Epidémiologie des rayonnements ionisants

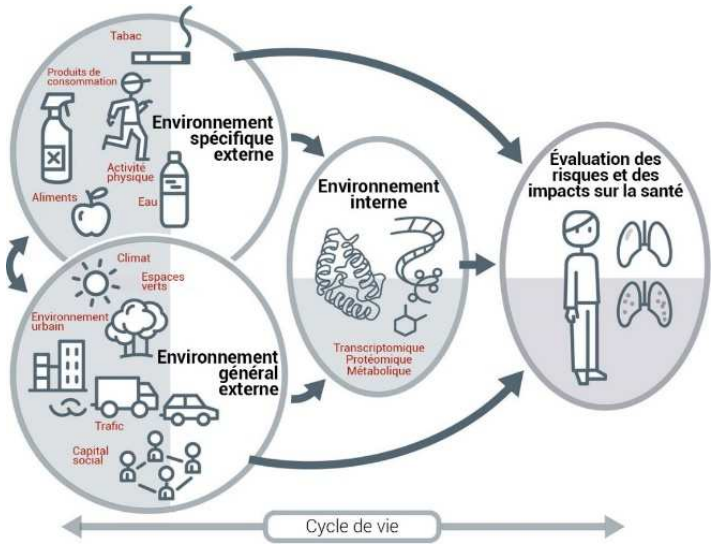
panorama et résultats récents

Epidémiologie

- « L'épidémiologie cherche à la fois à quantifier la fréquence d'un événement de santé dans une population, et à déterminer ses causes biologiques et médicales, environnementales, socio-économiques, etc. » (Inserm, 2009)

Science d'observation : pas de contrôle comme en expérimentation (>biais)

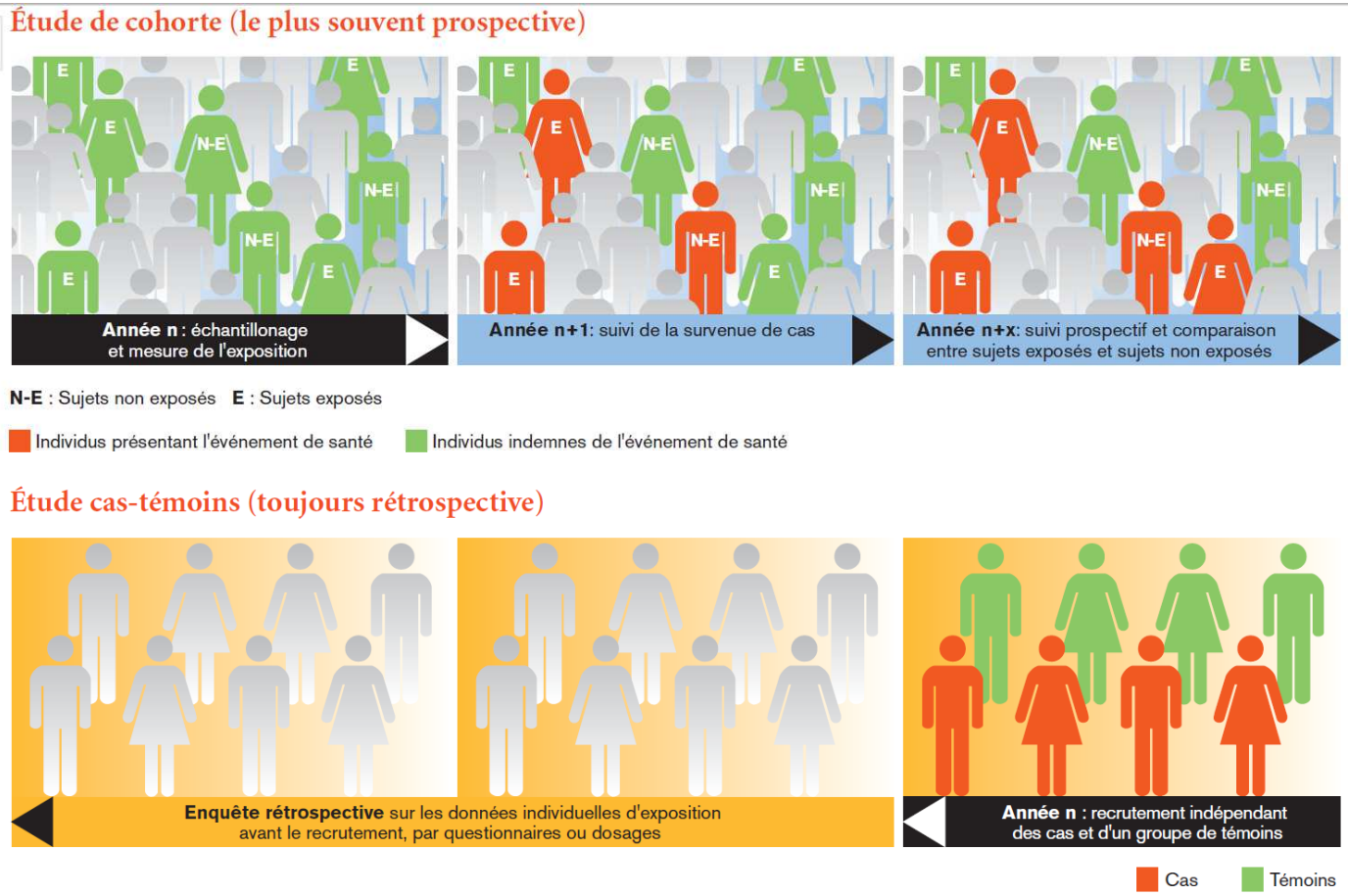
Considère l'homme dans son environnement: expositions multiples



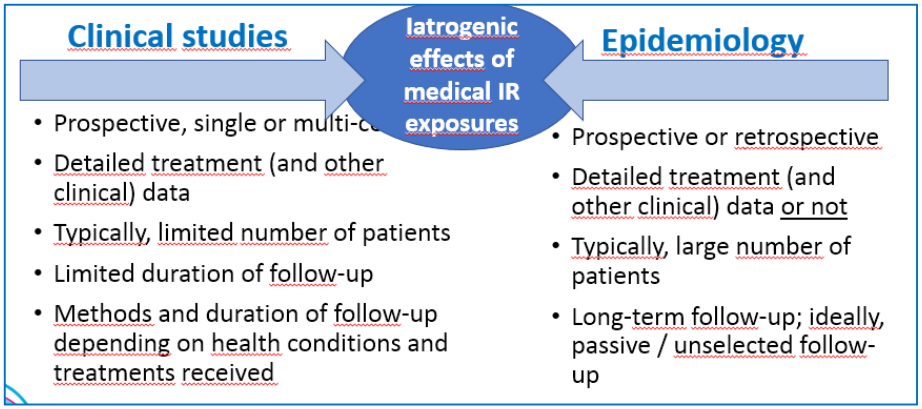
Epidémiologie

Inserm, 2009

- Co

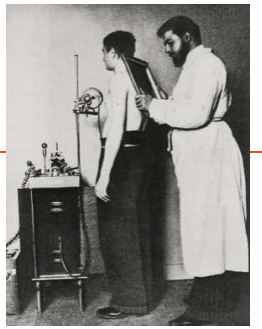


Epidémiologie des RI: champ d'application



- **Effets tardifs** des irradiations aux faibles et fortes doses
- Effets des irradiations aux **faibles doses**
- **Effets stochastiques** (la probabilité d'occurrence augmente avec la dose), effets **non spécifiques**

Epidémiologie des RI: champ d'application



Radiographie effectuée à Thion dans le service d'A Béclère, 1897.

1920	Médecins radiologues (1900-30)
1930	Peintres de cadrans lumineux (1910-30)
1940	Irradiations médicales pour affections non malignes, radio-diagnostique (1920-40)
1950	Survivants d'Hiroshima-Nagasaki (1945)
1960	Mineurs (uranium) (1940-90)
1970	Populations exposées aux retombées d'essais atomiques (1950-)
1970	Travailleurs du nucléaire (1950-)
1980	Populations exposées aux rayonnements naturels
1990	Populations exposées aux conséquences de l'accident de Tchernobyl (1986)
2010	Enfants exposés aux scanners (visée diagnostique) (1980-)
2011	Populations exposées aux conséquences de l'accident de Fukushima (2011)

Epidémiologie des RI: champ d'application

Sources d'exposition de la population

Expo. naturelles
- Rayonnements gamma et cosmiques
- Radon

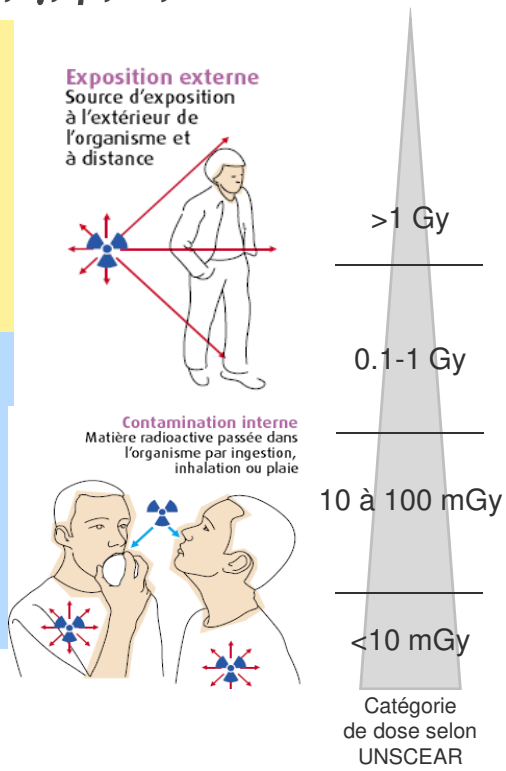
Expo.« accidentelles »
- Bombes atomiques
- Essais nucléaires
- Industrie nucléaire (contamination des milieux)

Expo. professionnelles
- Industrie nucléaire
- Mineurs d'uranium
- Professionnels médicaux
- Transport aérien
- Astronautes, etc.

Expo. médicales
- Radiothérapie
- Radiologie interventionnelle & diagnostique

Nous sommes tous exposés

X, γ, β, α, neutron



Epidémiologie des RI: principaux questionnements

Conditions d'irradiation

- Nature du rayonnement, transfert d'énergie linéique
- Mode d'irradiation (externe, interne), homogénéité de l'exposition
- Débit de dose, exposition aigüe (unique), fractionnée, chronique

Effets sanitaires

- Cancer
- Pathologies non cancer
- Effets transgénérationnels

Délai de latence, taux d'incidence, risque (vs. âge, temps)

Forme de la relation dose-réponse, effet des faibles doses (<1 Gy – 5 Gy)

Facteurs de susceptibilité / sensibilité

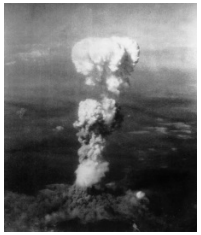
- Sexe, âge à l'exposition (dont *in utero*)
- Tabagisme, facteurs reproductifs, expositions à des agents chimiques
- Facteurs génétiques

