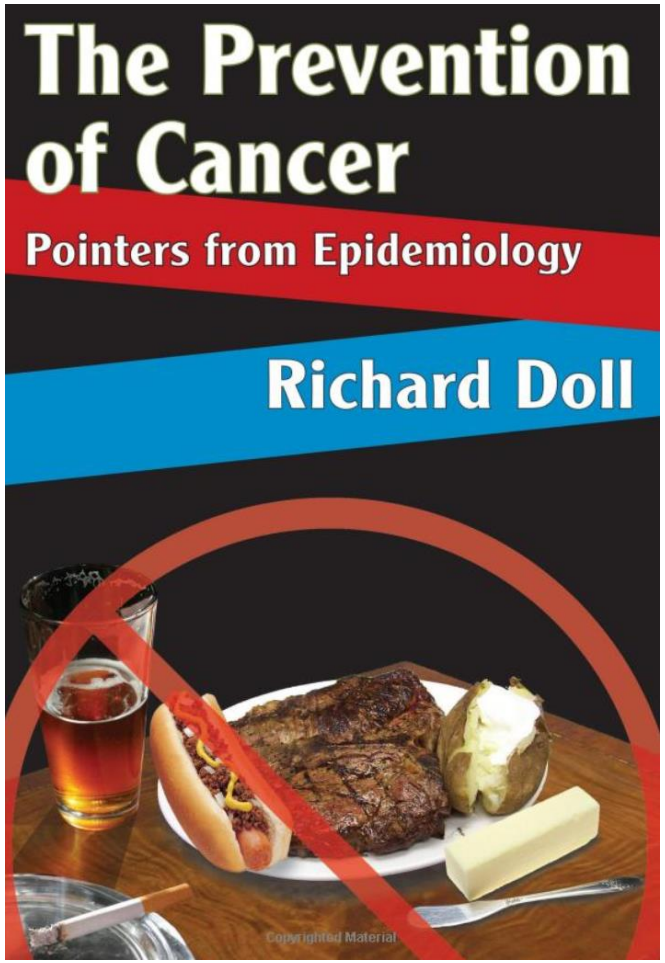
Life-style factors influencing individual risk of radiogenic cancer and risk transfer between populations



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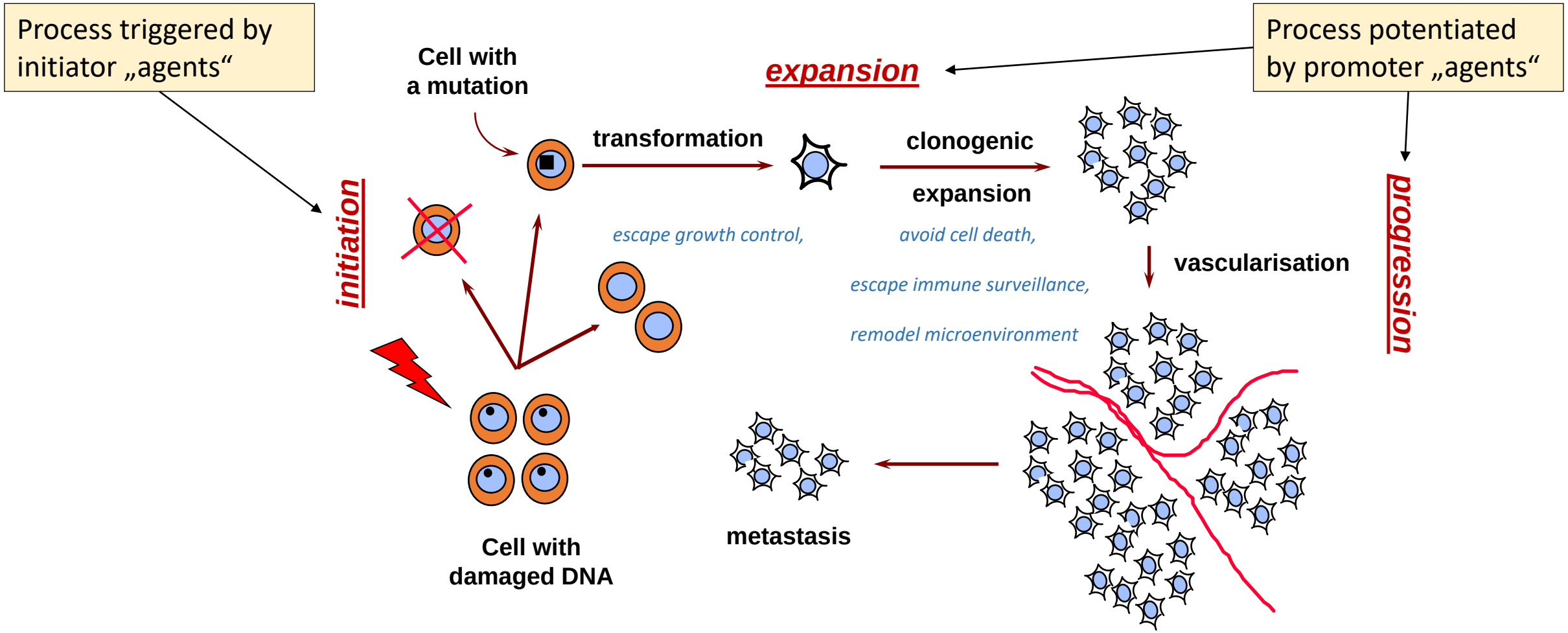
Radiation-induced tumor development and modes of interaction

