4	6	20
Each other type	<10	<10	<20	

^{*}Includes only nine cancer sites listed in Table 2. Detailed estimation of number of radiation-induced cases for all cancers is not possible, since estimates of organ-specific doses are not available for other cancers.

Table 3: Estimated number of radiation-induced cases of cancer per year in the UK by type of X-ray

^{*}Taken from worldwide survey.1



ORIGINAL INVESTIGATION

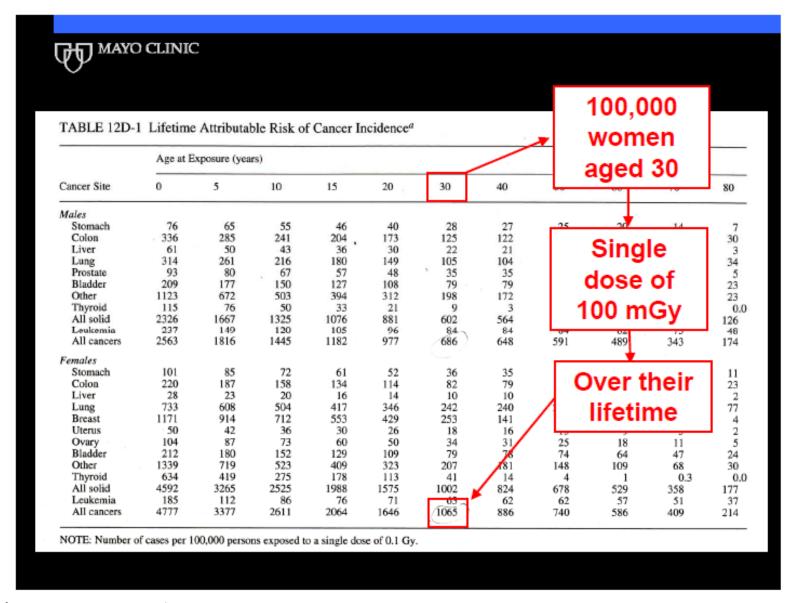
Projected Cancer Risks From Computed Tomographic Scans Performed in the United States in 2007

Amy Berrington de González, DPhil; Mahadevappa Mahesh, MS, PhD; Kwang-Pyo Kim, PhD; Mythreyi Bhargavan, PhD; Rebecca Lewis, MPH; Fred Mettler, MD; Charles Land, PhD

Using BEIR VII report, estimated radiation-related incident cancers

Estimated that 29,000 future cancers could be related to CT scans performed in the U.S. in 2007.....and would translate into about 14,500 cancer deaths.

Arch Intern Med. 2009;169(22):2078-2086



M.K. O'Connor, Mayo Clinic



Where does the estimate of 29,000 cancers come from ?

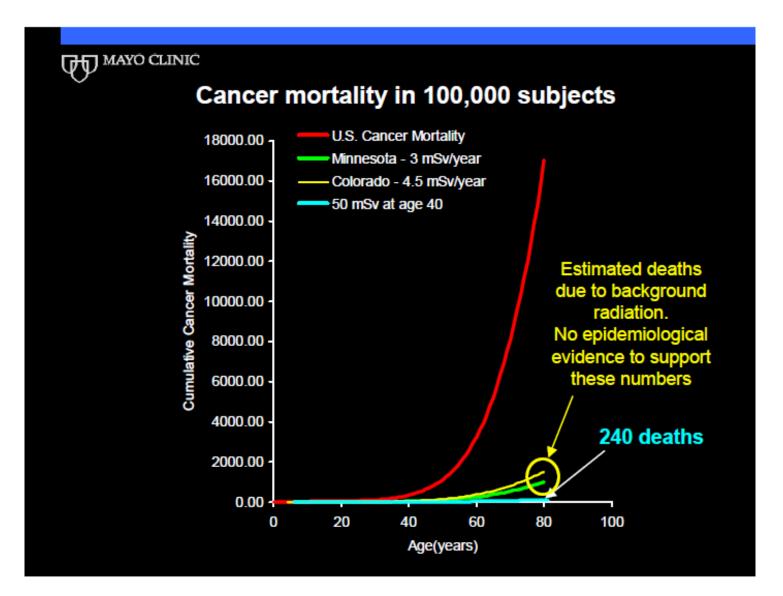
Based on Table 12D BEIR VII, and risk estimates for 56,900,000 patients

For comparison: 9,700,000 people will die of cancer

IF they all lived in Minnesota, (bkg rad = 3 mSv) we would expect 576,000 deaths from background radiation

IF they all lived in Colorado, (bkg rad = 4.5 mSv) we would expect 863,000 deaths from background radiation

Differences in residence = 287,000 cancers, or ~10 CT scans/patient



Cancers radio-induits: imagerie pédiatrique



We understand that every patient is different. We know that medical imaging helps your doctor with your care. So we perform only necessary medical imaging exams, and make sure it's the right test and the right radiation does for each patient — large or small.