Interactions RI – co-facteurs

Effets tardifs aux faibles doses : résultats récents

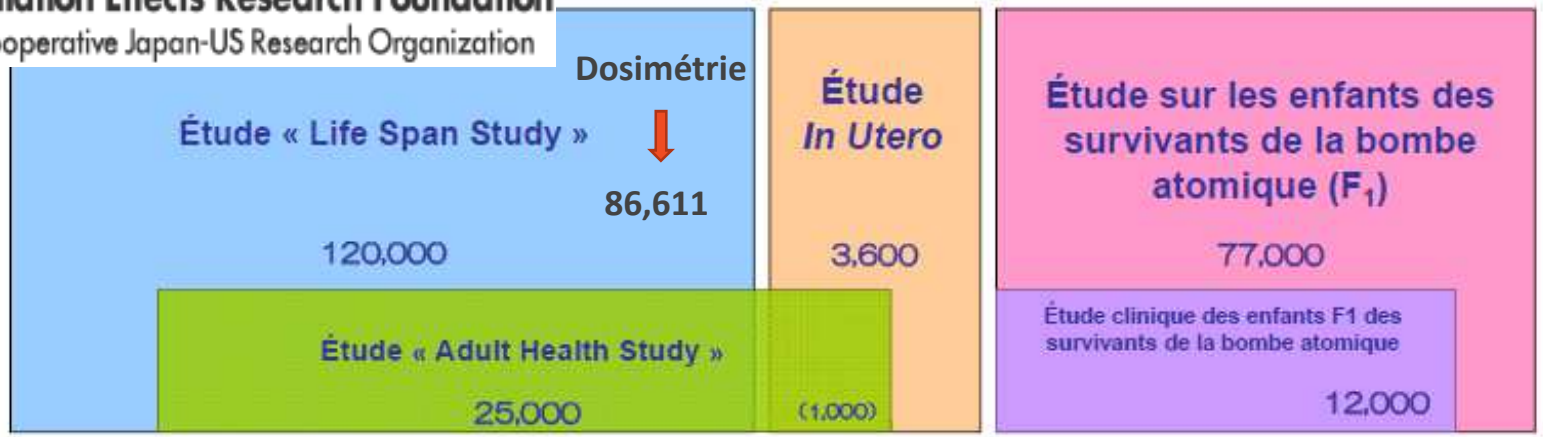
- Survivants des bombardements d'Hiroshima-Nagasaki
- Travailleurs du cycle du nucléaire
- Scanographie
- Médecine nucléaire

Survivants des bombardements d'Hiroshima-Nagasaki



- Bombardements en 1945, 660 000 habitants, ~200 000 décès
- Rayonnements externes γ et neutron, doses < 2Gy (<100 mGy pour 80% des individus, débit de dose très élevé)
- Suivi épidémiologique depuis 1950

放影研 RERF **Radiation Effects Research Foundation**
A Cooperative Japan-US Research Organization



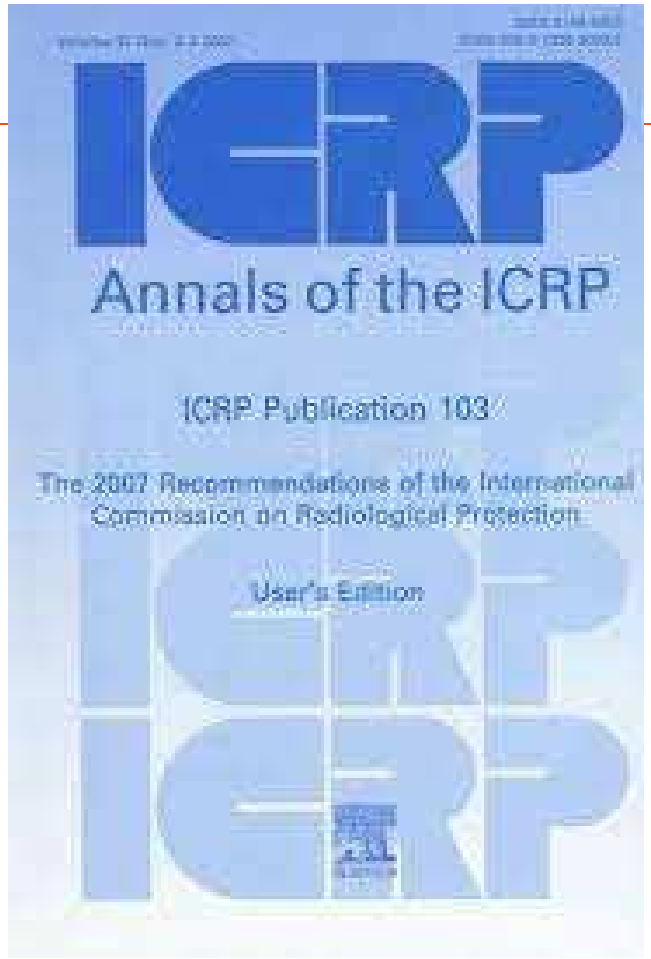
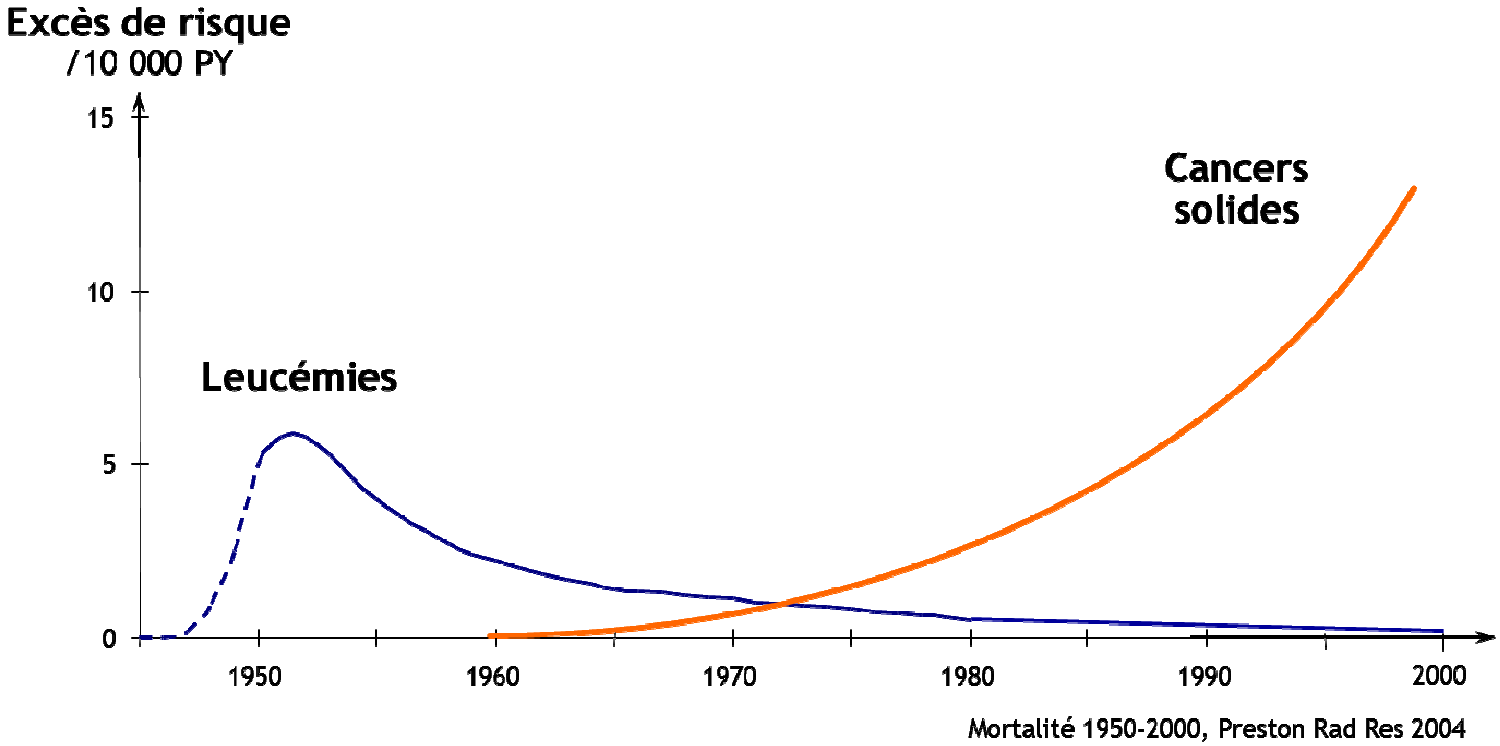


Table 2. Steps in the construction of the radiation detriment, from nominal risk coefficient to detriment for the general population and for workers (from Publication 103, ICRP 2007)

Organ/tissue	**Nominal risk coefficient** R *	Lethality fraction k	Min weight for non-fatal cancers q_{min}	Non-fatal case weight q	Relative cancer free life lost l	**Detriment** D *	Relative detriment
General population (ages 0-84 years at exposure)							
Oesophagus	15	0.93	0.1	0.935	0.87	13.1	0.023
Stomach	79	0.83	0.1	0.846	0.88	67.7	0.118
Colon	65	0.48	0.1	0.530	0.97	47.9	0.083
Liver	30	0.95	0.1	0.959	0.88	26.6	0.046
Lung	114	0.89	0.1	0.901	0.80	90.3	0.157
Bone	7	0.45	0.1	0.505	1.00	5.1	0.009
Skin	1000	0.002	0.0	0.002	1.00	4.0	0.007
Breast	112	0.29	0.1	0.365	1.29	79.8	0.139
Ovary	11	0.57	0.1	0.609	1.12	9.9	0.017
Bladder	43	0.29	0.1	0.357	0.71	16.7	0.029
Thyroid	33	0.07	0.2	0.253	1.29	12.7	0.022
Bone marrow	42	0.67	0.1	0.702	1.63	61.5	0.107
Other solid	144	0.49	0.1	0.541	1.03	113.5	0.198
Gonads (heritable)	20	0.80	0.1	0.820	1.32	25.4	0.044
Total	1715					574.2	1.000

[Cléro, JRP 2019]

Survivants des bombardements d'Hiroshima-Nagasaki



Survivants des bombardements d'Hiroshima-Nagasaki

Cancers

Excès de risque démontré:

- Leucémies
- Cavité orale
- Œsophage
- Estomac
- Colon
- Foie
- Poumon
- Peau (non mélanome)
- Sein (femmes)
- Ovaire
- Vessie, Tractus urinaire
- Prostate
- SNC : gliome, méningiome
- Thyroïde

[Preston, Radiat Res 2007
Hsu, Radiat Res 2013
Utada, JNCI Cancer Spectr 2018
Brenner, Radiat Res 2018
Sadakane, Radiat Res 2019
Brenner, Eur J Epidemiol 2020
Mabuchi et al., 2020
Utada, Radiat Res 2021
Grant, Radiat Res 2021]

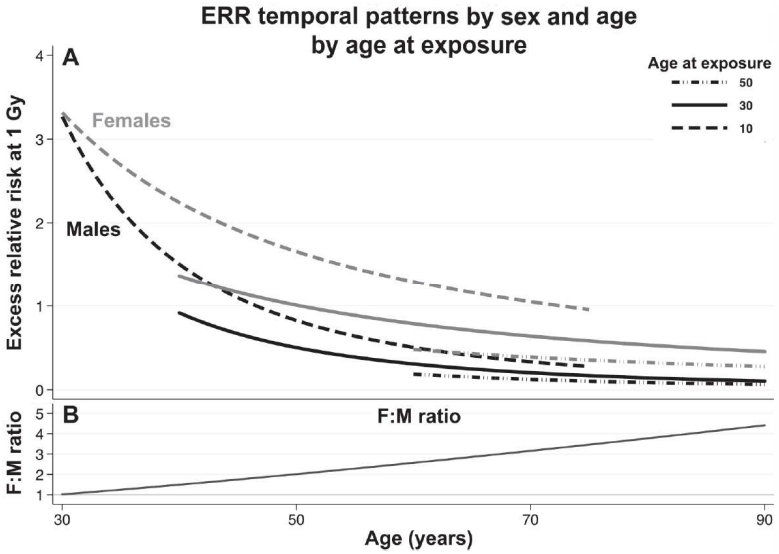
Suspecté: pancréas, rein, ovaire (séreux), sein (hommes), neurinome de l'acoustique, lymphome non-Hodgkin