Based on Müller and Streffer, 1987



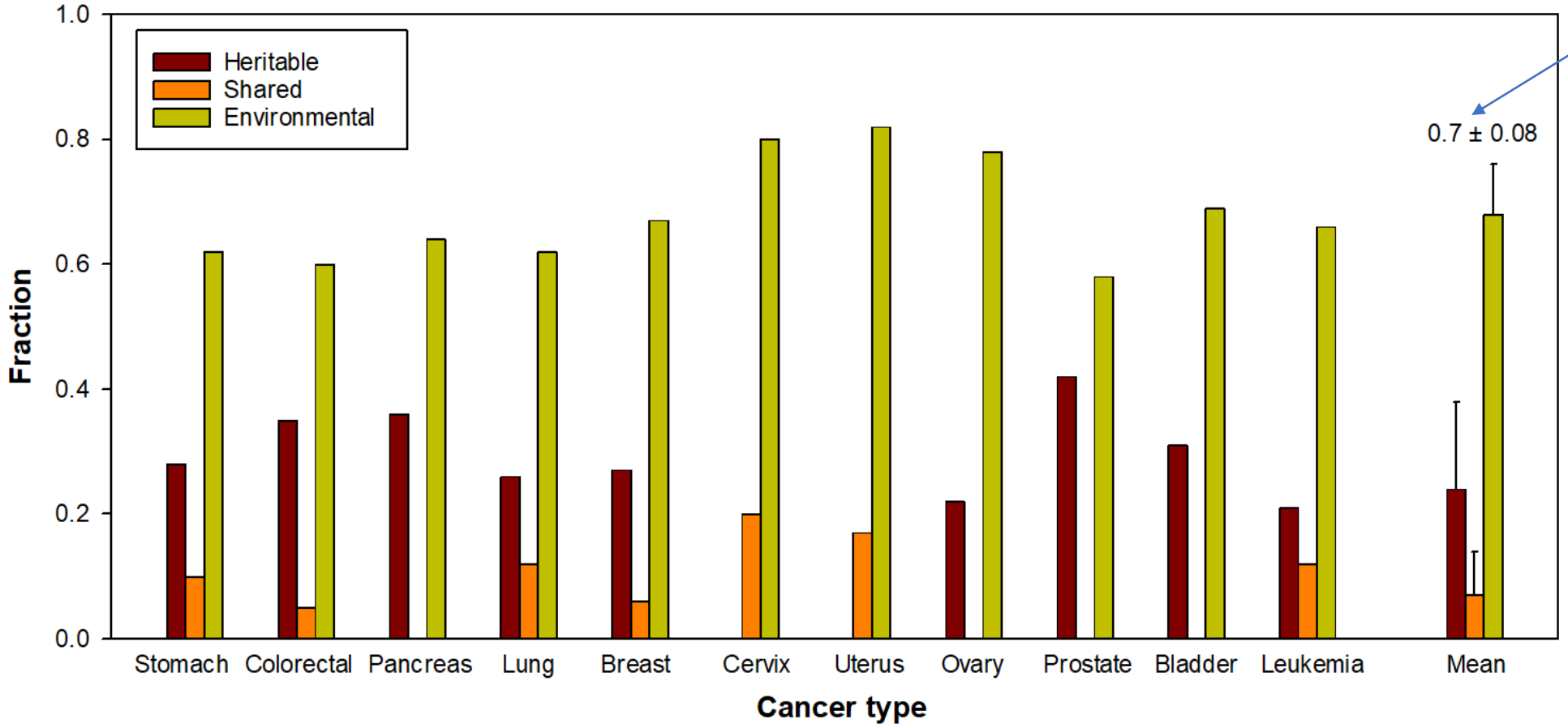
ICRP 103 and BEIR VII assume that radiation is mainly a cancer initiator. Co-exposure outcome can be described by:

- **Multiplicative model (interaction) -** if co-exposure factor is a promoter.
- **Additive model (no interaction) -** if co-exposure factor is an initiator.

Background incidence of cancer – contribution of heritable (non-modifiable) and environmental (modifiable) risk factors

Effects of heritable and environmental factors in cancers at various sites, according to data from Swedish, Danish and Finnish twin registries

Ca 70% of cancers are due to environmental factors



Source: Lichtenstein P et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 13:78-85, 2000.

