

Second primary cancer after radiotherapy in women with invasive cervical carcinoma

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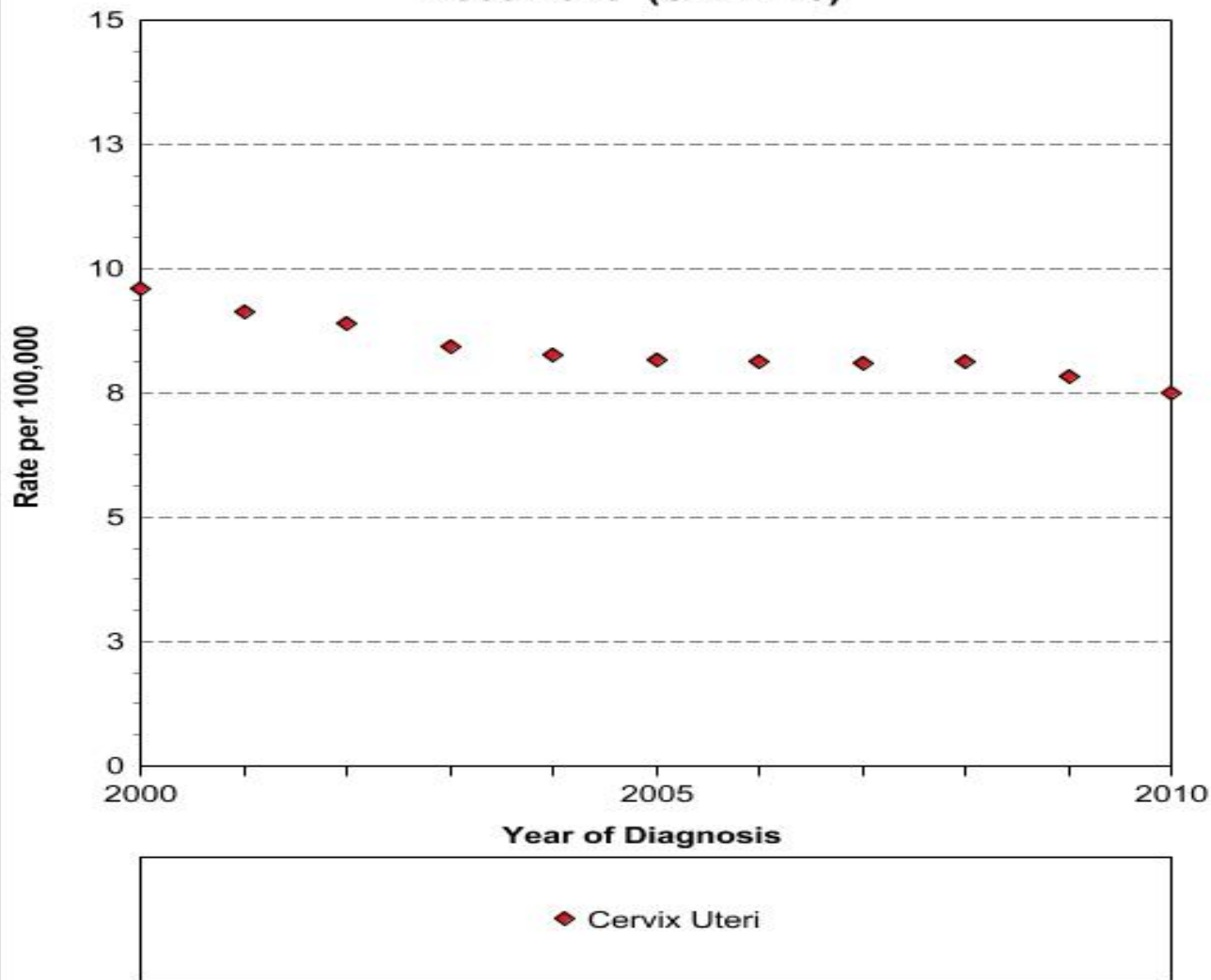
CERCIT Scholar

Introduction

Cervical Cancer

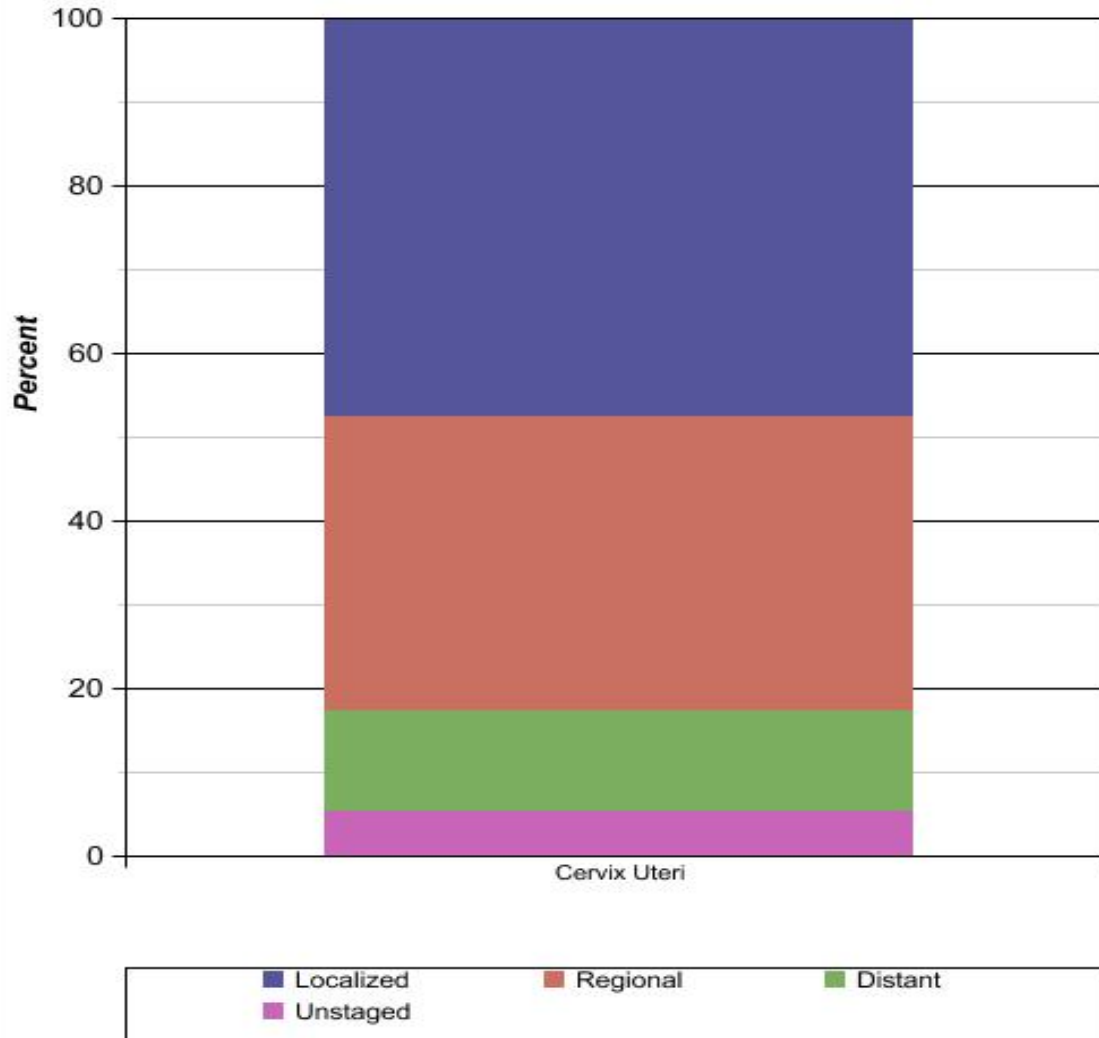
- In 2013
 - 12,340 new cases of cervical cancer
 - 4,030 deaths

**Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Female
2000-2010 (SEER 18)**



Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute.
Incidence source: SEER 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).

**Stage Distribution (SEER Summary Stage 2000)
By Cancer Site
All Ages, All Races, Female
2000-2010**



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Subsequent Malignancies in Cancer Survivors

- 18% of all cancer diagnoses in the US Surveillance, Epidemiology and End Results (SEER) cancer registries are second primary cancers
- Third most common cancer diagnosis
- Compared to the general population, cancer survivors have approximately 14% higher rate of cancer

Objectives

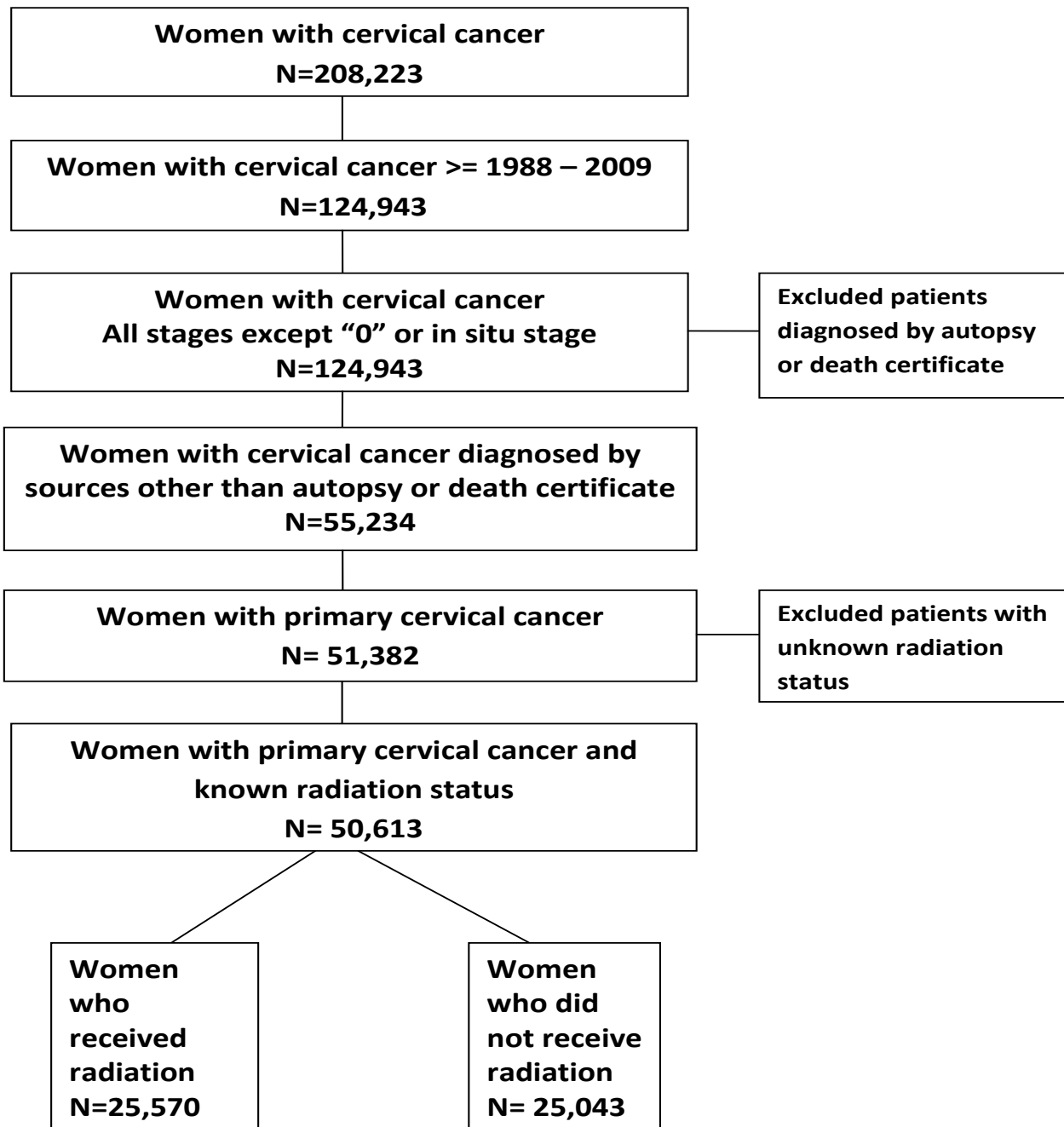
- Radiation has been widely used as primary treatment or adjuvant therapy of cervical carcinoma
- There is a growing concern whether other primary cancers can arise years later
- This study examines the risk of developing other primary cancers after receiving radiotherapy for cervical cancer