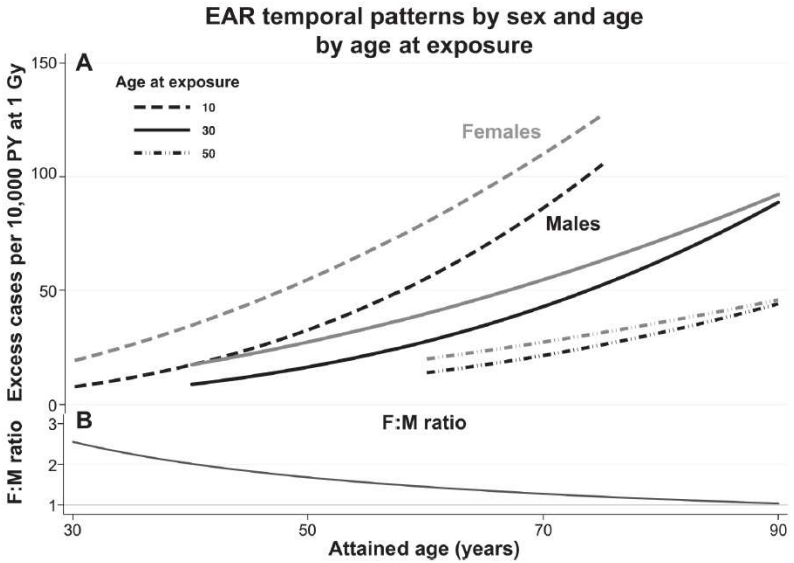
Pas d'excès de risque: col de l'utérus, ovaire (mucineux), vésicule biliaire, lymphome de Hodgkin, myélome multiple

Survivants des bombardements d'Hiroshima-Nagasaki

[Grant et al, Rad Res 2017]

Cancers solides (incidence 1958-2009)



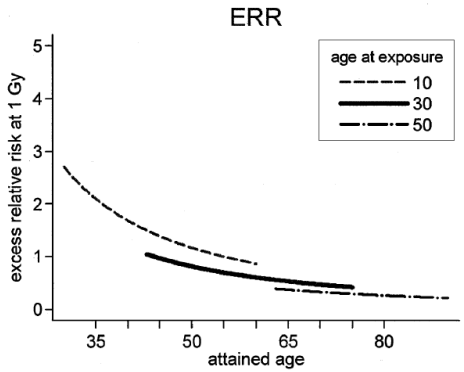


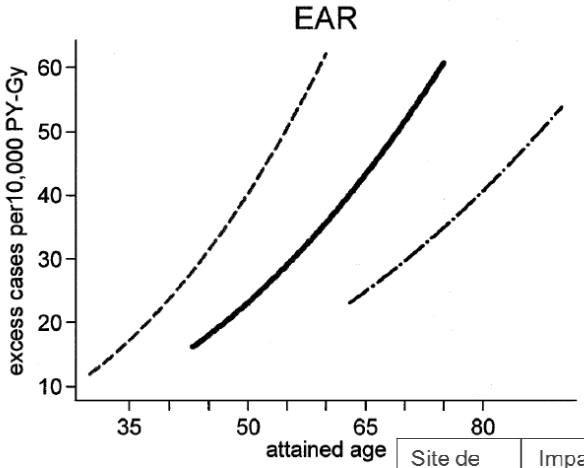
- **Relation dose-réponse linéaire** (hommes et femmes)
- **Excès de risque significatif pour des doses de 0 – 100 mGy, Pas de preuve d'existence de seuil**
- ERR décroit / EAR augmente avec âge atteint.

Survivants des bombardements d'Hiroshima-Nagasaki

Cancers: effet de l'âge à l'exposition

Tous cancers solides
[Grant et al, Rad Res 2017]





[UNSCEAR 2013]

83. The Committee has reviewed over 23 tumour sites for age-at-exposure effects. For about 15% of tumour types (e.g. bladder cancer), children appear to have about the same radiosensitivity as adults. For about 10% of tumour types (e.g. lung cancer), children appear less sensitive to external radiation exposure than adults. For about 20% of tumour types (e.g. oesophagus cancer), the data are too weak to draw a conclusion regarding differences in risk with age at exposure. Finally, for about 30% of tumour types (including Hodgkin's lymphoma, prostate, rectum and uterus cancer), there is only a weak or no relationship between radiation exposure and risk at any age of exposure.

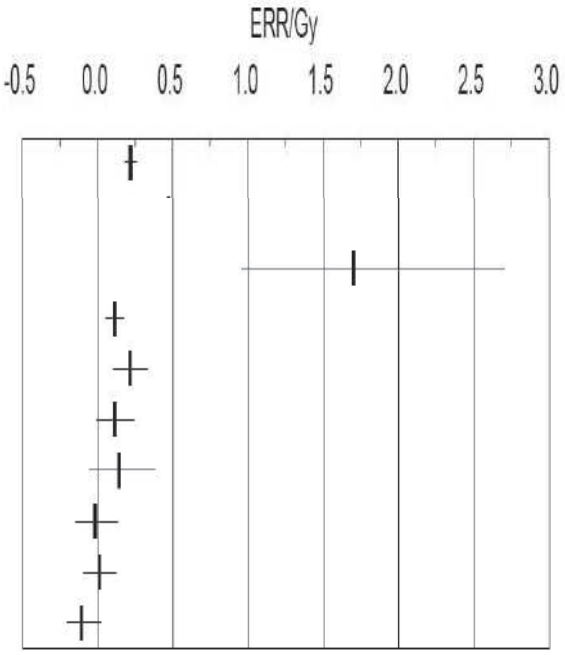
Site de cancer	Impact sur le risque radio-induit
Estomac	↑
Poumon	↓
Peau	↑
Sein	↑
Vessie	‹ ›
Cerveau	↑
Thyroïde	↑
Leucémie	↑

Survivants des bombardements d'Hiroshima-Nagasaki

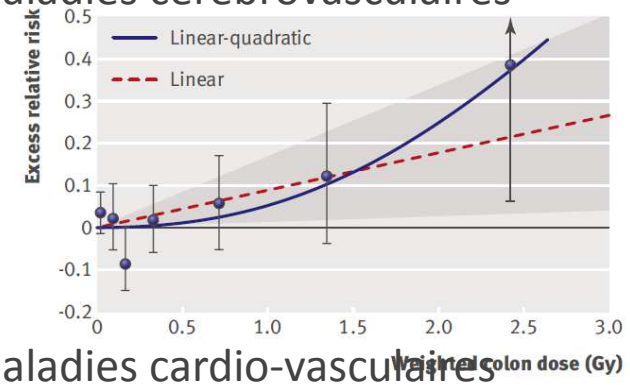
[Ozasa et al., Radiat Res 2012]
[Shimizu et al., BMJ 2010]

Décès par maladies non cancéreuses

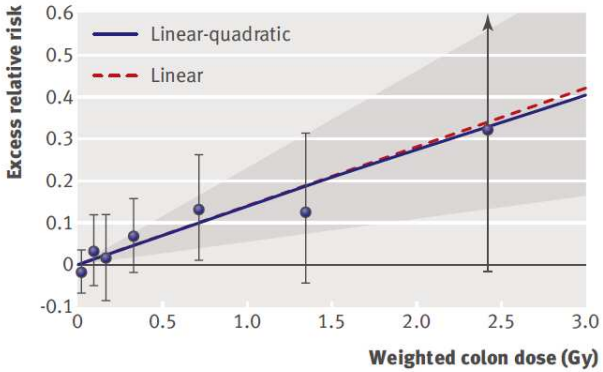
Cause of death	ERR/Gy [a] (95%CI [b])	Cases
All causes	0.22 (0.18, 0.26)	50,620
Non-neoplastic diseases and other causes		
Blood diseases	1.70 (0.96, 2.70)	238
Circulatory diseases	0.11 (0.05, 0.17)	19,054
Respiratory diseases	0.21 (0.10, 0.33)	5,119
Digestive diseases	0.11 (-0.01, 0.24)	3,394
Genitourinary diseases	0.14 (-0.06, 0.38)	1,309
Infectious diseases	-0.02 (-0.15, 0.13)	1,962
Other diseases	0.01 (-0.1, 0.12)	4,847
External causes	-0.11 (-0.21, 0.02)	2,432



Maladies cérébrovasculaires



Maladies cardio-vasculaires



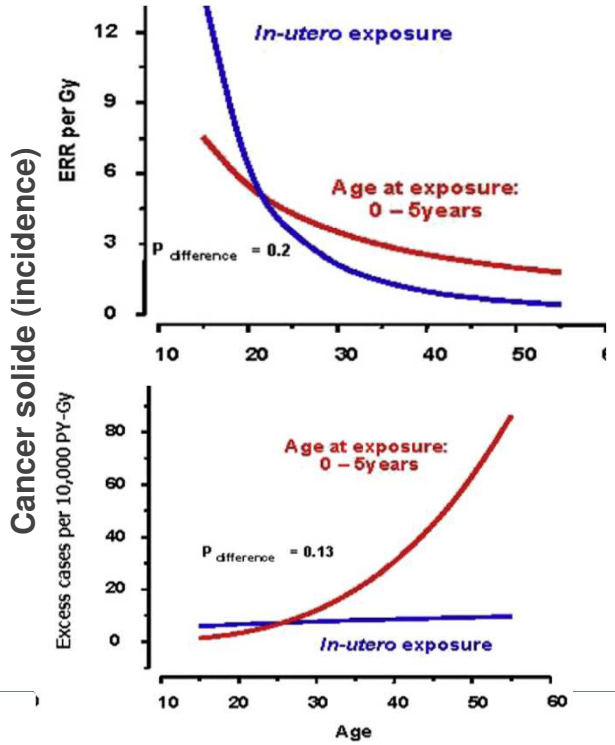
Survivants des bombardements d'Hiroshima-Nagasaki

[Preston, JNCI 2008; Tatsukawa, Radiat Res 2008; Sugiyama, EJE 2021]

Effets des expositions *in utero*

2,463 individus, suivi 1958-2012. Dose moyenne chez les exposés: 0,1 Gy (0 – 2,5 Gy), 80% exposés à <0.1 Gy

Effets	Résultats
Cancer solide (mortalité)	↑ uniquement chez les femmes
Cancer solide (incidence)	↑ significative. ERR/Sv décroit avec l'âge atteint, sex-ratio F/H (EAR)=2
Pathologies non-cancer (mortalité)	↑ expliquée par faible poids de naissance, petite taille de la tête, père décédé ou mère
Pathologies non-cancer (incidence)	Pas d'effet dose-réponse significatif (sous-cohorte; N=506)



Effets transgénérationnels

- Incidence pathologies non-cancer : pas d'association avec la dose reçue par les parents (11 951 enfants) *[Tatsukawa et al., J Radiol Prot 2013]*

- Mortalité par cancer ou pathologies non-cancer : pas d'association avec les doses maternelles ou paternelles (75 327 enfants), Dose moyenne aux gonades des parents exposés : 264 mSv, âge médian à la fin du suivi = 53 ans *[Grant et al., Lancet Oncol 2015]*

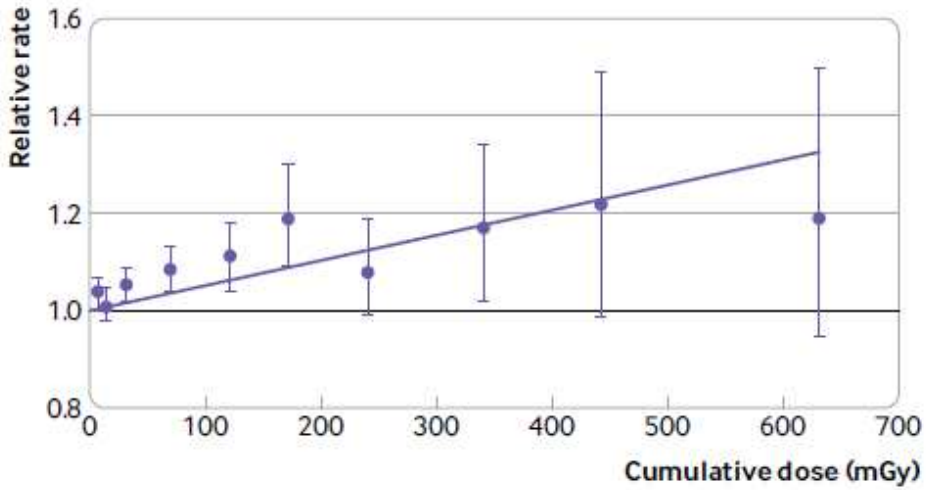
INWORKS (travailleurs du cycle du nucléaire, France-UK-US)