Background incidence of cancer – contribution of heritable (non-modifiable) and environmental (modifiable) risk factors

Additional arguments for the major contribution of environmental factors to cancer incidence

1. The incidence of different cancer types varies between countries, often by a factor of > 10
2. People who migrate to a different country acquire the cancer incidence of their adopted country
3. The incidence of some types of cancer has varied dramatically over time within a single country
4. Total incidence of all forms of cancer is stable throughout the world suggesting the induction is partly by chance (no individuals susceptible to all forms of cancer)

Sources:

- Golemis et al. Molecular mechanisms of the preventable causes of cancer in the United States Genes Dev. 32: 868–902, 2018.
- Doll R. The prevention of cancer, 1967.

Among the USA population a small number of "supercarcinogens" cause a large fraction of cancers

The supercarcinogens include **smoking, obesity, sunlight** and **infectious agents.**

Agent	Mechanism of action	Expected mode of action with radiation
Smoking	Mutagenesis (initiator) Epigenetic modifications (promoter) Immunomodulation (promoter)	Additive Multiplicative
Obesity (incl. physical activity and diet)	Metabolism (promoter) Cell signalling (pomoter) Immunomodulation (promoter) Mutagenesis – diet (initiator)	Multiplicative Additive
Sun light	Mutagenesis (initiator) Immunomodulation (promoter)	Additive Multiplicative
Infectious agents	Mutagenesis (initiator) Immunomodulation (promoter)	Additive Multiplicative
Pollutants (chemical drugs)	Mutagenesis (initiator) Immunomodulation (promoter)	Additive Multiplicative

No data on combined exposure with radiation

Source: Golemis A et al. Molecular mechanisms of the preventable causes of cancer in the United States Genes Dev. 32: 868–902, 2018.

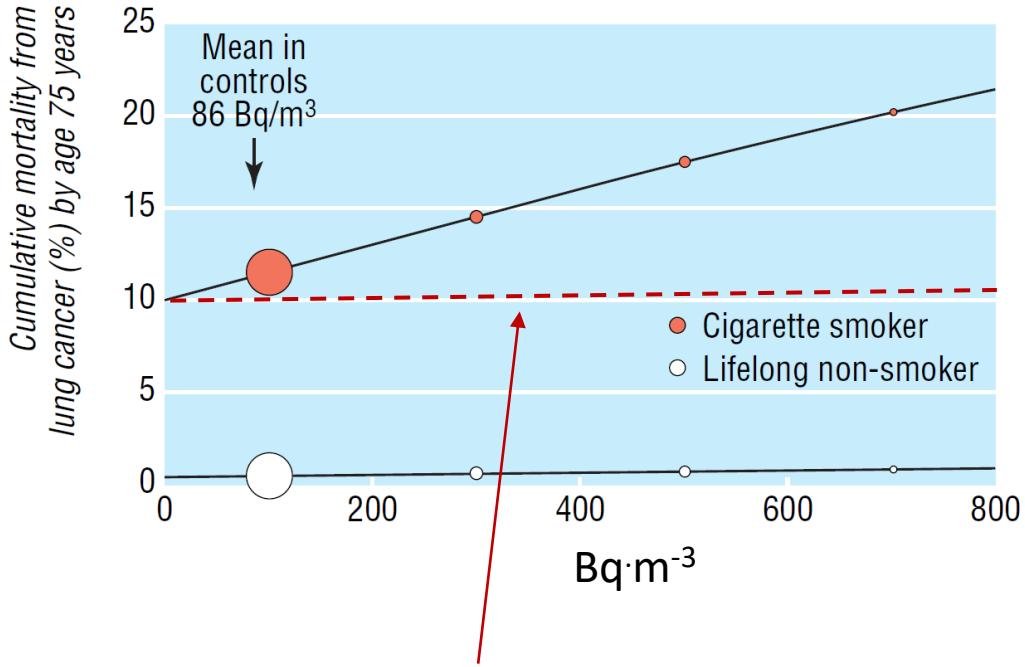
Smoking interacts with radon in causing lung cancer

Darby et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2004.

Cumulative absolute risks of lung cancer by age 75 years in smokers and non smokers

Cumulative mortality from lung cancer

$Bq \cdot m^{-3}$	non smokers	smokers
0	0.41%	10.1%
100	0.47%	16.0%
400	0.67%	21.6%



