Risk of secondary cancers after radiotherapy for benign diseases

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Radiogenic cancer risk:

The number of excess cancers in a population exposed to radiation

Absolute Risk

The probability of cancer induction following exposure to radiation

Example: ***Conceptus radiogenic risk***

Radiation risk for childhood cancer : 6% per Gy (6% per 1000 mGy)

If the conceptus dose is 10 mGy, the risk of excess childhood fatal cancer is 0.06%

Relative Risk

Designates the risk in comparison to the background cancer risk i.e. the spontaneous incidence

- **A relative risk of 1.0 indicates that there is no effect or exposure**
- **A relative risk of 1.4 indicates that exposure is associated with a 40% increase in cancer incidents above background rates**

Conceptus risk: Stewart et al found a 1.3-1.4 relative risk

Absolute risk: 0.06%
Bg risk: 0.2
Increase: 30%

Radiation Risk Assessment

Radiation risk assessment is not a precise science

Large uncertainty can be associated with a given radiation risk estimate

Is it important to know the risk of radiation-induced cancers after RT for benign diseases?

- **To provide information about risks to (referring physicians, ROs and) patients**
- **To balance benefits with risks**
- **To provide information to referring physicians useful for the follow-up of patients**

Benefit -risk assessment occurs at 3 levels

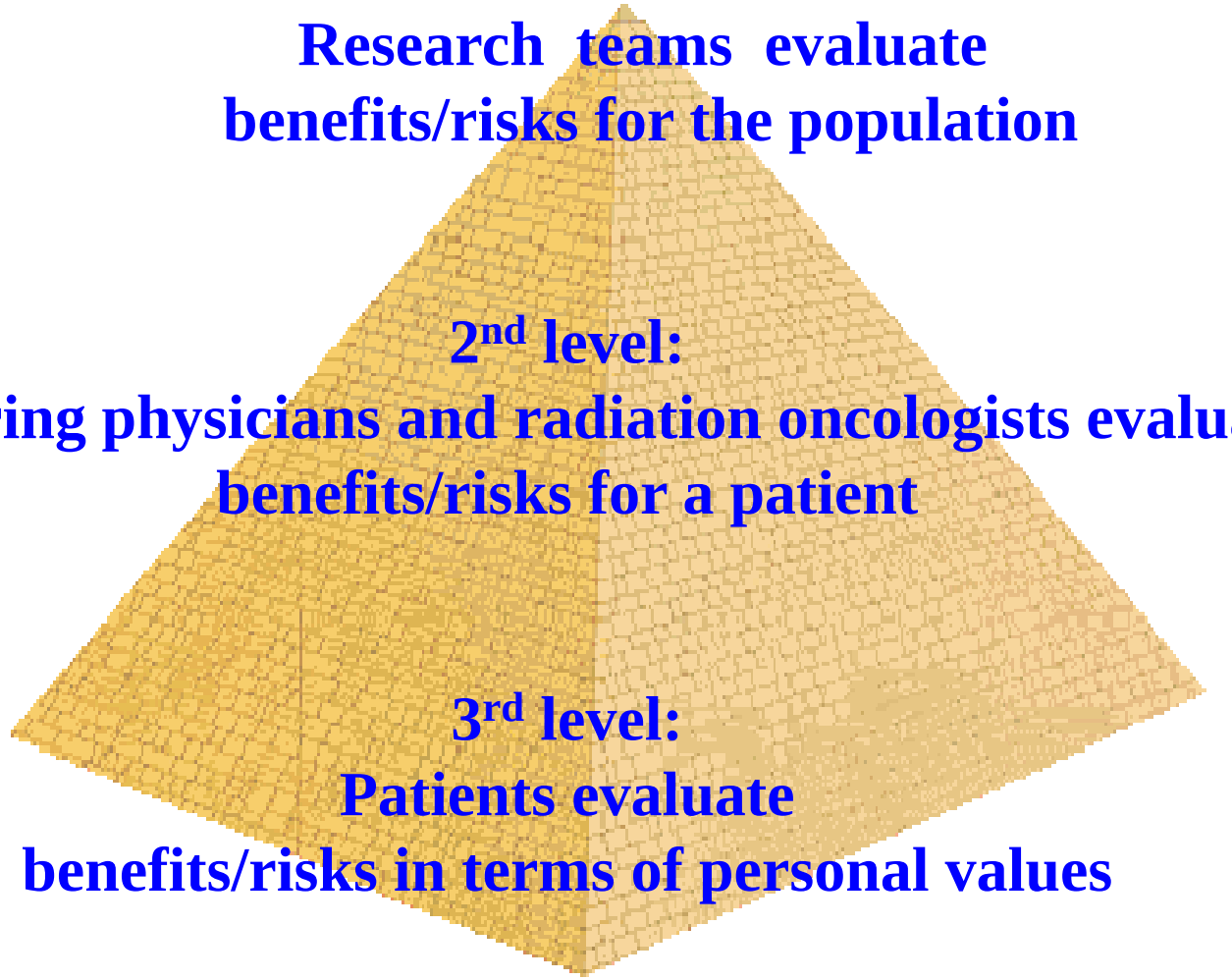
1st level:

Research teams evaluate benefits/risks for the population

They provide information about risk of secondary cancers after RT for benign diseases to weigh benefits and risks of RT against alternative therapies such as anti-inflammatory drugs. This information is important for radiation oncologists and referring physicians to evaluate benefits and risks of RT for a patient and inform the patient accordingly.

Benefit -risk assessment occurs at 3 levels

1st level:
Research teams evaluate
benefits/risks for the population



2nd level:
Referring physicians and radiation oncologists evaluate
benefits/risks for a patient

3rd level:
Patients evaluate
benefits/risks in terms of personal values

Utilization of RT in patients with benign diseases

Utilization in UK

	Numbers of centers treating	Total number treated per annum
Thyroid eye disease	19	81
Keloid	15	117
Heterotopic ossification	14	32
Glomus tumour	11	16
Acoustic Schwannoma	8	93
Pigmented Synovitis	4	4

RCR, A review of the use of RT in the UK for the treatment of benign clinical conditions and benign tumours

Utilization in Germany

Table 1. Development of radiotherapy for non-malignant diseases in Germany (number of treated patients from 1999 to 2004—results of patterns of care studies)

Non-malignant diseases (treatment groups)	1999	2004	Increase (%)
Inflammatory	456	503	10.9
Degenerative	12,600	23,754	88.5
Hyperproliferative	972	1252	28.8
Functional/other	6099	10,637	74.4
Overall	20,082	37,410	86.3

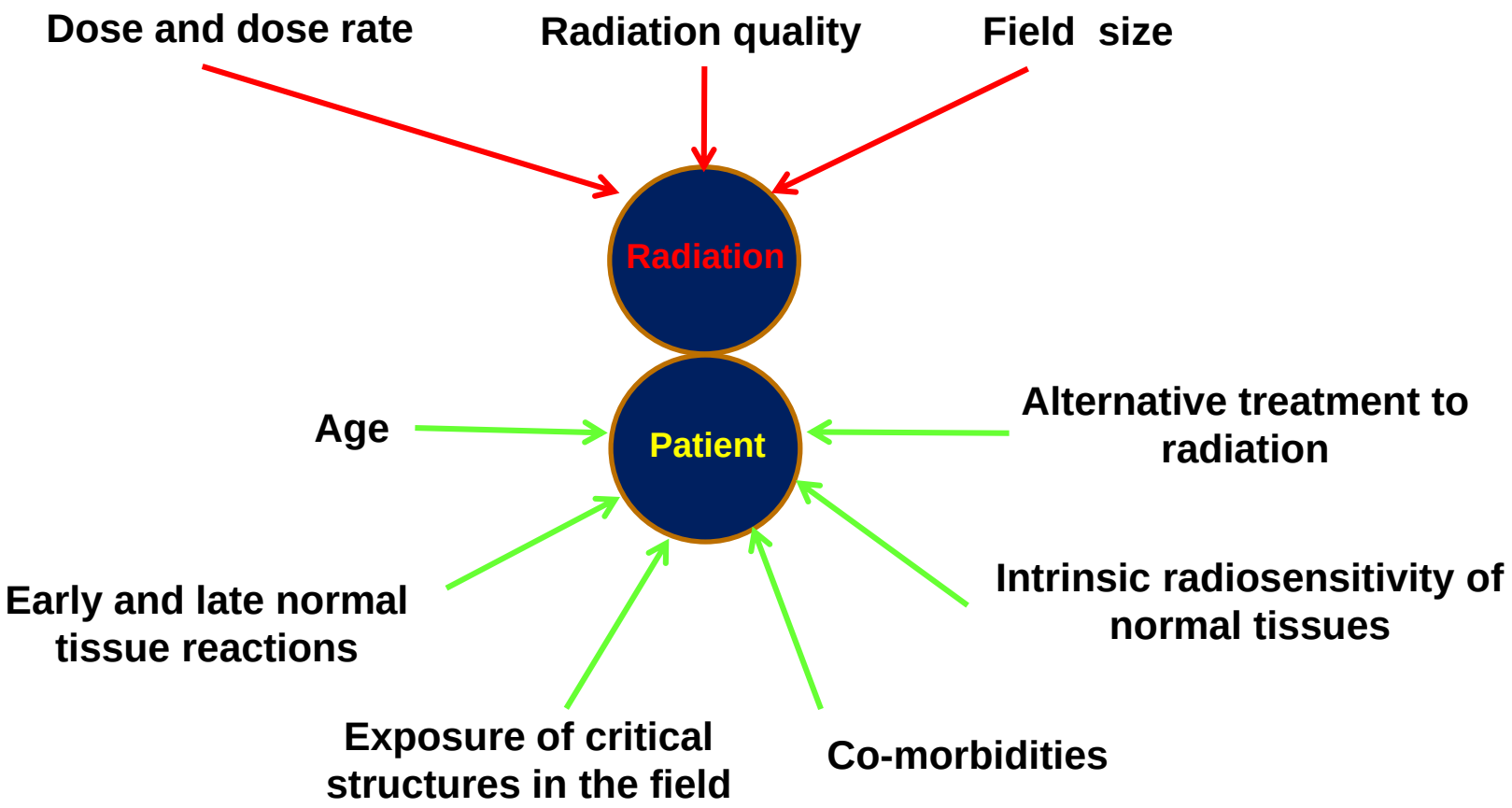
Seegenschmiedt MH et al BJR 2015;88:20150080

Recommendations for doses

Specific disease	Single dose (Gy)	Total dose (Gy)
Painful arthrosis of the knee joint	0.5–1.0	3.0–6.0
Painful arthrosis of the hip joint	0.5–1.0	3.0–6.0
Painful arthrosis of the hand and finger joints	0.5–1.0	3.0–6.0
Painful shoulder syndrome	0.5–1.0	3.0–6.0
Painful elbow syndrome	0.5–1.0	3.0–6.0
Painful trochanteric bursitis	0.5–1.0	3.0–6.0
Painful plantar fasciitis	0.5–1.0	3.0–6.0
Morbus Dupuytren	3.0	15.0 (repeat after 12 weeks)
Morbus Ledderhose	3.0	15.0 (repeat after 12 weeks)
Keloids	3.0	12.0
Peyronie's disease	2.0–3.0	10.0–20.0
Desmoid tumours	1.8–2.0	50.0–65.0
Symptomatic vertebral haemangiomas	1.8–2.0	34.0–36.0
Pigmented villonodular synovitis	1.8–2.0	36.0–40.0
Gorham Stout syndrome	1.8–2.0	36.0–45.0
Heterotopic ossification (pre-operative)	7.0	7.0
Heterotopic ossification (post-operative)	3.5	17.5
Graves orbitopathy (early inflammatory phase)	0.3–2.0	2.4–16.0
Graves orbitopathy (advanced inflammatory phase)	2.0	16.0–20.0

Factors influencing radiation-induced cancer risk

Factors influencing cancer risk



How do we estimate risk of radiation-induced cancer following RT for benign diseases?

