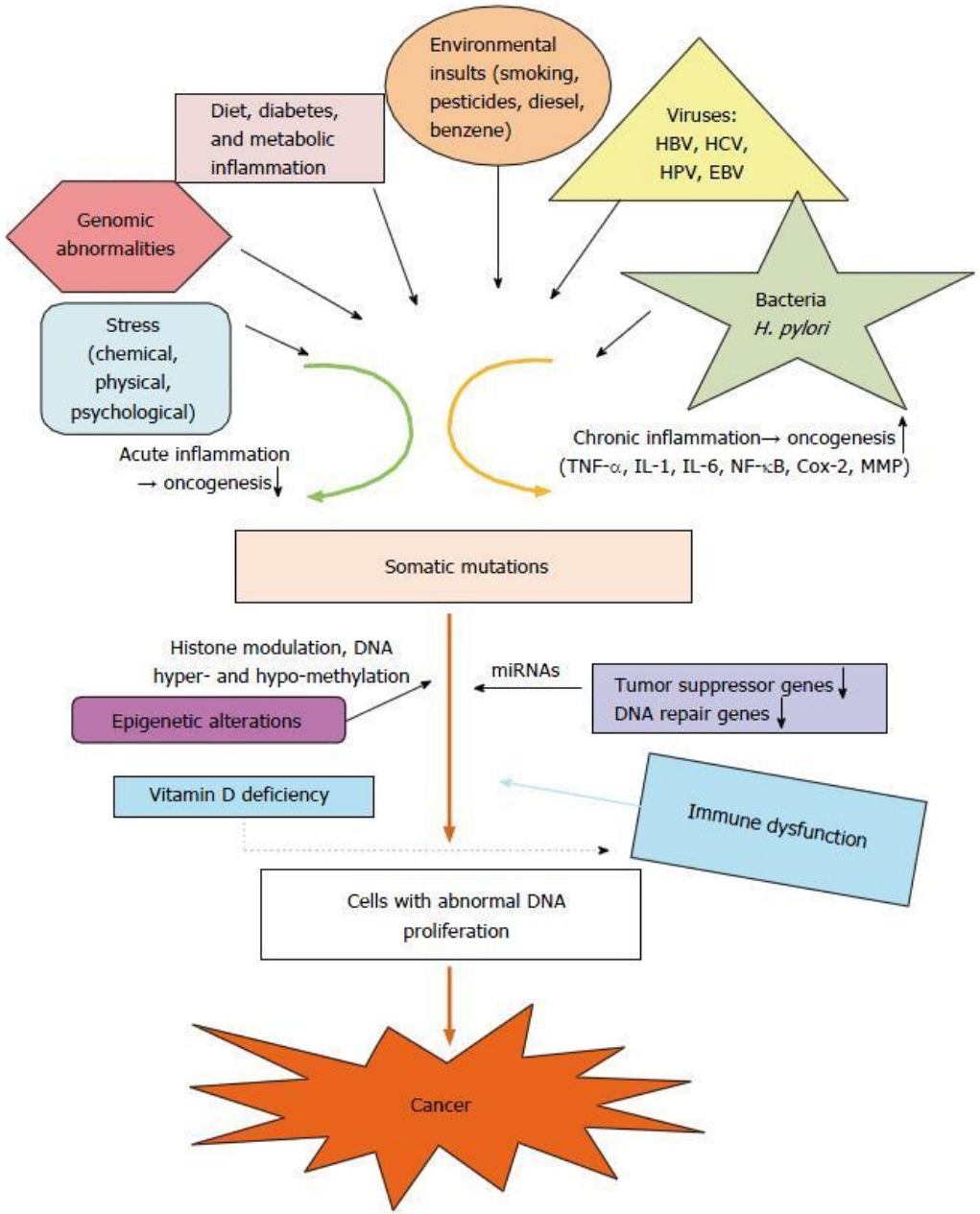
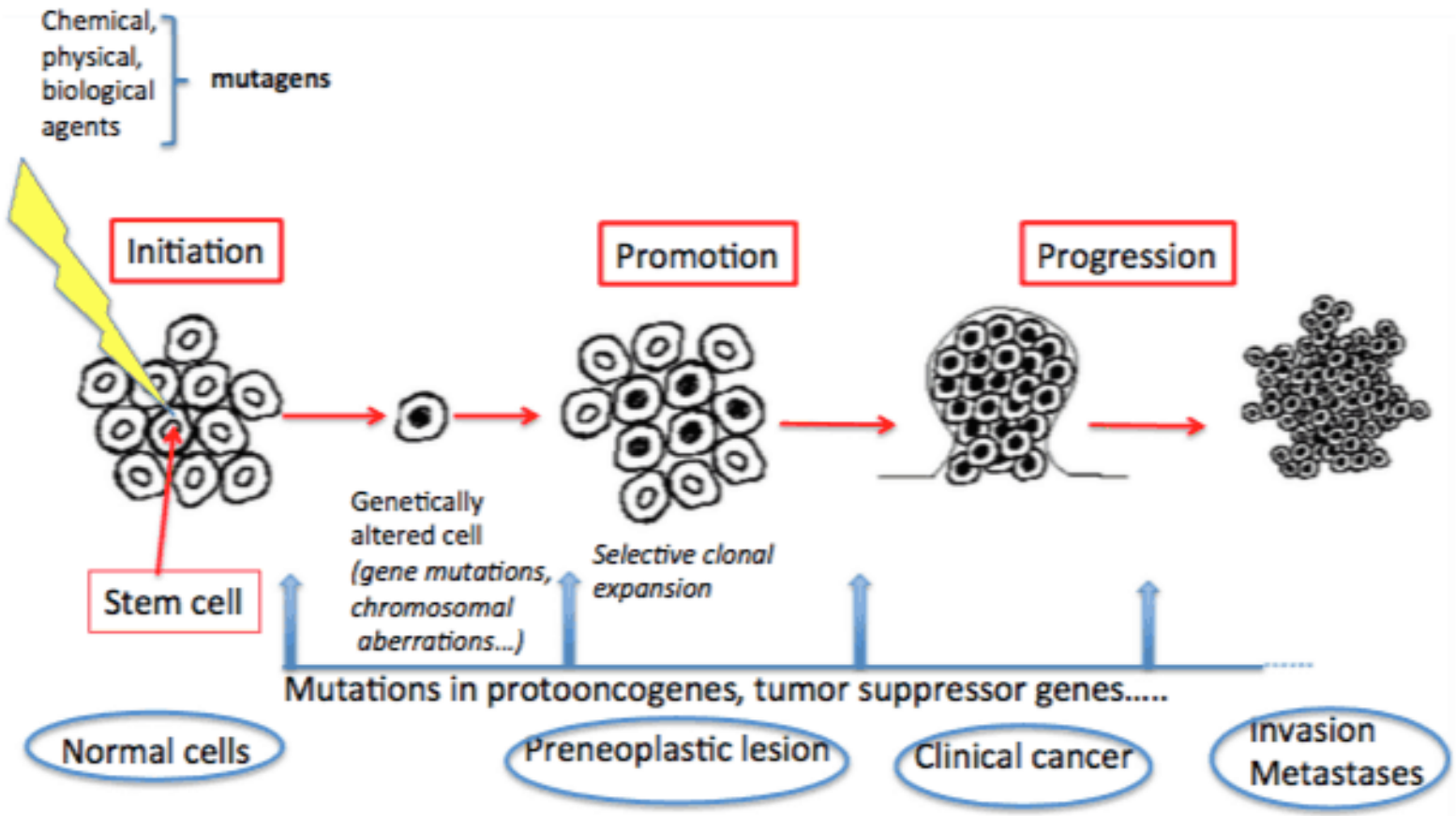
LAUREA MAGISTRALE BIOLOGIA MOLECOLARE E APPLICATA- Curriculum Biosanitario e della Nutrizione

