Experimental animal studies on cancer

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Role of animal studies

- **Information obtained from animal experiments can be used to complement epidemiological evidence.**
  - Smaller likelihood of uncontrollable biases
  - Opportunity to examine a wide range of modifying factors

- **We systematically reviewed the available evidence from animal studies on modifying factors of radiation-related cancer**

Modification by age and sex (1/3)

(a) Age at exposure

- **General:** Young animals are more susceptible than foetuses or adults
- **Specific organs:** Some varies by tissue

Tissue (*genetically modified)	**High susceptibility**	**Reference (example)**
All tumours	Neonatal–juvenile	Sasaki & Fukuda (2005) + 8 refs
Pituitary, medulloblastoma*, kidney*	Perinatal	Sasaki (1991), Pazzaglia et al. (2006, 2009), Tsuruoka et al. (2016, 2021), Kokubo et al. (2010), Castanera et al. (1971)
Thyroid, liver, skin, small intestine*, colon*, ovary, bone, kidney, lymphoma	Perinatal–young adult	Di Majo et al. (1990), Sasaki (1991) +20 refs
Breast	Peripubertal	Imaoka et al. (2023) + 8 refs
Myeloid leukaemia	Young adult–adult	Sasaki (1991) + 2 refs
Lung	Prenatal–neonatal Juvenile–young adult	Sasaki (1991), Yamada et al. (2017), Lundgren et al. (1980, 1995)

Modification by age and sex (2/3)

(b) Attained age

- ERR generally decreases and EAR increases with attained age, with some exceptions

Model	Outcome	Analysis	Animal	Modification	Reference
ERR	All tumours	Qualitative	Mouse	Decrease	Tanaka et al. 2017
	All solid	Qualitative	Mouse	Decrease	Sasaki & Fukuda 2005
	Breast cancer	Model	Rat	Decrease (power of −0.7)	Imaoka et al. 2023
	Lung cancer	Model	Rat	Increase (spline)	Yamada et al. 2017
EAR	All tumours	Qualitative	Mouse	Increase (<500 days)	Tanaka et al. 2017
	All tumours	Qualitative	Mouse	Increase	Sasaki 1991
	All tumours	Qualitative	Mouse	Increase	Sasaki et al. 1978
	All solid	Model	Mouse	Increase (power of ~1.5)	Sasaki & Fukuda 2005
	Breast cancer	Model	Rat	Increase (power of 0.6)	Imaoka et al. 2023
	Osteosarcoma	Model	Dog	Increase (exponential)	Bruenger et al. 1991
	Skin cancer	Model	Rat	Increase (power of 2)	Burns et al. 1993
	T-cell lymphoma	Qualitative	Mouse	Peak at 60–90 days post-IR	Dange et al. 2007

Modification by age and sex (3/3)

(c) Sex

- **Females:** More susceptible to all solid tumours and lymphoma
- **Males:** More susceptible to myeloid leukaemia and liver tumour

Outcome	Risk measure	Modification	Reference
All solid Lymphoma Myeloid leukaemia Soft tissue sarcoma	ERR sex ratio (95% CI)	M:F = 0.50 (0.34, 0.73) M:F = 0.56 (0.38, 0.84) M:F = 2.06 (0.55, 7.68) M:F = 1.39 (0.54, 3.55)	Chernyavskiy et al. 2017
Lung adenocarcinoma	ERR/Gy	M 1.05 : F 1.24	Suzuki et al. 2022
All (excl. ovary) Lymphoreticular Vascular Lung	EAR (10^{-4} mouse-days Gy^{-1})	M 6.27 ± 0.84 : F 8.60 ± 0.94 M 7.36 ± 1.08 : F 3.65 ± 1.13 M 6.67 ± 1.21 : F 5.54 ± 1.03 M 5.35 ± 0.87 : F 12.30 ± 1.43	Grahn et al. 1992

Lifestyle factors (1/2)

- **Cigarette smoke** increases radionuclide-related lung cancer

Smoking exposure	Radiation	Animal	Outcome	Modification	Reference
Lifetime	$^{239}PuO_2$	Rat	Lung cancer	Supra-additive	Mauderly et al. (2010)
Post-radionuclide	^{222}Rn	Rat	Lung cancer	Increase	Chameaud et al. (1982)