Expected dose response if effect of smoking and radon was additive

Smoking interacts with gamma radiation in causing lung cancer

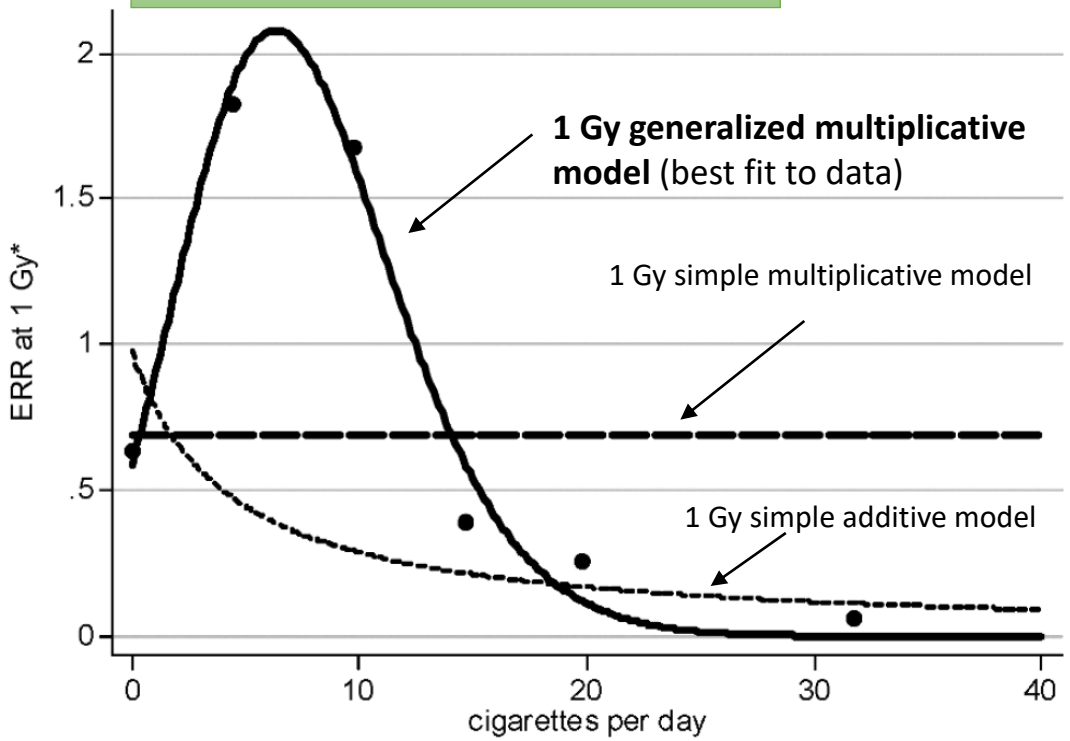
Stockholms universitet

Furukawa et al. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. Rad Res 174:72-82, 2010

Variation of the excess relative risk (ERR) per Gy with smoking intensity

Sex-averaged risk estimates at age 70 after radiation exposure at age 30

Radiation interacts with smoking only in cases smoking < 1 pack per day



* Gender-averaged excess risk relative to unexposed person with same smoking history

Radiation risks were not significantly higher for those who smoked before exposure as compared to those who started smoking after exposure

Smoking was assumed to start at age 20 so that smoking duration was fixed at 50 years in this figure. Radiation-associated excess risks for an exposure of 1 Gy relative to the risk of an unexposed person with the same smoking history.

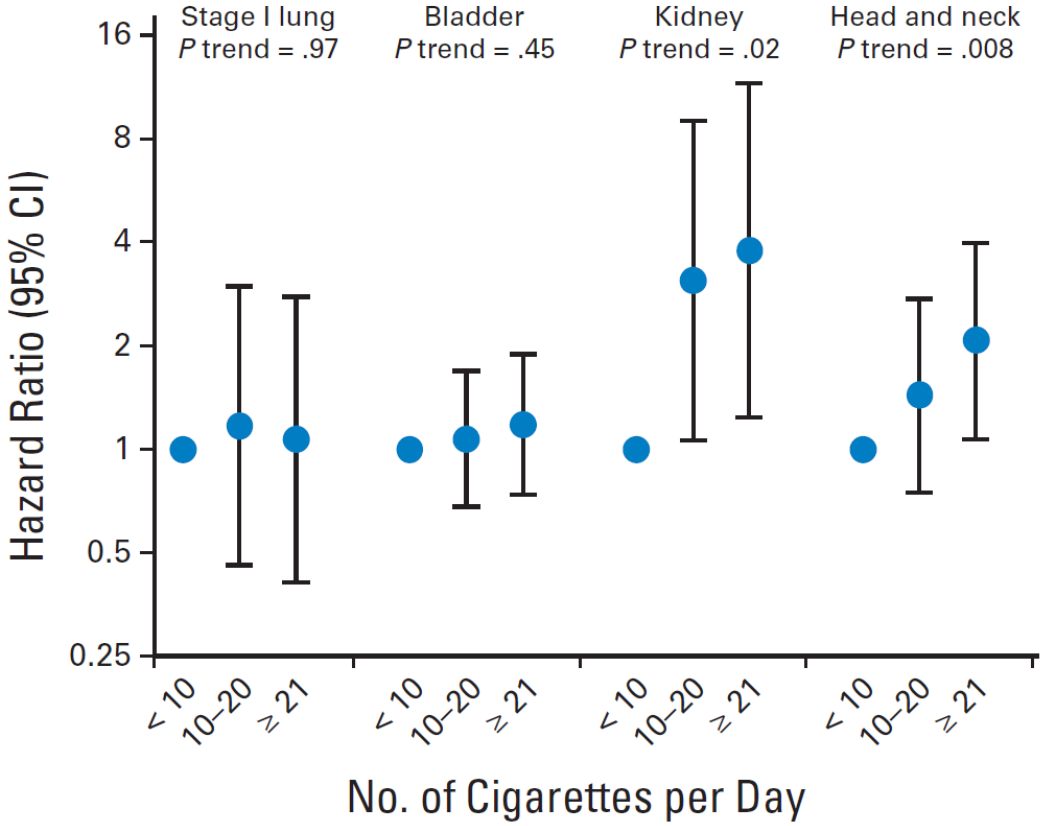
In the LSS, age at exposure is highly correlated with whether radiation exposure occurred before or after initiation of smoking, making it difficult to address this question. However, in an analysis in which the radiation effect was allowed to depend on whether one reported smoking before exposure, we found that radiation risks were not significantly higher for those who smoked before exposure as compared to those who started smoking after the exposure.