Epidemiological studies

- **very long term patient follow-up due to the long latency for cancer development after treatment**

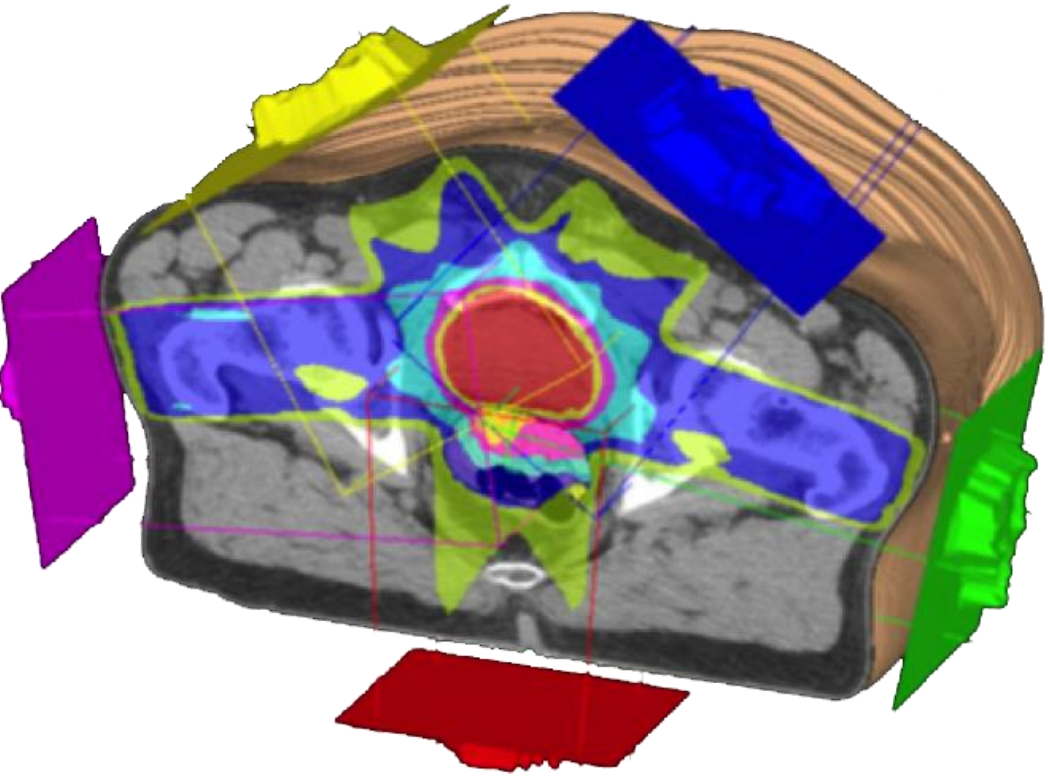
- **the collection of data is difficult based on the small number of subjects undergoing radiotherapy for a benign disease**

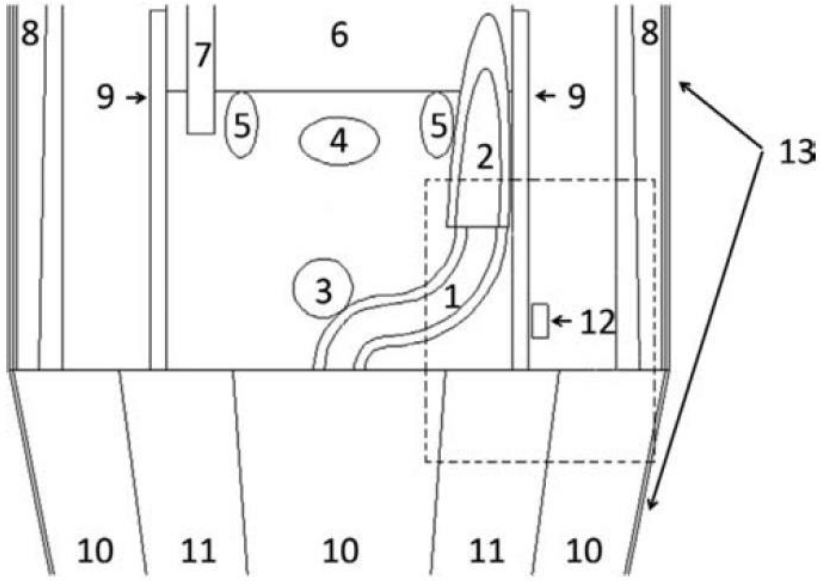
Vertebral hemangiomas

LAR in the partially in-field organs: 0.1 to 1.0 %

We should include in a properly designed study 10,000 of exposed patients to detect the 10 or 100 cases of cancer due to exposure

Phantom Studies





Effective dose vs. organ doses

Effective dose 'hides' differences in the doses delivered to various organs from CT examinations

CCTA: Dose with 256-slice scanning

Effective Dose: < 2.0 mSv (Prospective mode)

Breast Dose: 14 mGy
Lung Dose: 9 mGy

We can estimate radiation-induced

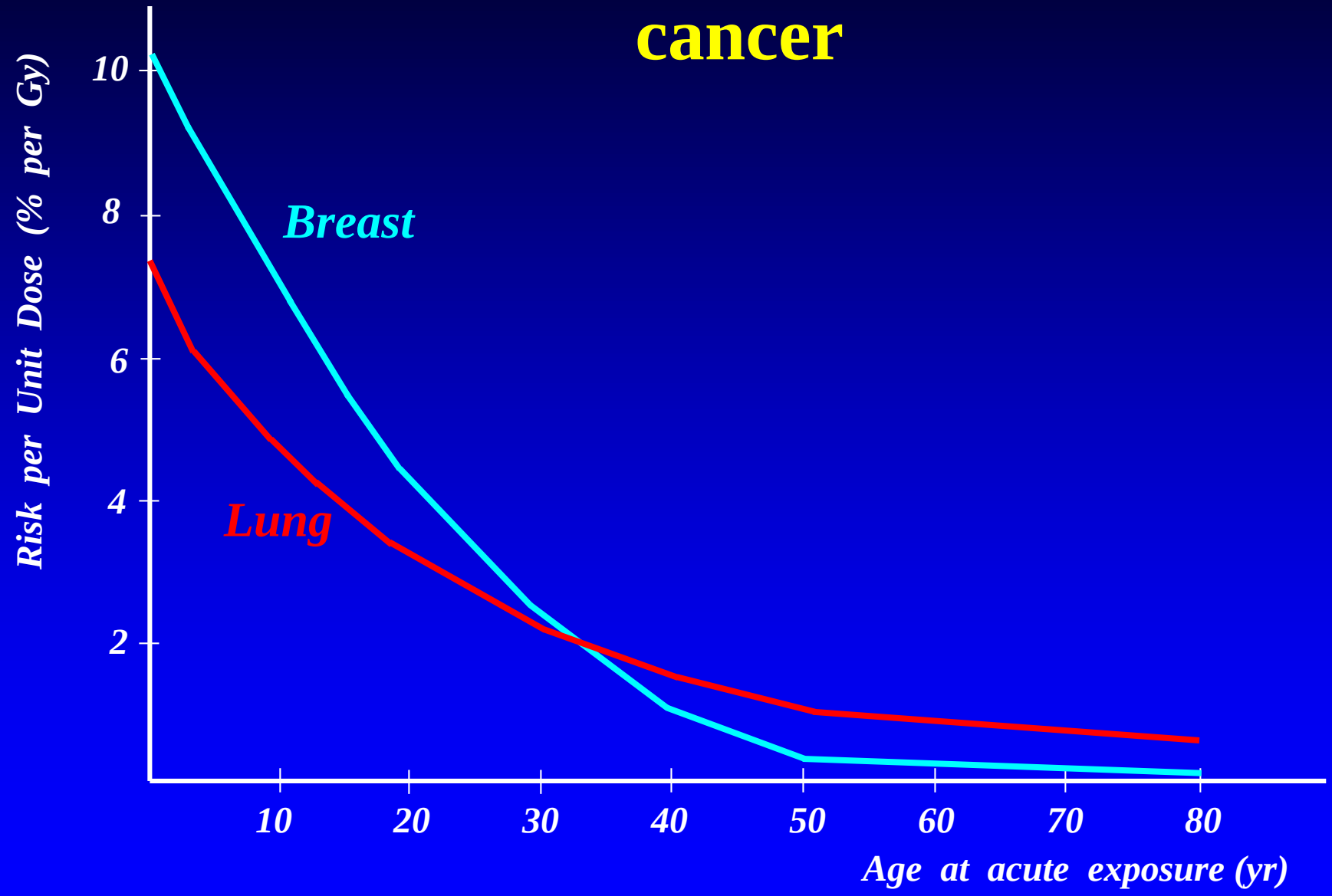
cancer risk using

- **BEIR VII coefficients (0.1-2.5 Gy)**
- **Mechanistic modeling (Dasu et al 2005, Schneider 2005, etc)**

LAR of cancer incidence (BEIR VII – Phase 2)