- **Body weight** increases radiation-related tumours in general

Diet	Timing	Animal	Outcome	Modification	Reference
Food intake	Post IR	Rat Mouse	All Leukaemia	Increase	Gross & Dreyfuss (1984, 1990) Gross & Dreyfuss (1986)
Carbohydrate	Post IR Pre IR Pre + post	Mouse Mouse Mouse	All, intestinal, myeloid leukaemia Myeloid leukaemia Myeloid leukaemia	Increase No Increase	Shang et al. (2014), Morioka et al. (2021), Yoshida et al. (1997, 2006) Yoshida et al. (2006) Yoshida et al. (1997)
Fat	Post IR Pre + post	Rat Rat	Breast cancer Breast cancer	Supra-multiplicative Increase	Imaoka et al. (2023) Silverman et al. (1980), Imaoka et al. (2016)

Lifestyle factors (2/2)

- **Female sex hormones** increase radiation-related breast cancer risk

Modifying factor	Timing	Modification	Reference
Diethylstilbestrol (DES)	Pre + post	Increase	Shellabarger et al. (1983) + 3 refs
		Supra-additivity	Shellabarger et al. (1978)
		Supra-additivity, increase	Holtzman et al. (1979) + 1 ref
	Post IR	Increase	Shellabarger et al. (1983)
Estradiol	Pre + post	Increase	Bartstra et al. (1998a) + 2 refs
Hyperprolactinemia	Post IR	Acceleration	Clifton et al. (1985)
Progesterone + DES	Pre + post	Decrease	Segaloff (1973)
Removal of ovary	Pre + post	Decrease	Clifton et al. (1985)
Tamoxifen	Post IR	Marked decrease	Lemon et al. (1989)
	Pre + post (short)	Decrease	Welsch et al. (1981)
	Post IR (short)	Decrease	Welsch et al. (1981)
Estriol	Post IR	Decrease	Lemon et al. (1989)
Ethinylestriol	Post IR	Decrease	Lemon et al. (1989)
Parity	Post IR	Decrease or no effect (depending on age at exposure)	Takabatake et al. (2018)

Underlying conditions

- **Diabetes, collagen vascular disease:** No evidence found

- **Inflammation** increases radiation-related cancer in some studies.

Modifying factor	Animal	Outcome	Modification	Reference
Gastritis, antigen-induced	Mouse	Stomach cancer	Increase	Hirose et al. (1976)
Inflammation, implant-induced	Mouse	Salivary gland carcinoma	Increase	Eulderink and van Rijssel (1972)
Inflammation, implant-induced	Mouse	Myeloid leukaemia	Increase (male) Non-significant (female)	Yoshida et al. (1993)
	Mouse	Myeloid leukaemia	No change	Yoshida et al. (1993)
Fibrosis, implant-induced	Rat	Soft tissue tumours	Non-significant	Eltze et al. (2006)
Colitis, chemically induced	Mouse Mlh1$^{-/-}$	Colon neoplasms	Non-significant	Morioka et al. (2015)
Anti-inflammatory agent	Rat	Colon neoplasms	Decrease	Northway et al. (1990)

Other environmental factors (1/2)

- **UV and sunlight** increase X-ray-induced skin cancer

Modifier	Animal	Modification	Reference
Solar dermatosis	Dog	Increase	Nikula et al. (1992)
Simulated solar radiation (incl. UV)	Mouse	Increase	Lerche et al. (2013)

- **Chemical carcinogens** are generally additive to radiation-related risk

Class	Chemicals	Outcome	Modification	Reference
Alkylating	BHP	Lung	Additive	Iwata et al. (2013)
	DEN	Liver focus	No effect, supra-additive	Kim et al. (1994) +2 refs
	DMH	Colon	Increase	Sharp & Crouse (1989)
	ENU	Lymphoma	Supra-additive	Kakinuma et al. (2012) +1 ref
		Nervous	Decrease	Hasgekar et al. (1986) +2 refs
	MNNG	Gastric cancer	No effect	Fujii et al. (1980)
	MNU	Breast, intestine	Additive, multiplicative	Imaoka et al. (2014) +3 refs
Adduct-forming	2AA, AAF, DAAF	All, skin, liver	Increase	Myers & McGregor (1982) +3 refs
	BrdU	All	Increase	Anisimov & Osipova (1993)
	DMBA, 4NQO	Skin, oral, lung	No effect, increase	Lurie (1977) +5 refs
	MAM	Intestinal	Increase	Tanaka et al. (1993) +2 refs
	PhIP, MCA	Breast	Additive	Imaoka et al. (2014) +1 ref
	Urethane	All, lymphoma, lung	Increase	Myers (1976) +3 refs