Smoking effect on radiotherapy associated risk of second primary cancer among bladder, kidney, head and neck, and lung cancer patients

Shiels et al. Cigarette Smoking Prior to First Cancer and Risk of Second Smoking-Associated Cancers Among Survivors of Bladder, Kidney, Head and Neck, and Stage I Lung Cancers. JCO 32: 3989-3996, 2014.

Association between cigarettes smoked per day at baseline and subsequent risk of second smoking-associated cancers among current smokers with stage I lung, bladder, kidney, and head/neck cancers. Points represent odds ratios and lines represent 95% CIs.

The problem of smoking-related mortality.
As cigarette smoking is associated with additional diverse causes of mortality, and deaths preclude second cancer diagnoses from occurring, competing deaths may distort the observed associations between smoking and second cancer risk.



Smoking-associated cancers: H&N, stomach, colorectum, liver, pancreas, larynx, lung, uterine cervix, ovary, urinary bladder, kidney and ureter, and myeloid leukemia.

Smoking and alcohol drinking effect on radiotherapy associated risk of second primary cancer and mortality among breast cancer patients

DiMarzio et al. Smoking and alcohol drinking effect on radiotherapy associated risk of second primary cancer and mortality among breast cancer patients. Cancer Epidemiology 57: 97–103, 2018.

smoking*radiotherapy interaction term

Table 3
Second Primary Cancer Risk According to Smoking Status and Radiotherapy.[a]

Cancer groups	Observed numbers of SPCs	ever-smokers/ no RT	never-smokers/ RT	ever-smokers/ RT	
Breast:	*n*	*HR 95% CI*	*HR 95% CI*	*HR 95% CI*	*P-value* [d]
Total	376	0.82 0.60-1.11	1.27 0.97-1.65	1.26 0.94-1.72	0.36
Ipsilateral [b]	113	1.17 0.72-1.89	1.08 0.66-1.75	0.83 0.43-1.61	0.31
Contralateral [c]	254	0.68 0.46-1.00	1.36 0.99-1.86	1.40 0.98-2.01	0.16
Non-Breast:					
Total	326	1.32 0.93-1.87	**1.64 1.17-2.29**	**3.02 2.17-4.20**	0.14
Lung	53	**3.80 1.58-9.22**	1.59 0.59-4.32	**4.98 2.06-12.05**	0.74
Hematological	33	0.23 0.03-1.86	1.65 0.60-4.49	**4.16 1.64-10.54**	< 0.001
Gastrointestinal	68	1.71 0.84-3.48	0.71 0.31-1.64	**2.46 1.26-4.81**	0.17
Gynecological	77	0.56 0.23-1.34	**1.93 1.05-3.53**	**2.84 1.53-5.29**	0.07
Urological	20	0.87 0.16-4.78	2.32 0.66-8.18	**4.02 1.13-14.26**	0.51
Thyroid	26	1.49 0.52-4.26	1.48 0.53-4.16	1.16 0.33-4.04	0.42
Skin	24	2.07 0.66-6.54	2.15 0.66-6.92	2.25 0.63-8.01	0.4
Other sites	25	0.80 0.27-1.07	1.43 0.59-3.52	1.85 0.71-4.80	0.52

Conclusion: Patients who receive radiotherapy and smoke before or at time of BC diagnosis have an increased risk for specific second primary cancer (SPC). Smoking interacts with radiation only for hematological cancers, not for lung cancer.

Obesity and risk of second primary cancer among breast cancer patients

Druesne-Pecollo N et al. Breast Cancer Res Treat 135:647–654, 2012.

Obesity was associated to significantly increased risks of second primary cancer of:

- contralateral breast (RR = 1.37, 95 % CI: 1.20–1.57),
- breast (RR = 1.40, 95 % CI: 1.24–1.58),
- endometrium (RR = 1.96, 95 % CI: 1.43–2.70),
- colon and rectum (RR = 1.89, 95 % CI: 1.28–2.79)

For a BMI increase of 5 kg/m^2, dose–response meta-analyses resulted in significantly increased RRs for:
contralateral breast (RR= 1.12 95 % CI: 1.06–1.20)
breast (RR = 1.14 (95 % CI: 1.07–1.21).