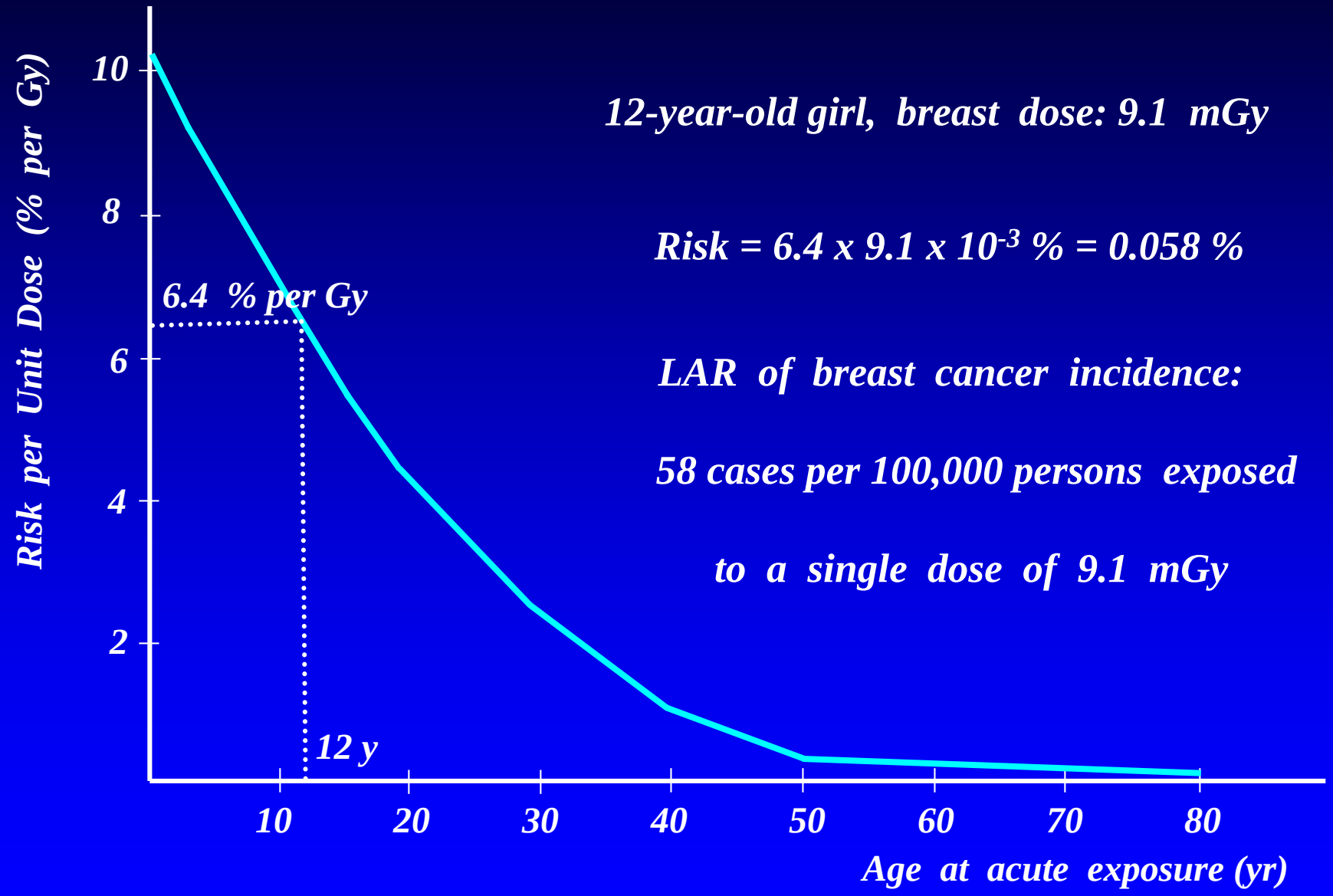
Cancer Site	Age at exposure (years)										
	0	5	10	15	20	30	40	50	60	70	80
Males											
Stomach	76	65	55	46	40	28	27	25	20	14	7
Colon	336	285	241	204	173	125	122	113	94	65	30
Liver	61	50	43	36	30	22	21	19	14	8	3
Lung	314	261	216	180	149	105	104	101	89	65	34
Prostate	93	80	67	57	48	35	35	33	26	14	5
Bladder	209	177	150	127	108	79	79	76	66	47	23
Other	1123	672	503	394	312	198	172	140	98	57	23
Thyroid	115	76	50	33	21	9	3	1	0.3	0.1	0.0
All solid	2326	1667	1325	1076	881	602	564	507	407	270	126
Leukemia	237	149	120	105	96	84	84	84	82	73	48
All cancers	2563	1816	1445	1182	977	686	648	591	489	343	174

Risk coefficients for breast and lung cancer



Source : BEIR VII (2006)

Radiogenic risks for breast cancer



12-year-old girl, breast dose: 9.1 mGy

Risk = 6.4 x 9.1 x 10^{-3} % = 0.058 %

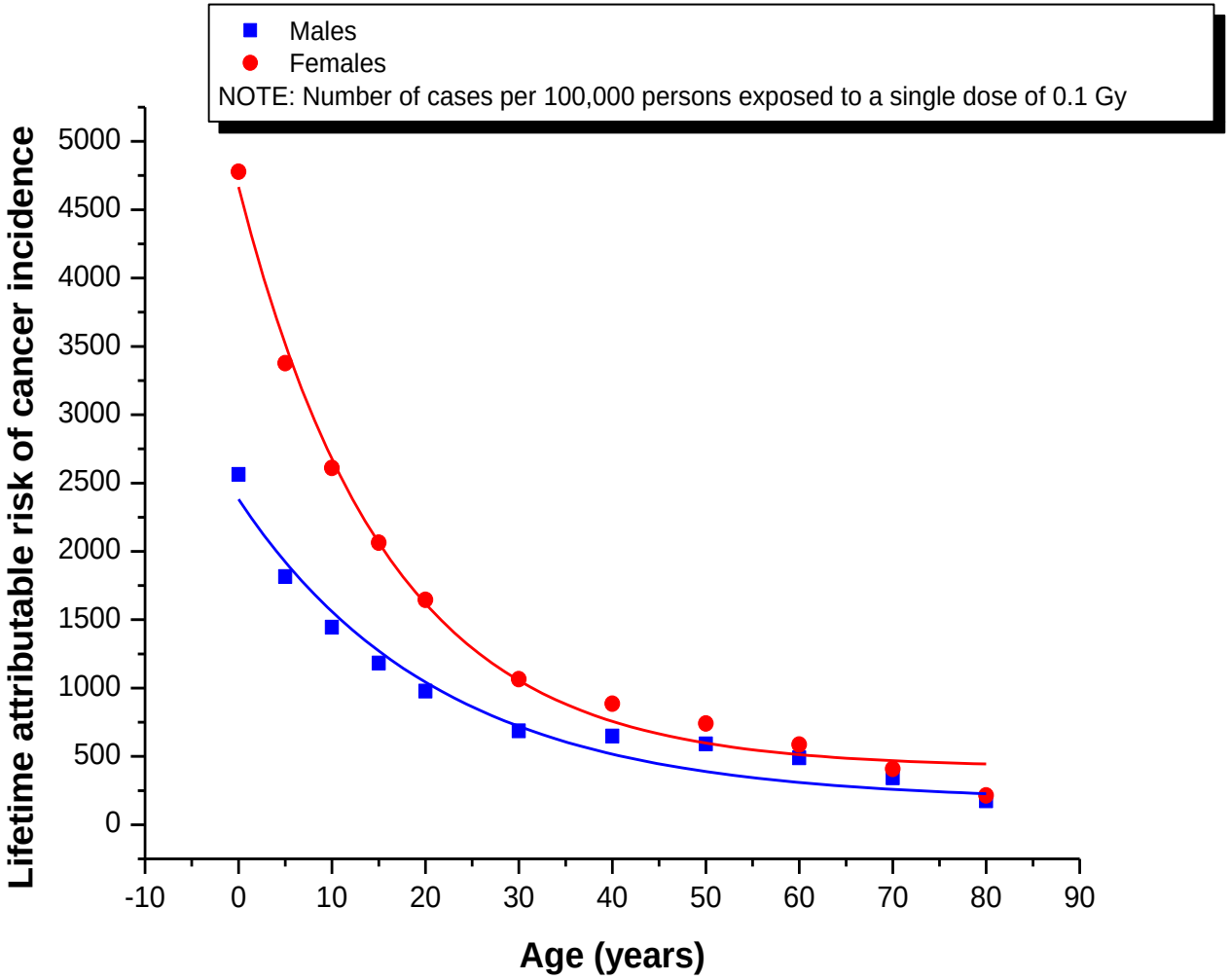
LAR of breast cancer incidence:

58 cases per 100,000 persons exposed

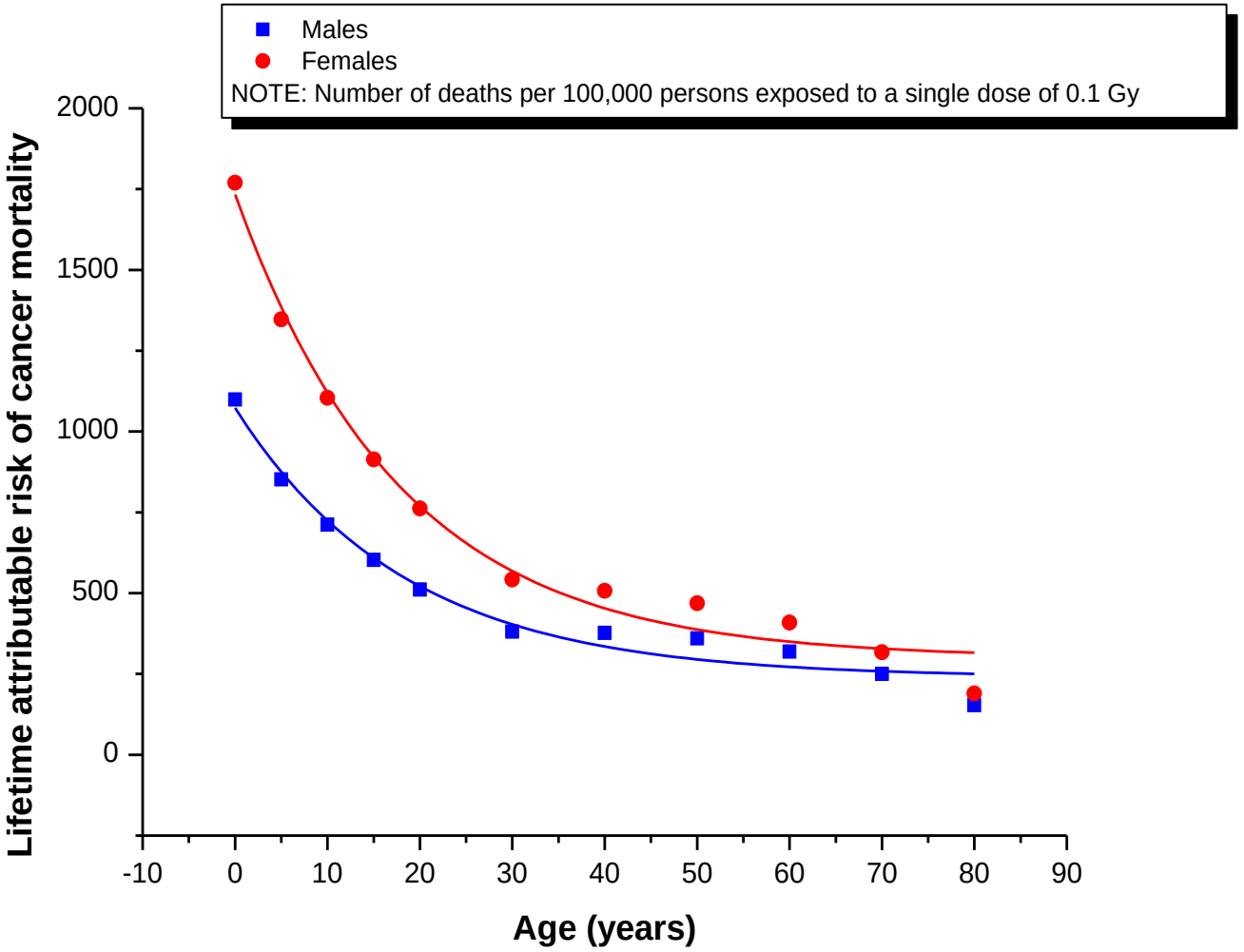
to a single dose of 9.1 mGy

Source : BEIR VII (2006)

LAR of cancer incidence



LAR of cancer mortality



We can estimate radiation-induced cancer risk using

- **BEIR VII coefficients (0.1-2.5 Gy)**
- **Mechanistic modeling (Dasu et al 2005, Schneider 2005, etc)**

Cancer risk estimates based on non-linear models

$$\mathrm{OED} = \frac{1}{V_t} \sum_i V_{D_i} \frac{e^{-a_i' D_i}}{a_i' R} \left[1 - 2R + R^2 e^{a_i' D_i} - (1-R)^2 e^{-\frac{a_i' R}{1-R} D_i} \right]$$

where V_t is total colon volume, V_{D_i} is the colon volume corresponding to a bin D_i, R=0.99 is the repopulation parameter for colon and a_i' is the colon cell kill factor

Schneider *et al*, Theor. Biol. Med. Modell. 8, 27, 2011

EAR for organ cancer induction

$$\mathrm{EAR} = \beta' \,\mathrm{OED} \exp\left[\gamma_e (age_e - 30) + \gamma_a \ln\left(\frac{age_a}{70}\right)\right]$$

where β' is the initial slope of radiation-induced colon malignancies in the low-dose region for a population in Western countries, age_e is the patient's age at the time of irradiation, age_a is the attained age, and γ_e, γ_a are the required age parameters

LAR for organ cancer induction

$$\mathrm{LAR} = \int_{\mathrm{age}_e + L}^{\mathrm{age}_{a,\max}} \mathrm{EAR}(D_t, \mathrm{age}_e, \mathrm{age}_a) \frac{S(\mathrm{age}_a)}{S(\mathrm{age}_e)} d(\mathrm{age}_a)$$

where L is a typical risk free latent period of 5 yr for solid cancer development[17] and $\mathrm{age}_{a,\max}$ is the final attained age.

How can we realize the magnitude of the radiotherapy-induced cancer risk?

Browse the SEER Cancer Statistics Review (CSR) 1975–2011

The navigation below allows you to jump to any table or figure within the SEER Cancer Statistics Review.

1. First select the CSR Section, then a Table/Figure from that section.
2. Use the Submit button to view the table or figure. You will have options to download a printer-friendly version (PDF) or the data table (CSV) as well.

To learn more about the Cancer Statistics Review and the statistics presented in this report, refer to the About the CSR (PDF) and Technical Notes (PDF) pages.

Section: - Lung and Bronchus

Table/Figure: Select Table/Figure

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- Select Table/Figure
- Table 15.1: Trends in SEER Incidence and US Mortality, Both Sexes
- Table 15.2: Trends in SEER Incidence and US Mortality, Males
- Table 15.3: Trends in SEER Incidence and US Mortality, Females
- Table 15.4: Trends in SEER Incidence (Small Cell and Non-small Cell Cancer)
- Table 15.5: Annual Delay-adjusted Incidence Rates
- Table 15.6: Annual Incidence Rates
- Table 15.7: Annual Incidence Rates (Small Cell Cancer)
- Table 15.8: Annual Incidence Rates (Non-Small Cell Cancer)
- Table 15.9: Annual Death Rates
- Table 15.10: Incidence and Mortality Rates by Age
- Table 15.11: Incidence Rates by Age (Small Cell and Non-Small Cell Cancer)
- Table 15.12: 5-year Relative and Period Survival
- Table 15.13: 5-year Relative and Period Survival (Small Cell Cancer)
- Table 15.14: 5-year Relative and Period Survival (Non-Small Cell Cancer)
- Table 15.15: Relative Survival by Year of Diagnosis, Both Sexes
- Table 15.16: Relative Survival by Year of Diagnosis, Males
- Table 15.17: Relative Survival by Year of Diagnosis, Females
- Table 15.18: Risk of Developing/Dying
- Table 15.19: Risk of Developing/Dying

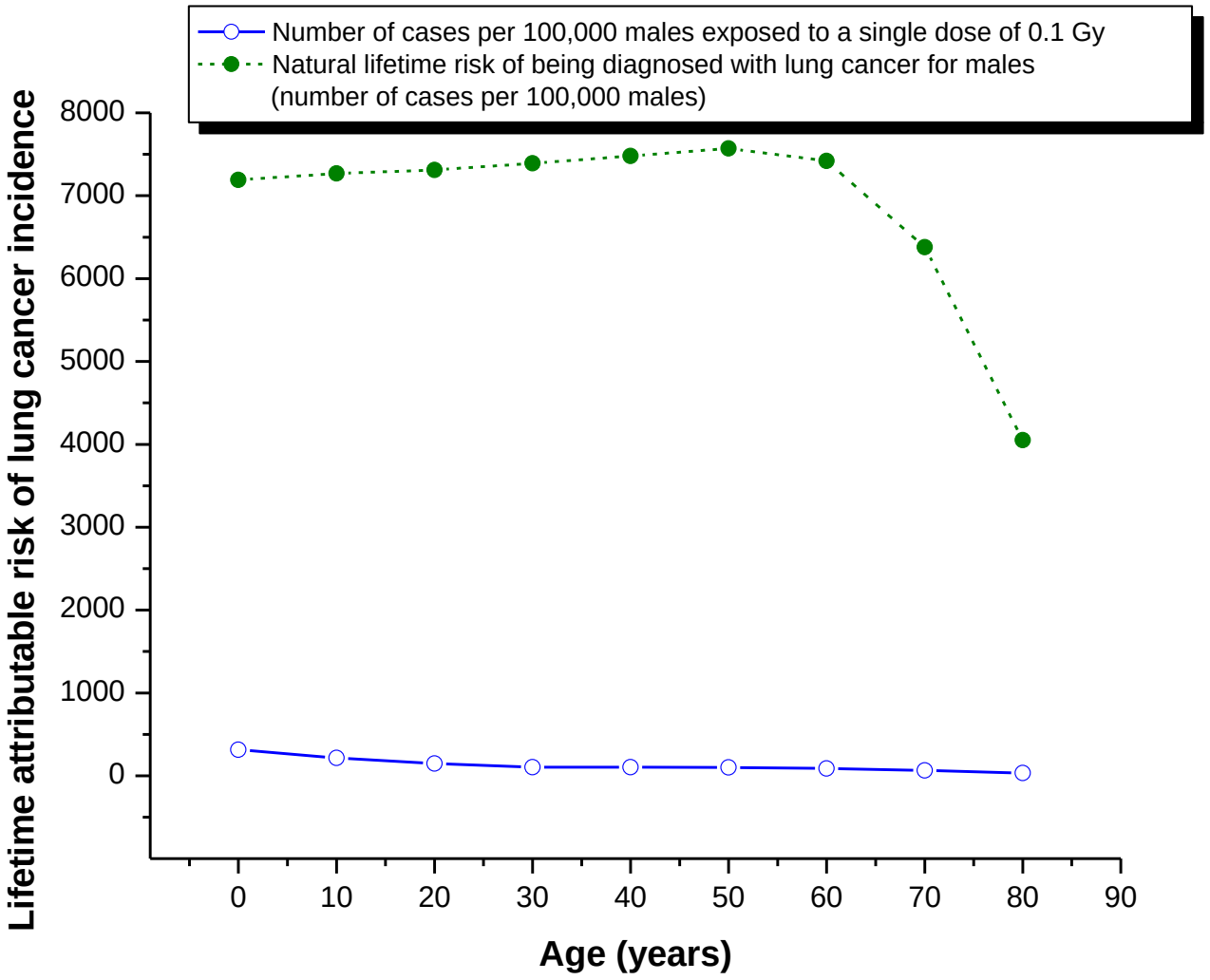
Table 15.18

Cancer of the Lung and Bronchus (Invasive)