[Richardson, BMJ 2023]

310,000 workers with individual monitoring data for external exposure to ionising radiation; Mean follow-up time= 35 ans; Mean cumulative dose to colon = 21 mGy

Photons (100 – 3,000 keV) +neutrons

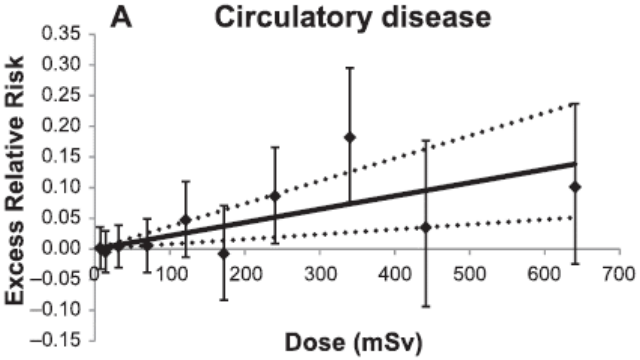
- Linear association between protracted low dose external IR exposure and solid cancer mortality; but some evidence for a steeper slope at lower doses (0 – 200 mGy)
- Significant increase of risk at 0-50 mGy cumulative dose ranges
- No evidence supporting the relevance of a Dose and Dose Rate Effectiveness Factor (DDREF)

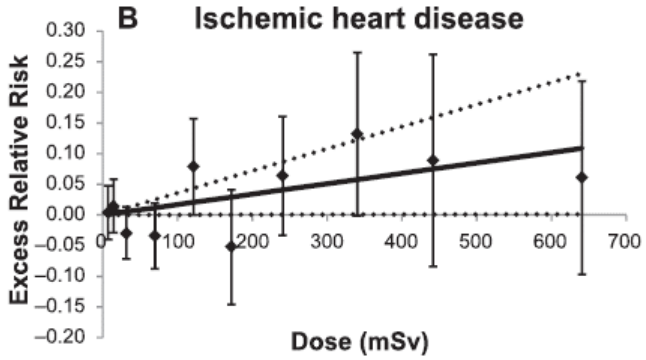


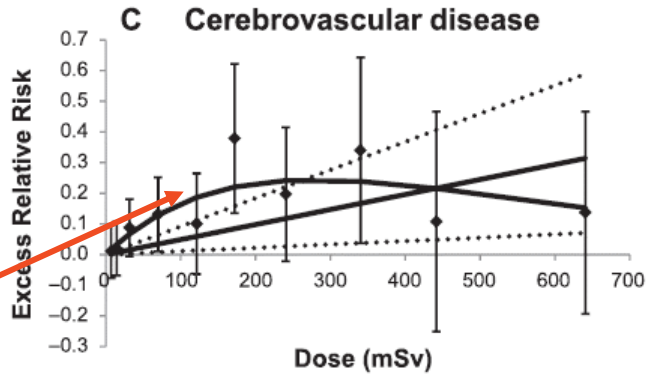
INWORKS : ERR/Gy = 0.52 (90%IC: 0.27 to 0.77)
vs. LSS, males exposed at ages 20-60 years : ERR/Sv = 0.32 (95%IC: 0.01 to 0.50)

INWORKS (travailleurs du cycle du nucléaire, France-UK-US)

[Gillies et al., Radiat Res 2017]



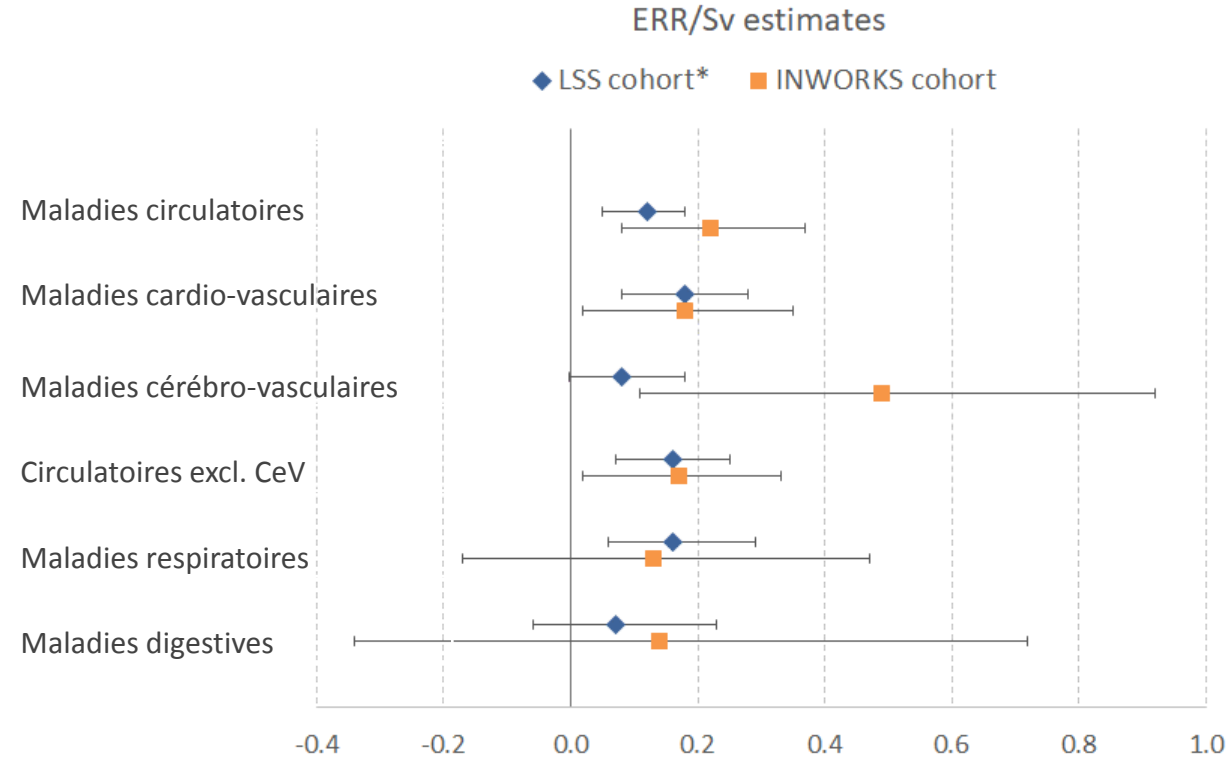




Modèle linéaire-exponentiel :
ERR(d) = $\beta_1 d\exp(\beta_2 d)$

INWORKS (travailleurs du cycle du nucléaire, France-UK-US) vs. Life Span Study

[Gillies et al., Radiat Res 2017]



* adultes exposés entre 20 et 60 ans avec une dose au côlon < 2 Gy

Scanographie – x-rays

EPI-CT

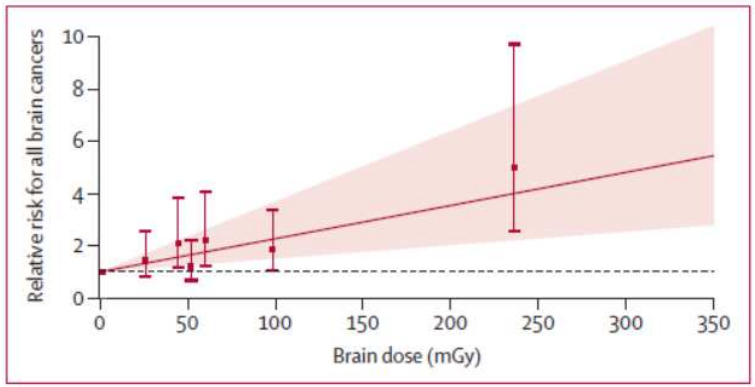
[Hauptmann, Lancet Oncol 2023]

Tumeurs malignes du cerveau

EPI-CT: 948,000 individus, suivi médian= 6 ans, 165 cas (121 gliomes). CT en 1977- 2014, 9 pays européens, âge médian (range) = 11 ans (0–22), dose médiane cumulée au cerveau = 44 mGy

Une manipulatrice radio prépare un enfant à un scanner cérébral. © Philippe Castano/IRSN

- Augmentation significative de risque pour des doses au cerveau de 40 –50 mGy
- Risque absolu : 1 tumeur cérébrale (glioma) radio-induite / 10 000 scanners de la tête, durant les 5-15 premières années de suivi



Scanographie – x-rays

EPI-CT

[Hauptmann, Lancet Oncol 2023]

Tumeurs malignes du cerveau

	ERR / 100 mGy	IC à 95%
CT, tous	1·27	(0·51 to 2·69)
CT, sauf UK	0·91	(0·12 to 2·83)
CT, sauf UK, gliomes	0·65	(-0·03 to 2·45)
CT, sauf 3% les plus exposés	0·94	(0·09 to 2·54)
Life Span Study (agex <20 ans, suivi ≤20 ans)	0.61	(0·01 to 6·39)

BJC British Journal of Cancer

[Thi-Van-Trinh, *Br J Cancer 2022*]

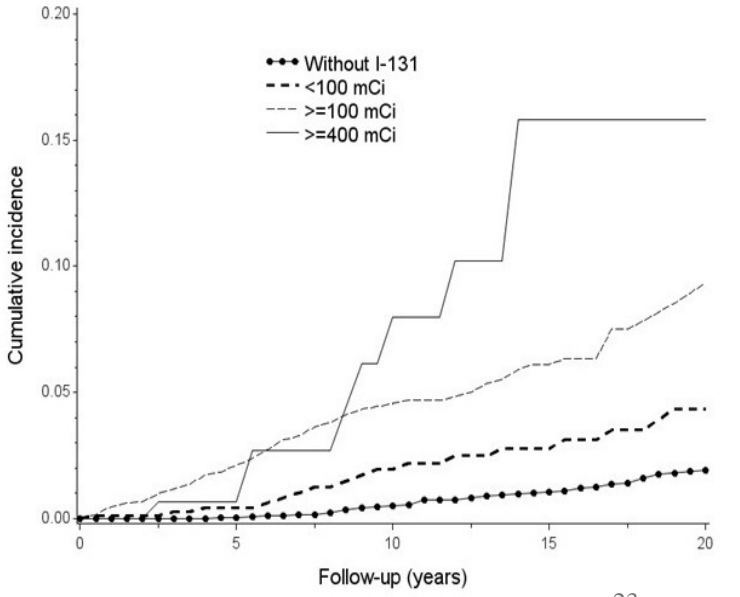
Cancer du sein après traitement d'un cancer de la thyroide (I-131)

8,500 femmes, âge moyen 45 ans au diagnostic de cancer de la thyroïde

Activité cumulée I-131, médiane (min–max)= 100 (10–1597) mCi

- Incidence cumulée à 10 ans avec I-131 = 4% (95% CI: 3–5%) vs. 0.5% sans I-131
- Relation dose-réponse linéaire
- Risque absolu, ≥100 mCi : 4 cas de cancer du sein en excès / 10,000 personnes-années
- Risque absolu, ≥400 mCi : 42 cas de cancer du sein en excès / 10,000 PA

Cumulative incidence of breast cancer after thyroid cancer.