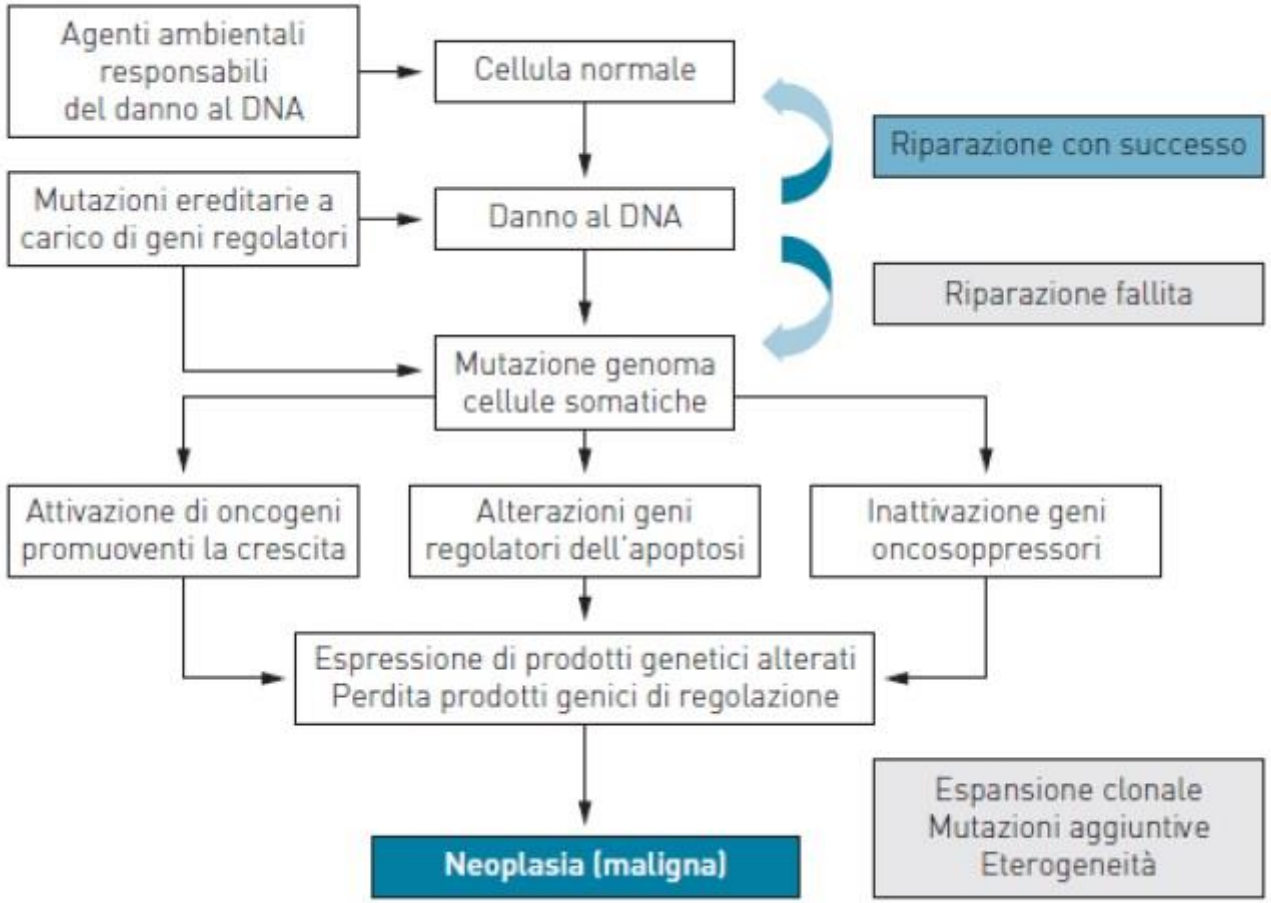
Corso di ONCOLOGIA

28 ottobre 2019


Environmental insults (smoking, pesticides, diesel, benzene)
Diet, diabetes, and metabolic inflammation
Viruses: HBV, HCV, HPV, EBV
Genomic abnormalities
Bacteria H. pylori
Stress (chemical, physical, psychological)
Acute inflammation → oncogenesis
Chronic inflammation→ oncogenesis (TNF-α, IL-1, IL-6, NF-κB, Cox-2, MMP)
Somatic mutations
Histone modulation, DNA hyper- and hypo-methylation
miRNAs
Tumor suppressor genes
DNA repair genes
Epigenetic alterations
Vitamin D deficiency
Immune dysfunction
Cells with abnormal DNA proliferation
Cancer


Chemical, physical, biological agents
mutagens
Initiation
Promotion
Progression
Stem cell
Genetically altered cell (gene mutations, chromosomal aberrations…)
Selective clonal expansion
Mutations in protooncogenes, tumor suppressor genes…..
Normal cells
Preneoplastic lesion
Clinical cancer
Invasion Metastases

«vie cancerogenetiche»



Sitemi di riparazione umani

- Riparazione di mismatch
- Correzione diretta
- Excisione di basi (specifica)
- Excisione di nucleotidi

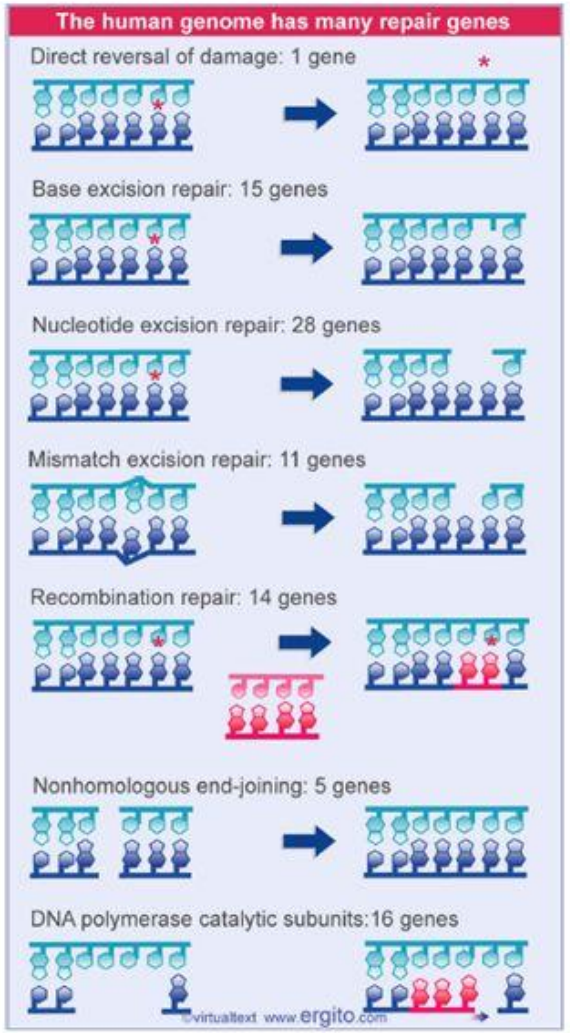


Figure 15.37 Repair genes can be classified into pathways that use different mechanisms to reverse or bypass damage to DNA.

- small mutational damage to the dividing cell by exogenous factors (e.g. by radiation, chemical carcinogens etc) is also repaired.
- *p53 gene is held responsible* for detection and repair of DNA damage
- if this system of DNA repair is defective as happens in some inherited mutations (mutator genes), the defect in unrepaired DNA is passed to the next progeny of cells and cancer results.