Other environmental factors (2/2)

- **Protective chemicals** decrease radiation-related cancer in animals

Chemicals	Timing	Outcome	Modification	Reference
Protectants				
Radioprotectors and radical scavengers	Pre	All, hematopoietic, breast, liver, lung, sarcoma	Decrease	Cook et al. (2018) +14 refs
Antioxidants	Post, pre + post	All, breast, lymphoma, lung	Decrease	Inano et al. (1999) +5 refs
NO scavengers	Pre + post	Breast	Decrease	Inano and Onoda (2003)
NO synthase inhibitor	Post	Pituitary	Decrease	Ueno et al. (2009)
Food ingredients				
Vitamins	Pre + post, post	Lung, lymphoma, parathyroid	Decrease	Kennedy et al. (2008) +2 refs
Minerals	Pre + post, post	Skin, thyroid (C cell)	No effect	Zackheim et al. (1993) +2 refs
Soybean protease inhibitor	Pre + post	Lymphoma	Decrease	Kennedy et al. (2008) +1 ref
Sugar beet fibre	Pre + post	Colon (foci)	Decrease, no effect	Nagai et al. (2000) +1 ref
Meadowsweet extract	Post	Breast	Decrease	Bespalov et al. (2017)
Potato extract	Post	Liver (foci)	Decrease	Kim et al. (1994)
Vitamin A	Pre + post	Lung	Increase	Mian et al. (1984)
Iodine (low/high)	Pre + post	Thyroid	Increase	Boltze et al. (2002)

Other biological factors

- **DNA repair deficiencies** increase, decrease, or have no effect on radiation-related cancer, depending on the affected gene and tissue type

Class	Modifying factor	Animal model	Outcome	Modification	Reference
Non-homologous end joining	$Prkdc^{scid/+}$	Mouse	Solid tumours	No effect	Ishii-Ohba et al. (2007)
	$Prkdc^{scid/scid}$	Mouse	Solid tumours	No effect	Ishii-Ohba et al. (2007)
	$Prkdc^{-/-}$	$Ptch1^{+/-}$ mouse	Medulloblastoma	Decrease	Tanori et al. (2019)
	$Prkdc^{BALB/BALB}$	$Apc^{Min/+}$ mouse	Breast tumour	Decrease	Haines et al. (2015)
	$Prkdc^{BALB/BALB}$	$Apc^{Min/+}$ mouse	Intestinal tumour	Increase	Haines et al. (2015)
Homologous recombination repair	$Rad54^{-/-}$	$Ptch1^{+/-}$ mouse	Medulloblastoma	Increase	Tanori et al. (2019)
	$Xrcc2^{+/-}$	$Apc^{Min/+}$ mouse	Breast tumour	Increase	Haines et al. (2015)
	$Xrcc2^{+/-}$	$Apc^{Min/+}$ mouse	Intestinal tumour	No effect	Haines et al. (2015)
	$Brca1^{+/-}$	Mouse	Ovarian tumour	Increase	Jeng et al. (2007)
	$Brca1^{+/-}$	Rat	Breast cancer	Increase	Nakamura et al. (2022)
Mismatch repair	$Mlh1^{-/-}$	Mouse, DSS-treated	Colon neoplasms	Increase	Morioka et al. (2015)
DNA damage response	$Atm^{-/-}$	Mouse	All neoplasms	No effect	Yamamoto et al. (2011)
	$Atm^{+/-}$	Mouse	All neoplasms	No effect	Yamamoto et al. (2011)
	$Atm^{+/-}$	Mouse	Breast cancer	No effect	Umesako et al. (2005)
	$Atm^{+/-}$	$Trp53^{+/-}$ mouse	Breast cancer	No effect	Umesako et al. (2005)
Phenotype	Slow γH2AX decay	Mouse	Lung cancer	Increase	Ochola et al. (2019)

Genetic/epigenetic factors (1/2)

- **Animal strain** influences radiation-related cancer in a tissue-specific manner