Effet des faibles doses: en résumé

- Excès de risque de cancers solides, leucémies et tumeurs bénignes démontrés à des doses de 0 – 100 mGy; Relation dose-réponse linéaire la plus plausible; pas de seuil démontré; hétérogénéité des résultats selon études / sources d'exposition faible

- Excès de risque de pathologies cardio- et cérébro-vasculaires démontrés à des doses de 0 – 500 mGy. Relation dose-réponse linéaire pour path. cardiaques

- Pas de diminution de risque pour exposition chronique et fractionnée vs. exposition unique

RESEARCH

OPEN ACCESS

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Ionising radiation and cardiovascular disease: systematic review and meta-analysis

Mark P Little,[1] Tamara V Azizova,[2] David B Richardson,[3] Soile Tapio,[4] Marie-Odile Bernier,[5] Michaela Kreuzer,[6] Francis A Cucinotta,[7] Dimitry Bazyka,[8] Vadim Chumak,[8] Victor K Ivanov,[9]

Radiothérapie externe :

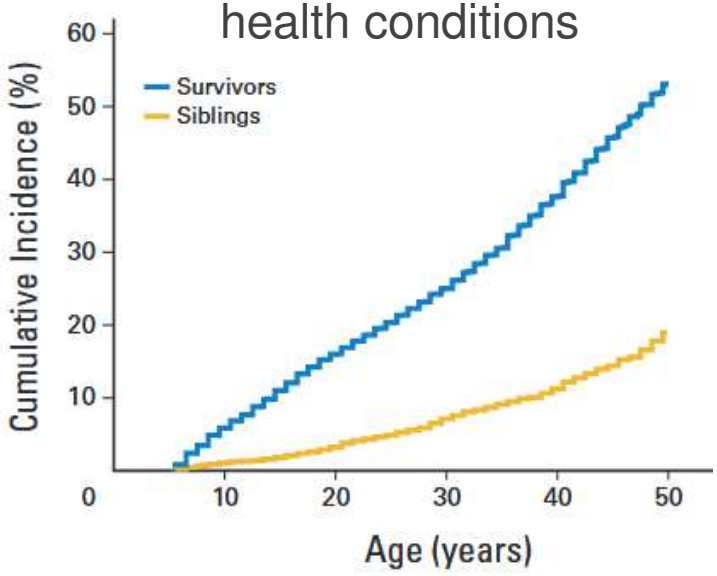
Effets tardifs

Effets tardifs après cancer

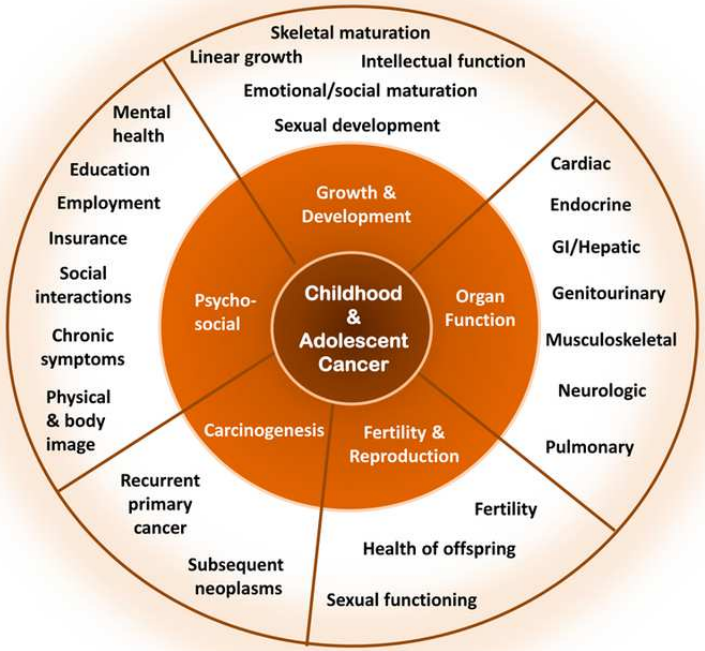
[Robison, Nat Rev Cancer 2014
Armstrong et al JCO 2014]

Half of childhood cancer survivors developed one or more severe, disabling, life-threatening or fatal health condition.s before the age of 50 years

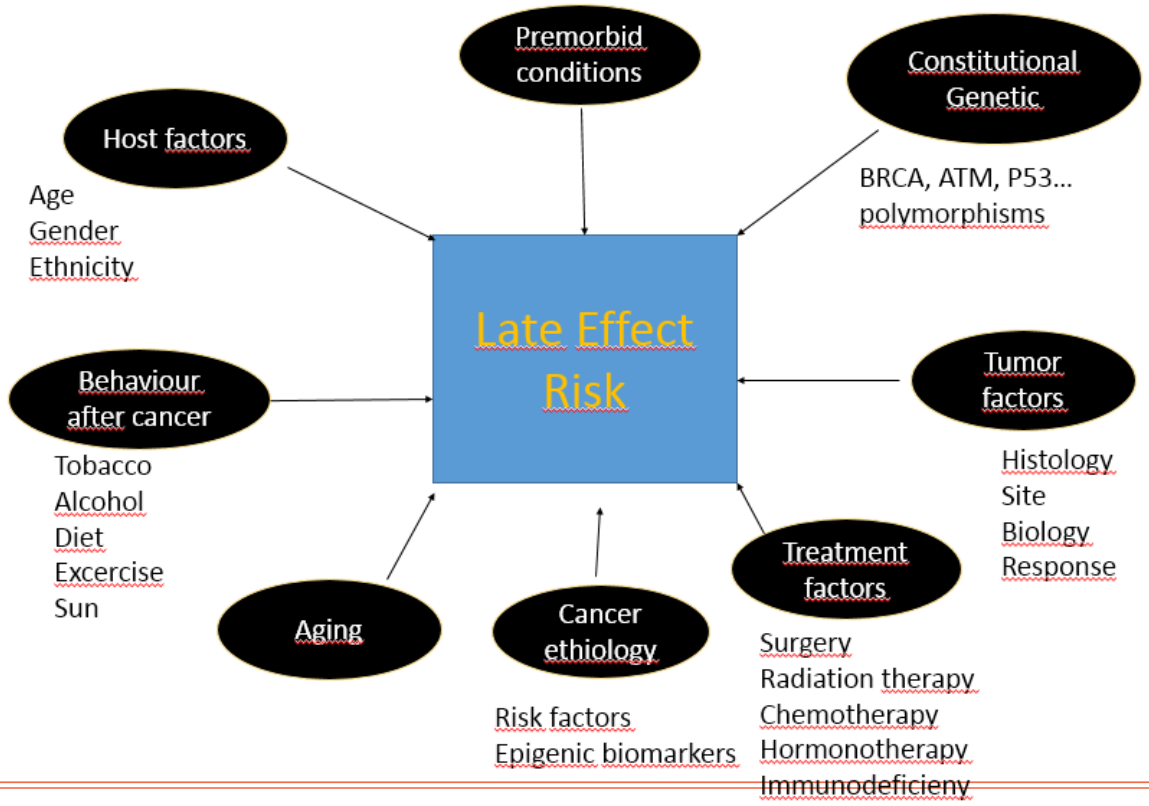
Grade 3-5 chronic health conditions



Spectrum of health-related and quality of life outcomes among long-term survivors of childhood and adolescent cancers.



Effets tardifs après cancer: rôle de la radiothérapie?



Effets tardifs post-RTX : second cancers

CCSS THE CHILDHOOD CANCER SURVIVOR STUDY

[Turcotte, JAMA 2017]

JAMA | Original Investigation

Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015

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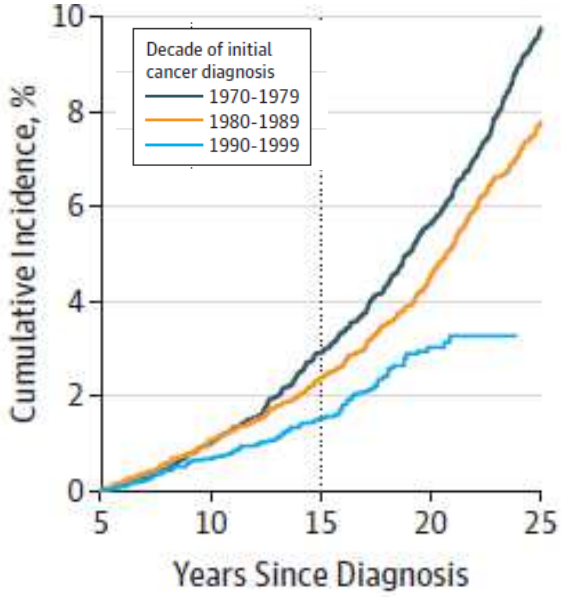
Childhood Cancer Survivor Study: 23,603 five-year survivors of cancer diagnosed in 1970-1999 in the U.S. and Canada at age <21 years

- % treated with RT decreased: 77% in the 1970s to 33% to 1990s
- median RT dose also decreased over time (30 Gy in the 1970s to 26 Gy in the 1990s)
- % treated with alkylating agents, anthracyclines and epipodophyllotoxins and platinum increased over time, but median doses decreased, except for platinum and epipodophyllotoxins

Mean follow-up time: 20 years



No. at risk					
1970s	6223	5806	5535	4981	4046
1980s	9430	8823	7842	6353	1811
1990s	7950	7521	4474	902	0

Effets tardifs post-RTX : second cancers

CCSS THE CHILDHOOD CANCER SURVIVOR STUDY

[Turcotte, JAMA 2017]

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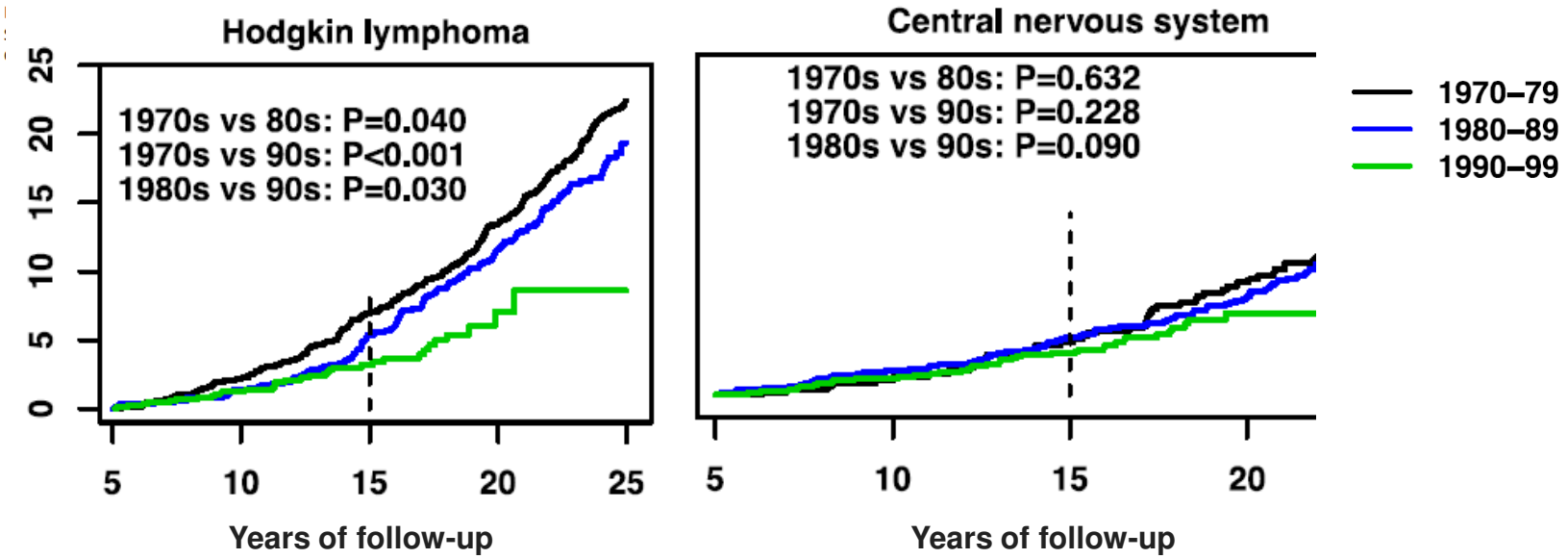


Effets tardifs post-RTX : second cancers

CCSS THE CHILDHOOD CANCER SURVIVOR STUDY

[Turcotte, JAMA 2017]