From the discussion:

The observation that excess body weight increased the risk of second primary cancers at sites for which a relationship is well established for first primary cancers suggests that this positive association may result from a life-long exposure, **rather than from a specific effect after the first breast cancer diagnosis.**

Obesity and risk of second primary cancers among colorectal cancer (CRC) patients

A pooled analysis of prospective cohort studies

Source: Gibson TM et al. J Clin Oncol 32:4004-4011, 2014

Associations Between Prediagnostic BMI and Risk of Either a Second Obesity-Associated Cancer Among CRC Survivors or a First Obesity-Associated Cancer Among All Participants at Baseline of the Five Cohort Studies

	Second primary cancer risk				First primary cancer risk			
	Overweight		Obese		Overweight		Obese	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All obesity associated cancers	**1.39**	**1.1-1.9**	**1.5**	**1.1-2.1**	**1.2**	**1.1-1.2**	**1.6**	**1.6-1.7**
Breast	1.36	0.9-2.1	1.2	0.7-1.9	1.1	1.1-1.2	1.4	1.3-1.4
Kidney	1.57	0.7-3.4	1.3	0.5-3.3	1.4	1.3-1.5	2.2	2.0-2.4
Pancreas	1.8	0.7-4.8	2.6	0.9-7.0	1.1	1.1-1.2	1.2	1.1-1.3
Esophagus	1.6	0.3-8.1	1.2	0.2-9.1	1.4	1.2-1.6	2.0	1.7-2.4
Endometrium	0.6	0.2-2.2	3.2	1.1-9.4	1.3	1.2-1.4	2.9	2.6-3.1

Blue: not significant

From the discussion:

The magnitude of the increased risk was similar to that observed for these cancers as first primary malignancies in the cohort. Elevated cancer risks in colorectal cancer survivors compared with the general population may be related to increased prevalence of overweight or obesity **rather than increased susceptibility to obesity-associated carcinogenesis**.

Obesity

Influence of diet and metabolism on hematopoietic stem cells and leukemia development following ionizing radiation exposure

Source: Karabulutoglu et al. IJRB 95:452-479, 2019

Conclusion: The review summarizes the current knowledge on how alterations in dietary and metabolic factors could alter the risk of leukemia development following ionizing radiation exposure by inhibiting or even reversing the leukemic progression.

Although clinical evidence is currently underdeveloped, experiments with animal models have provide evidence for possible dietary modification of the risk of radiation-induced malignancies including leukemia.

Infectious agents and radiation-induced cancer

Stockholms universitet

Sharp GB et al. Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. Int J Cancer, 103:531-537, 2003.

RR for hepatocellular carcinoma was **28.7** in hepatitis C virus -infected persons exposed to radiation compared to those negative for liver irradiation and the virus. The expected RR for this comparison would be **7.3**.

Conclusion

Hepatitis C virus infection combined with liver irradiation significantly elevated hepatocellular carcinoma risks after controlling for the effects of hepatitis C virus and liver irradiation alone, as well as for cirrhosis status and other factors.

Infectious agents and radiation-induced cancer

Ohishi et al. Impact of Radiation and Hepatitis Virus Infection on Risk of Hepatocellular Carcinoma (among atomic bomb survivors) **Hepatology. 53:1237-1245, 2011**

Table 2. Risk of HCC for Radiation and HBV or HCV Infection Status

Variables	Number of Cases/Controls	Unadjusted RR (95% CI)		Adjusted* RR (95%CI)	
		Alone†	Joint‡	Alone†	Joint‡
Radiation (at 1Gy)	186/600	1.40 (1.07-1.89)	1.39 (0.93-2.26)	1.67 (1.22-2.35)	1.82 (1.09-3.34)
HBV+/HCV −	24/14	34 (13-106)	30 (11-91)	63 (20-241)	50 (16-184)
HBV−/HCV +	119/35	57 (27-140)	58 (28-147)	83 (36-231)	87 (37-251)

Abbreviations: CI, confidence interval; RR, relative risk.
*Adjusted for categorical alcohol consumption, BMI 10 yrs before diagnosis, and smoking habit.
†Radiation dose to the liver and hepatitis virus infection status were fit separately.
‡Radiation dose to the liver and hepatitis virus infection status were fit simultaneously.

From the discussion:

Radiation exposure and HBV and HCV infection are associated independently with increased HCC risk. In particular, radiation exposure was a significant risk factor for non-B, non-C HCC with no apparent confounding by alcohol consumption, BMI, or smoking habit.

Chemical agents and radiation-induced cancer

Reviews of experimental and epidemiological data

- UNSCEAR 1982. Annex L: Biological effects of radiation in combination with other physical, chemical or biological agents.
- UNSCEAR 2000. ANNEX H: Combined effects of radiation and other agents.

Overall conclusions from UNSCEAR 1982 and 2000 reports

With the exception of radiation and smoking, there is little indication from epidemiological data for a need to adjust for strong antagonistic or synergistic combined effects of radiation and chemical agents.