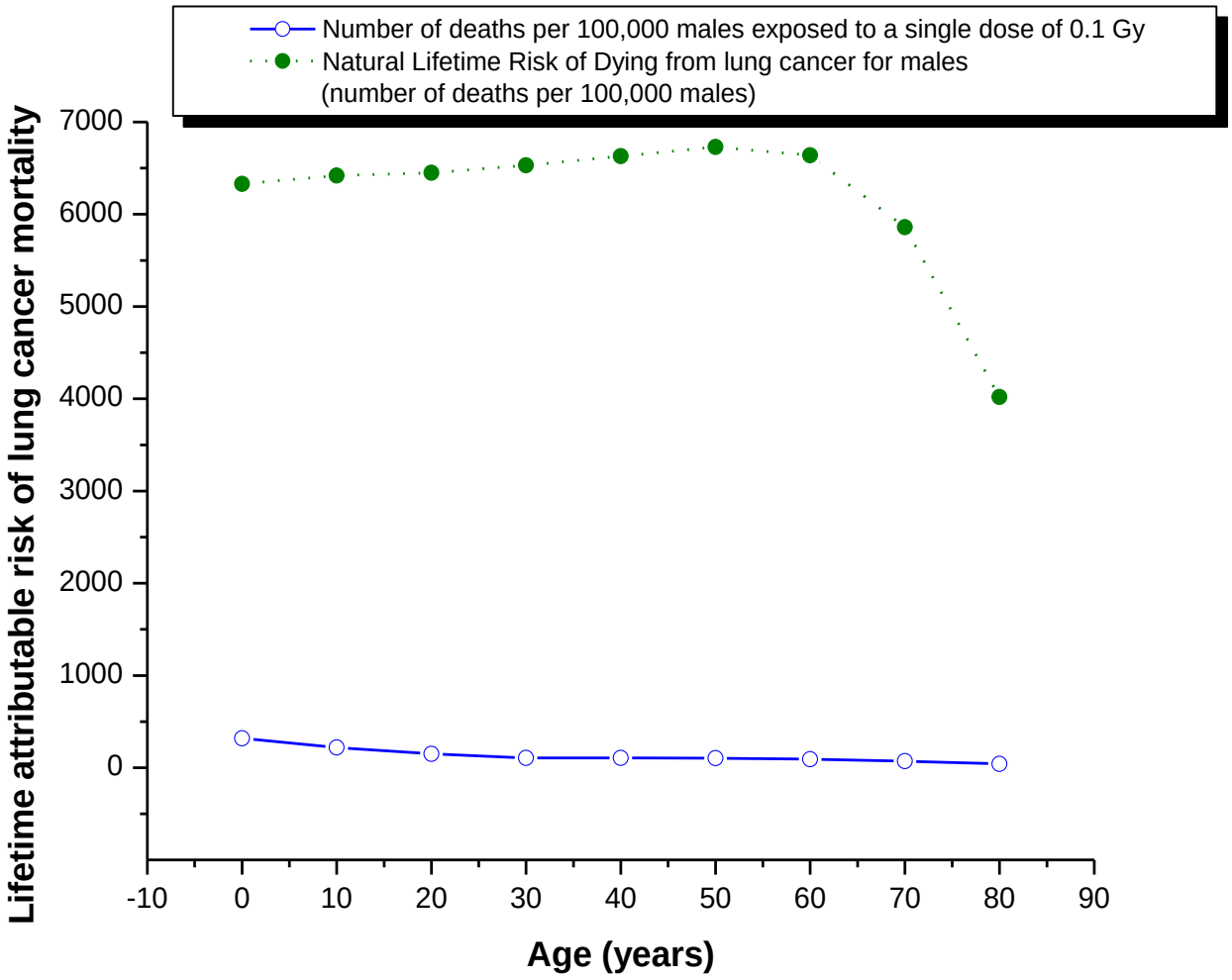
**Risk of Being Diagnosed With Cancer in 10, 20 and 30 Years,
Lifetime Risk of Being Diagnosed with Cancer Given Alive and Cancer-Free at Current Age, and
Lifetime Risk of Dying from Cancer Given Alive at Current Age
Both Sexes, 2009-2011 By Race/Ethnicity**

Race/ Ethnicity	Current Age	Risk of Being Diagnosed with Cancer				Risk of Dying from Cancer
		+10 yrs	+20 yrs	+30 yrs	Eventually	Eventually
All Races	0	0.00	0.00	0.01	6.75	5.66
	10	0.00	0.01	0.03	6.83	5.73
	20	0.01	0.03	0.18	6.85	5.75
	30	0.02	0.18	0.80	6.90	5.80
	40	0.16	0.78	2.43	6.96	5.87
	50	0.64	2.33	4.94	6.99	5.91
	60	1.79	4.56	6.39	6.74	5.74
	70	3.15	5.23	-	5.63	4.93
	80	2.83	-	-	3.37	3.19
White	0	0.00	0.00	0.01	6.92	5.79
	10	0.00	0.01	0.03	6.98	5.85
	20	0.01	0.03	0.18	7.01	5.87
	30	0.02	0.18	0.79	7.06	5.92
	40	0.15	0.77	2.46	7.12	5.98
	50	0.64	2.37	5.08	7.15	6.02
	60	1.84	4.72	6.57	6.91	5.86
	70	3.27	5.38	-	5.76	5.02
	80	2.89	-	-	3.41	3.22
Black	0	0.00	0.00	0.01	6.47	5.21
	10	0.00	0.01	0.03	6.61	5.33
	20	0.00	0.03	0.23	6.64	5.35
	30	0.02	0.23	1.11	6.72	5.42
	40	0.21	1.11	2.96	6.83	5.52
	50	0.93	2.86	5.25	6.88	5.59
	60	2.12	4.75	6.24	6.55	5.40
	70	3.21	5.02	-	5.39	4.58
	80	2.68	-	-	3.23	3.02
Asian/ Pacific Islander	0	0.00	0.00	0.01	5.55	4.30
	10	0.00	0.00	0.03	5.59	4.33
	20	0.00	0.03	0.13	5.60	4.34
	30	0.02	0.12	0.50	5.62	4.35
	40	0.10	0.48	1.47	5.63	4.36
	50	0.39	1.39	3.19	5.60	4.36
	60	1.04	2.89	4.69	5.38	4.25
	70	1.99	3.93	-	4.66	3.88
	80	2.33	-	-	3.21	2.97

Radiogenic vs. nominal LIR



Radiogenic vs. nominal LIR



Benign diseases and risk from RT

- **Pigmented villonodular synovitis**
- **Heterotopic ossification of the hip**
- **Vertebral hemangioma**

Radiation dose and cancer risk to out-of-field and partially in-field organs from radiotherapy for symptomatic vertebral hemangiomas

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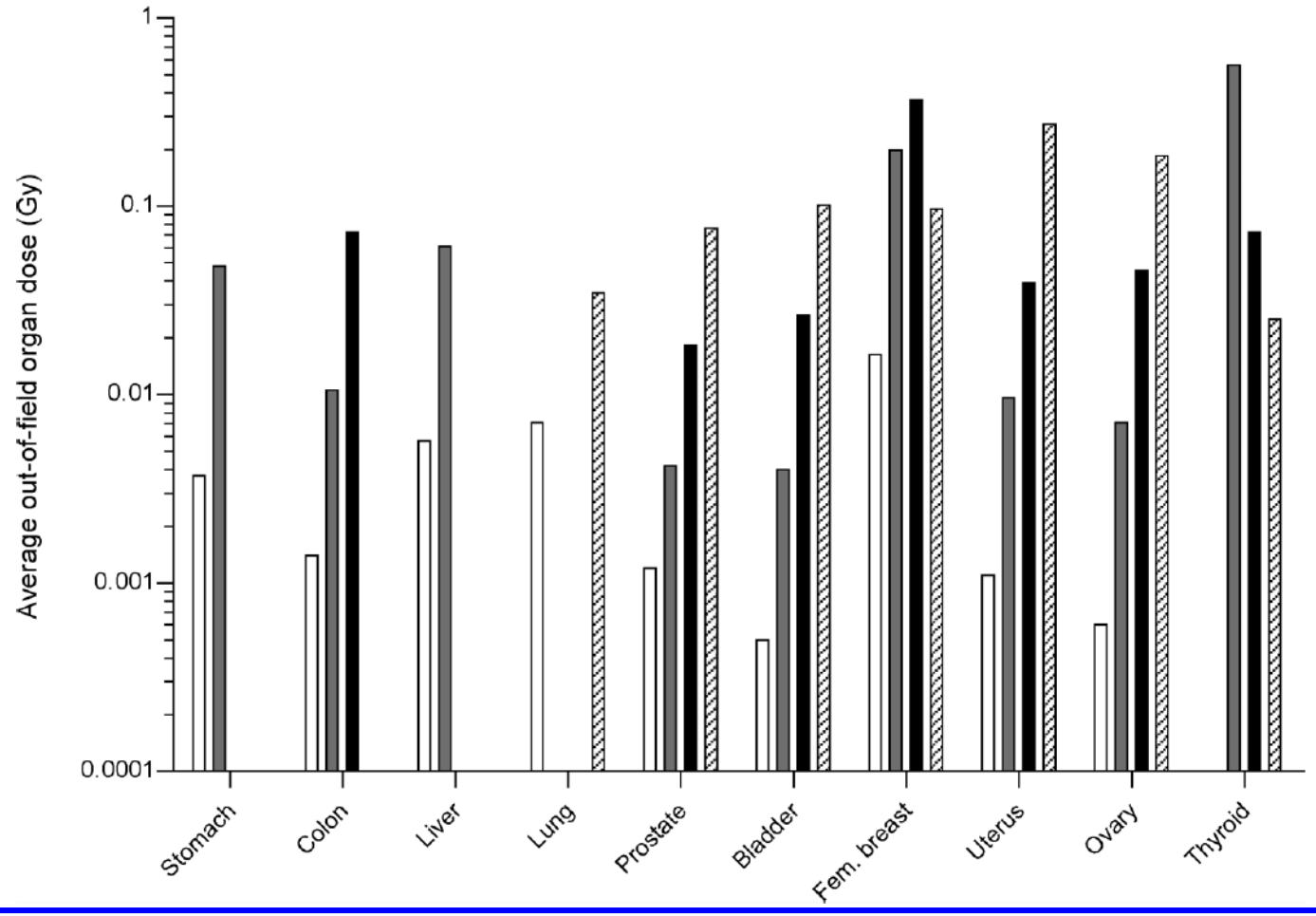
Purpose: Vertebral hemangiomas (VHs) are the most common benign tumors of the spine that may cause bone resorption. Megavoltage irradiation is usually the treatment of choice for the management of symptomatic VHs. The current study was conducted to estimate the risk for carcinogenesis from radiotherapy of this benign disease on the basis of the calculated radiation doses to healthy organs.