Data Source

- Data were obtained from the SEER program from 1988 to 2009
- We included invasive stage I-IV cervical carcinoma cases according to the International Federation of Gynecology and Obstetrics (FIGO) classification

Methods

- Kaplan-Meier estimator for survival curve
- Cox proportional hazard models were developed to estimate the risk of second primary cancer (SPC) overtime among women diagnosed with cervical cancer and treated with and without radiation
- These models were controlled for other covariates including patient characteristics and tumor characteristics
- Level of significance was set at $P < 0.05$



Demographics

Age (Years)	Radiation (%) N= 25,570	No Radiation (%) N= 25,043
Mean Age	52.8 ± 14.9 years	46.6 ± 28.5 years
0-19	14 (0.05%)	88 (0.35%)
20-39	5088 (19.90%)	9891 (39.50%)
40-59	12382 (48.42%)	10317(41.20%)
60-79	6657 (26.03%)	3801 (15.19%)
80-99	1423 (5.57%)	922 (3.68%)
>100	6 (0.02%)	24 (0.10%)

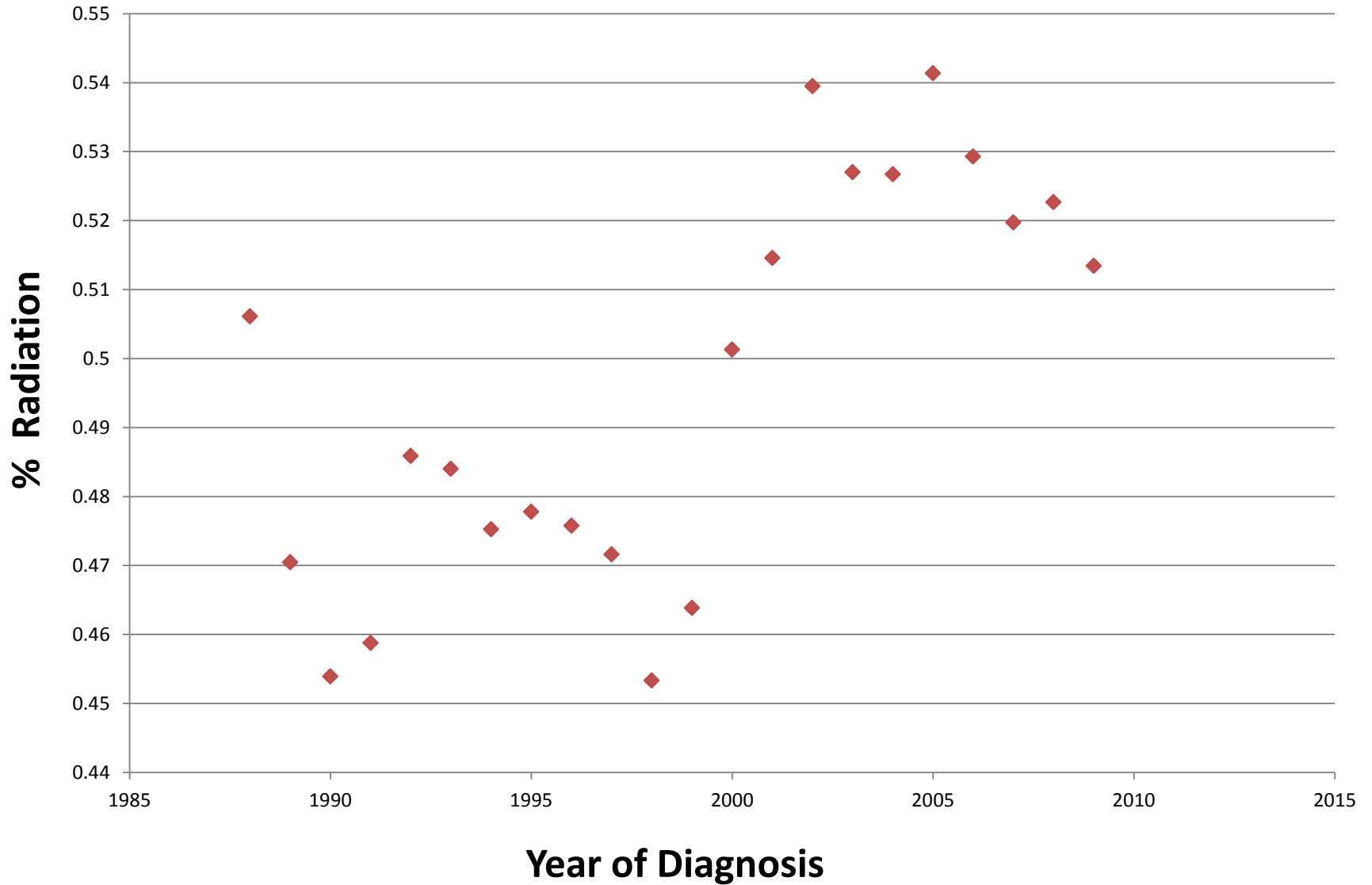
Demographics

Race	Radiation (%) N= 25,570	No Radiation (%) N= 25,043
White	13582 (53.12%)	14412 (57.55%)
Black	4051 (15.84%)	2847 (11.37%)
Hispanic	5329 (20.84%)	4937(19.71%)
Other / unknown	2608 (10.20%)	2847 (11.37%)

Demographics

Marital Status at Diagnosis	Radiation (%) N= 25,570	No Radiation (%) N= 25,043
Single	6052 (23.67%)	6089 (24.31%)
Married	10678 (41.76%)	11909 (47.55%)
Separated	8840 (34.57%)	7045 (28.13%)

Women Radiated by Year of Diagnosis (%)



Surgical Procedure

Surgical Procedure	Radiation (%) N= 25,570	No Radiation (%) N= 25,043
Yes	9609 (37.58%)	20314 (81.12%)
No	15961 (62.42%)	4729 (18.88%)

Tumor Characteristics

Stage at Diagnosis	Radiation (%) N= 25,570	No Radiation (%) N= 25,043
Localized	6159 (24.09%)	19188 (76.62%)
Regional	15389 (60.18%)	2291 (9.15%)
Distant	3295 (12.89%)	1486 (5.93%)
Unstaged	727 (2.84%)	2078 (8.30%)

Tumor Characteristics

Tumor Grade	Radiation (%) N= 25,570	No Radiation (%) N= 25,043
Well differentiated	1408 (5.51%)	2717 (10.85%)
Moderately differentiated	7674 (30.01%)	5655 (22.58%)
Poorly differentiated	9473 (37.05%)	4624 (18.46%)
Undifferentiated	776 (3.03%)	476 (1.90%)
Unknown	6239 (24.40%)	11571 (46.20%)

Second Primary Tumor Over 20 Years Follow up

Heavily Irradiated Sites	Radiation (%) N= 25,570	No Radiation (%) N= 25,043	P-value (Log-Rank < 0.05)
Small Intestine	7 (0.1%)	8 (0.1%)	0.6799
Colon	121 (2.5%)	69 (0.8%)	0.0001
Rectum and Anus	57 (1.2%)	39 (0.4%)	0.0002
Urinary Bladder	92 (1.9%)	37 (0.4%)	<0.0001
Vagina	114 (1.3%)	167 (1.1%)	0.1787
Ovary	61 (0.8%)	71 (0.5%)	0.8002
Corpus Uterine	88 (1.9%)	74 (0.4%)	0.0225
Bone	4 (0.05%)	1 (0%)	0.0503
Soft Tissue including Heart	16 (0.2%)	9 (0.2%)	0.0079
ANY	545 (9.2%)	462 (3.6%)	< 0.0001