Table 3. Relative Rates of Overall and Subsequent Neoplasm Subtypes, per 5-Year Treatment Era, Without and With Adjustment for Treatment Variables[a]

		Subsequent Neoplasm		Subsequent Malignant Neoplasm		Meningioma		Nonmelanoma Skin Cancer	
Treatment Era		RR (95% CI)	*P* Values	RR (95% CI)	*P* Values	RR (95% CI)	*P* Values	RR (95% CI)	*P* Values
Not adjusted for any treatment (A)		0.81 (0.76-0.86)	<.001	0.87 (0.82-0.93)	<.001	0.85 (0.75-0.97)	.03	0.75 (0.67-0.84)	<.001
Adjusted for:									
All treatments except maximum radiation dose (B)		0.84 (0.78-0.90)	<.001	0.87 (0.81-0.94)	<.001	0.80 (0.68-0.92)	.003	0.81 (0.71-0.92)	.001
Maximum radiation dose (C)		0.93 (0.87-0.99)	.02	0.96 (0.90-1.02)	.20	1.01 (0.87-1.17)	.90	0.87 (0.78-0.97)	.01
All treatments (D)		0.91 (0.84-0.98)	.01	0.93 (0.86-1.00)	.047	0.94 (0.81-1.10)	.47	0.87 (0.76-1.00)	.048
Statistical significance for the coefficient difference	A vs B		.10	A vs B	>.99	A vs B	.02	A vs B	.046
	A vs C		<.001	A vs C	<.001	A vs C	<.001	A vs C	<.001
	A vs D		<.001	A vs D	<.001	A vs D	<.001	A vs D	.03
	B vs C		<.001	B vs C	<.001	B vs C	.02	B vs C	<.001
	B vs D		<.001	B vs D	<.001	B vs D	<.001	B vs D	<.001
	C vs D		.24	C vs D	.046	C vs D	.90	C vs D	.10

Abbreviation: RR, relative rate.

[a] Separate models were developed for each outcome, adjusting for sex, age at initial cancer diagnosis, attained age as cubic spline. Models adjusting for treatment included maximum radiation dose to the body, splenectomy, cyclophosphamide equivalent dose, anthracycline dose, epipodophyllotoxin dose, and platinum dose.

After adjusting for sex, age at diagnosis, and attained age, RRs declined for every 5-year increment of treatment era

No change when adjusting for all treatments except radiation dose

"RT dose changes were the chief contributor to the era-associated decline of subsequent neoplasm rates and [..] RT dose changes were the only component of the treatment variables significantly associated with the decline of subsequent neoplasm rates over time"

Leucémies : effet de la RT

[Allodji, Int J Cancer 2022]

Etude internationale : France, Royaume-Uni, Etats-Unis, Canada, Italie, Pays-Bas

TABLE 2 Risk of secondary leukemia in relation to radiotherapy or/and chemotherapy

Treatment characteristics	Cases/controls	Univariate analyses Odds ratio[a] (95% CI)	Multivariable analysis Odds ratio[a] (95% CI)
Radiotherapy			
No	50/224	1.0 (Reference)	1.0 (Reference)
Yes	97/298	1.6 (1.0-2.4)	1.5 (0.99-2.3)
P value for heterogeneity		.03	.06
Chemotherapy			
No	15/151	1.0 (Reference)	1.0 (Reference)
Yes	132/371	6.2 (2.9-13.3)	5.5 (2.6-12.0)
P value for heterogeneity		<.0001	<.0001
Treatment combination			
Nor radiotherapy nor chemotherapy	2/65	1.0 (Reference)	
Radiotherapy alone	13/86	6.4 (1.3-30.3)	
Chemotherapy alone	48/159	19.0 (3.8-94.7)	
Radiotherapy and chemotherapy	84/212	24.6 (5.0-120.8)	
P value for heterogeneity		.0001	

Abbreviation: 95% CI, 95% confidence interval.
[a]Conditional logistic regression matched on gender, age at childhood cancer diagnosis and follow-up, and the multivariable analysis, adjusted for radiotherapy, chemotherapy and year of diagnosis.

Effet prépondérant de la chimio
(Inhibiteurs des topoisomérases II, cyclophosphamide)

Leucémies : effet de la RT

[Allodji, Int J Cancer 2022]

Appendix Table A7: Risk of secondary leukemia in relation to radiotherapy (RT) and selected chemotherapy groups in pooled data according to the interval (≤ or > 10 years) after childhood cancer, according to average radiation dose to active bone marrow (ABM) and chemotherapy, by type of leukemia

Treatment characteristics	Cases/ controls	Odds ratio[$] (95% CI)
All leukemias	**147/522**	
Delay after FPN ≤ 10 years and no RT	41/124	25.4 (7.9-82.3)
Delay after FPN ≤ 10 years and RT	78/158	34.8 (10.8-111.8)
Delay after FPN > 10 years and no RT	**9/100**	**1.0 (Reference)**
Delay after FPN > 10 years and RT	19/140	1.2 (0.43-3.2)
[§]P-value for interaction		*0.9*
Delay after FPN ≤ 10 years and no Topo II	37/142	25.2 (7.2-88.5)
Delay after FPN ≤ 10 years and Topo II	82/140	93.9 (24.7-357.3)
Delay after FPN > 10 years and no Topo II	**13/153**	**1.0 (Reference**
Delay after FPN > 10 years and Topo II	15/87	3.2 (0.99-10.2)
[§]P-value for interaction		*0.9*
Delay after FPN ≤ 10 years and no AA	38/116	40.6 (10.6-155.5)
Delay after FPN ≤ 10 years and AA	81/166	48.2 (12.0-194.8)
Delay after FPN > 10 years and no AA	**10/130**	**1.0 (Reference**
Delay after FPN > 10 years and AA	18/110	2.2 (0.66-7.1)
[§]P-value for interaction		*0.2*

↑ risque dans les 10 premières années de suivi seulement

FPN: first primary neoplasm

Sarcomes osseux : effet de la RT

[Reulen, JCO 2023]

TABLE 3. OR and AR% for Different Levels of Cumulative Radiation Exposure to Site of Development of Subsequent Primary Bone Cancer (in case) and Same Site for the Corresponding Control

Dose, Gy	Mean Dose, Gy	Mean Years to Bone Cancer	Cases, No.	Controls, No.	OR (95%CI)	AR%
0	0.0	13.6	37	87	1.00 (ref)	0
<1	0.2	14.0	49	80	1.15 (0.52 to 2.53)	13
1-4	2.4	13.4	18	17	4.78 (1.16 to 19.63)	79
5-9	7.3	12.9	19	8	9.56 (2.44 to 37.36)	90
10-19	14.0	13.0	26	10	11.35 (2.90 to 44.42)	91
20-39	30.1	13.8	45	12	16.72 (4.66 to 60.01)	94
≥40	49.4	14.8	25	3	78.49 (9.20 to 669.86)	99
Missing			9	11	$P_{\text{linear trend}} < .001$	

Relation dose(RT)-réponse linéaire (?)

[Hawkins, JNCI 1996]

Radiation dose, cGy	No. of patients (median dose, cGy) Control	Case	terval); *P* value Adjusted* for alkylating agent exposure
Incomplete information	52	9	
0	61	10	1.0†
1-999	79 (10)	13 (8)	0.7 (0.2-2.2); *P* = .537
1000-2999	15 (1740)	7 (2160)	12.4 (0.9-163.3); *P* = .055
3000-4999	7 (3750)	15 (4150)	93.4 (6.8-1285.4); *P*<.001
≥5000	6 (5525)	5 (7570)	64.7 (3.8-1103.4); *P* = .004
Total	220	59	

+ augmentation de risque (effet propre) avec procarbazine, ifosfamide, et cyclophosphamide

Sarcomes osseux : effet de la RT

Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies
PanCareSurFup

[Reulen, JCO 2023]

TABLE 6. Evaluation of Potential Effect Modifiers of the Radiation Dose Response

Modification Parameter of Baseline Model	Cases, No.	Controls, No.	EOR/Gy (95% CI)	$P_{heterogeneity}$
Sex				
Males	134	132	1.43 (0.35 to 7.87)	
Females	85	85	1.52 (0.28 to 11.13)	.96
Type of childhood cancer[a]				
Retinoblastoma	70	70	1.17 (0.07 to 25.45)	
Bone sarcoma	38	7	11.46 (0.37 to 232.8)	
Soft-tissue sarcoma	35	21	53.63 (2.09 to 700.6)	
Other	85	130	1.17 (0.29 to 5.26)	.005
Age at childhood cancer diagnosis, years				
0-4	126	128	0.93 (0.26 to 4.09)	
5-9	48	46	2.46 (0.41 to 18.04)	
10-19	45	43	6.97 (454.6[b])	.49
Time between childhood cancer and bone cancer, years				
0-9	70	74	1.40 (0.19 to 27.18)	
10-19	108	104	3.35 (0.63 to 21.77)	
>20	41	39	0.38 (0.06 to 3.50)	.30
Arms/legs	109	107	1.06 (0.24 to 5.20)	.26
Alkylating agents				
No	93	144	1.20 (0.30 to 5.17)	
Yes	123	73	2.89 (17.11[c])	.12
Cyclophosphamide[a]				
No	132	162	1.02 (0.29 to 3.91)	
Yes	76	50	1.16 (0.27 to 6.13)	.83
Ifosfamide[a]				
No	183	207	1.57 (0.49 to 5.35)	
Yes	29	10	12.48 (1.59 to 106.7)	.01
Procarbazine[a]				
No	204	210	1.23 (0.38 to 4.43)	
Yes	11	6	6.32 (131.10[b])	.13
Anthracyclines[c]				
No	132	168	1.05 (0.33 to 3.78)	
Yes	84	48	2.02 (0.43 to 11.79)	.23
Antimetabolites[c]				
No	169	169	1.03 (0.33 to 3.43)	
Yes	46	47	1.24 (0.30 to 5.26)	.70
Epipodophyllotoxins[c]				

facteurs génétiques ?

Cancer colorectal : effet de la RT

[Allodji, Pediatr Blood Cancer 2019]

TABLE 4 Risk of subsequent CRC after childhood cancer in relation to cumulative radiation dose at the site of CRC and specific chemotherapy agents or regimen—multivariable analyses

Treatment characteristics	Cases/ controls	Univariable analyses Odds ratio (95% CI)	Multivariable analysis Odds ratio (95% CI)
Dose category (mean), Gy			
No RT	3/39	OR = 1	OR = 1
0–4.99 (0.79 Gy)	14/64	3.7 (1.1–15.9)	3 (0.9–12.9)
5–19.99 (11.74 Gy)	8/28	5.5 (1.3–26.9)	4.1 (1.0–20.6)
20–29.99 (25.60 Gy)	4/6	13.7 (2.3–91.2)	8.9 (1.4–64.9)
≥30 (35.61 Gy)	7/3	33 (6.2–226)	19.3 (3.4–141.8)
P value for trend		**<.0001**	**0.0009**
Dose category of anthracyclines (mean), g/m^2			
No	22/108	OR = 1	OR = 1
0–0.29 (0.21 g/m^2)	7/15	3.3 (1–11.7)	3.3 (0.9–13.8)
≥0.30 (0.50 g/m^2)	7/17	3 (0.9–10.5)	3.2 (0.8–15.1)
P value for trend		0.06	0.06
Dose category of MOPP (mean), g/m^2			
No	27/128	OR = 1	OR = 1
0–5.29 (2.84 g/m^2)	4/6	3.1 (0.8–11.3)	2.2 (0.5–10.3)
≥5.30 (9.11 g/m^2)	5/6	4.8 (1.2–21.4)	2.4 (0.5–11.8)
P value for trend		**0.01**	0.16
Model			AIC = 97.00