Medical Physics 2016;43(4):1841-1848

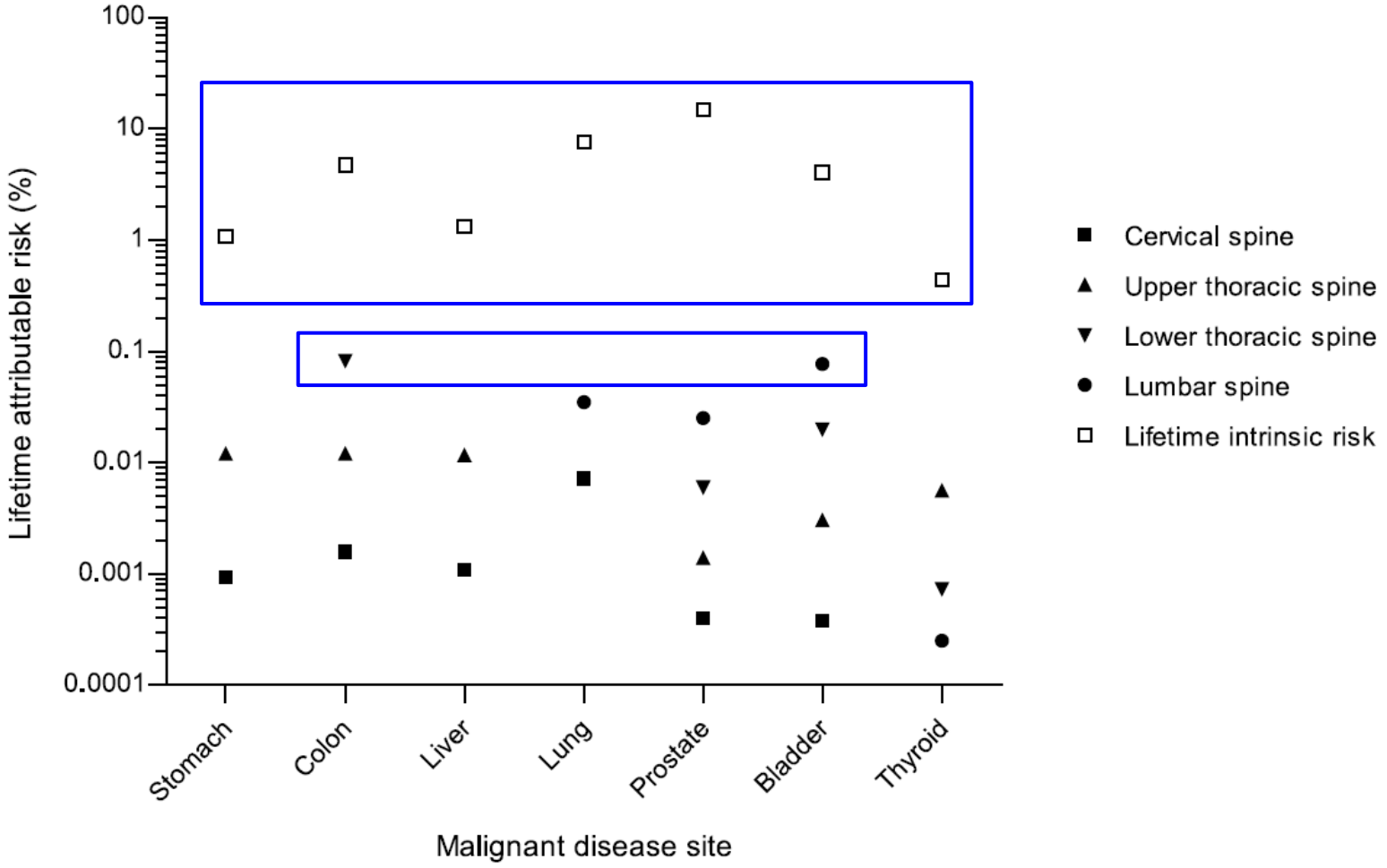
Dose received by out-of-field organs

34 Gy to the target site

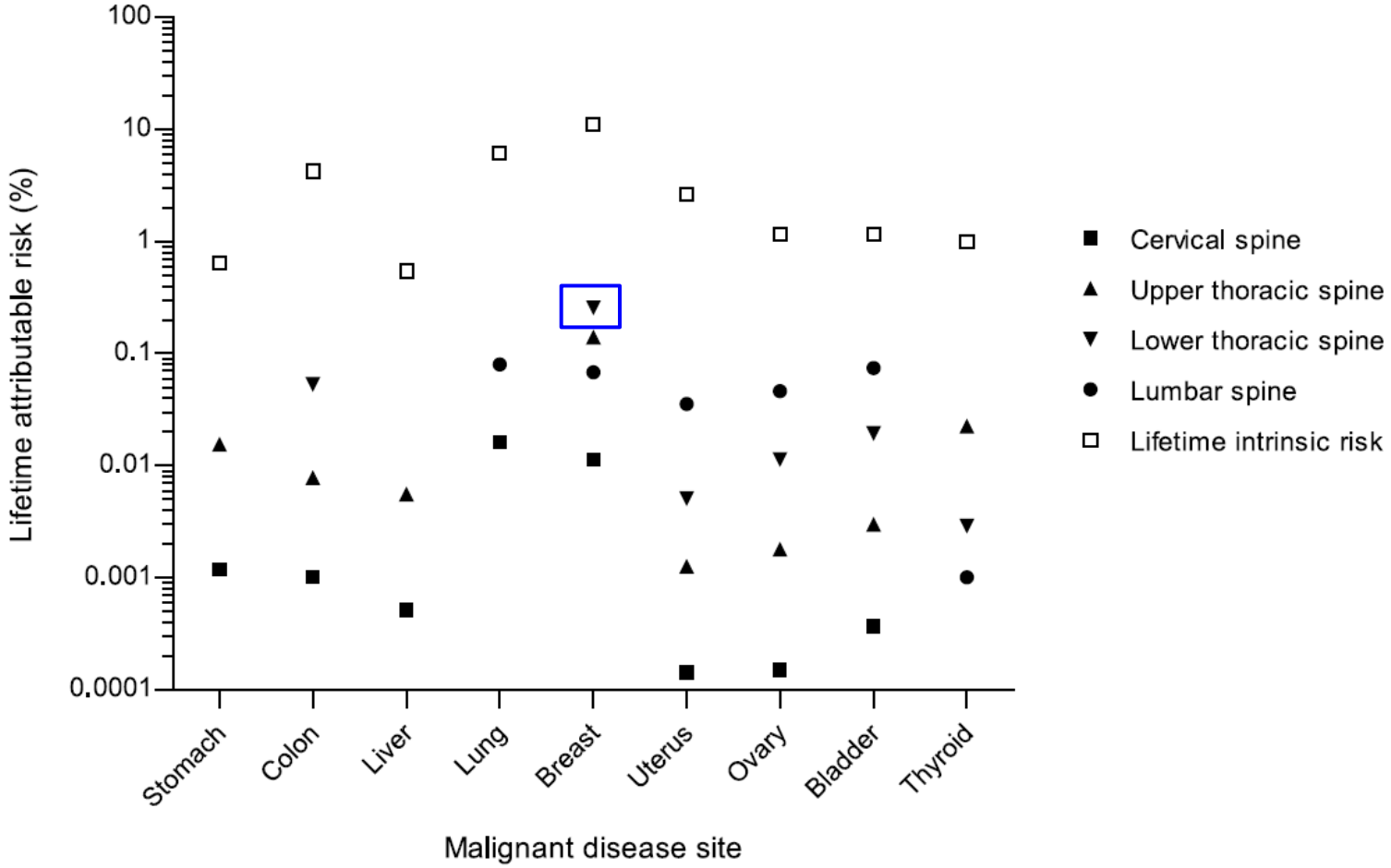
Organ dose range 4.9 x 10^{-4} to 0.56 Gy



