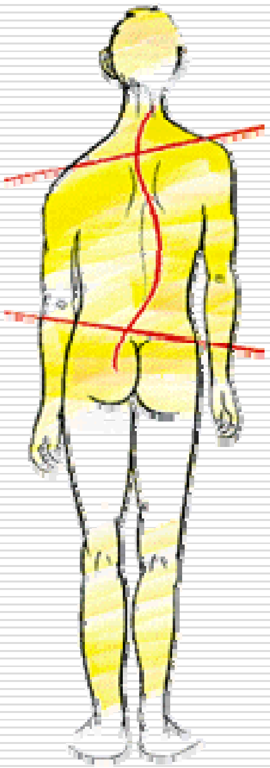
National Cancer Institute

Radiation exposure and cancer risk in the US Scoliosis Cohort Study

Cécile M. Ronckers

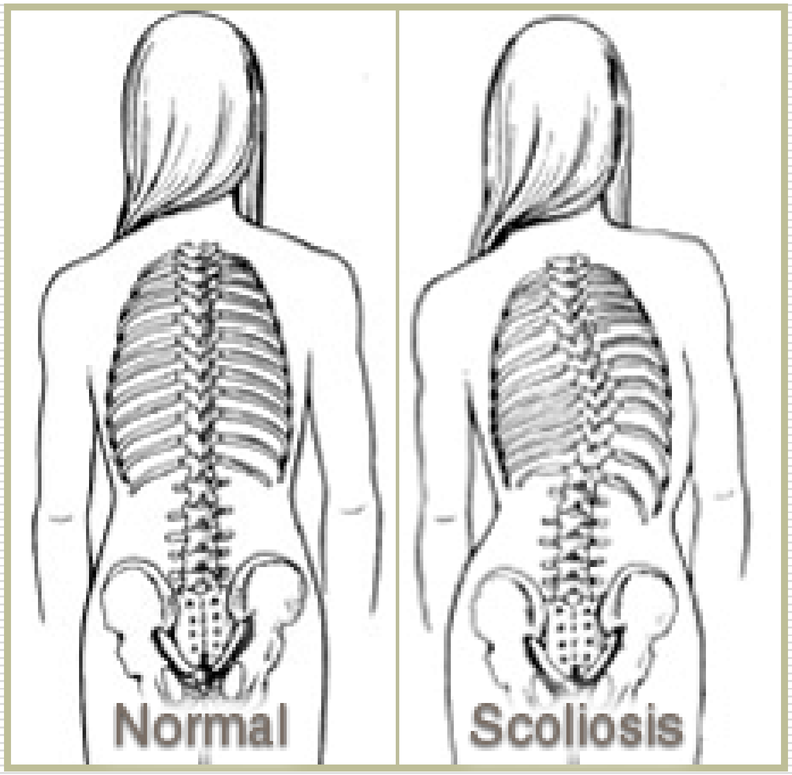


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Background

- Abnormal spinal curvature of at least 10°



Background

- Typical age at diagnosis
  - Congenital 0-3 yrs
  - Juvenile 4-9 yrs
  - Adolescent idiopathic 10-16 yrs
- Curve progression
  - F-M ratio 10:1
  - 10% progress → require treatment
  - Frequent monitoring using X-rays
  - Radiation exposure of the chest

Age at radiation exposure: sensitive subgroups?

- Atomic bomb survivors
  - Age at exposure 10-19 yrs confers highest risk of breast cancer (McGregor 1977)
- Oestrogen window hypothesis (Korenman, 1980)
  - Unopposed estrogen exposure between breast budding and menarche → risk window for mammary cancer induction
- Chest RT for Hodgkin lymphoma
  - Age at radiotherapy 10-19 yrs: highest risk (Bhatia 1996)