Treatment characteristics	Cases / Controls	Odds ratio (95% CI)	P-values
Model 1 (AIC=98.48)			
Treatment combination			
No Radiotherapy / No Anthracyclines	1/27	OR=1	**0.006**
No Radiotherapy / Anthracyclines	2/12	5.4 (0.51-78.6)	
0-19.99 Gy / No Anthracyclines	15/72	6.4 (1.27-65.3)	
0-19.99 Gy / Anthracyclines	7/20	10.6 (1.76-119)	
20-29.99 Gy / Anthracyclines or not	4/6	20.8 (2.57-277.1)	
≥ 30 Gy / Anthracyclines or not	7/3	57.6 (7.92-754.8)	
Model 2 (AIC= 97.78)			
Treatment combination			
No Radiotherapy / No MOPP	2/37	OR=1	**0.003**
No Radiotherapy / MOPP	1/2	6.7 (0.36-148.9)	
0-19.99 Gy / No MOPP	17/85	3.5 (0.98-19.2)	
0-19.99 Gy / MOPP	5/7	10.2 (2.22-63)	
20-29.99 Gy / MOPP or not	4/6	11.4 (1.83-89.3)	
≥ 30 Gy / MOPP or not	7/3	32.9 (6-253.9)	

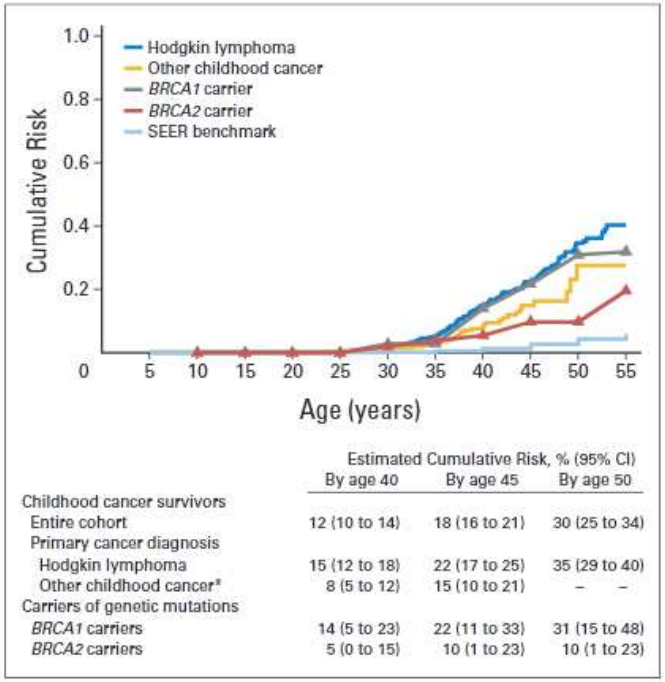
Interactions additives RT – chimio

Abbreviations: AIC, Akaike information criterion that is an estimator of the relative quality of statistical models for a given set of data; MOPP, mechlorethamine, vincristine, procarbazine with or without prednisone; Model refers to the multivariable model included the cumulative radiation dose at the site of CRC (dose category), anthracyclines (dose category) and MOPP (dose category); RT, radiotherapy.

Cancer du sein : effet de la RT

CCSS THE CHILDHOOD CANCER SURVIVOR STUDY

[Moskovitz JCO 2014]



	Estimated Cumulative Risk, % (95% CI)		
	By age 40	By age 45	By age 50
Childhood cancer survivors			
Entire cohort	12 (10 to 14)	18 (16 to 21)	30 (25 to 34)
Primary cancer diagnosis			
Hodgkin lymphoma	15 (12 to 18)	22 (17 to 25)	35 (29 to 40)
Other childhood cancer[a]	8 (5 to 12)	15 (10 to 21)	– –
Carriers of genetic mutations			
BRCA1 carriers	14 (5 to 23)	22 (11 to 33)	31 (15 to 48)
BRCA2 carriers	5 (0 to 15)	10 (1 to 23)	10 (1 to 23)

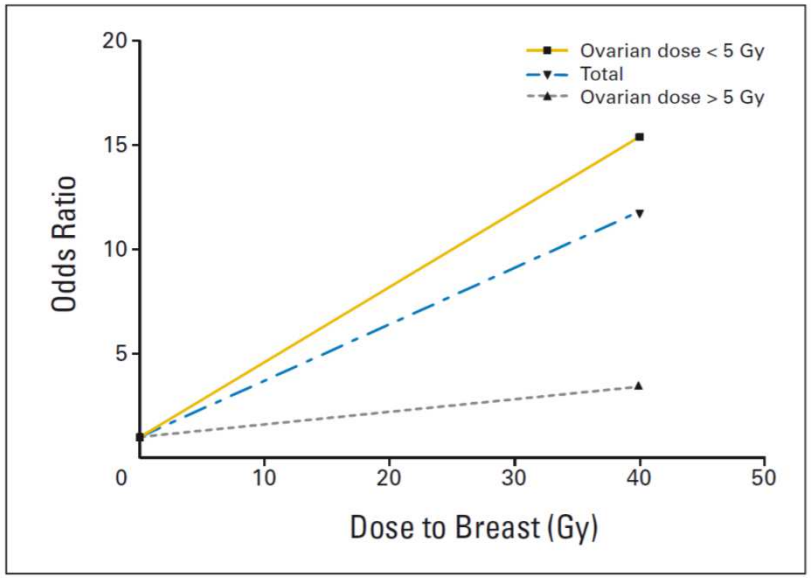


Fig 2. Fitted breast cancer risk by radiation dose to the breast and ovary.

Median time from childhood cancer diagnosis to onset of breast cancer = 23 years (range,7-41)
Median age at breast cancer diagnosis = 39 years (range, 24-59).

Cancer du sein : effet de la RT

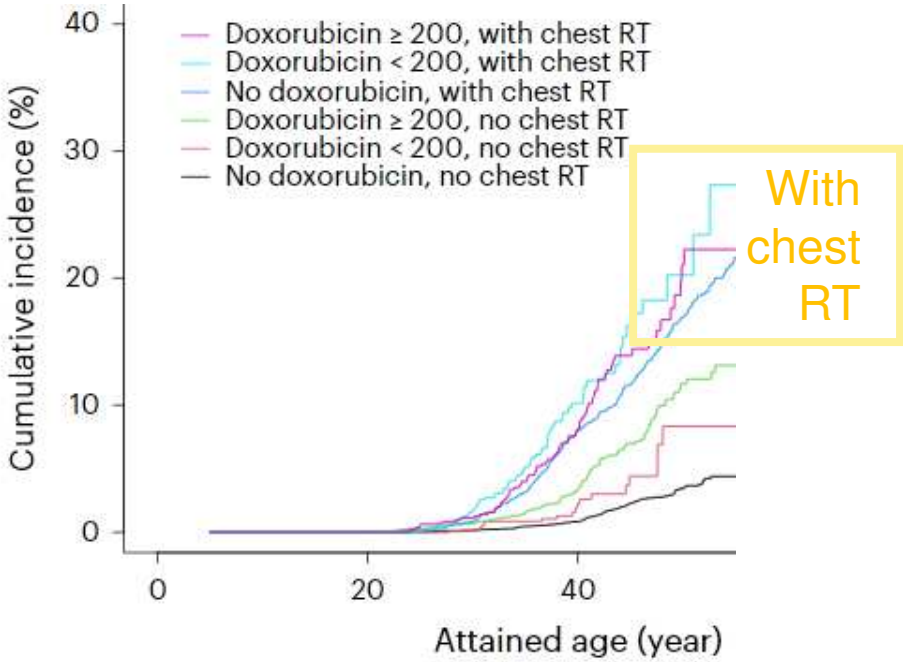
[Wang, Nature Med 2023]

Pooled cohort of 17,903 five-year survivors of childhood cancer (1946–2012)

- Median follow-up time after primary cancer diagnosis = 25 years (IQR: 19–33)
- 782 cases (mostly invasive)
- Median age at BC diagnosis = 40 years (IQR: 34–45)

>Additive effect between cumulative doxorubicin dose and chest radiation

Fig. 2 | Cumulative incidence of subsequent breast cancer in female 5-year childhood cancer survivors by cumulative doxorubicin dose, stratified by chest radiotherapy status (primary cancer diagnosis year 1946–2012).

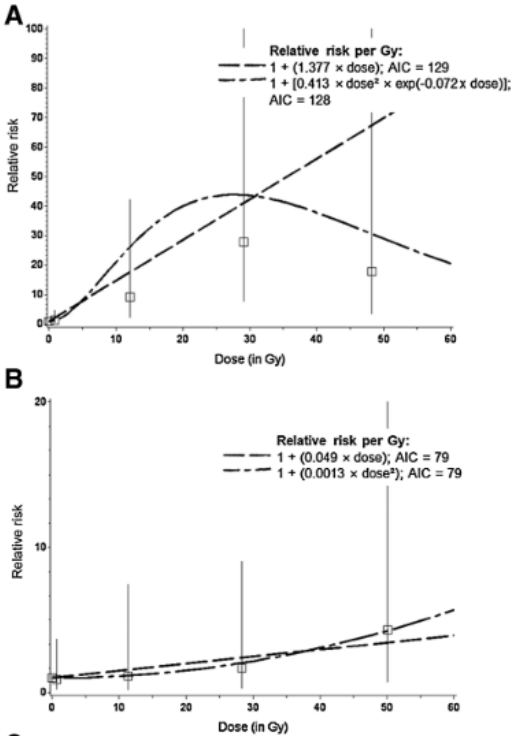


Tumeurs du SNC

[Journy, CEBP 2021]

Table 2. OR of SPN of the CNS associated with reported genetic syndromes predisposing to CNS tumors, type of first cancer, and radiation dose categories.

	Cases/controls, *n*	Model with clinical factors only OR (95% CI)	Model with therapeutic factors only OR (95% CI)	Model with clinical + therapeutic factors OR (95% CI)
Meningioma				
Genetic syndrome				
No	71/326	1.0 (Ref.)	—	1.0 (Ref.)
Yes	15/14	3.5 (1.4–9.4†)	—	4.0 (1.3–12.9†)
First cancer type				
Non-CNS tumor	29/301	1.0 (Ref.)	—	1.0 (Ref.)
CNS tumor	57/39	15.7 (8.2–33.2)	—	3.4 (1.5–8.3)
Radiation dose, in Gy				
0 (no radiotherapy)	5/138	—	1.0 (Ref.)	1.0 (Ref.)
0–<5 (mean: 0.8)	14/153	—	2.2 (0.8–6.5†)	1.43 (0.5–4.7)
5 to <20 (mean: 12.1)	11/15	—	20.7 (5.6–82.8†)	9.24 (2.4–42.2)
20 to <40 (mean: 29.1)	42/25	—	68.8 (22.1–241.5†)	27.86 (7.8–124.0)
≥40 (mean: 48.2)	14/9	—	61.1 (15.2–269.1†)	17.80 (3.6–103.0)
Glioma				
Genetic syndrome				
No	26/179	1.0 (Ref.)	—	1.0 (Ref.)
Yes	21/9	10.5 (3.1–39.4†)	—	11.0 (3.1–43.5)
First cancer type				
Non-CNS tumor	13/166	1.0 (Ref.)	—	1.0 (Ref.)
CNS tumor	34/22	10.0 (4.1†–26.2)	—	6.7 (2.2†–20.0†)
Radiation dose, in Gy				
0 (no radiotherapy)	14/89	—	1.0 (Ref.)	1.0 (Ref.)
0 to <5 (mean: 0.7)	7/73	—	0.6 (0.2†–1.7†)	0.9 (0.2–3.7)
5 to <20 (mean: 11.3)	11/8	—	9.3 (2.8–32.5†)	1.2 (0.2–7.5)
20 to <40 (mean: 28.3)	5/13	—	3.2 (0.8–12.0†)	1.7 (0.3–9.0)
≥40 (mean: 50.1)	10/5	—	11.9 (3.5–43.9†)	4.3 (0.7–31.1)



Tumeurs du SNC

[Journy, CEBP 2021
Withrow, JAMA Oncol 2022]