LAR for out-of-field cancer development for 50-yr-old male patients



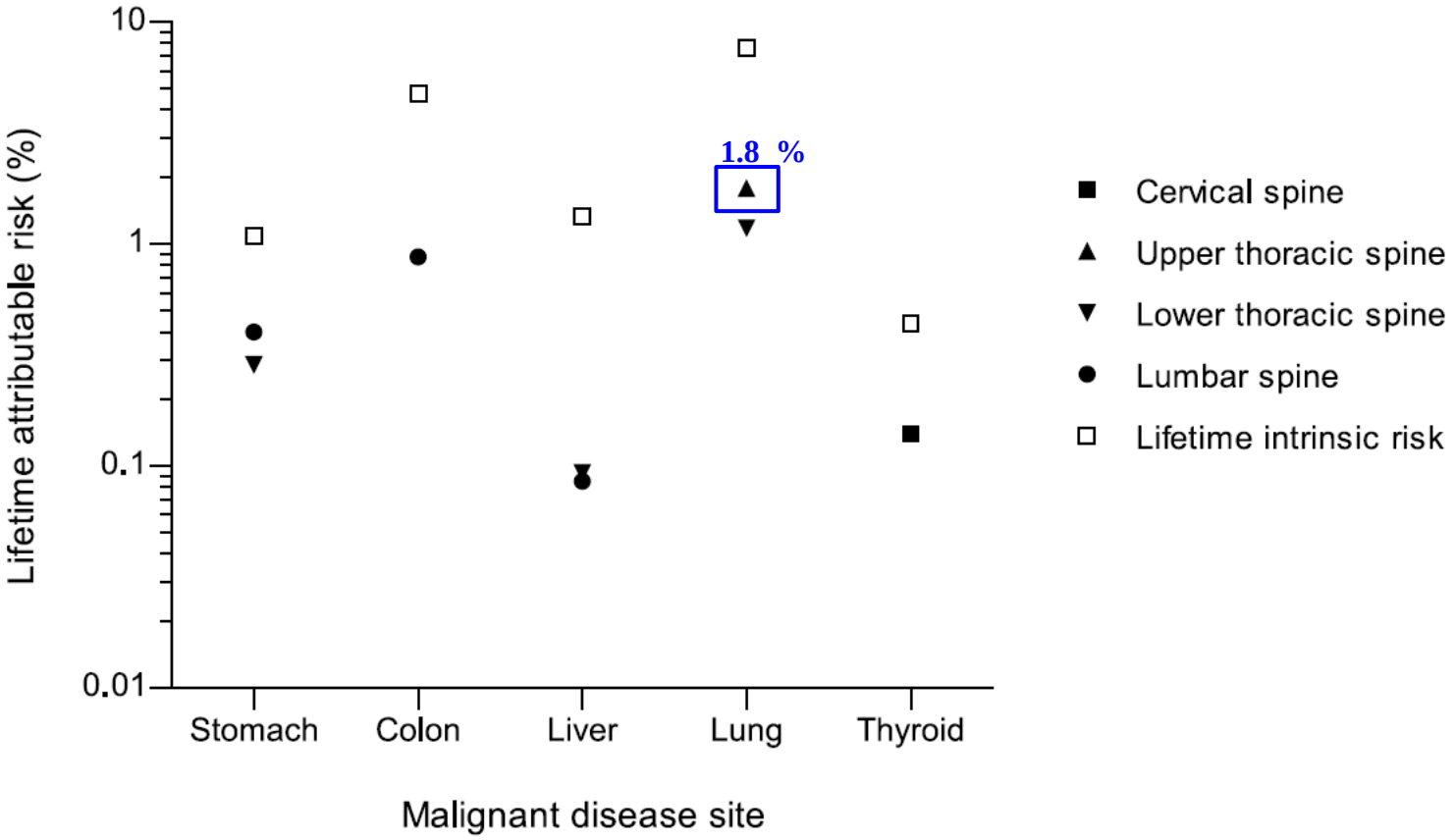
LAR for out-of-field cancer development



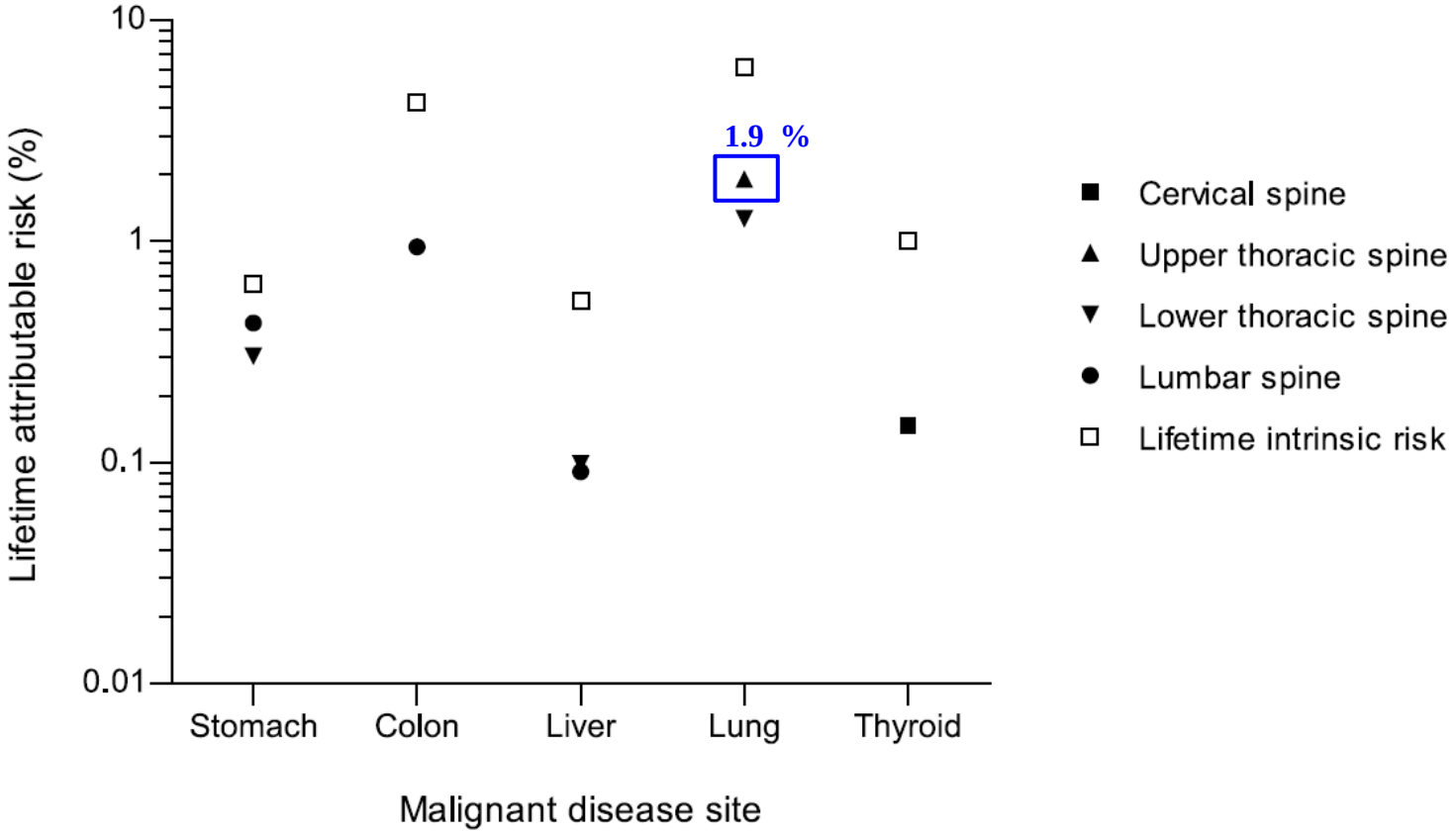
Doses of the partially in-field organs

Treatment site	Organ	OED (Gy)
Cervical spine	Thyroid	5.15
Upper thoracic spine	Lung	1.59
Lower thoracic spine	Lung	1.06
	Stomach	0.37
	Liver	0.43
Lumbar spine	Stomach	0.52
	Liver	0.39
	Colon	3.03

LAR in the partially in-field organs (M)



LAR in the partially in-field organs (F)



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Organ-specific radiation-induced cancer risk estimates due to radiotherapy for benign pigmented villonodular synovitis

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Abstract

Pigmented villonodular synovitis (PVNS) is a benign disease affecting synovial membranes of young and middle-aged adults. The aggressive treatment of this disorder often involves external-beam irradiation. This study was motivated by the lack of data relating to the radiation exposure of healthy tissues and radiotherapy-induced cancer risk. Monte Carlo methodology was employed to simulate a patient's irradiation for PVNS in the knee and hip joints with a 6 MV photon beam. The average radiation dose received by twenty-two out-of-field critical organs of the human body was calculated. These calculations were combined with the appropriate organ-, age- and gender-specific risk coefficients of the BEIR-VII model to estimate the lifetime probability of cancer development. The risk for carcinogenesis to colon, which was partly included in the treatment fields used for hip irradiation, was determined with a non-linear mechanistic model and differential dose-volume histograms obtained by CT-based 3D radiotherapy planning. Risk assessments were compared with the nominal lifetime intrinsic risk (LIR) values. Knee irradiation to 36 Gy resulted in out-of-field organ doses of 0.2–24.6 mGy. The corresponding range from hip radiotherapy was 1.2–455.1 mGy whereas the organ equivalent dose for the colon was up to 654.9 mGy. The organ-specific cancer risks from knee irradiation for PVNS were found to be inconsequential since they were at least 161.5 times lower than the LIRs irrespective of the patient's age and gender. The bladder and colon cancer risk from radiotherapy in the hip

Pigmented villonodular synovitis

3 subtypes:

- **PV tenosynovitis that affects the finger joints**
- **Localized PVNS that involves the knee joint**
- **Diffuse PVNS that affects the knee and hip joint**

Pigmented villonodular synovitis

Common symptoms:

- **Chronic pain and an impairment of joint function**

Treatment:

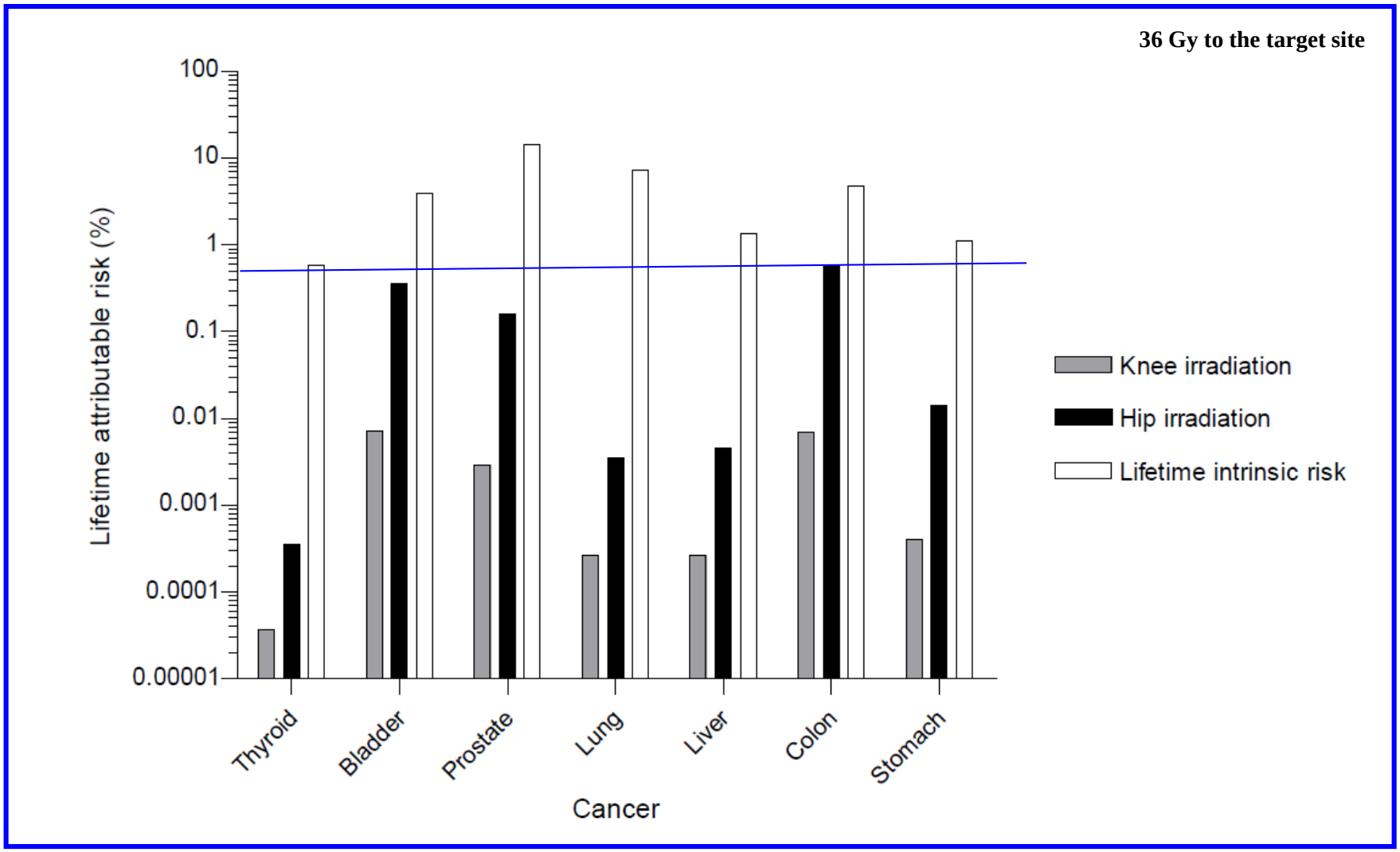
- **Surgical synovectomy**

recurrence after the excision of local and diffuse PVNS is up to 29 % and 56 %, respectively. RT has been given postoperatively to reduce the risk of recurrence following synovectomy.