Radiation protection is important for children and adults. If you have questions, ask your radiology professional before the test, and you can learn more at the websites imagewisely.org and imagegently.org.







Cancers radio-induits: imagerie pédiatrique

Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study

W-Y Huang^{1,2}, C-H Muo³, C-Y Lin⁴, Y-M Jen¹, M-H Yang^{2,5}, J-C Lin¹, F-C Sung^{3,6} and C-H Kao*,^{6,7}

Table	1. Incidence and adjusted	d hazard ratio of cancer t	type compared with the u	nexposed cohort
I able	I. IIICIGETICE and adjusted	a nazara rado or cancer i	type compared with the d	Hexposed Wholl

	Unexposed cohort N=97668			Expos	ure cohort N = 24			
Subtype (ICD-9-CM)	Case	Person-years	IR	Case	Person-years	IR	HR	(95% CI)
Overall (140–208, 225, 227.3 and 227.4)	122	428 381	28.48	39	106216	36.72	1.29	(0.90–1.85)
Brain tumour	•	•				•		
Malignat and Benign	30	428 381	7.00	19	106216	17.89	2.56	(1.44-4.54)**
Malignant (191, 192, 194.3 and 194.4)	11	428 381	2.57	5	106216	4.71	1.84	(0.64-5.29)
Benign (225, 227.3 and 227.4)	19	428 381	4.44	14	106216	13.18	2.97	(1.49-5.93)**
Leukaemia (204–208)	17	428 381	3.97	8	106 2 16	7.53	1.90	(0.82-4.40)
ALL (204.0)	10	428 381	2.33	6	106216	5.65	2.43	(0.88-6.68)
AML (205.0)	7	428 381	1.63	2	106216	1.88	1.15	(0.24-5.53)
Other cancers	75	428 381	17.51	12	106216	11.30	0.65	(0.35-1.19)

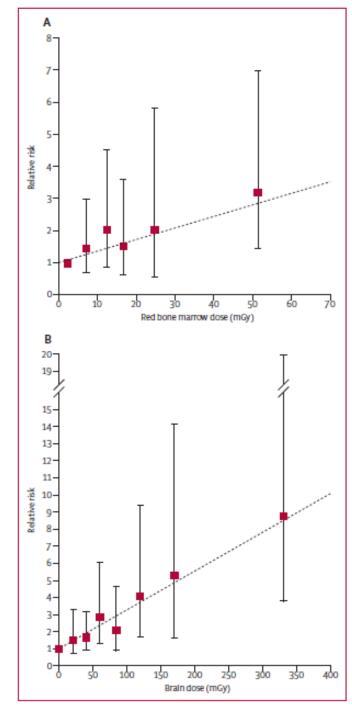
Abbreviations: ALL = acute lymphoid leukaemia; AML = acute myeloid leukaemia; CI = confidence interval; HR = hazard ratio; IR = incidence rate per 100 000 person-years. HR adjusted for age and sex. **P < 0.01.

Cancers radio-induits: imagerie pédiatrique

Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study

	Cases	ERR per mGy (95% CI)	p value (test fo dose-response				
Red bone marrow dose							
All leukaemia, including myelodysplastic syndromes	74	0-036 (0-005 to 0-120)	0-0097				
Acute lymphoblastic leukaemia	26	1719* (>0 to 1773†)	0-0053				
Acute myeloid leukaemia	18	0-021 (-0-042† to 0-155)	0.2653				
Myelodysplastic syndromes	9	6-098* (>0 to 145-4†)	0-0032				
Leukaemia excluding myelodysplastic syndromes	65	0-019 (-0-012† to 0-079)	0.1436				
Brain dose							
All brain	135	0-023 (0-010 to 0-049)	< 0.0001				
Glioma	65	0-019 (0-003 to 0-070)	0-0033				
Schwannoma and meningioma	20	0-033 (0-002 to 0-439)	0-0195				
ERR—excess relative risk. *Iteratively reweighted least-squares algorithm falled to converge, so parameter estimates might be unreliable. †Calculated using Wald-based CI.							

Pearce et al., Lancet, 2012



Cancers radio-induits: en imagerie médicale (F. Jamar)

Même si le risque de cancer radio-induit ne peut être considéré comme nul, Il n'y a de limite que celle de la raison qui veut:

Que tout acte soit potentiellement plus utile que dangereux **JUSTIFICATION**

Que tout acte soit effectué dans les meilleures conditions

OPTIMISATION

Le médecin doit rassurer le patient, pas lui-même

« La morphine a été inventée pour permettre aux médecins de dormir tranquille » S. Guitry

Cancers radio-induits - relativité

RISKS





Expected reduction of life

Unmarried man	3500 days
Smoking man	2250 days
Unmarried woman	1600 days
30% overweight	1300 days
Cancer	980 days
Construction work	300 days
Car accident	207 days
Accident at home	95 days
Administrative work	30 days
Radiological examination	6 days
Cancer Construction work Car accident Accident at home Administrative work	980 days 300 days 207 days 95 days 30 days