Méningiome

- Temps médian depuis 1er cancer = 30 ans
- Forte association (linéaire ?) avec dose de radiation
- Excès de risque / Gy persistant après >25-30 ans de suivi
- Risque / Gy augmenté chez les femmes et les individus les plus jeunes au diagnostic du 1er cancer
- Risque x3–5 avec méthotrexate (effet propre) – pas d'interaction avec RT

Gliome

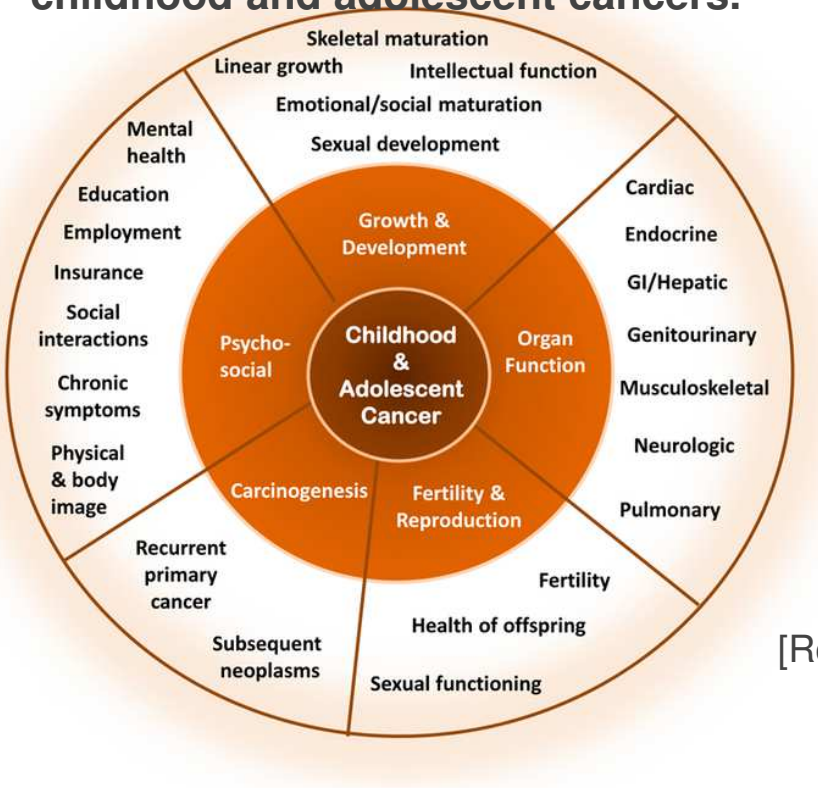
- Temps médian depuis 1er cancer = 17 ans
- Faible contribution de la dose de radiation à l'excès de risque post-RT (facteurs génétiques+++)
- Excès de risque / Gy restreint aux 10-15 ans de suivi post-RT

Second cancers: rôle de la radiothérapie

Site/ type of cancer	Median time (yrs)	EBRT effect	ERR / Gy	Minimal dose with signif. effect
Leukemia	4	Non – linear	1.6 (95%CI:0.1 to 14.3)	>12 Gy OR (vs. no RT)= 2.3 (1.1-4.6)
Meningioma	30	Linear (?)	1.4 (95%CI: 0.6-3.6)	4 to 24 Gy (mean: 16 Gy) OR (vs. no RT)= 14.4 (5.7-36.4)
Bone	~15	Linear (?)	1.3 (95%CI, 0.4 to 4.5)	1 to 4 Gy (mean: 2 Gy) OR (vs. no RT)= 4.8 (95% CI, 1.2 to 19.6)
Colorectal	30	Linear	0.2 (97.5%CI: 0.02–1.4)	5 to 20 Gy (mean: 12 Gy) OR (vs. no RT)= 4.1 (95% CI: 1.0–20.6)
Glioma	17	Linear	0.05 (95%CI: 0–0.3)	>=40 Gy (mean: 50 Gy) OR (vs. no RT)= 11.9 (3.5–43.9)

Effets tardifs post-RTX : autres effets que seconds cancers

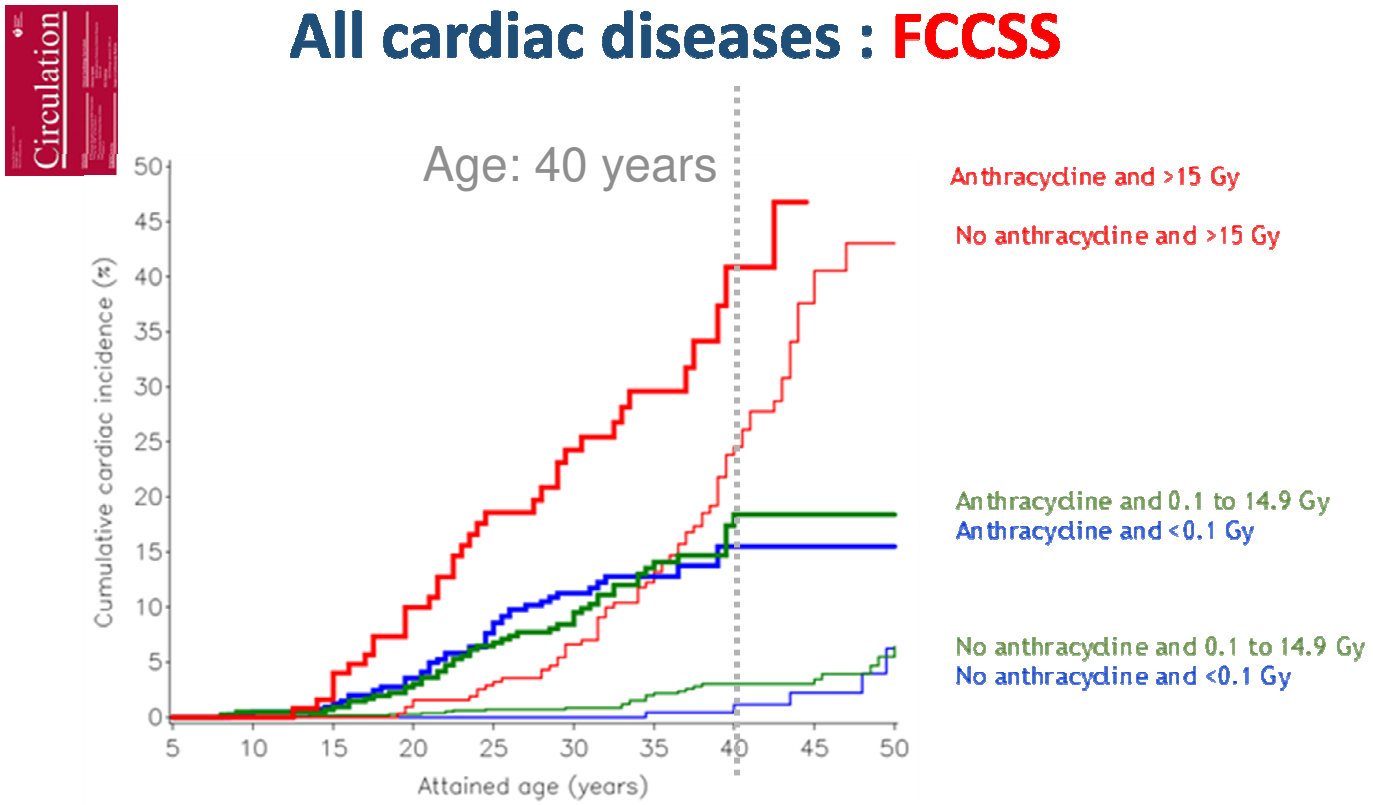
Spectrum of health-related and quality of life outcomes among long-term survivors of childhood and adolescent cancers.



[Robison, Nat Rev Cancer 2014]

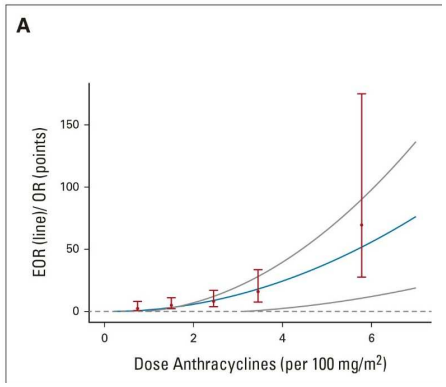
Effets tardifs post-RTX : Pathologies cardiovasculaires

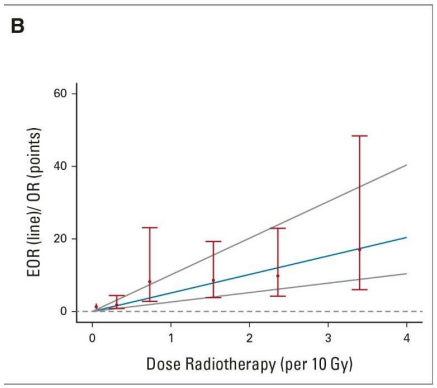
[Haddy Circulation 2016]



Effets tardifs post-RTX : Pathologies cardiovasculaires

[De Baat JCO 2022]





Grade 3-5 Heart Failure

TABLE 3. Multivariable Conditional Logistic Regression Models[a] of Grade 3-5 Heart Failure by Volume of the Heart Exposed to the Individual Patients' Maximum Heart RT Dose

Variable	Volume of the Heart, %	Cases,[b] No.	Controls, No.	OR (95% CI)	*P*
5 to < 15 Gy[c]	No RT	166	215	Ref	—
	0 to < 10	117	179	1.3 (0.7 to 2.2)	.4
	10 to < 50	7	5	1.9 (0.4 to 8.9)	.4
	≥ 50	27	5	5.6 (1.5 to 20.6)	.01
	Missing[d]	8	7		
≥ 15 Gy	No RT	166	215	Ref	—
	0 to < 10	176	213	1.9 (1.1 to 3.1)	.01
	10 to < 50	21	18	3.4 (1.1 to 9.0)	.01
	50 to < 90	68	39	9.4 (4.4 to 20.1)	< .0001
	≥ 90	61	8	14.6 (6.0 to 35.5)	< .0001
	Missing[d]	8	7		

Effets tardifs post-RTX : Accidents cérébraux vasculaires

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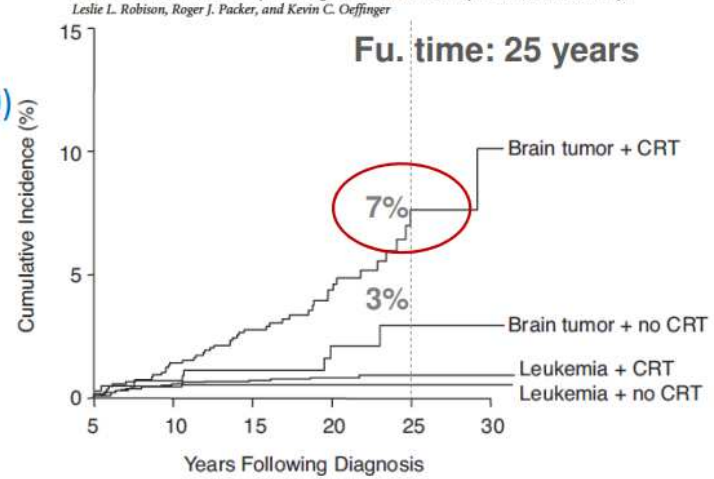
U.S.
N=14,000,
(Brain tumors, N=1,900)

Late-Occurring Stroke Among Long-Term Survivors of Childhood Leukemia and Brain Tumors: A Report From the Childhood Cancer Survivor Study

Daniel C. Bowers, Yan Liu, Wendy Leisenring, Elizabeth McNeil, Marilyn Stovall, James G. Gurney, Leslie L. Robison, Roger J. Packer, and Kevin C. Oeffinger



CRT: cranial radiation therapy

Avancées techniques en radiothérapie :

Impact en termes d'effets tardifs ?

Équipe « épidémiologie des radiations » Inserm U1018

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