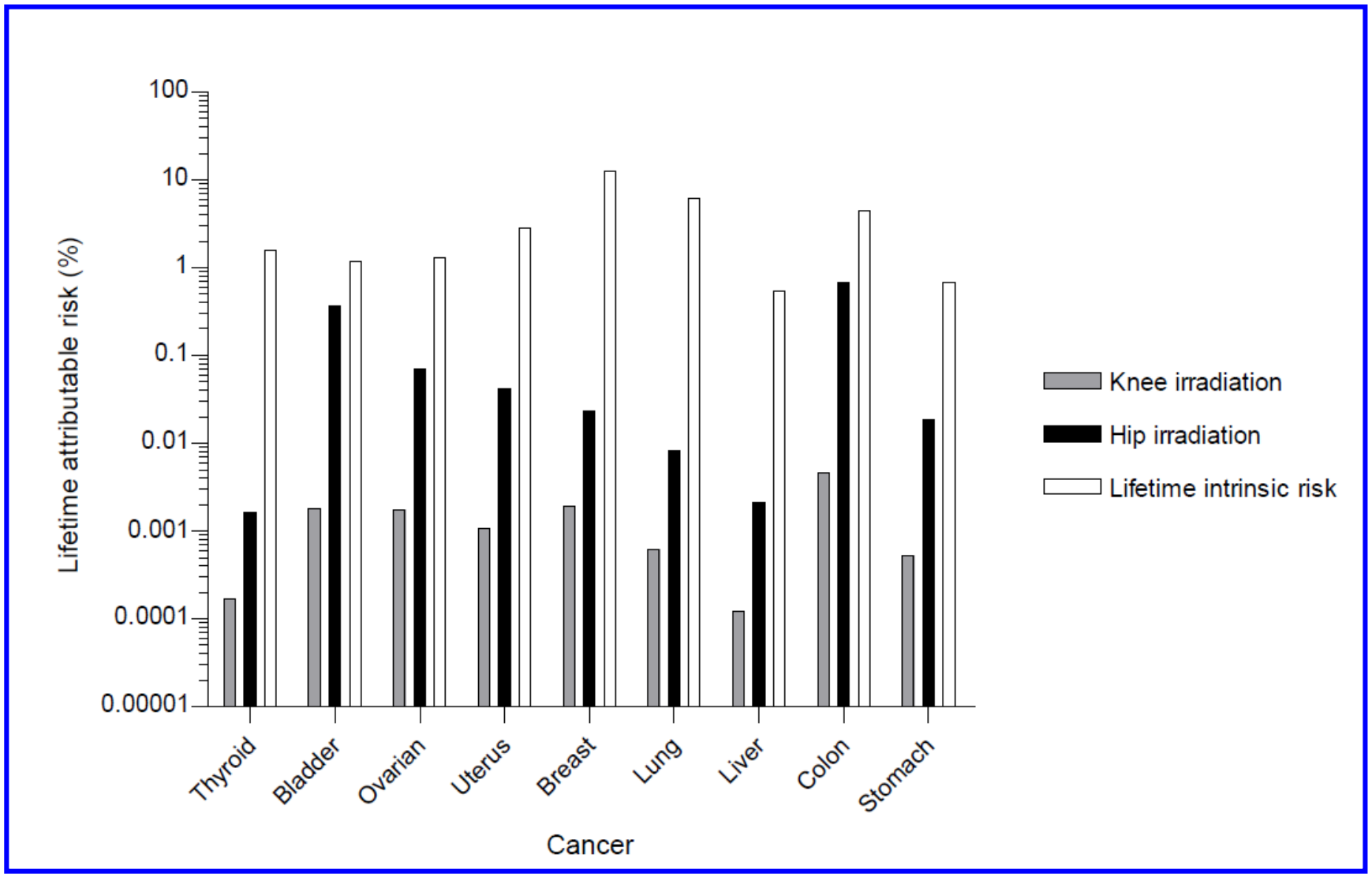
Dose received by out-of-field organs

Organ	Total organ dose (mGy)	
	Knee irradiation	Hip irradiation
Lungs	0.25	3.36
Colon	5.55	- 655 mGy
Stomach	1.42	51.22
Breasts	0.75	9.30
Ovaries	5.11	203.12
Testicles	24.62	384.34
Bladder	9.09	455.13
Oesophagus	0.73	12.40
Liver	1.21	20.72
Thyroid	0.41	4.00
Brain	0.15	1.17
Salivary glands	0.38	1.85
Adrenals	1.18	30.08
Gallbladder	1.93	46.92
Heart	0.60	13.52
Kidneys	2.01	46.26
Pancreas	1.09	36.27
Spleen	1.47	45.07
Thymus	0.29	6.70
Uterus	5.87	229.34
Prostate	8.15	447.57
Oral mucosa	0.28	1.44

LAR for cancer induction (30 y M)



LAR for cancer induction (30-y F)



Cancer risk estimates from radiation therapy for heterotopic ossification prophylaxis after total hip arthroplasty

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Purpose: Heterotopic ossification (HO) is a frequent complication following total hip arthroplasty. This study was conducted to calculate the radiation dose to organs-at-risk and estimate the probability of cancer induction from radiotherapy for HO prophylaxis.

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TABLE I. Organ doses from radiation therapy for heterotopic ossification prophylaxis with a target dose of 7 Gy given by equally weighted anteroposterior and posteroanterior fields.

	Organ dose (mGy)								
	Small field size: 12 × 14 cm^2			Medium field size: 13 × 16 cm^2			Large field size: 14 × 18 cm^2		
Organ	AP field	PA field	Total	AP field	PA field	Total	AP field	PA field	Total
Colon	307.2	293.1	600.3	325.7	323.8	649.5	371.9	369.2	741.1
Stomach	8.1	6.9	15.0	9.1	8.1	17.2	10.3	9.4	19.7
Liver	3.1	2.8	5.9	3.5	3.3	6.8	4.0	3.7	7.7
Lung	0.5	0.5	1.0	0.5	0.6	1.1	0.6	0.7	1.3
Prostate	73.3	73.3	146.6	87.8	88.0	175.8	103.7	103.8	207.5
Bladder	71.3	101.0	172.3	89.9	128.3	218.2	111.0	191.9	302.9
Thyroid	0.6	0.4	1.0	0.8	0.5	1.3	0.8	0.6	1.4
Breast	1.5	1.4	2.9	1.8	1.7	3.5	2.2	1.8	4.0
Uterus	38.9	43.2	82.1	50.0	55.6	105.6	64.3	72.7	137.0
Ovary	49.3	49.5	98.8	68.0	68.2	136.2	95.9	95.9	191.8
Out-of-field colon	3.9	3.9	7.8	4.7	4.8	9.5	5.6	5.8	11.4

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TABLE II. Organ doses from radiation therapy for heterotopic ossification prophylaxis with a target dose of 7 Gy given by equally weighted anteroposterior and posteroanterior blocked fields of size 13 × 16 cm^2.

	Organ dose (mGy)		
Organ	AP field	PA field	Total
Colon	73.1	73.2	146.3
Stomach	8.1	6.8	14.9
Liver	2.7	2.4	5.1
Lung	0.7	0.7	1.4
Prostate	52.6	53.1	105.7
Bladder	48.0	58.1	104.4
Thyroid	1.2	0.8	2.0
Breast	2.9	1.8	4.7
Uterus	30.8	31.8	62.6
Ovary	35.2	34.8	70.0

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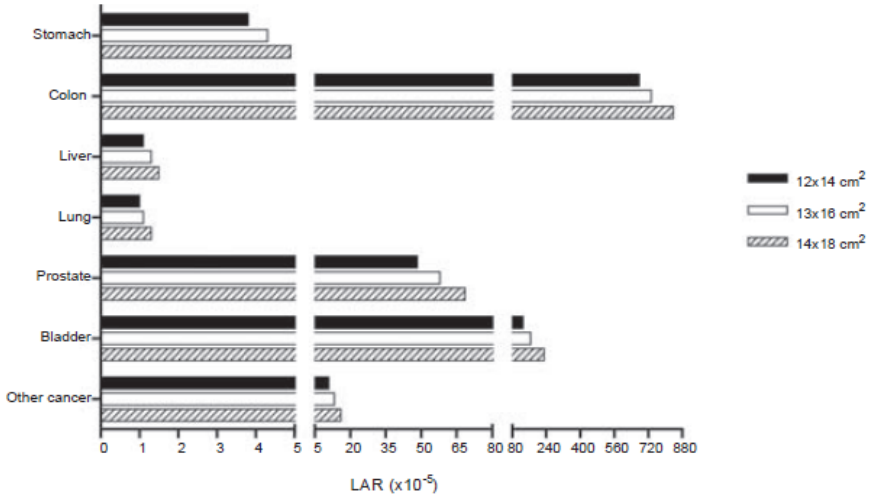
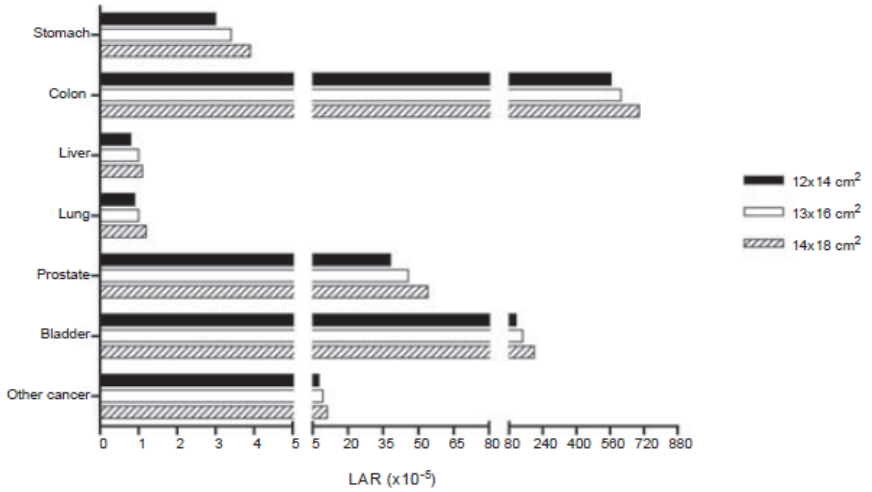


(a)



(b)

Cancer risk estimates for (a) 50- and (b) 60-year-old male patients undergoing open field radiation therapy for heterotopic ossification prophylaxis.

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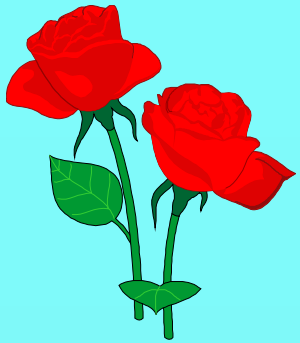
Messages to take home

1. It is important to know the risk of radiation-induced cancers after radiotherapy for benign diseases to:
   * provide information about risks to patients
   * balance benefits and risks
   * take it into consideration during follow up

2. Estimation of radiation-induced cancer risk following radiotherapy for benign diseases using MC, is possible using phantoms and BEIR VII data and mechanistic modeling

3. Studies are needed to provide organ doses and risks attributable to radiotherapy for benign diseases



Thank you !