

The issue of second malignancies

Risks associated with radiotherapy



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Spinocellular carcinoma of a dentist's finger

QuickTime™ et

un module de décompression

photo CD sont requis pour visualiser cette image.

QuickTime™ et

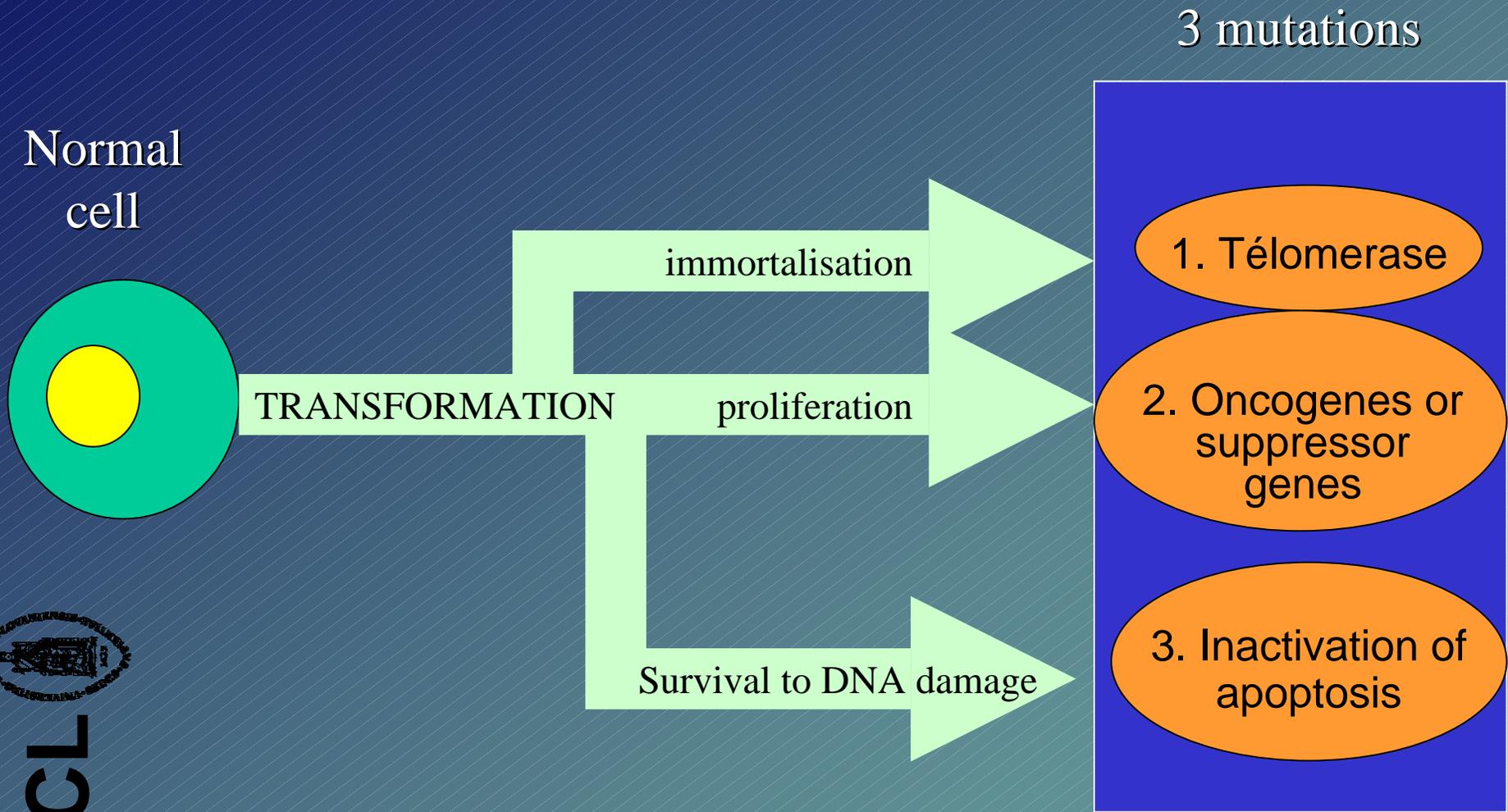
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What is cancer?



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Magnitude uncertain



- One in 10 cancer diagnoses are second (or higher) malignancies.
- What is the contribution of radiotherapy?



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What is radiation induced cancer?

- Cancers in A-bomb survivors mainly in tissues lining the body (no sarcomas).
- Cancers in patients treated with radiotherapy in lining tissues (low dose regions), *and* in soft tissues (high dose regions).
- No differences with “spontaneous” cancers.
- Impossible to assert that a given cancer actually *is* radiation-induced.
- Controversies arising from confounding factors (lifestyle, genetic predisposition).