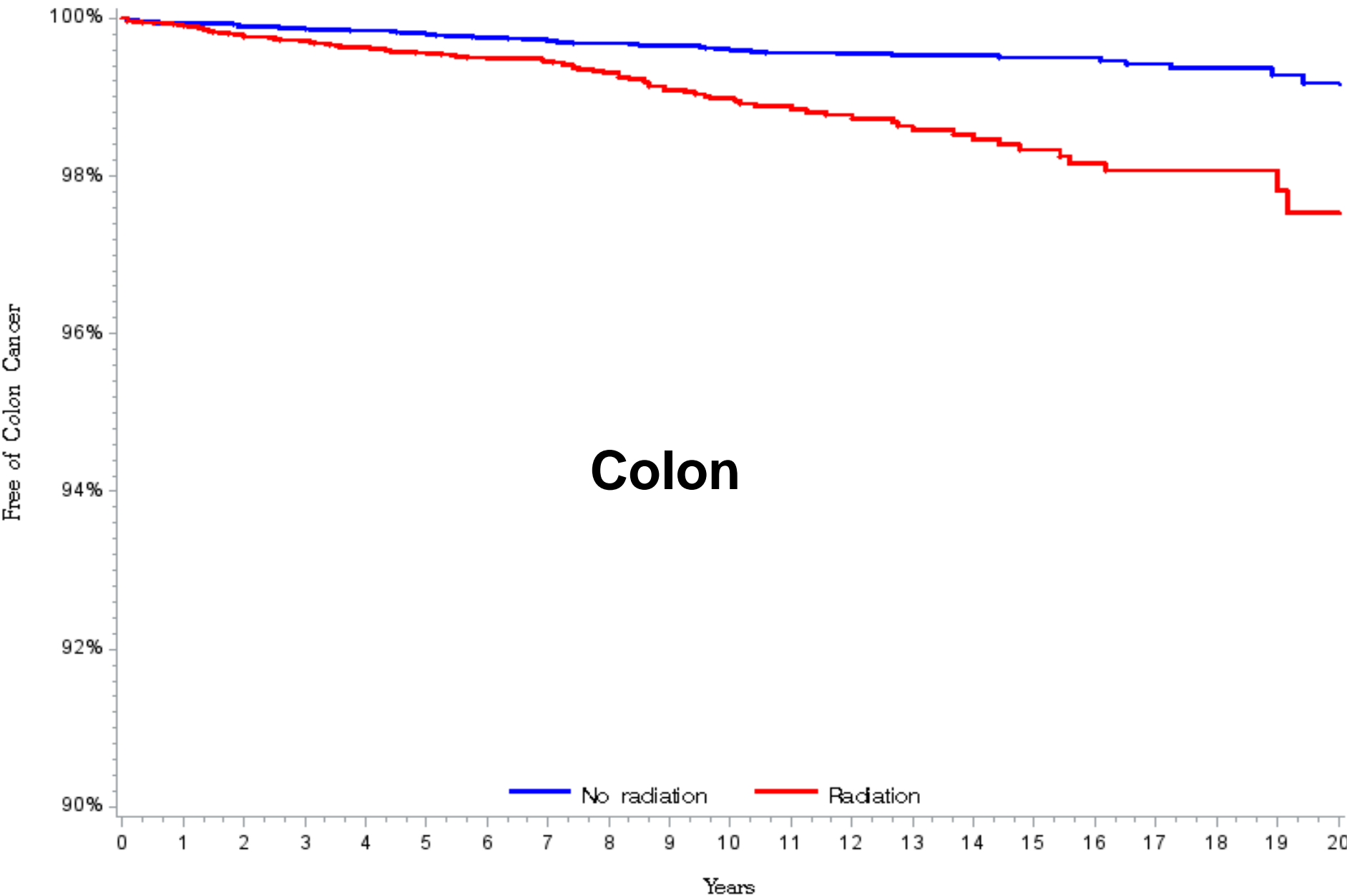
Second Primary Tumor Over 20 Years Follow up

Moderately Irradiated Sites	Radiation (%) N= 25,570	No Radiation (%) N= 25,043	P-value (Log-Rank)
Stomach, Liver, Gallbladder	39 (0.8%)	40 (0.6%)	0.0529
Pancreas	44 (1.2%)	13 (0.2%)	<0.0001
Kidney	36 (1.5%)	32 (0.4%)	0.0617
ANY	119 (3.4%)	85 (1.2%)	<0.0001

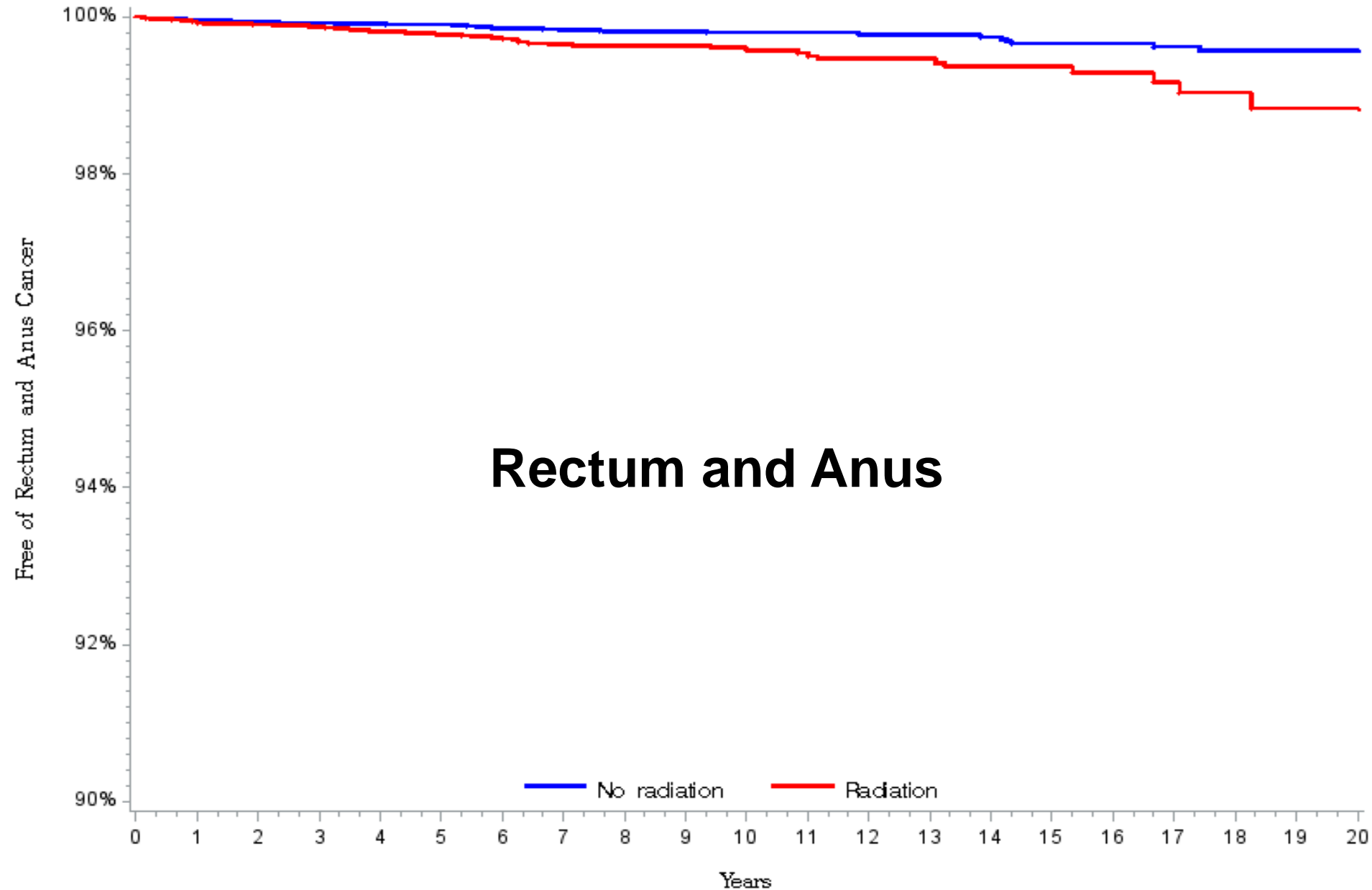
Second Primary Tumor Over 20 Years Follow up

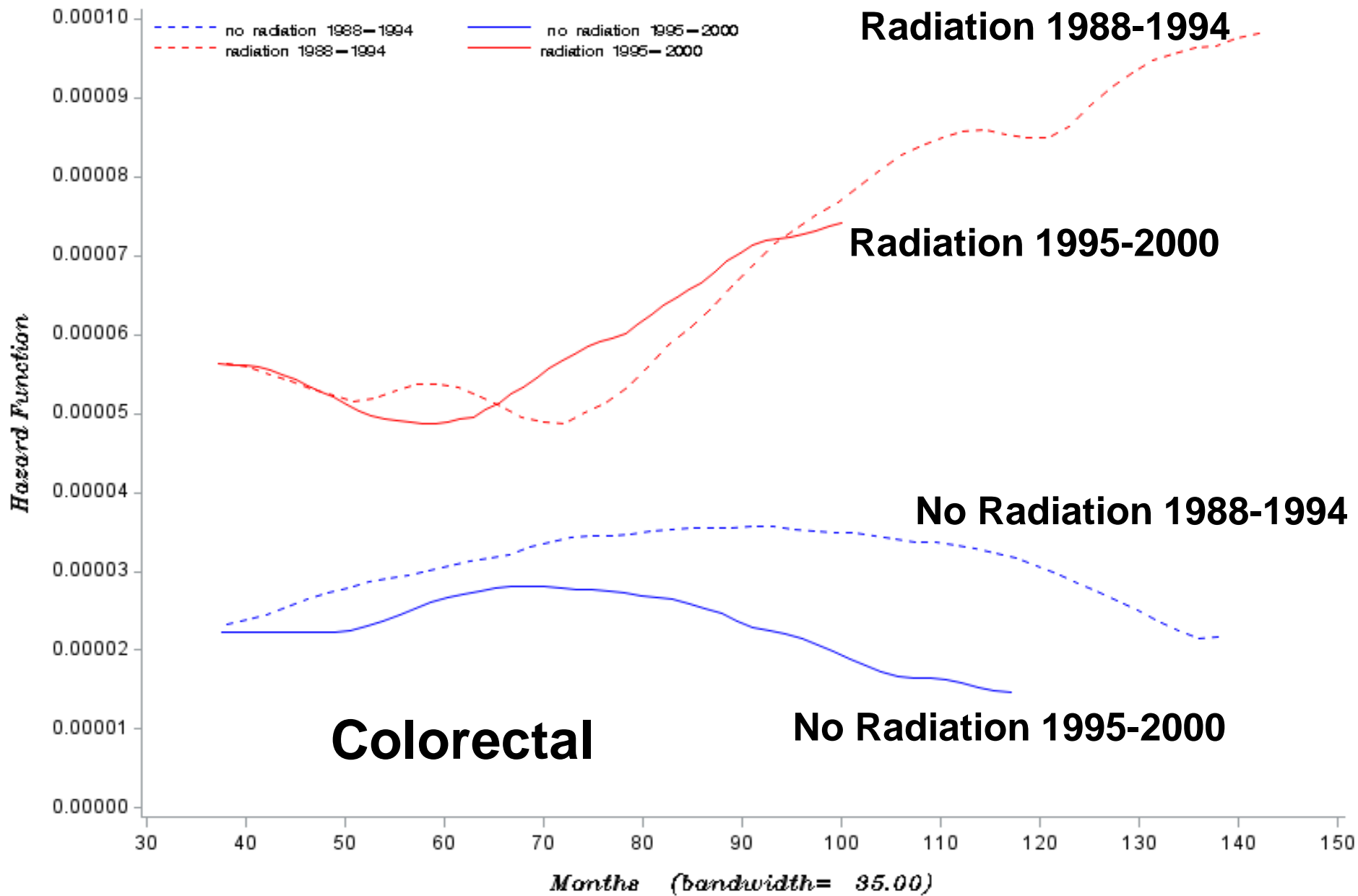
Lightly Irradiated Sites	Radiation (%) N= 25,570	No Radiation (%) N= 25,043	P-value (Log-Rank)
Lip/Tongue/Salivary Gland/Mouth	15 (0.27%)	13(0.1%)	0.2355
Pharynx	10 (0.24%)	6 (0.08%)	0.0485
Esophagus	0 (0%)	0 (0%)	..
Nose, Nasal Cavity, Middle Ear	0 (0%)	0 (0%)	..
Larynx	5 (0.05%)	12 (0.09%)	0.3747
Trachea/Bronchus/Lung/Mediastinum	421 (6.12%)	217 (2.67%)	<0.0001
Pleura	0 (0%)	0(0%)	..
Breast	308 (5.9%)	322 (3.9%)	<0.0001
Eye	0 (0%)	1 (0%)	0.4600
Brain/CNS	20 (0.71%)	27 (0.52%)	0.5063
Thyroid	38 (0.45%)	37 (0.40%)	0.1138
ANY	817 (13.3%)	626 (8.5%)	<0.0001