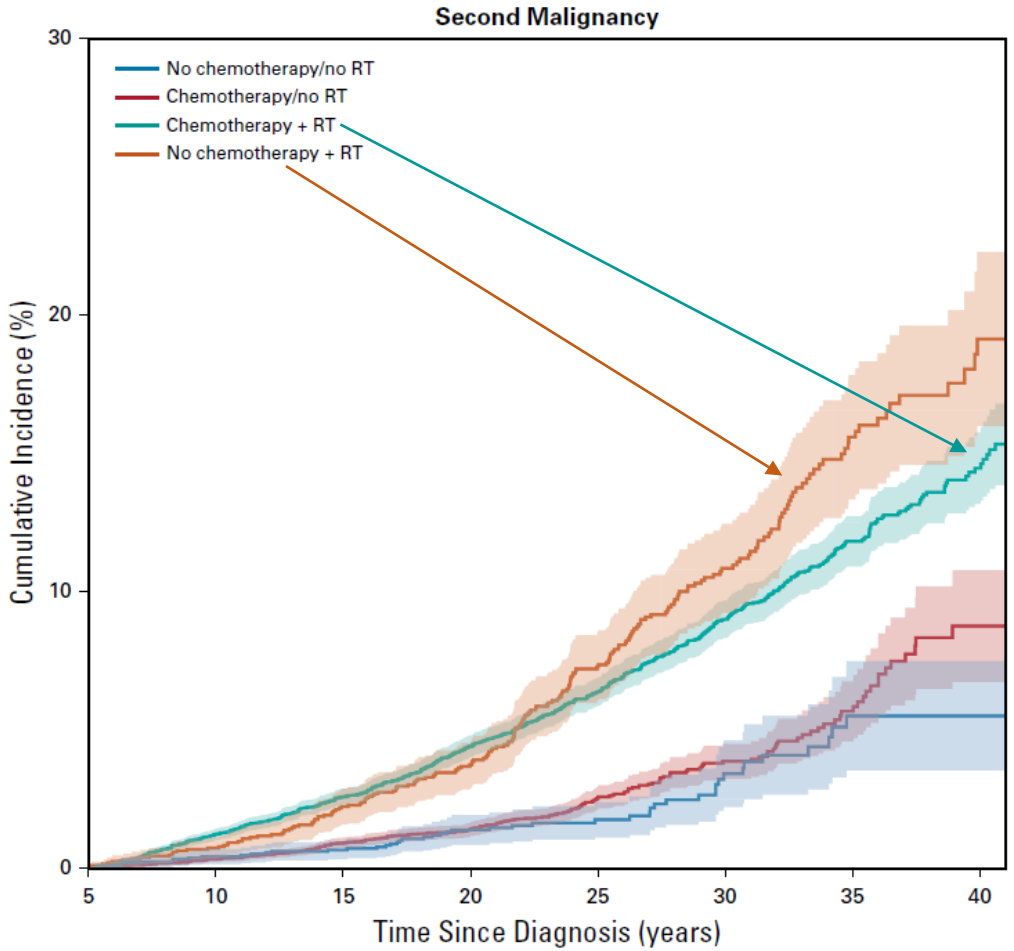
Chemical agents and radiation-induced cancer

Chemotherapy reduces the second primary cancer (SPC) risk after radiotherapy

D`angio et al. 1976
Cancer 37:1177-1185.

Actinomycin-D reduces the risk of SPC in a cohort of patients with various primary cancers.
Cocktail of cyclophosphamide, vina alkaloids and antifolic acid has no effect of the risk of SPC.

Turcotte et al. 2009
J Clin Oncol 37:3310-3319.



Cumulative incidence of SPC by childhood cancer treatment.
RT: radiation therapy

Chemotherapy: alkylating agents, anthracyclines, platinum.

Possible mechanism: cell overkill.

Substantiates the notion that radiation is a cancer inducer and not promoter

Chemical agents and radiation-induced cancer

Chemotherapy reduces the second primary cancer (SPC) risk after radiotherapy

Alodji et al. Role of radiotherapy and chemotherapy in the risk of leukemia after childhood cancer: An international pooled analysis. Int J Cancer 148: 2079-2089, 2021.

TABLE 4 Excess odds ratio of secondary leukemia per Gy of weighted average radiation dose to the active bone marrow (EOR/Gy) in a linear multiplicative model, according to chemotherapy status

	Patients without chemotherapy	Patients receiving chemotherapy	*P* values
EOR/Gy (95% CI)	1.55 (0.14-14.3)	0.02 (–0.01-0.09)	.006[a]

Abbreviations: 95% CI, 95% confidence interval; EOR/Gy, excess odds ratio of secondary leukemia per Gy of weighted average radiation dose to the active bone marrow.

[a]*P* value from likelihood ratio test (comparison of two nested models—that is, the first one including radiotherapy dose to ABM and chemotherapy vs the second one with adding an interaction term of dose to ABM × chemotherapy to the first model).

Chemical agents and radiation-induced cancer

Chemotherapy potentiates the second primary cancer (SPC) risk after radiotherapy

Guerin et al. Concomitant chemo-radiotherapy and local dose of radiation as risk factors for second malignant neoplasms after solid cancer in childhood: A case–control study. Int. J. Cancer 120:96-102, 2006.

A cohort of 4,581 patients, at least 2-year survivors, treated for a solid cancer occurred between 0 and 15 years, in 8 centers in France and Great Britain, between 1942 and 1986.
Pooled impact of alkylating agents, platinum compounds, bleomycin, anthracyclins, antimetabolites.