The examples of mutator genes exist in the following inherited disorders associated with increased propensity to cancer:

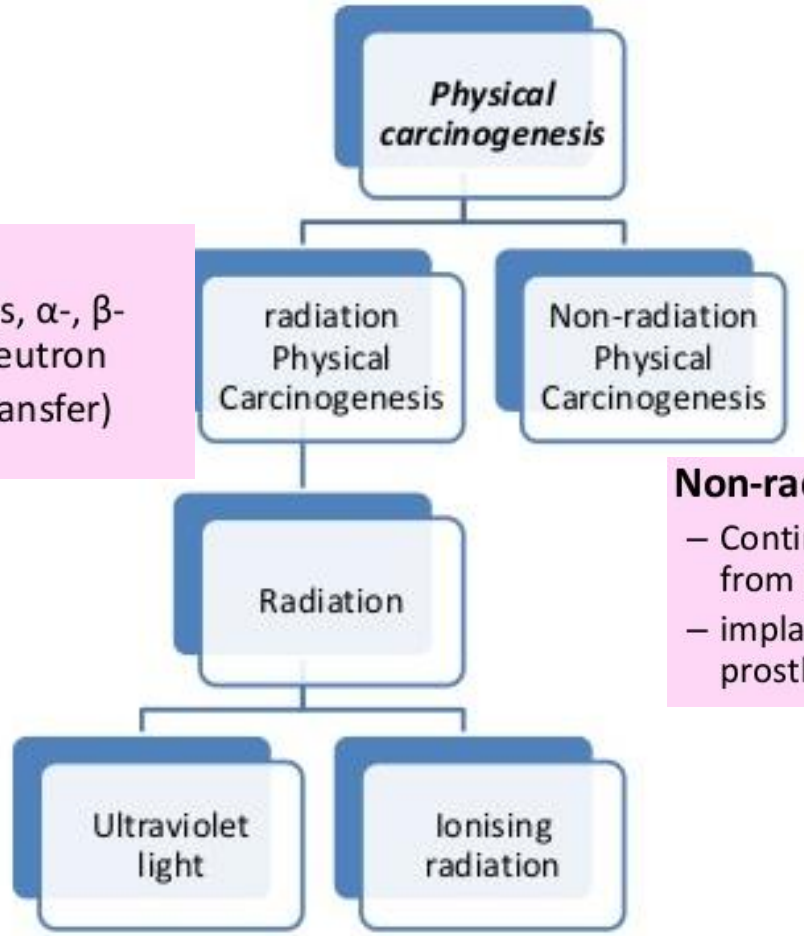
- Xeroderma pigmentosa:
  - an inherited disorder in which there is defect in DNA repair mechanism. Upon exposure to sunlight, the UV radiation damage to DNA cannot be repaired. Thus, such patients are more prone to various forms of skin cancers.
- Bloom syndrome:
  - damage by ionising radiation which cannot be repaired due to inherited defect and the patients have increased risk to develop cancers, particularly leukaemia
  - cells from persons with Bloom syndrome exhibit a striking genomic instability that is characterized by hyper-recombination and hyper-mutation

- Mechanism: The most important is induction of mutation;inhibition of cell division, inactivation of enzymes and sometimes causing cell death.
- most important biochemical effect of UV radiation is the formation of **pyrimidine dimers** in DNA:
  - Uv-induced DNA damage in normal individuals is repaired, while in the predisposed persons who are excessively exposed to sunlight such damage remain unrepaired.
- Xeroderma pigmentosum is predisposed to skin cancers at younger age (under 20 years of age).
- Ataxia telangiectasia is predisposed to leukaemia.
- Bloom's syndrome is predisposed to all types of cancers.
- Fanconi's anaemia with increased risk to develop cancer.

Cancerogenesi Fisica

Radiation

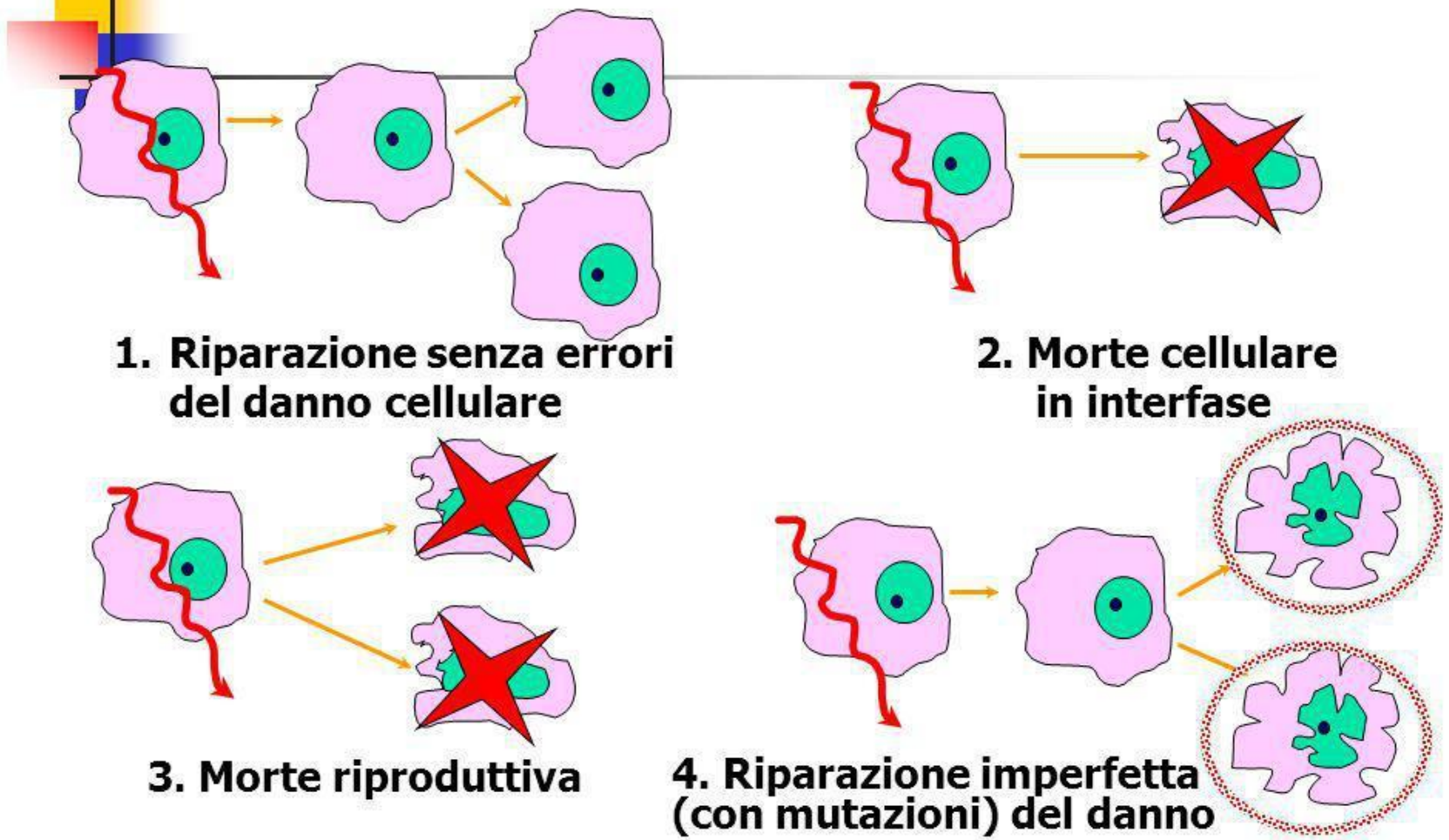
- ultraviolet light and ionising radiation like X-rays, α-, β- and γ-rays, radioactive isotopes, protons and neutron
- Higher dose and with high LET (linear energy transfer) caused carcinogenic effect



Non-radiation

- Continous mechanical injury to the tissues such as from intrinsic stone
- implants of inert materials such as plastic, glass etc in prostheses