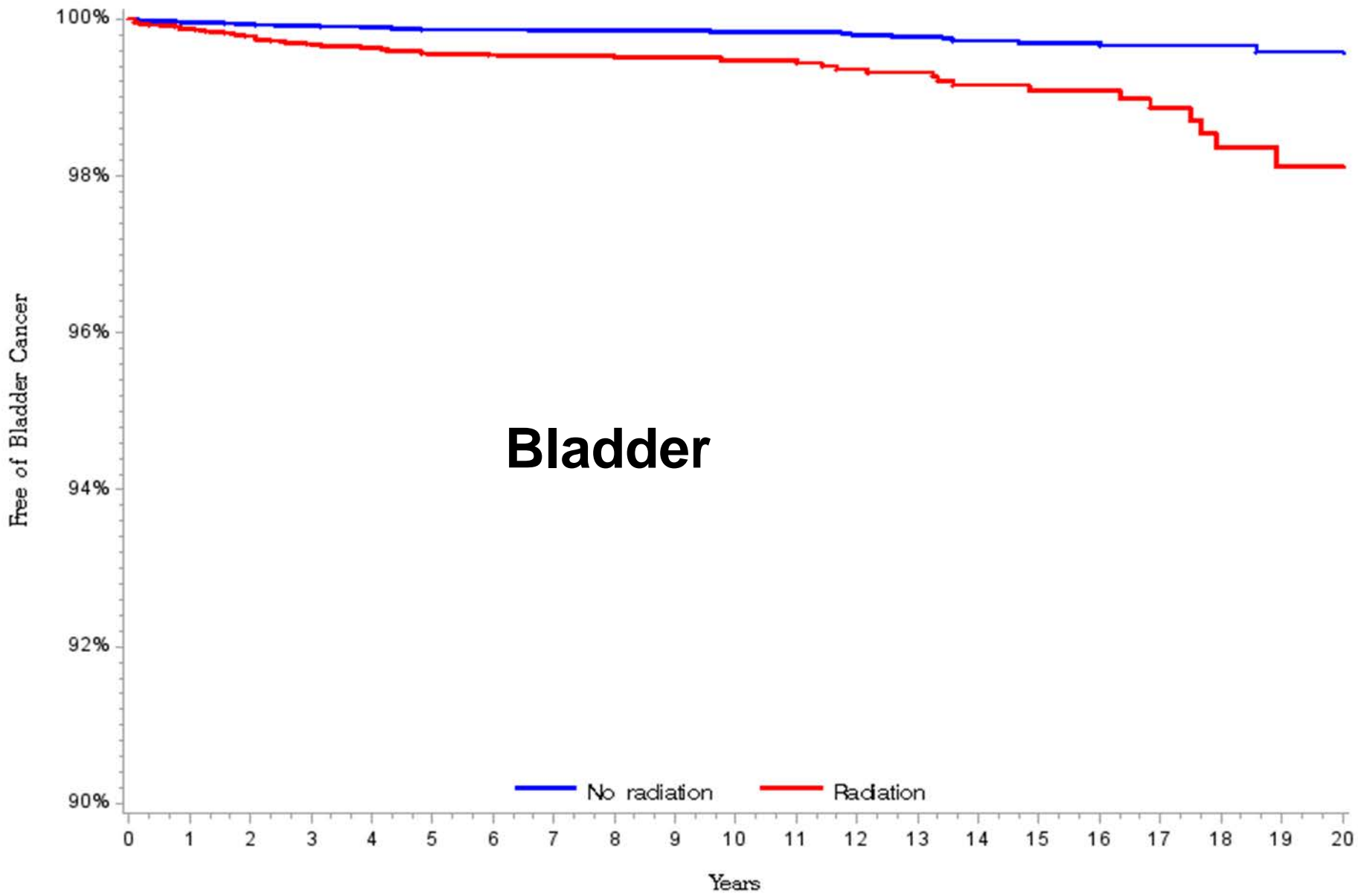
Colon

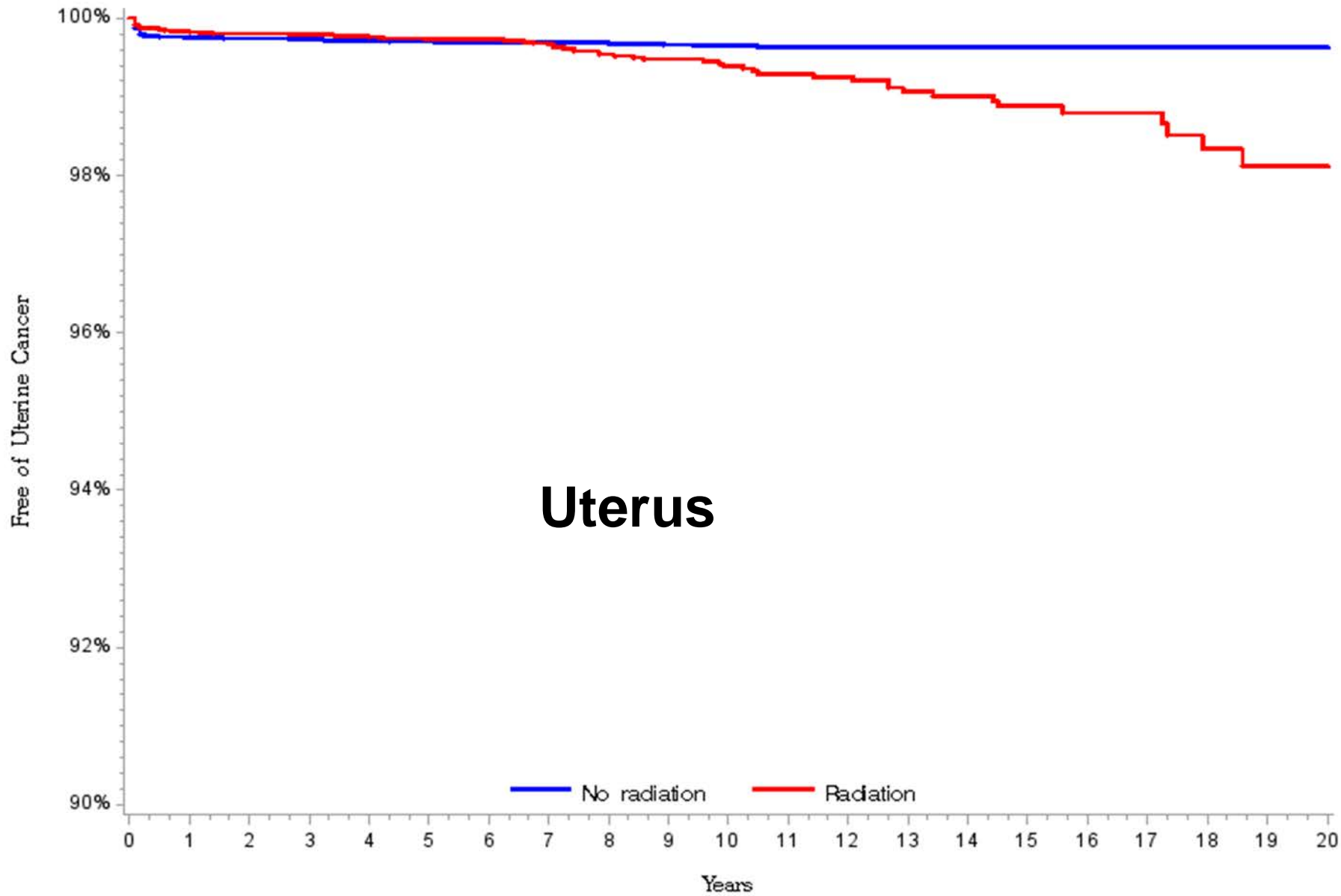


Rectum and Anus

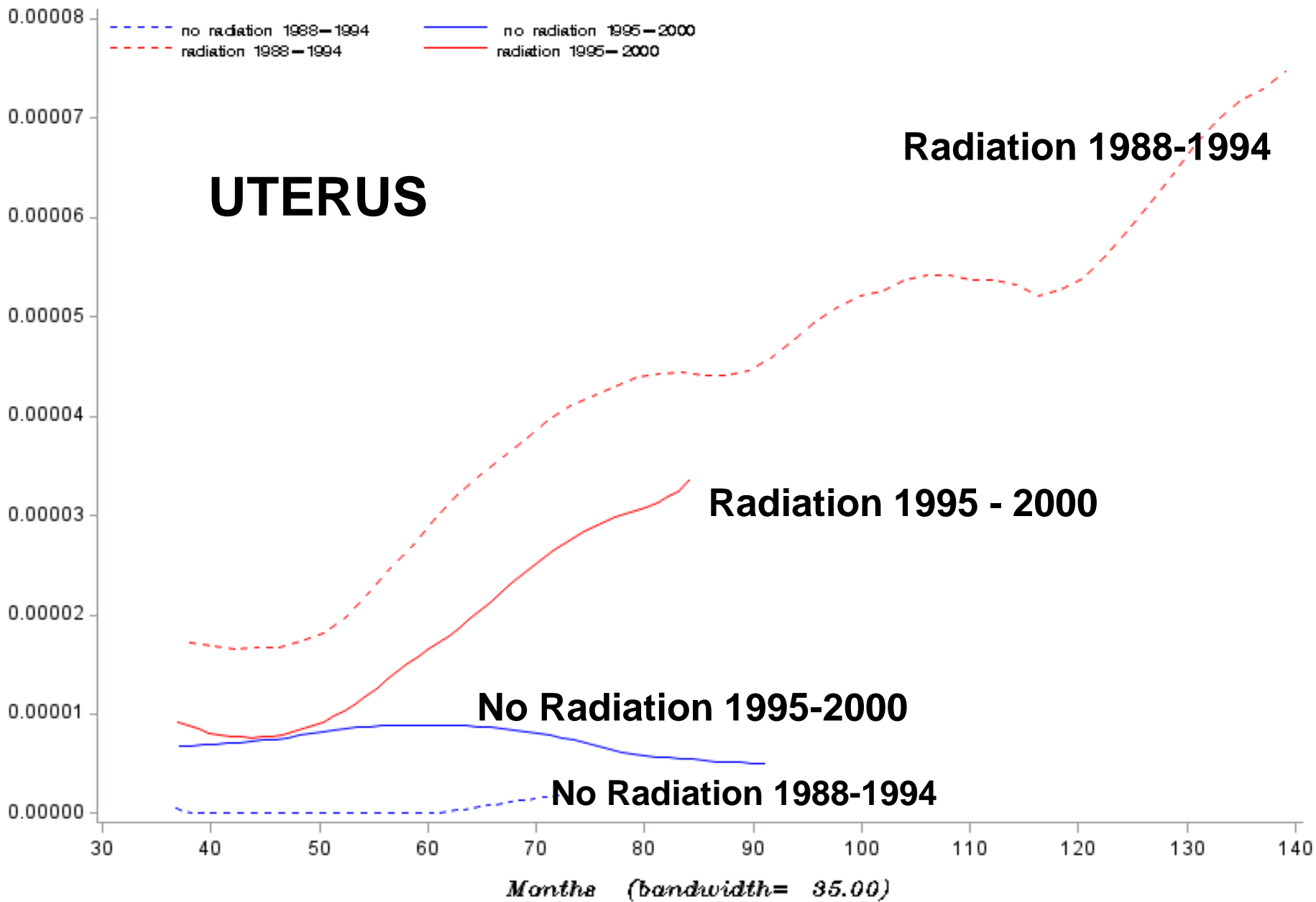




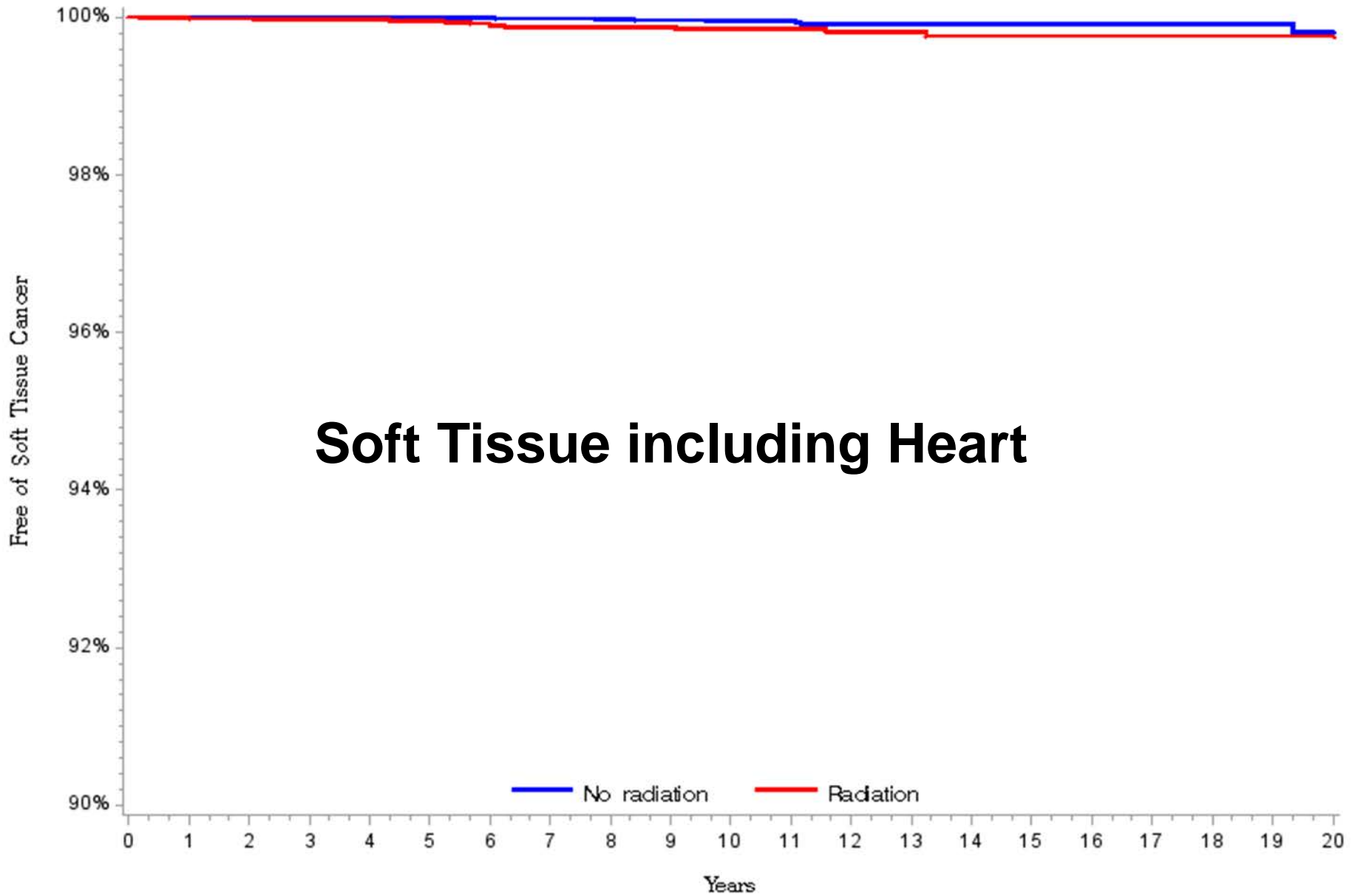