Objectives

1. Breast cancer risk and radiation dose-response

2. Variation in sensitivity to radiation-induced breast cancer by breast development stage

Methods: medical information

- Pediatric cohort of female patients diagnosed with abnormal spinal curvature between 1912 and 1965 in 14 U.S. orthopedic centers
- Diagnostic/treatment characteristics from pediatric medical file
- Archival data from radiographic films and reports available for >137,000 examinations to allow for individual radiation dosimetry

Estimated radiation dose to the breast (cGy) for a full-spine view

Age at radiographic exam/view	1920-39	1940-59	1960-75	1976-89
≥ 13 yrs AP				
≥ 13 yrs PA				
≥ 13 yrs lateral				
<13, AP				
<13 PA				
<13 lateral				

Estimated radiation dose to the breast (cGy) for a full-spine view

Age at radiographic exam/view	1920-39	1940-59	1960-75	1976-89
≥ 13 yrs AP	1.176	0.588	0.350	0.090
≥ 13 yrs PA	0.010	0.005	0.005	0.005

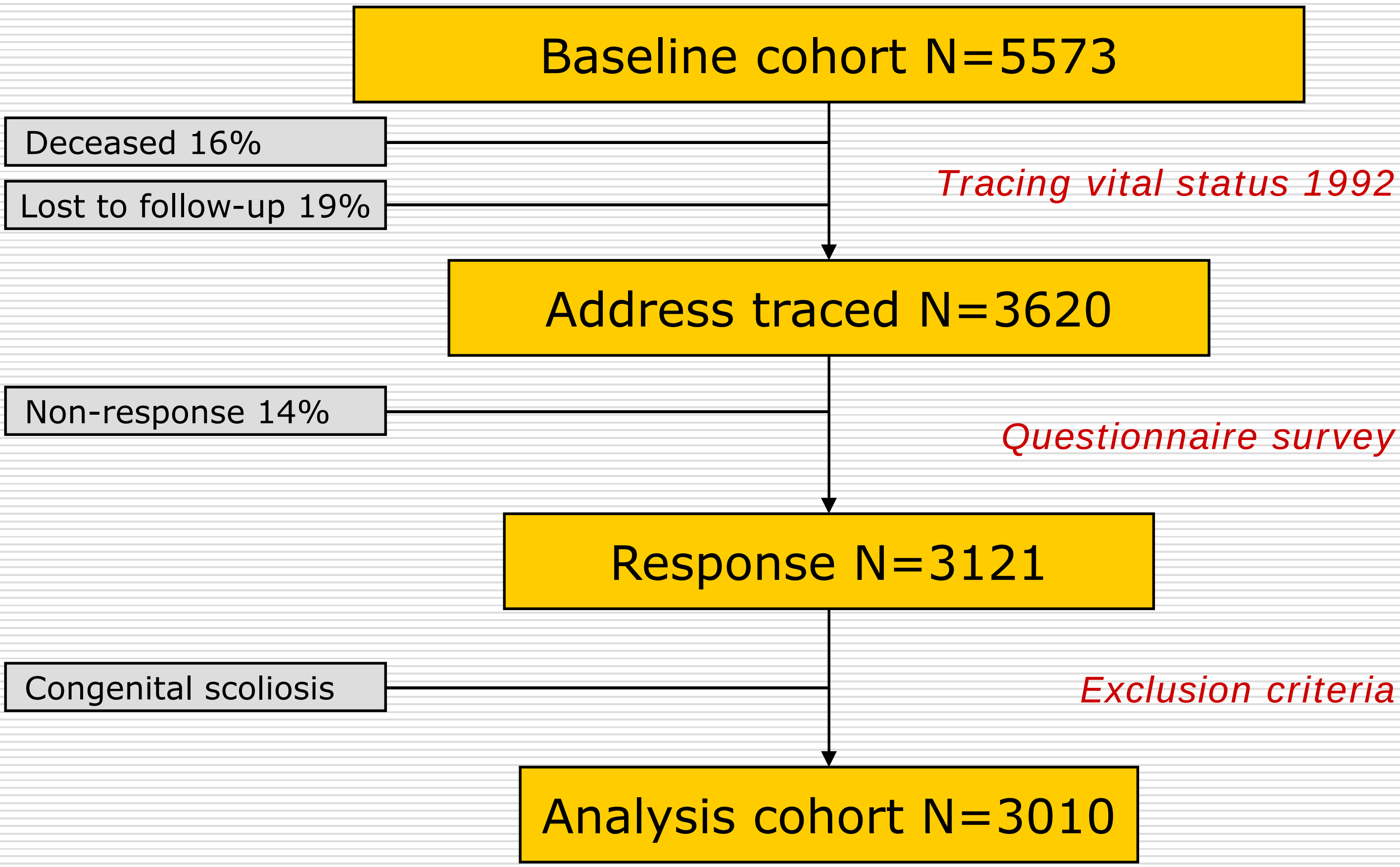
Estimated radiation dose to the breast (cGy) for a full-spine view