Effetti delle radiazioni ionizzanti a livello cellulare

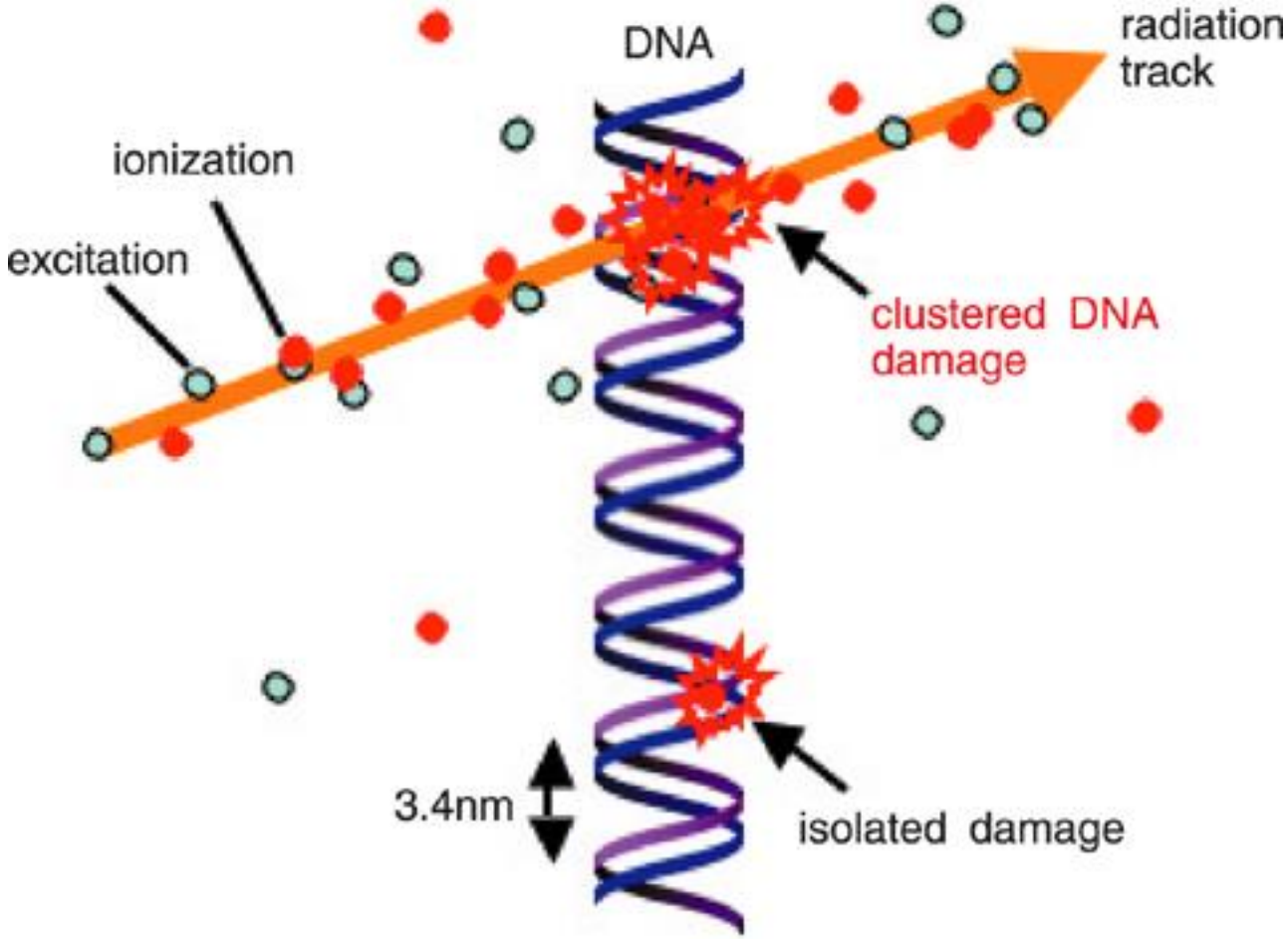


Radiazioni Ionizzanti

Raggi X, raggi gamma, particelle alfa, beta, protoni, neutroni e radiazione cosmica.

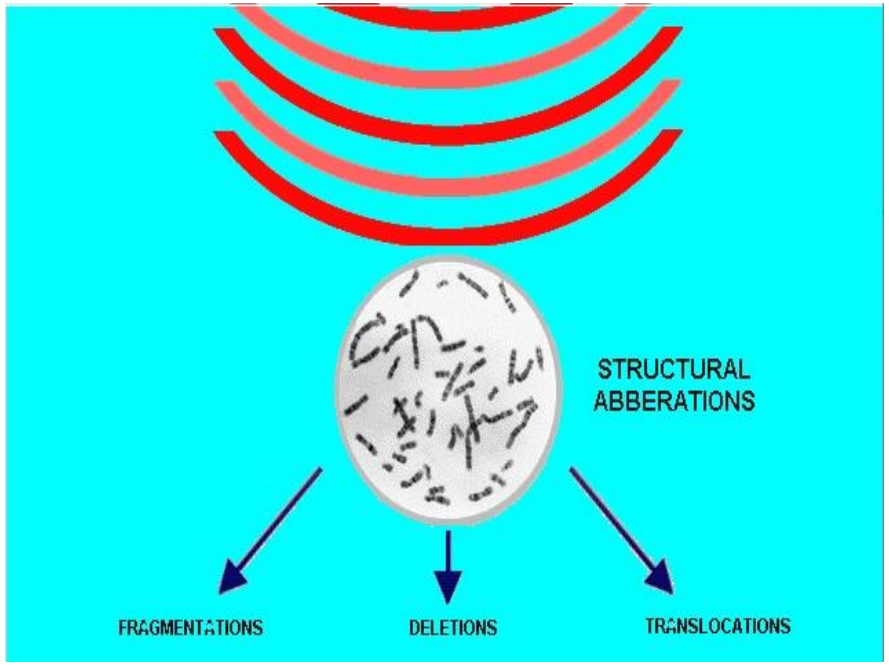
Tutte le radiazioni ionizzanti sono cancerogene, con particolare sensibilità per:

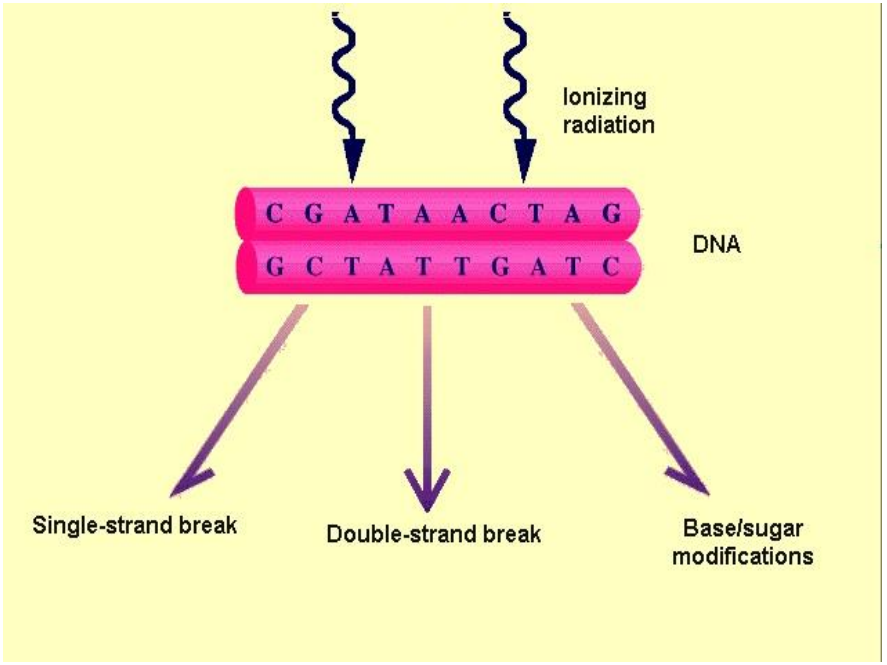
- Midollo osseo: leucemia acuta
- Tiroide: l'adk della tiroide si sviluppa nel 9% dei soggetti esposti a radiazioni durante infazia o adolescenza.
- Polmone: aumento dell'incidenza dell'adk polmonare in minatory esposti al gas Radon (emettitore alfa)


DNA
radiation track
ionization
excitation
clustered DNA damage
3.4nm
isolated damage

Le proprietà oncogene delle radiazioni ionizzanti sono associate ai loro effetti mutageni;

- Rottura cromosomica, traslocazioni e mutazioni puntiformi;
- Il tipo di danno più rilevante è il “double strand break”;
- Dosi non letali possono indurre instabilità genomica che promuove la cancerogenesi.