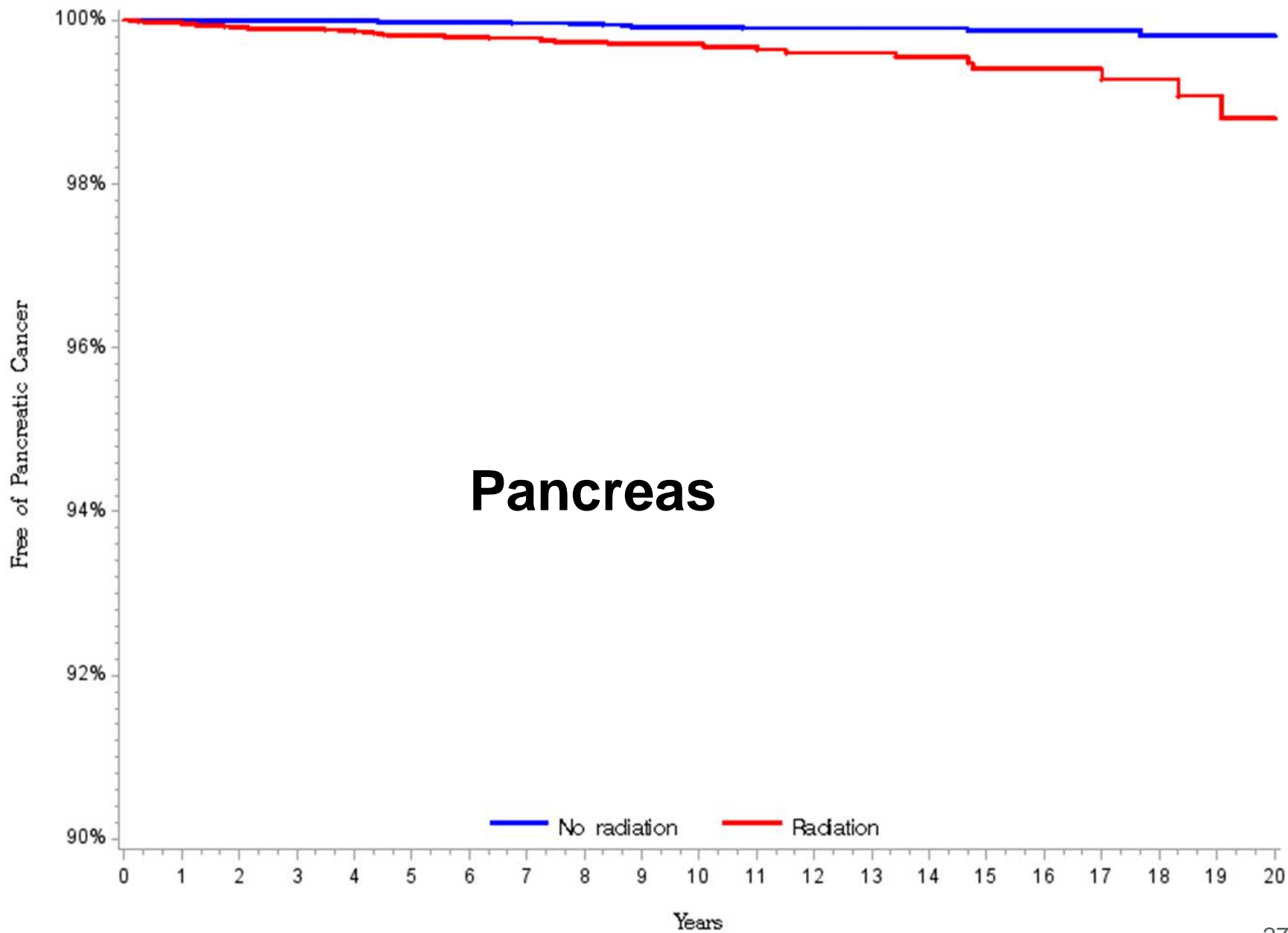
UTERUS

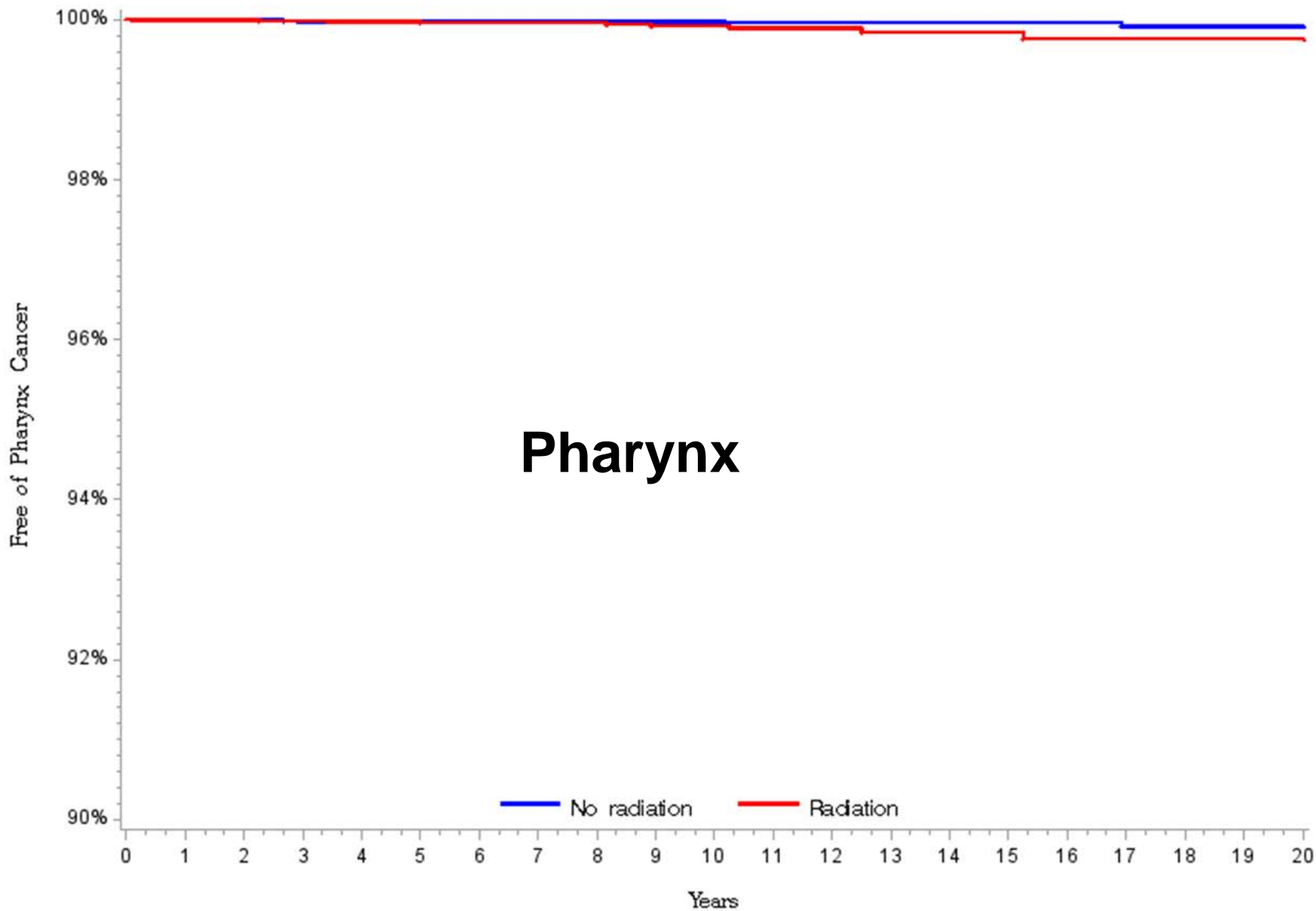


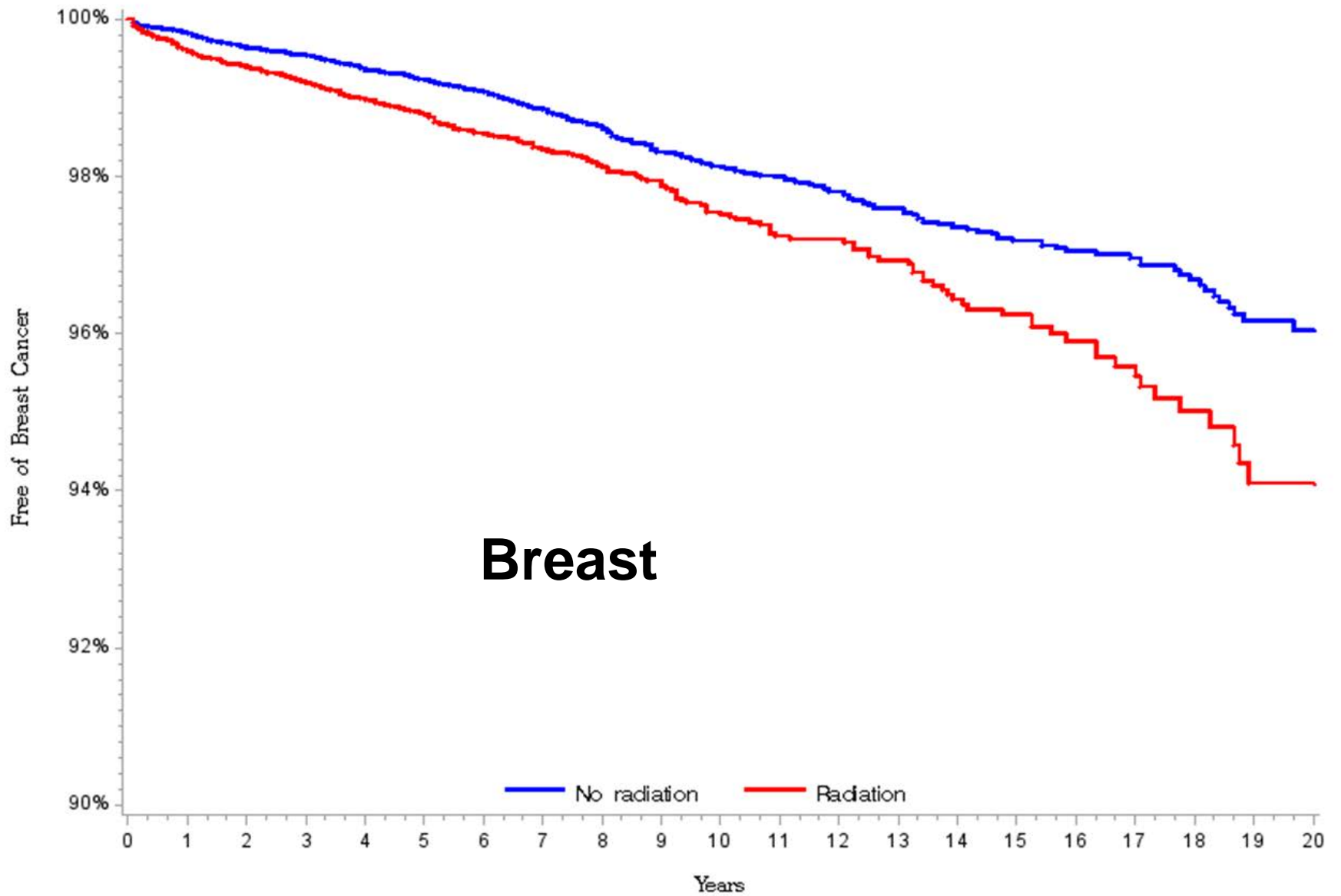
Soft Tissue including Heart