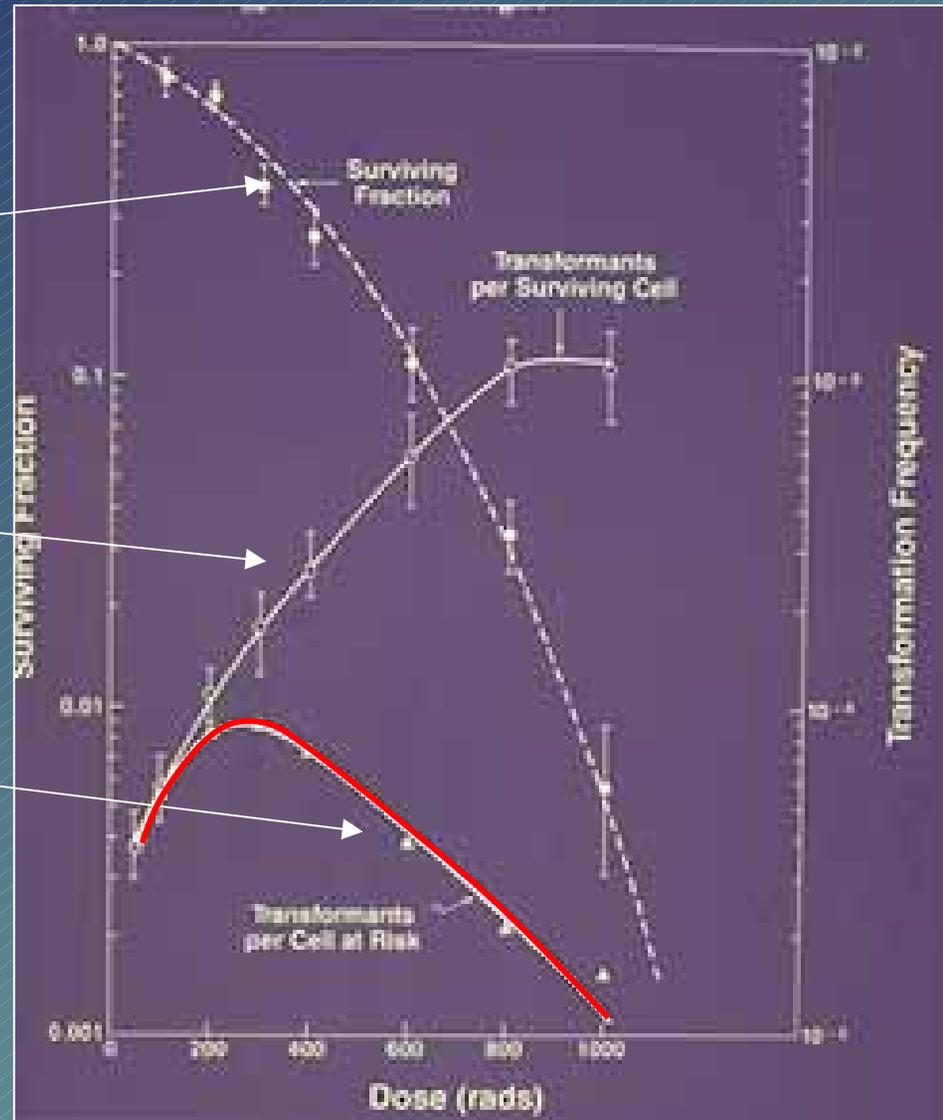


Cancer induction: a bell-shaped curve

Survival rate

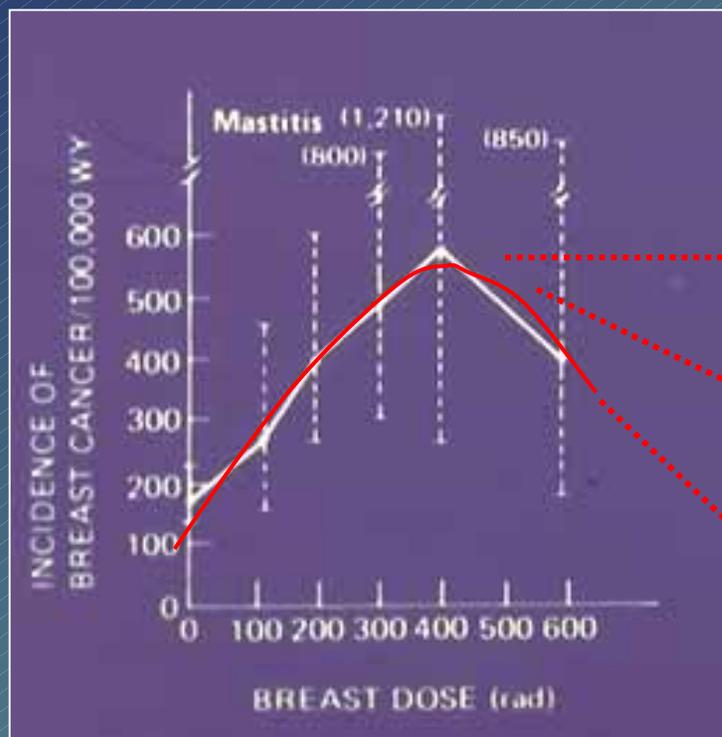
Frequency of transformation

Sum of the 2 curves :
cancerogenesis



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Breast cancer induction in women irradiated for acute mastitis



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Not all data show a clear bell-shaped curve. There is considerable uncertainty in human data.

Cancer as a result of radiation exposure

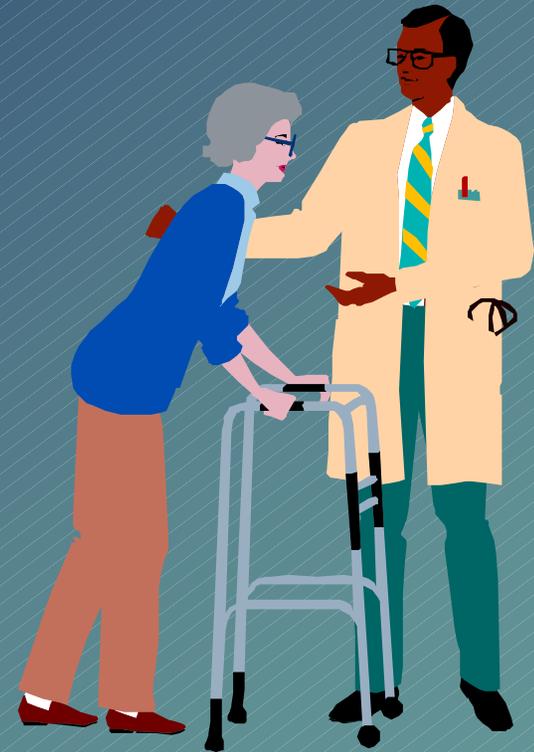
- Several epidemiological series
- Some examples
 - Male cockpit crew members with >5000h flight have an excess risk of leukaemia of 5.1 (1.03-14.0 91) .
 - No excess foetal death and congenital malformation in babies born to nuclear industry employees.
 - Decrease in overall cancer incidence and mortality in people treated for hyperthyroidism with radioiodine (RR 0.83, range 0.77-0.90).



Radiation induced cancer

(BMJ 284: 449, 1982)

- 14,111 patients irradiated for ankylosing spondylitis in UK.
- Fivefold excess of death from leukaemia (O/E : 31 vs.. 6.5).
- Risk greater 3-5 y after treatment and disappeared after 18 years.
- All neoplasm : O/E = 397/256
- Risk increased 10y after irradiation.
- Dose range 1-7 Gy in field



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Normal latency for radiation induced large bowel carcinoma after a first treatment for pelvic malignancy

<i>Latency (yr)</i>	<i>Patient n_i</i>	<i>Cumulative %</i>
² 10	16	30
11-20	22	73
21-30	12	94
31-40	2	98
³ 40	1	100



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Cancer 57: 728, 1986

Breast cancer in women with scoliosis exposed to multiple diagnostic X rays

- 1.030 women seen between 1935 and 1965.
- Mean age 12.3 year.
- Individual X-rays between 0 and 618 films (0-1.59 Gy)
- Average period of observation was 26 years.
- O/E = 11/6
- RR 1.82 (1.0-3.0)
- RR increased with time and with n° of films



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JNCI 81: 1307, 1989

Mortality from breast cancer after irradiation during fluoroscopic examination for tuberculosis treatment

Relative risk per 1 Gy	
<i>Age at first exposure</i>	<i>Relative risk</i>
10 Ğ 14	4.46
15 Ğ 24	1.77
25 Ğ 34	1.25
³ 35	1.10

- 31,710 women admitted between 1930 and 1952.