Age at radiographic exam/view	1920-39	1940-59	1960-75	1976-89
≥ 13 yrs AP	1.176	0.588	0.350	0.090
≥ 13 yrs PA	0.010	0.005	0.005	0.005
≥ 13 yrs lateral	0.600	0.300	0.225	NA
<13, AP	**1.560**	0.780	0.470	0.125
<13 PA	0.006	**0.003**	**0.003**	**0.003**
<13 lateral	0.600	0.300	0.225	NA

Tracing and follow-up

- Nation-wide tracing for vital status and address
- NDI+ and state death certificates for cause of death
- Questionnaire survey
  - Breast cancer occurrences
  - Cancer risk factor information
  - Medical confirmation of breast tumors

Study Population



Population Characteristics

Characteristic	Median	Maximum
Age at scoliosis diagnosis, yrs	12	19
Age at end of follow-up , yrs	48	84
No. of radiographs involving breast	21	332
Estimated cumulative radiation dose to the breast, cGy	9	111

Data Analysis

- Outcome: occurrence of invasive breast cancer
- Poisson regression, internal comparisons
- Relative Risk = Exp $(\alpha_0 + \Sigma\alpha_k x_k) \times (1 + \beta \text{dose})$

Results incidence analysis

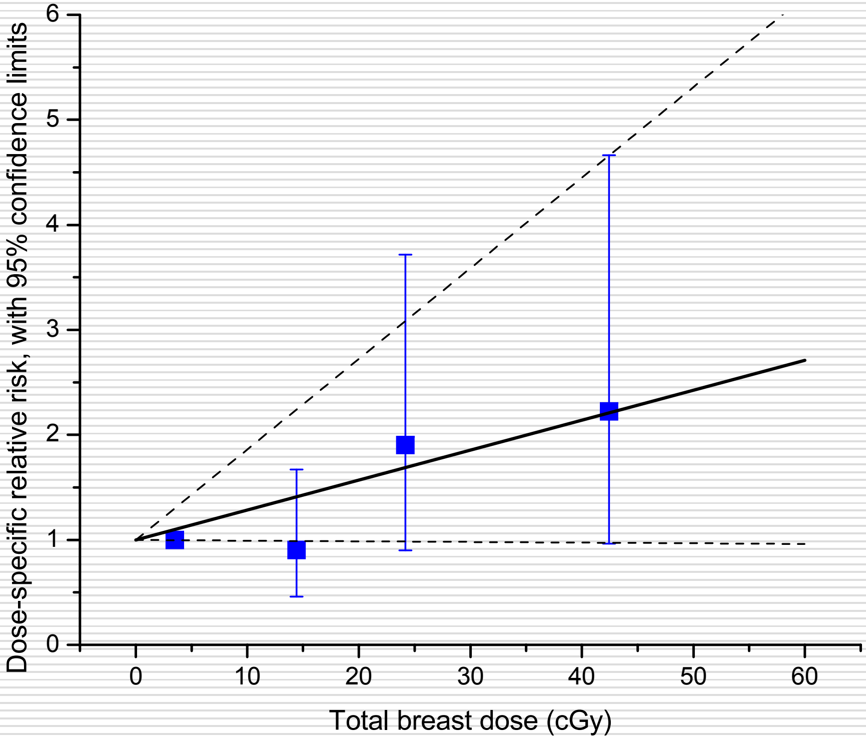
Risk of breast cancer by radiation dose

Mean dose (cGy)	PYR	N cases	RR (95% CI)
3.5	69,825	45	1.0
14.4	29,536	13	0.9 (0.5-1.7)
24.2	11,644	11	1.9 (1.0-3.9)
42.4	7,573	9	2.2 (1.0-4.9)

ERR/Gy = 2.9 (95% CI -0.1-8.6)

Results incidence analysis

Risk of breast cancer by radiation dose



Mean dose (cGy)	PYR	N cases	RR (95% CI)
3.5	69,825	45	1.0
14.4	29,536	13	0.9 (0.5-1.7)
24.2	11,644	11	1.9 (1.0-3.9)
42.4	7,573	9	2.2 (1.0-4.9)

ERR/Gy = 2.9 (95% CI -0.1-8.6)

Data Analysis

- Modification of dose response by window of breast development at exposure
- 4 breast development stages individually defined by ages at breast budding, menarche, and first live birth
- Each of 137,000 X-ray exposures allocated to 1 of 4 breast development stages, using age at procedure, to obtain 4 cumulative $doses_k$
- $RR = background \times (1 + \boldsymbol{\Sigma}\beta_k \mathbf{dose}_k)$

Results

Sensitivity to radiation-induced breast cancer by breast development stage at radiation exposure

Breast development stage at time of X-ray	Average dose (cGy)	Any dose