Le radiazioni elettromagnetiche sono radiazioni ionizzanti indirette che depositano energia nel tessuto tramite elettroni secondari.

Questi elettroni possono danneggiare il DNA direttamente o interagire con l'acqua e formare radicali che interagiscono con DNA e protein.

Alterazione dei processi biochimici che porta a: morte cellular, neoplasia (tessuto somatico) e alterazioni genertiche ereditabili (cellule germinali)

Radiazioni non Ionizzanti (Luce Ultravioletta)

Formazione di dimeri di pirimidine sul DNA: comparsa di mutazioni.

Il danno è riparato dal sistema NER (Nucleotide Excision Repair): con esposizione protratta a UV il sistema può non essere funzionante e questo può causare la comparsa di un tumore cutaneo.

Individui con difetti genetici del sistema NER sono maggiormente suscettibili al danno da UV.

Evidenze epidemiologiche collegano gli UV a:

- Carcinoma squamocellulare
- Carcinoma basocellulare
- Melanoma in soggetti di carnagione chiara (la melanina protegge dalla penetrazione degli UV)

- Mechanism: The most important is induction of mutation;inhibition of cell division, inactivation of enzymes and sometimes causing cell death.
- most important biochemical effect of UV radiation is the formation of **pyrimidine dimers** in DNA:
  - Uv-induced DNA damage in normal individuals is repaired, while in the predisposed persons who are excessively exposed to sunlight such damage remain unrepaired.
- Xeroderma pigmentosum is predisposed to skin cancers at younger age (under 20 years of age).
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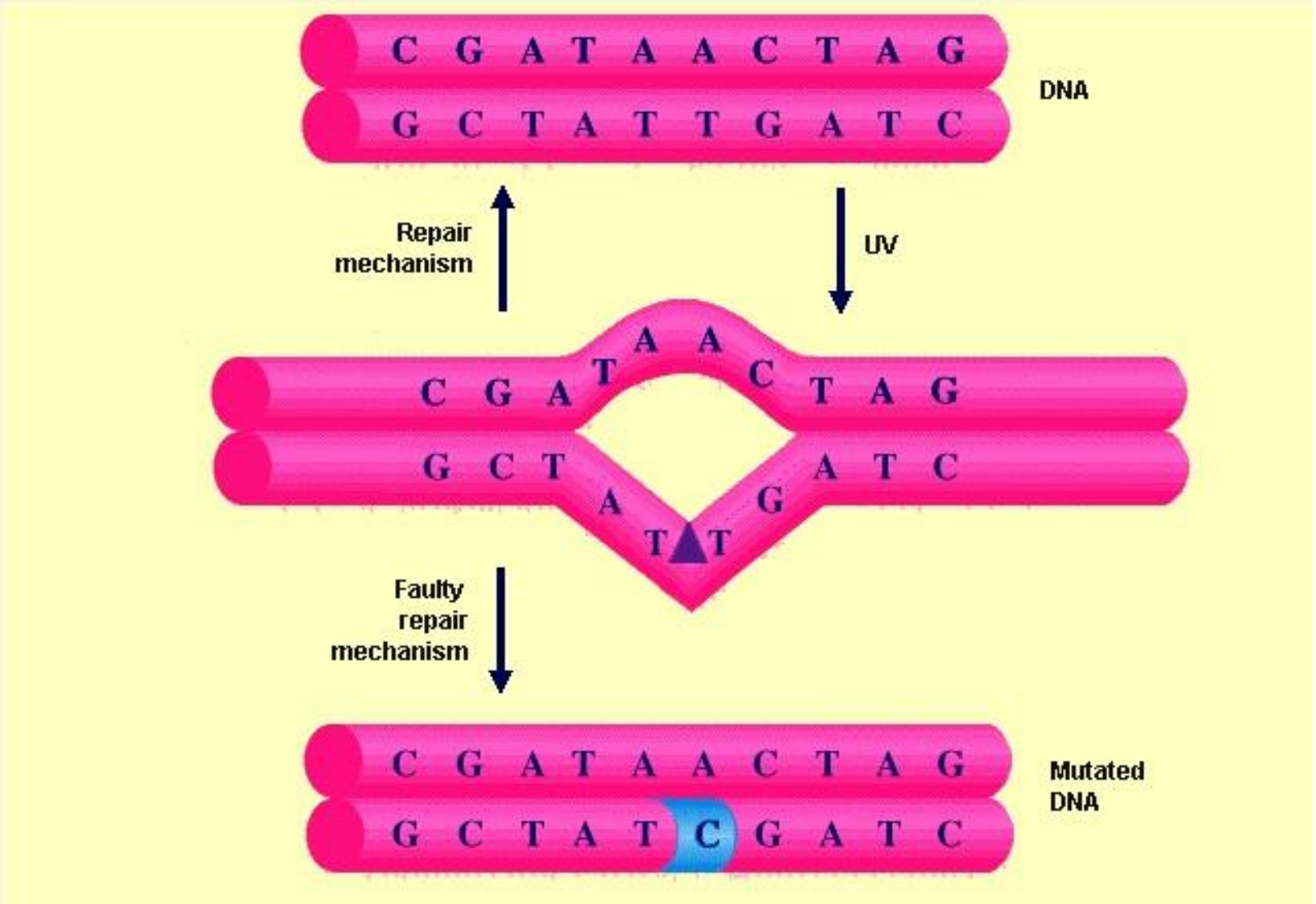
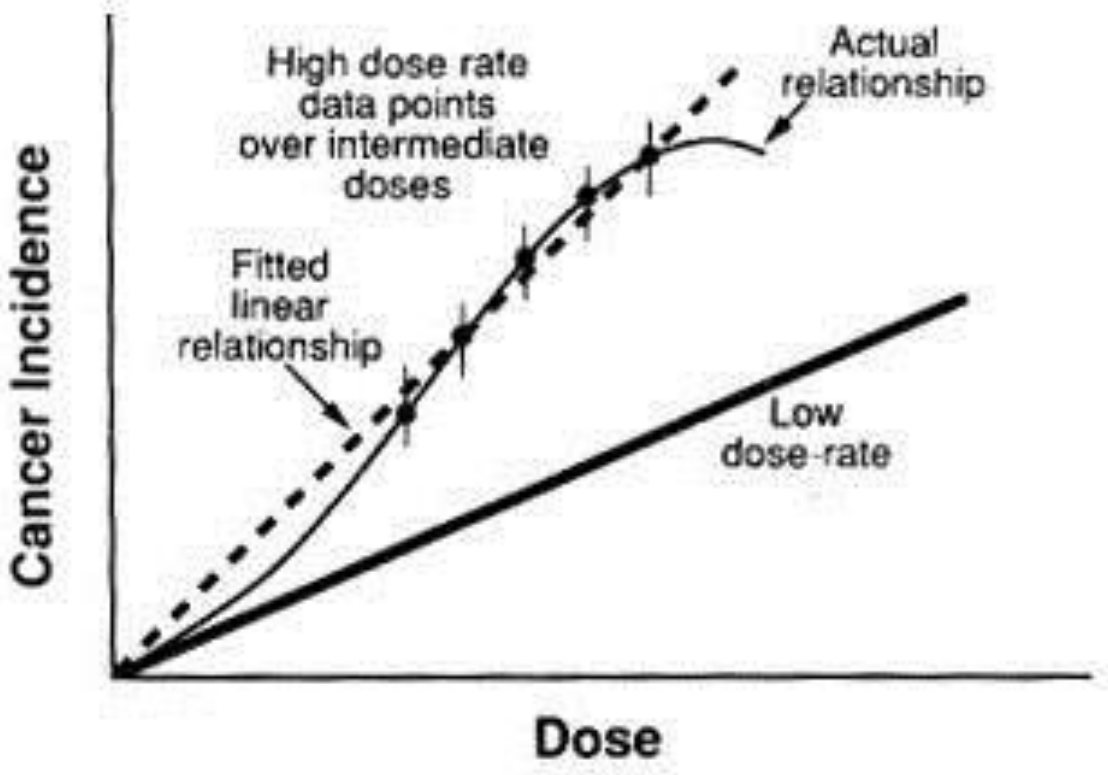