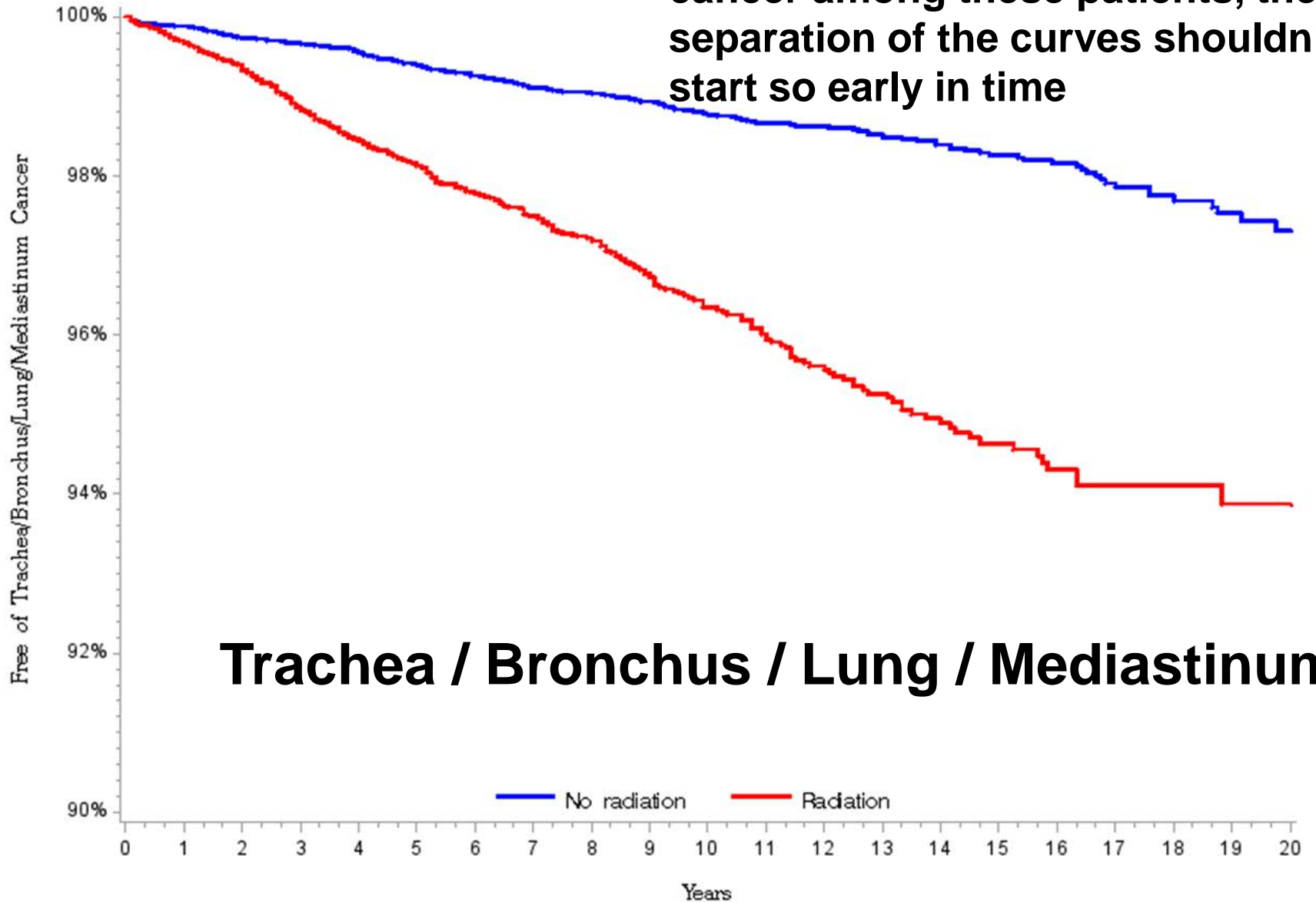
Pancreas







If radiation was the cause of lung cancer among these patients, the separation of the curves shouldn't start so early in time