NEJM 321:1285, 1989



Mortality from breast cancer after irradiation during fluoroscopic examination for tuberculosis treatment

<i>Time since first exposure</i>	<i>Relative risk</i>
5 Ğ 14	1.47
15 Ğ 24	1.40
25 Ğ 34	1.48
³ 35	1.24

Effect of time since first exposure to 1 Gy of radiation as predicted by relative-risk model



Latency longer in children

- Bowel cancer induced by high single dose delivered in the frame of sterilisation experiments by Nazis in Auschwitz (1943)

Three young women, aged 17 and 19, were victims of a war crime in 1943; all three developed colon cancer 40 years later, whereas the usual latency is 20 years. Similar observation made in Hiroshima & Nagasaki survivors.



Overall risk?

IJROBP 17: 623, 1989

- Cumberlin et al. Published estimates of the expected number of SMN induced in selected sensitive sites by scattered radiation during radiation therapy for cancer, based on 192,761 new patients with cancer treated in 1987.
- The model projected a 0.7 % incidence for leukaemia and 0.3 % for solid tumours.



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Second malignant tumours after Hodgkin's disease (AML)

NEJM 322: 7-13, 1990

- 1 % after radiotherapy alone.
- 9 % after chemotherapy alone (leukemogenic drugs).
- 7.7 % after RT and CT.

Risk of second brain tumour after conservative surgery and RT for pituitary adenoma...

J Clin Endocrinol Metab 90: 800-4, 2005

- 426 patients, 5749 person-years (1962-94)
- 11 tumours (5 **meningiomas**, 6 others)
- Cumulative risk : 2.4% at 20 years (0.9-4.4%)



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Second cancer after pelvic radiotherapy for cervix cancer (relative risk)

JNCI 74: 955-75, 1985

<i>Tissues receiving high doses</i>	
bladder	4.5
rectum	1.8
vagina	2.7
Bone?	1.3
Uterus?	1.3
Cecum?	1.5
NHL	2.5
<i>Tissues receiving low doses</i>	
stomach	2.1
leukaemia	2.1



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Second cancer after radiotherapy for prostate cancer (SEER data).

Cancer 88: 398-406, 2000

- Risk of second tumour of any type after 5 years : 6%
- Risk of second tumour of any type after 10 years : 34%
- Most dramatic increase for bladder (77%) and rectum (105%), for 10y and longer.
- Risk for sarcoma in heavily irradiated tissues is 145% after 5y and longer.



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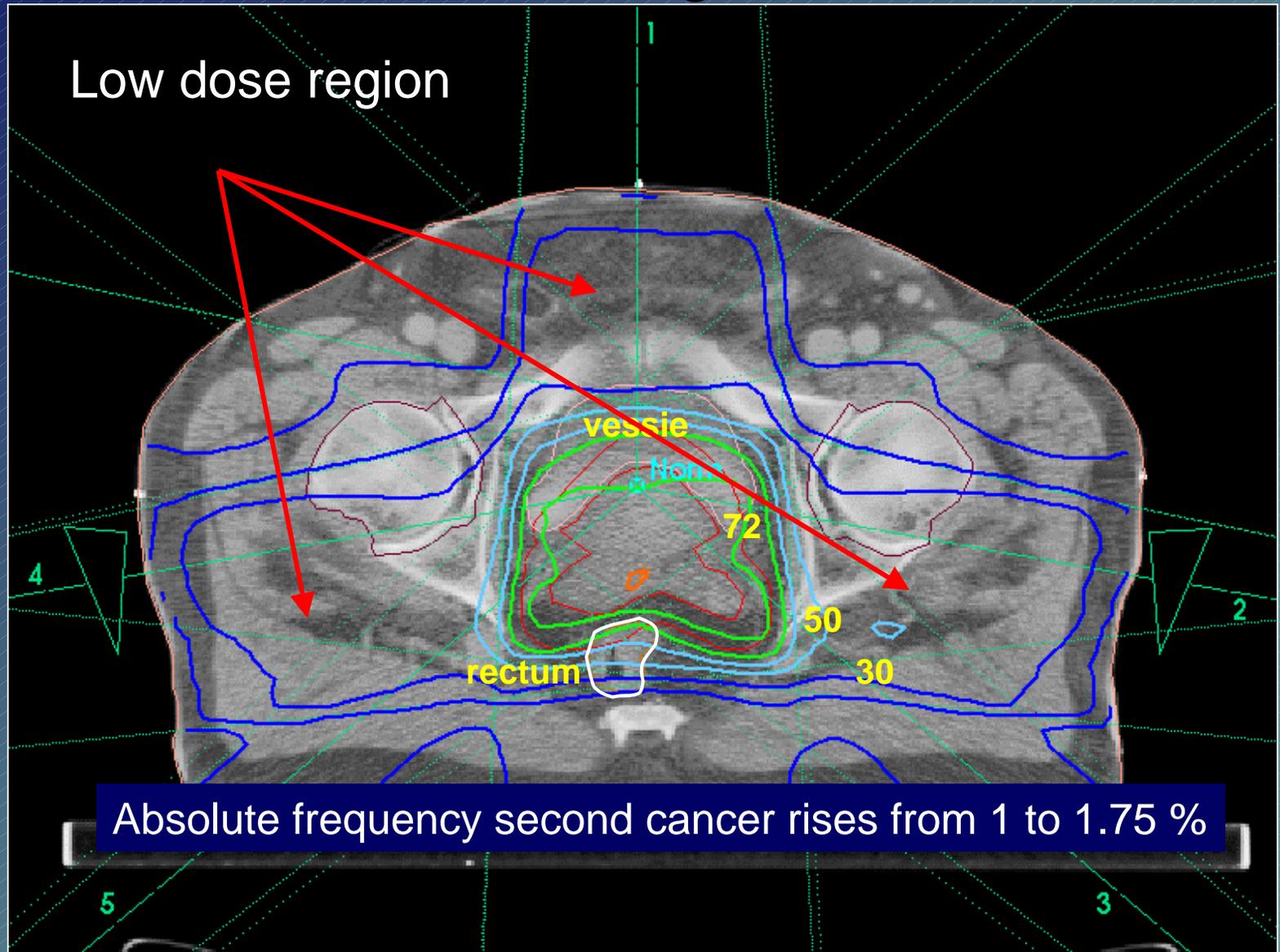
Radiation and genetic factors in the risk of second malignant neoplasm's after a first cancer in childhood