TABLE VI – CRUDE AND ADJUSTED ODD RATIOS OF SECOND CANCER ACCORDING TO TREATMENT MODALITIES

Treatment modalities	Cases (%)–Controls (%)	Crude OR (95% CI)	*p*-value*	Adjusted OR[1] (95% CI)	*p*-value*
No RT, no CT	6–9	1	10^{-4}	1	$<10^{-4}$
RT alone	23–30	1.4 (0.6–3.4)		1.0 (0.4–2.6)	
CT alone	14–19	1.7 (0.6–4.8)		1.8 (0.6–5.0)	
Sequential CT and RT	15–14	2.6 (0.9–7.4)		1.8 (0.6–5.2)	
Concomitant CT and RT	42–27	4.9 (1.8–13)		3.4 (1.2–9.2)	

95% CI, 95% confidence interval; RT, radiotherapy; CT, chemotherapy.
*Test of heterogeneity.
[1]Adjusted for the local dose of radiation.

Chemical agents and radiation-induced cancer

Chemotherapy potentiates the second primary cancer (SPC) risk after radiotherapy

Veiga et al. Association of Breast Cancer Risk After Childhood Cancer With Radiation Dose to the Breast and Anthracycline Use A Report From the Childhood Cancer Survivor Study. JAMA Pediatrics 2019

Table 3. Odds Ratio for Breast Cancer According to Estimated Radiation Dose to the Breast Cancer Location and Receipt of Anthracyclines[a,b]

	Anthracyclines				Potentiating effect
	No		Yes		
Breast Dose[b]	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	
All Breast Cases					
0 to <1 Gy	16/292	1 [Reference]	43/231	3.3 (1.6-6.8)	3.3
1 to <10 Gy	21/116	2.1 (0.9-4.8)	10/36	3.7 (1.4-10.3)	1.8
≥10 Gy	108/188	9.6 (4.4-20.7)	33/28	19.1 (7.6-48.0)	2.0
ER+ Invasive Cases					
0 to <1 Gy	6/129	1 [Reference]	17/94	5.0 (1.6-15.7)	5.0
1 to <10 Gy	8/46	3.5 (0.9 to13.2)	4/20	3.3 (0.7-15.7)	0.9
≥10 Gy	55/81	21.2 (6.5-69.5)	14/9	35.7 (8.5-150.0)	1.7
ER- Invasive Cases					
0 to <1 Gy	4/38	1 [Reference]	12/41	2.4 (0.6-9.8)	2.4
1 to <10 Gy	2/22	1.4 (0.2-10.2)	3/6	8.7 (0.7-109.2)	6.2
≥10 Gy	15/31	13.3 (2.4-75.3)	3/4	22.8 (2.1-240.5)	1.7

Do supercarcinogens interact with radiation?

Agent	Mechanism of action	Expected mode of action with radiation	Evidence
Smoking	Mutagenesis (initiator) Epigenetic modifications (promoter) Immunomodulation (promoter)	Additive Multiplicative	Radon studies and LSS suggest interaction
Obesity (incl. physical activity and diet)	Metabolism (promoter) Cell signalling (pomoter) Immunomodulation (promoter) Mutagenesis – diet (initiator)	Multiplicative Additive	Results from cancer patients indicate no interaction
Infectious agents	Mutagenesis (initiator) Immunomodulation (promoter)	Additive Multiplicative	LSS results contradictory
Pollutants (chemical drugs)	Mutagenesis (initiator) Immunomodulation (promoter)	Additive Multiplicative	Results from cancer patients contradictory. UNSCEAR claims no interaction

The problem of risk transfer between cohorts

Cancer risk factors from LSS are used to predict cancer incidence in other cohorts. Two possible ways exist:

Transfer of **excess absolute risk (EAR)**: radiation induces a certain number of cancers independently of the background assuming **no interaction** between radiation and the background

Transfer of **excess relative risk (ERR)**: radiation potentiates the background risk of cancer assuming **an interaction** between radiation and the background

Which model is recommended by BEIR VII (2006) and ICRP (2007)?

The problem of risk transfer between cohorts

Recommendations of BEIR VII and ICRP

BEIR VII: “At present, neither knowledge of biological mechanisms nor data from epidemiologic studies are sufficient to allow definitive conclusions regarding the appropriate method for transporting risks, although **mechanistic considerations suggest somewhat greater support for relative risk than for absolute risk transport**”.

ICRP 103: “For most sites, the difference between Japanese and US rates is considerably less than 12-fold, which means that inability to discriminate between the additive and multiplicative transfer models is less consequential. However, among the sites considered for the present report, only for lung, breast, and thyroid was it considered that there was sufficient information to justify a representative value other than 50:50”.

	ICRP			BEIR VII	
	EAR	**ERR**		**EAR**	**ERR**
Leukemia	100	0		30	70
Breast	100	0		100	0
Lung	70	30		70	30
Thyroid	0	100		0	100
Skin	0	100		30	70
All other	50	50		30	70


Thank you for your attention