Trachea / Bronchus / Lung / Mediastinum

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

Limitation of this study. Lack of control for smoking

Previous or current smoking is a risk factor for increased cancer stage at diagnosis in a wide range of malignancies



Advanced cancer stage increases the risk of requiring radiation for tumor control



Smoking increases the risk of developing lung cancer and cervical cancer

Proportional Hazard

Site	Time	Hazard Ratio	95% CI
Uterus	< = 5 years	0.64	0.41 – 0.98
	> 5 years	8.49	3.44 – 20.91
Colon/Rectum/Anus	< = 6 years	1.17	0.82 – 1.66
	> 6 years	2.10	1.34 – 3.27
Bladder	< = 10 years	1.58	0.95 – 2.65
	> 10 years	2.37	0.96 – 5.90
Breast		1.19	0.97 – 1.46
Lung		1.61	1.30 – 1.99

Conclusions

- Uterine cancer risk is increased more significantly after 5 years of completing radiation in women with invasive cervical cancer
- Colorectal cancer risk is increased more significantly after 6 years of completing radiation in women with invasive cervical cancer
- Bladder cancer risk is increased more significantly after 10 years of completing radiation in women with invasive cervical cancer

Conclusions

- Lung and breast cancer risk are increased in women with invasive cervical cancer, but no time effect was seen

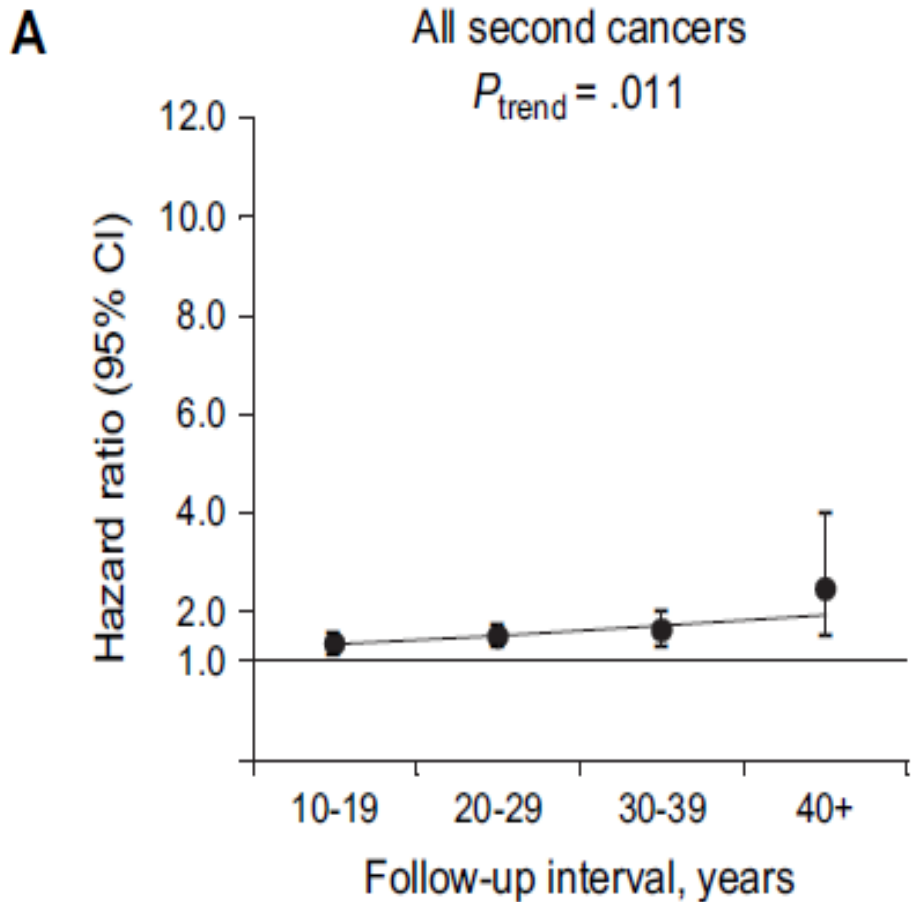
Comparing our results to current literature

JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

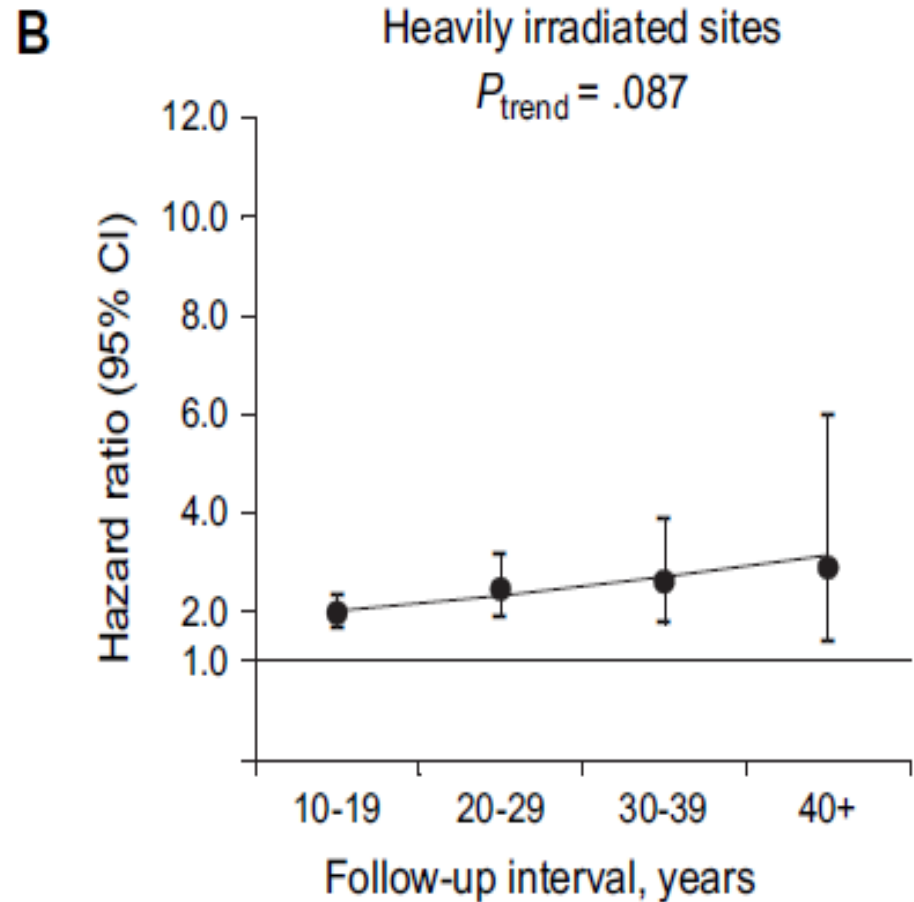
ARTICLE |

Second Cancers Among 104760 Survivors of Cervical Cancer: Evaluation of Long-Term Risk

Anil K. Chaturvedi, Eric A. Engels, Ethel S. Gilbert, Bingshu E. Chen, Hans Storm, Charles F. Lynch, Per Hall, Froydis Langmark, Eero Pukkala, Magnus Kaijser, Michael Andersson, Sophie D. Fosså, Heikki Joensuu, John D. Boice, Ruth A. Kleinerman, Lois B. Travis



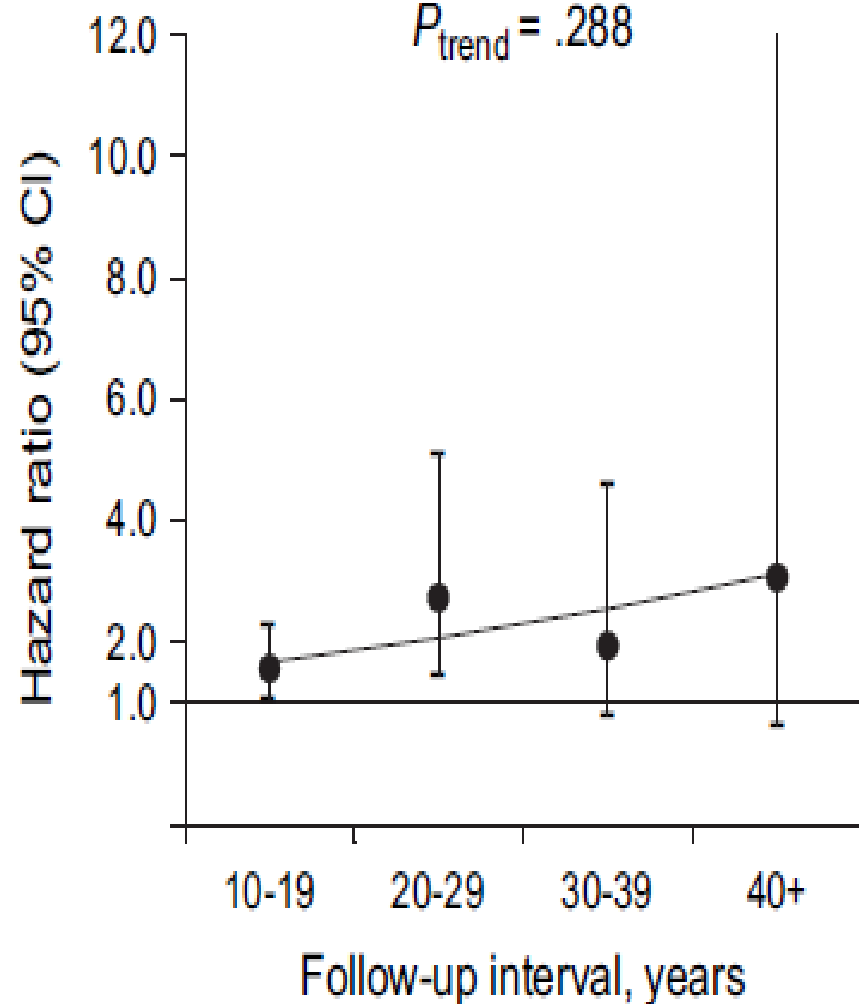
# events	2691	1888	886	225
Person-years	290345.	139539.	46292.	8665.