<i>factors</i>	<i>Odds ratio (95 % CI)</i>	<i>p</i>
<i>FI 0-2 vs. 0</i>	1.7 (0.1-21)	0.01
<i>FI ³ 2 vs. 0</i>	6.6 (1.5-29)	
<i>FI 0 & <0.5 Gy</i>	1	Ns
<i>FI 0 & ³ 0.5 Gy</i>	4.1 (0.8-21.3)	Ns
<i>FI >0 & <0.5 Gy</i>	8.3 (0.7-10.4)	Ns
<i>FI >0 & ³ 0.5 Gy</i>	15.5 (2.1-114)	0.01

FI = family index. A coefficient including n° of relatives with cancer, at a given age, with a given level of kinship



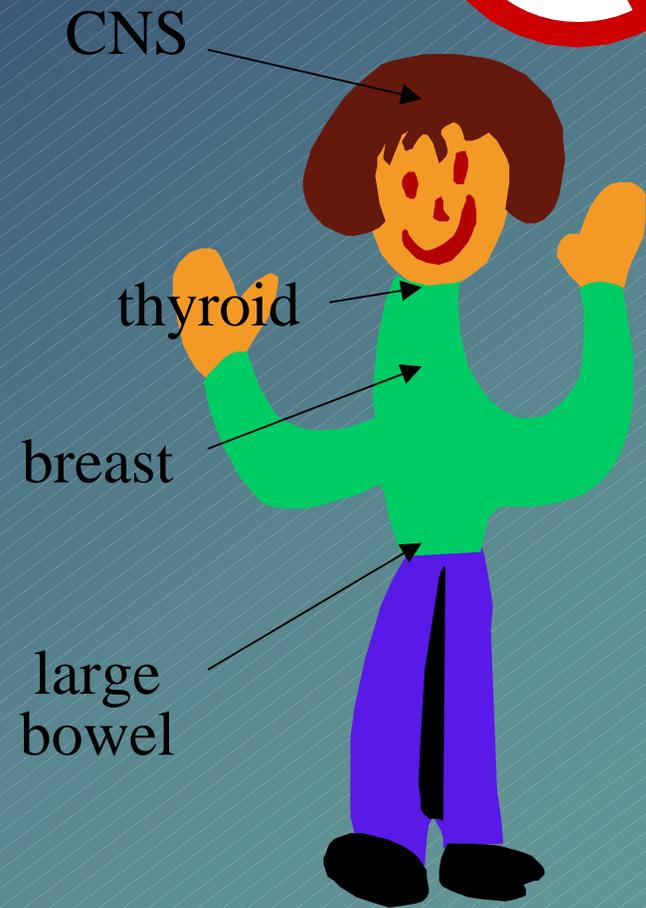
Dose distribution : new techniques increase the volume receiving low doses



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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.



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