C G A T A A C T A G
G C T A T T G A T C
DNA
Repair mechanism
UV
C G A T A A C T A G
G C T A T T G A T C
Faulty repair mechanism
C G A T A A C T A G
G C T A T C G A T C
Mutated DNA

Non-radiation carcinogenesis:

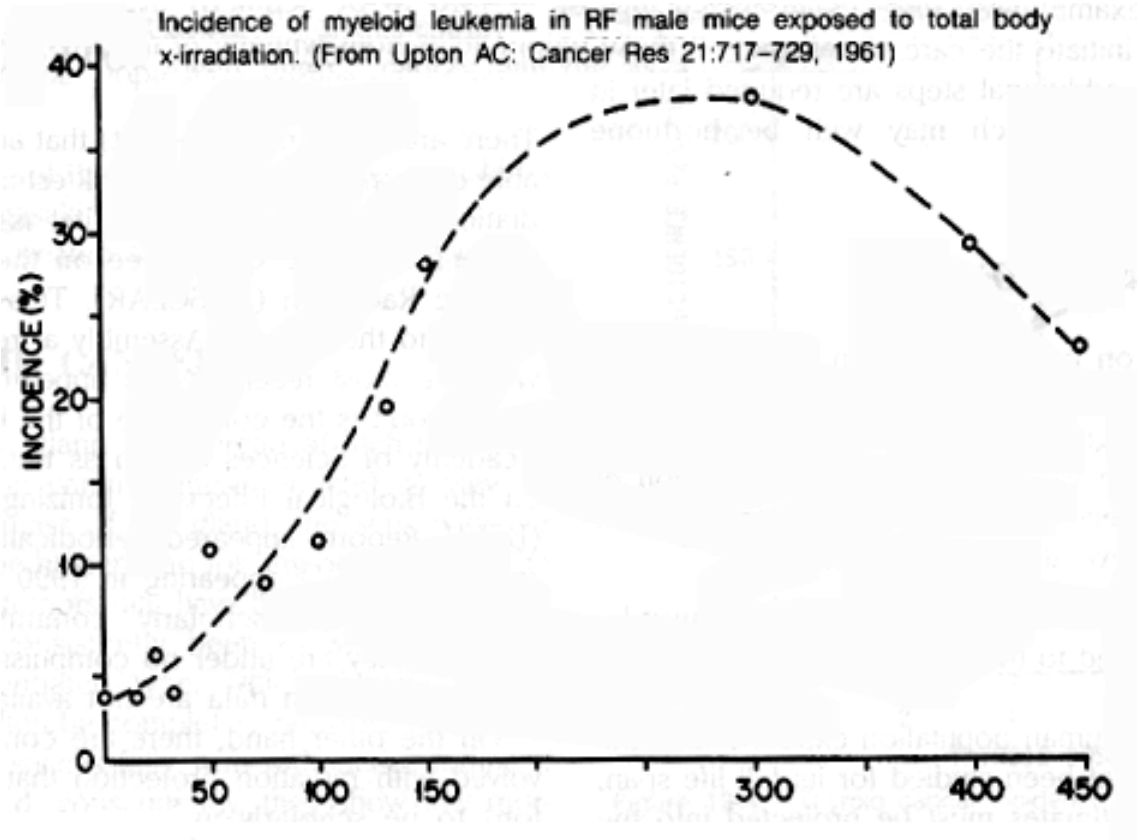
- Mechanical injury to the tissues such as from stones in the gallbladder, stones in the urinary tract, and healed scars following burns or trauma- increased risk of carcinoma in these tissues - evidence is not convincing.

- Other examples of physical agents in carcinogenesis are the implants of inert materials such as plastic, glass etc in prostheses or otherwise, and foreign bodies observed to cause tumour development

I tumori indotti da radiazioni sono dose-dipendenti



Leucemia radio-indotta



Tumori radio-indotti nel topo

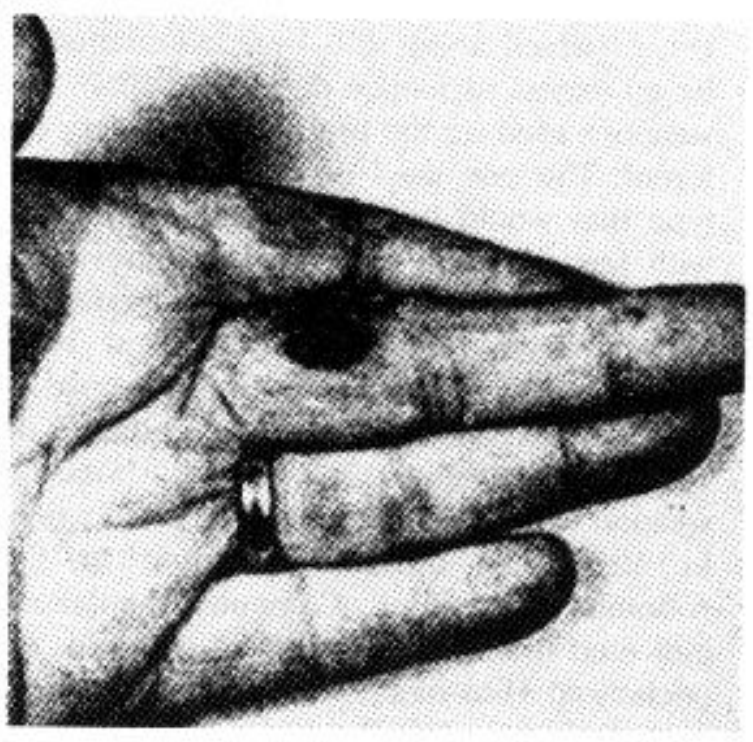
- Tumori polmonari
- Tumori ossei
- Tumori mammari
- Tumori ovarici
- Tumori uterini
- Tumori cutanei
- Tumori del tratto digerente
- Tumori tiroidei
- Tumori ipofisari
- Tumori surrenali

Alterations in Oncogenes in Radiation-Induced Cancer[a]

Type of Cancer	*Ras* Oncogenes
Mouse lymphoma[b]	Activated c-*ras*
Mouse thymomas[c]	Activated k-*ras*
Rat skin carcinoma[d,e] and rat thyroid tumor[e]	Activated k-*ras*
Mouse thymomas (RF/J)[f]	Mutated (k-*ras* and N-*ras*)
Mouse thymomas (C57BL/6J, and canine leukemia[g]	Activated N-ras
Murine osteosarcoma[h]	Activated H-*ras*