# events	969	789	437	133
Person-years	290345.	139539.	46292.	8665.

C

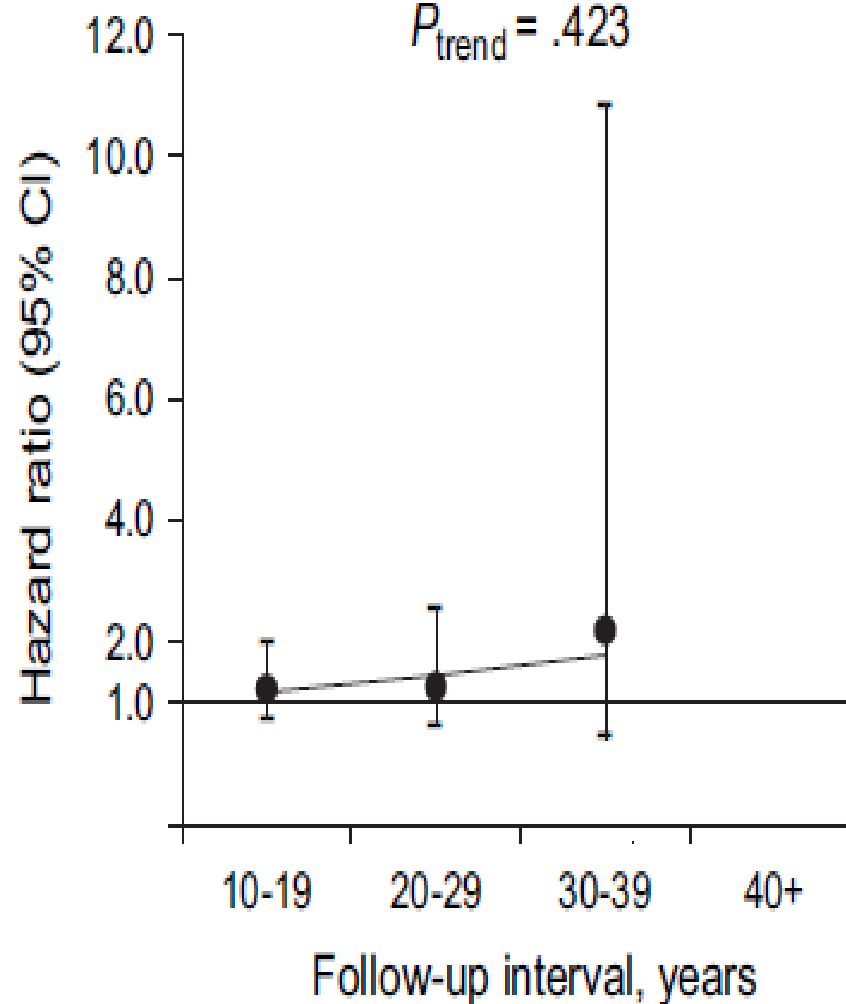
Rectum/anus

 $P_{\text{trend}} = .288$ 

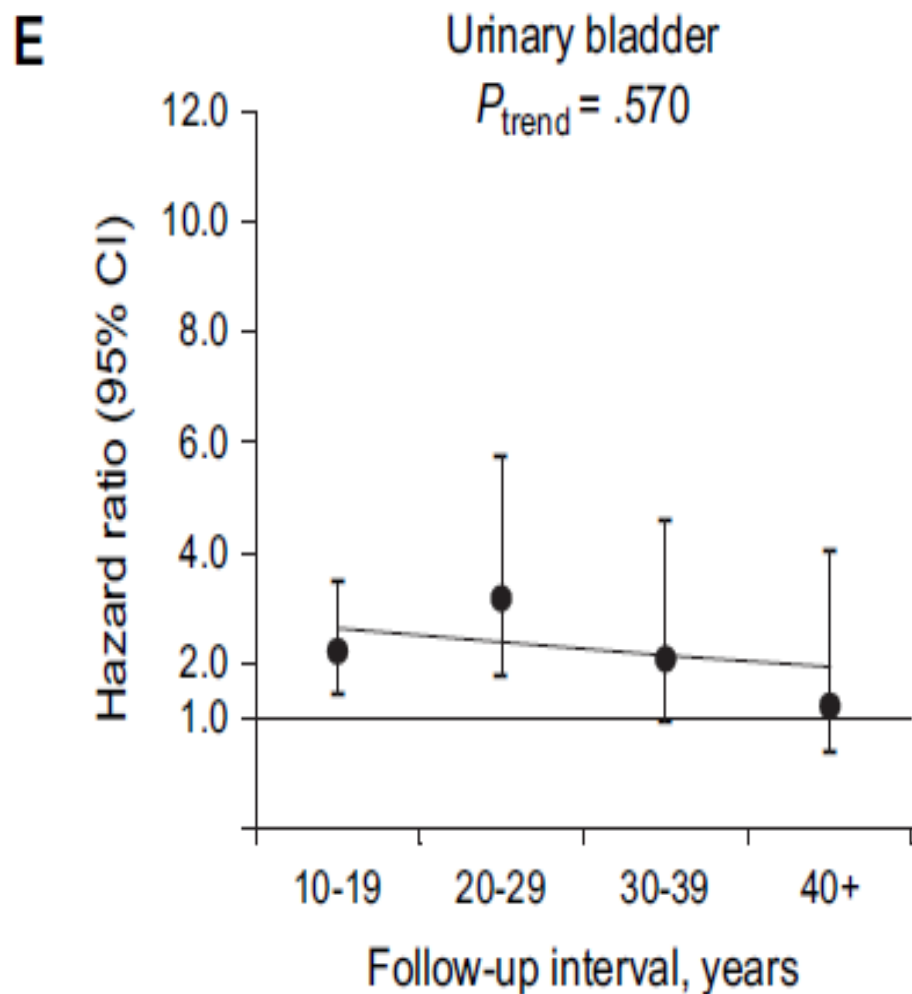
# events	195	142	94	38
Person-years	290345.	139539.	46292.	8665.

D

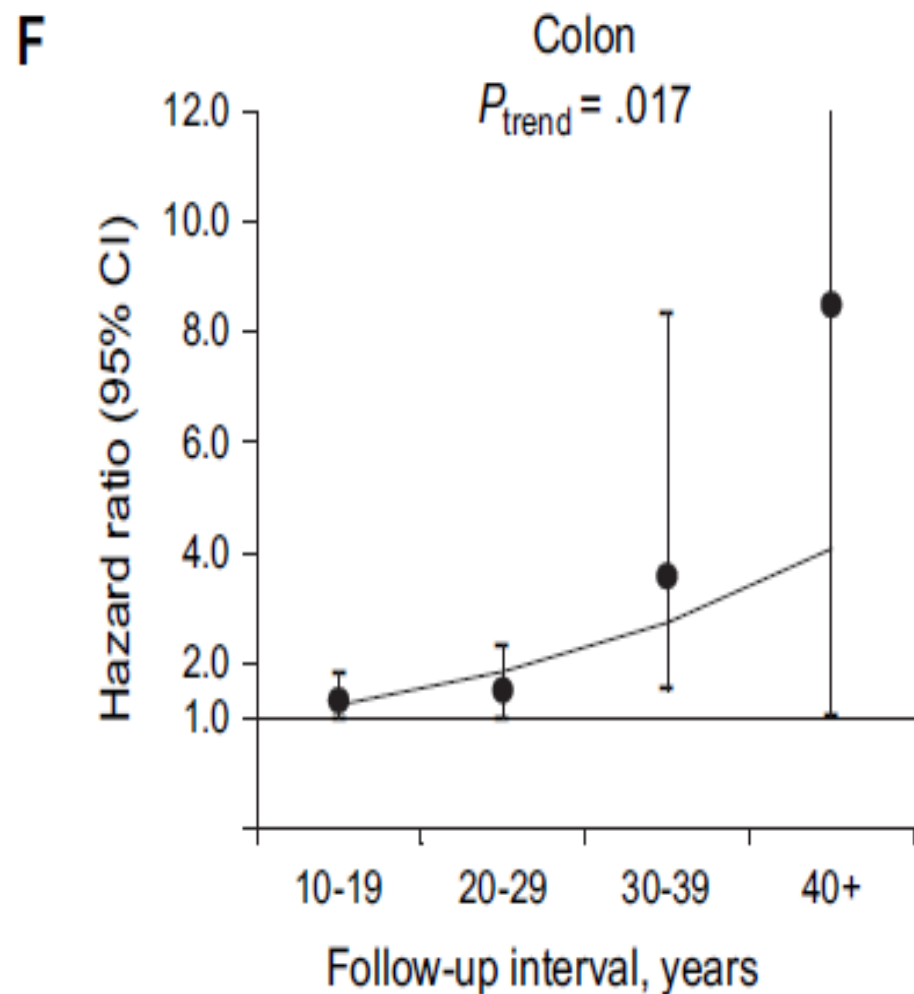
Female genital

 $P_{\text{trend}} = .423$ 

# events	98	83	43	15
Person-years	290345.	139539.	46292.	8665.



	10-19	20-29	30-39	40+
# events	158	172	118	32
Person-years	290345.	139539.	46292.	8665.



	10-19	20-29	30-39	40+
# events	249	198	86	29
Person-years	290345.	139539.	46292.	8665.

References

- Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. *The lancet oncology*. Apr 2011;12(4):353-360.
- Chaturvedi AK, Engels EA, Gilbert ES, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. *J Natl Cancer Inst*. Nov 7 2007;99(21):1634-1643.
- Tewari KS, DiSaia PJ. Radiation therapy for gynecologic cancer. *The journal of obstetrics and gynaecology research*. Jun 2002;28(3):123-140.

Acknowledgments

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- Yong-Fang Kuo, PhD