Outcome	Susceptible strain	Resistant strain	Animal	Reference
Thymic lymphoma	C57BL/6	C3H, SEG/Pas, SPRET/Ei, Swiss Webster, A/J, CBA/J	Mouse	Santos et al. (2009) +5 refs
	BALB/c	MSM, STS, A/J	Mouse	Okumoto et al. (1995) +8 refs
	C57BL/10	C3H, STS	Mouse	Kamisaku et al. (2000)
Myeloid leukaemia	CBA, 129Sv2	C57BL/6	Mouse	Patel et al. (2016)
	C3H, RFM, LP, SJL, CBA/Ca, CBA/H, BALB/c	C57BL/6, DBA/2, AKR, A, NOD, NON	Mouse	Darakhshan et al. (2006)
B-cell lymphoma	Swiss Webster	C57BL/6	Mouse	Hattori et al. (1988)
Breast cancer	ACI	Sprague-Dawley	Rat, DES-treated	Shellabarger et al. (1978)
	Sprague-Dawley	ACI, F344, Wistar, Copenhagen	Rat	Imaoka et al. (2007) +2 refs
	BALB/c	SPRET/EiJ, DBA2, C57BL/6	Mouse	Ullrich et al. (1996) +2 refs
Intestinal adenoma	BALB/c	C57BL/6	Mouse, $Apc^{Min/+}$	Degg et al. (2003) +1 ref
Lung cancer	A/J	C57BL/6	Mouse	Groch et al. (1997)
	F344	Wistar	Rat	Sanders & Lundgren (1995)
	2•4, 4•22	15•16, 87•20	Hamster	Little et al. (1973)
Liver tumour	C3H	C57BL/6	Mouse	Ito et al. (1992)
	F344	Sprague-Dawley	Rat	Lee et al. (1998)
Solid tumours	C3H	C57BL/6	Mouse	Edmondson et al. (2015)

Genetic/epigenetic factors (2/2)

- **Cancer-predisposing mutations** increase radiation-related cancer

Outcome	Gene modification	Syndrome	Modification	Reference
All neoplasms	$Trp53^{+/-}$, $Trp53^{-/-}$	Li-Fraumeni	Increase	Carlisle et al. (2010), Kemp et al. (1994)
	Tg(Trp53 mutant)	—	Increase	Lee et al. (1994)
	$Nbn^{+/-}$	Nijmegen	No effect	Dumon-Jones et al. (2003)
	$Cdkn1a^{+/-}$	MEN	Antagonistic	Martin-Caballero et al. (2001)
	$Cdkn1a^{-/-}$	—	Increase	Jackson et al. (2003)
	$Nf1^{+/-}$	Neurofibromatosis	Increase	Choi et al. (2012), Nakamura et al. (2011)
Myeloid leukaemia	$Sfpi1^{+/-}$	—	Increase	Genik et al. (2014b)
Thymic lymphoma	$Hip2k^{+/-}$	—	Increase	Mao et al. (2012)
	$Mt1^{-/-}$ $Mt2^{-/-}$	—	Increase	Shibuya et al. (2008)
	$Pten^{+/-}$	Cowden	Increase	Mao et al. (2003)
	$Trp63^{+/-}$	EEC	No effect	Perez-Losada et al. (2005)
	$Trp73^{+/-}$	—	No effect	Perez-Losada et al. (2005)
Lymphoma	Tg(Pim1)	—	Increase	van der Houven van Oordt et al. (1998)
Breast tumour	$Apc^{Min/+}$	FAP	Increase	Imaoka et al. (2006)
Intestinal tumour	$Apc^{1638N/+}$	FAP	Increase	van der Houven van Oordt et al. (1997)
Medulloblastoma	$Ptch1^{+/-}$	Gorlin	Increase	Pazzaglia et al. (2002a)
Sarcoma	$Ptch1^{+/-}$	Gorlin	No effect	Pazzaglia et al. (2002a)
Digestive tract tumour	$Pax6^{+/-}$	Gillespie	Increase	Nitta et al. (2007)

EEC, ectrodactyly-ectodermal dysplasia-clefting; FAP, familial adenomatous polyposis; MEN, multiple endocrine neoplasia

Conclusions

- **Young age at exposure** increases the risk of all solid tumours, with variation between tissues
- **Attained age** decreases ERR and increases EAR for all solid tumours, with variation between tissues
- **Female sex** is associated with higher radiation-related risk for all solid tumours, with variation between tissues
- **Cigarette smoke** increases radionuclide-related lung cancer risk
- **Body weight** increases radiation-related risk for all tumours and for some specific tumours
- **Female sex hormones** increase radiation-related risk of breast cancer
- **Chemical carcinogens** generally increase, whereas some protective chemicals decrease, radiation-related cancer; quantitative evidence is limited
- **Genetic factors** influence radiation-related tumours in a tissue-specific manner; quantitative evidence is limited

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