Esempi di tumori radio-indotti

Marie Curie



dentisti

Importanza dell'età al momento dell'esposizione

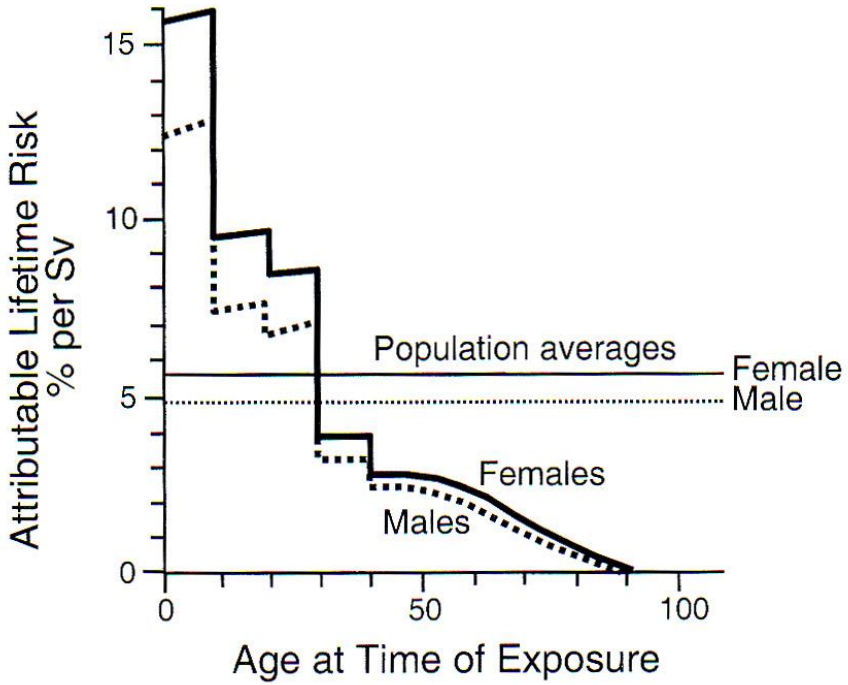


FIGURE 10.8 The attributable lifetime risk from a single small dose of radiation at various ages at the time of exposure. Note the dramatic decrease in radiosensitivity with age. The higher risk for the younger age-groups is not expressed until late in life. These estimates are based on a relative risk model and on a dose and dose-rate effectiveness factor (DDREF) of 2. (Adapted from ICRP: Recommendations. *Annals of the ICRP Publication 60*, Oxford, England, Pergamon Press, 1990.)

Maggiore suscettibilità in bambini e giovani

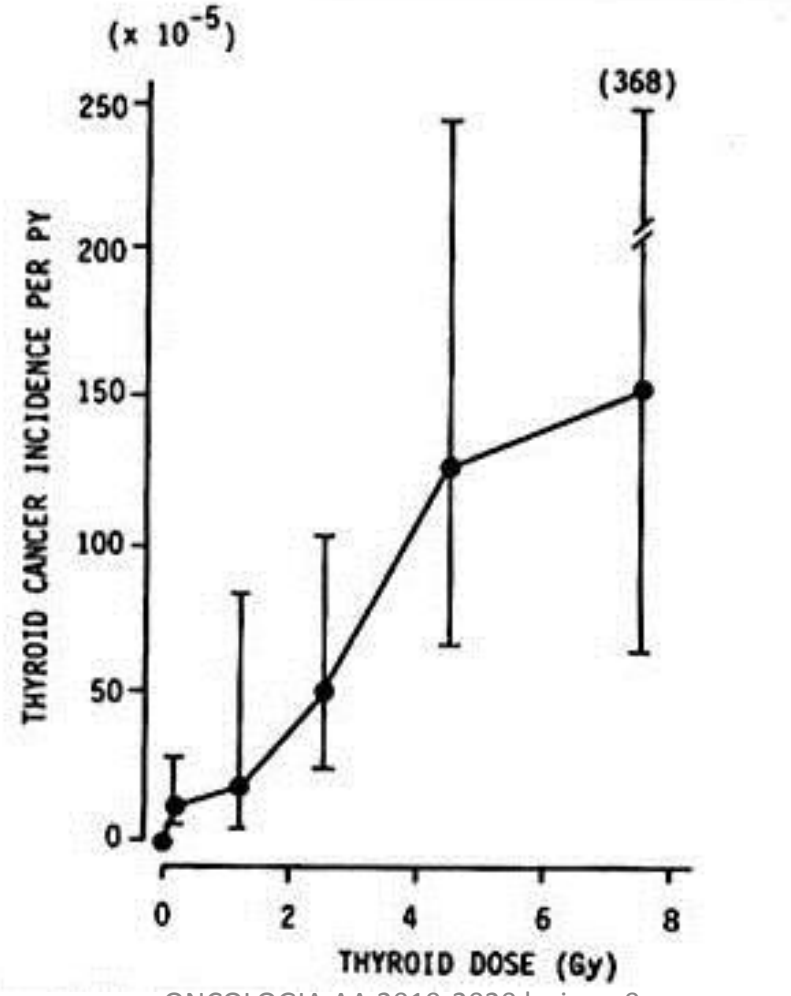
Leucemia

- Sopravvissuti alla bomba atomica di Hiroshima e Nagasaki
- Pazienti con spondilite anchilosante (dopo trattamento)

Tumori Tiroide

- Sopravvissuti alla bomba atomica di Hiroshima e Nagasaki
- Popolazione delle Isole Marshall esposta a Iodio-131
- Bambini trattati con raggi X per timo ingrossato Bambini trattati per patologie di tonsille e nasofaringe
- Bambini trattati con raggi X per *tinea capitis*

Incidenza Tumori Tiroidei radio-indotti



Tumori radio-indotti in seguito a Radioterapia

Incidence of Second Malignancy in Hodgkin's Disease Within 10 Years After Treatment Involving Radiation and/or Chemotherapy

Treatment Modality	Type of Malignancy	Incidence of Second Malignancy within 10 Years (% of Survivors)
Radiation therapy[a]	Solid tumor	12
Radiation therapy	Leukemia	0
Chemotherapy	Solid tumor	0
Chemotherapy	Leukemia	5.5
Radiation therapy	Solid tumor	0
Chemotherapy (MOPP)[b]	Leukemia	5.4
Radiation therapy	Solid tumor	2.1
Chemotherapy (MABOP)[c]	Leukemia	3.8
Radiation therapy	Solid tumor	0
Chemotherapy (ABVD)[d]	Leukemia	0
Radiation therapy	Solid tumor	12
Chemotherapy (other)	Leukemia	2.9

[a] Radiation therapy = 3000–5000 rads.
[b] MOPP = mustine, vincristine, procarbazine, and prednisone.
[c] MABOP = MOPP with adriamycin and bleomycin substituted for procarbazine.
[d] ABVD = adriamycin, bleomycin, vinblastine, and dacarbazine.

Data from Valagussa, P., Santoro, A., Kenda, R., Fossati-Bellani, F., Franchi, F., Banfi, A., Rieke, F., and Bonadonna, G., *Br. Med. J.*, 280, 216, 1980.

Basalioma

Incidence of Basal Cell Carcinoma Among Long-Term Survivors of Radiation Treatment

Number of Treated Patients	Latent Period	Basal Cell Carcinoma as a Second Malignancy (% of Total Patients)	Reference
13 patients of medulloblastoma treated with radiation	6 months to 3 years	100	10
3 patients treated with radiation	1–4 years	100	10
1 child treated with radiation shortly after birth	5 years	100	12
1 child received radiation treatment at the age of 5	23 years	100	13

Iodio 131

Cancer Incidence After a Therapeutic Dose of ^{131}I

Type of Cancer	Dose (cGy)	Value Higher than Normal (%)
Lung	7	32
Kidney	5	39
Stomach		33
Thyroid	>10,000	29
Parathyroid	No estimate	78
Brain	No estimate	30

Data are summarized from the work of Holm et al.[36]

Stima del rischio di tumori radio-indotti

TABLE 10.1

Summary of the 1958–1994 Cancer Incidence Data in A-Bomb Survivors

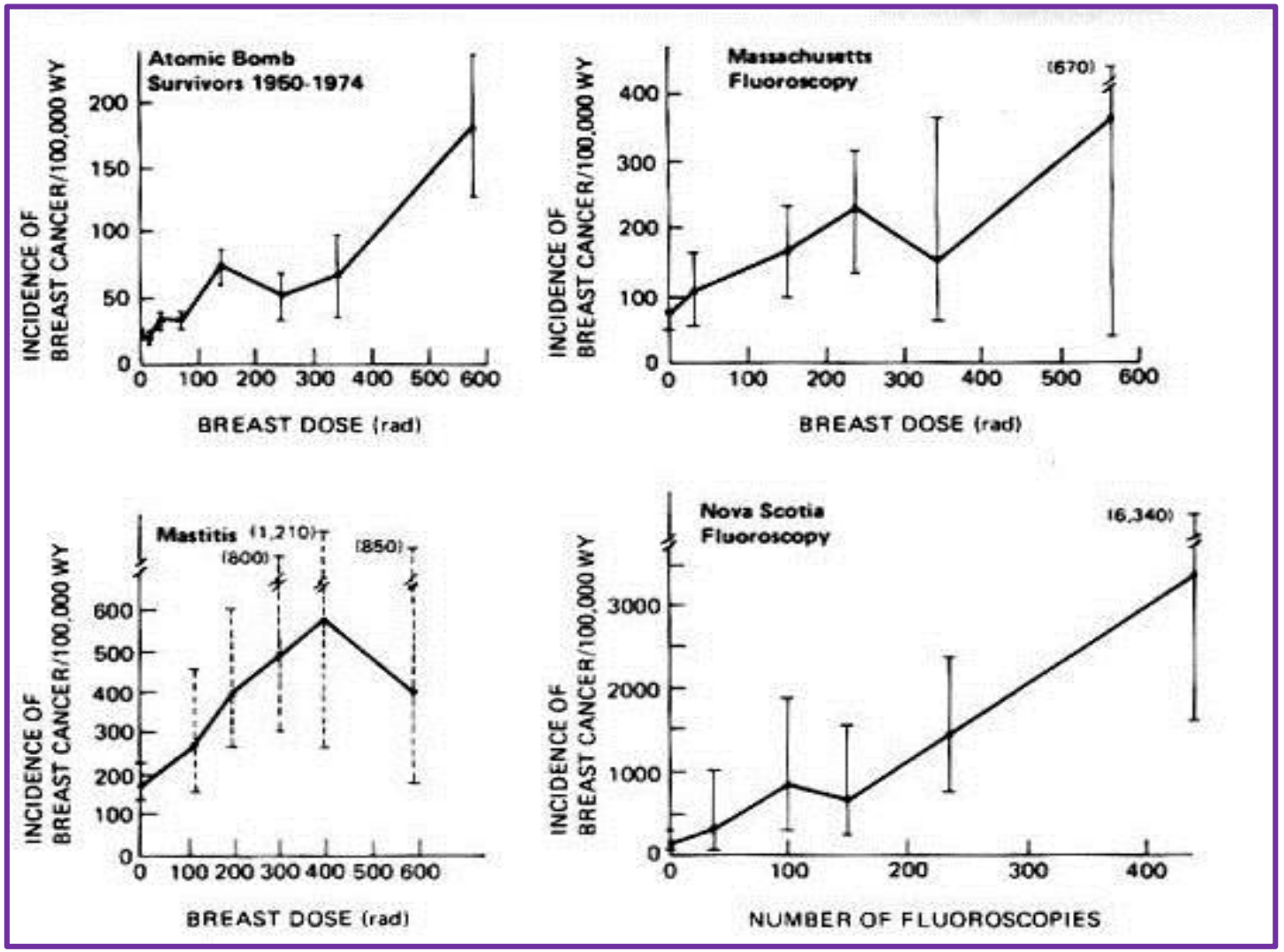
Colon Dose, Sv	Number of Subjects	Solid Cancers	Estimated Excess
Beyond >3,000 m	23,493	3,230	0
<0.005 Sv within <3,000 m	10,159	1,301	1
0.005–0.1	30,524	4,119	77
0.1–0.2	4,775	739	60
0.2–0.5	5,862	982	164
0.5–1	3,048	582	177
1–2	1,570	376	165
>2	470	126	80

Based on Pierce DA, Preston DL: Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiation Research* 154:178–186, 2003.

Incidenza Tumore della Mammella

Donne sopravvissute alla bomba atomica di Hiroshima e Nagasaki

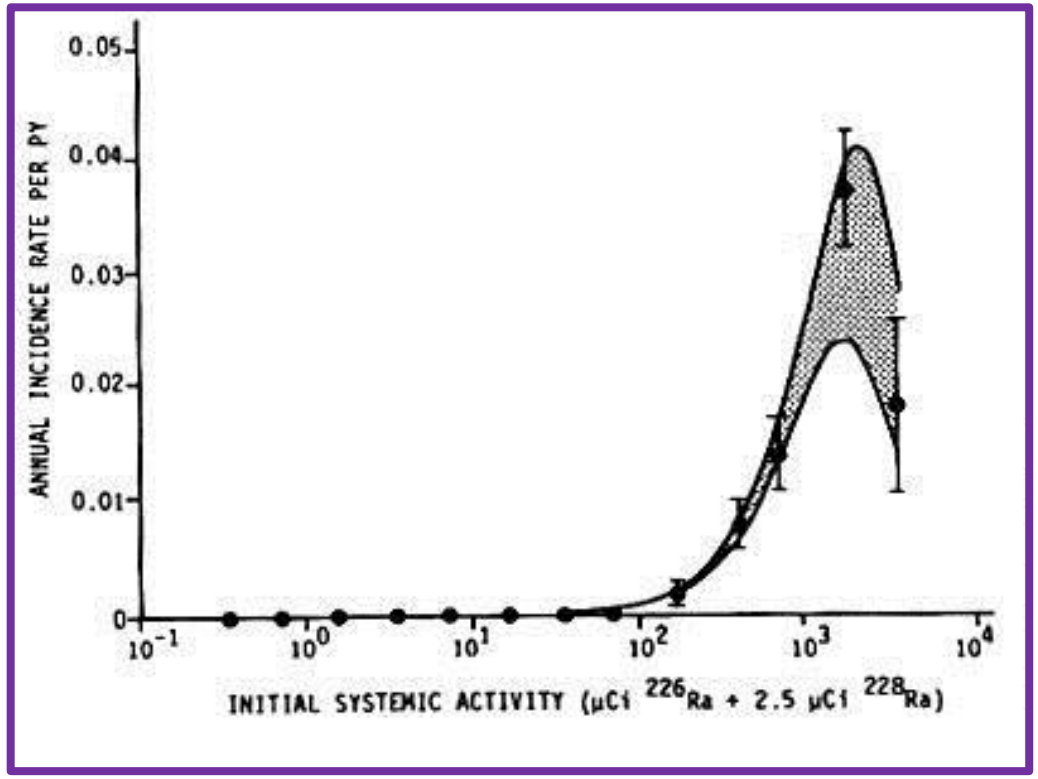
Donne trattate per mastite post-partum ed altre condizioni benigne



Donne con TBC polmonare sottoposte a fluoroscopia

Tumori Ossei

- Soggetti giovani (soprattutto donne) che hanno ingerito Radio dopo aver trattato elementi del quadrante degli orologi
- Pazienti con TBC o spondilite anchilosante, trattati con Radio-224



Tumori Polmone

- Soggetti esposti ad una sorgente esterna di radiazioni
- Pazienti con spondilite anchilosante
- Minatori esposti al gas Radon

Tumori Cutanei

- Basaliomi e tumori squamocellulari sono più frequenti in radiologi, dentisti e tecnici dei raggi X

Oncogeni e Oncosoppressori presenti nei tumori umani radio-indotti

- Mutazioni puntiformi di Ras
- RET in tumori tiroidei
- Amplificazione di *c-myc* in altri tumori radio-indotti
- Mutazioni di p53 in:
    - tumori del polmone associate ad esposizione di Radon (minatori)
    - tumori della tiroide in bambini esposti a radiazioni (incidente nucleare di Chernobyl)

Stima della mortalità per alcuni tumori radio-indotti

TABLE 10.2

Excess Cancer Mortality: Lifetime Risk per 100,000 at 0.1 Sv

	BEIR V (U.S. Population)			
	Males	Females	UNSCEAR 88 (Japanese Population)	
Breast	—	70	Breast	60
Respiratory	190	150	Lung	151
Digestive system	170	290	Stomach	126
			Colon	79
Other solid	300	220	Other solid	194
Leukemia	110	80	Leukemia	100
Total	770	810	Total	710