Before breast budding	1.7	23%
Between budding and menarche	2.7	41%
After menarche, before 1st child	7.1	78%
After birth of first child	0.1	9%

Results

Sensitivity to radiation-induced breast cancer by breast development stage at radiation exposure

Breast development stage at time of X-ray	Average dose (cGy)	Any dose	ERR/Gy
Before breast budding	1.7	23%	-0.2
Between budding and menarche	2.7	41%	1.7
After menarche, before 1st child	7.1	78%	15.9
After birth of first child	0.1	9%	4.4

Results

Sensitivity to radiation-induced breast cancer by breast development stage at exposure

- Exposure between menarche and birth of first child appears to account for most of the overall dose-response

- However
  - Model linear in total cumulative dose fits as well as one in which dose response is allowed to depend on developmental stage at exposure (p=0.57)
  - Few women had high-dose exposures before menarche

Age at radiation exposure: sensitive subgroups?

- Atomic bomb survivors
  - Age at exposure (ATB) 10-19 yrs confers highest risk of breast cancer (McGregor 1977)

Age at radiation exposure: sensitive subgroups?

- Atomic bomb survivors
  - Age at exposure (ATB) 10-19 yrs confers highest risk of breast cancer (McGregor 1977)
  - Caveat: 0 cases in group 0-9 yrs ATB
  - Longer follow-up (Tokunaga 1987)
    - Risk in groups 0-9 and 10-19 yrs ATB comparable
    - Women <20 yrs ATB: higher risk than women ≥20 yrs ATB

Age at radiation exposure: sensitive subgroups?

- Chest RT for Hodgkin lymphoma
  - Age at radiotherapy 10-19 yrs: highest risk (Bhatia 1996)

Age at radiation exposure: sensitive subgroups?

- Chest RT for Hodgkin lymphoma
  - Age at radiotherapy 10-19 yrs: highest risk (Bhatia 1996)
  - Caveats: few diagnosed before age 10 yrs & role of attained age
  - Longer follow-up (Bhatia 2004; Yasui 2003)
    - more cases among survivors aged 0-9 at diagnosis of HL
    - new analysis method taking into account age-related increase of breast cancer risk
    - Risk among <10 yr and 10-16 yr olds at RT comparable

Strengths

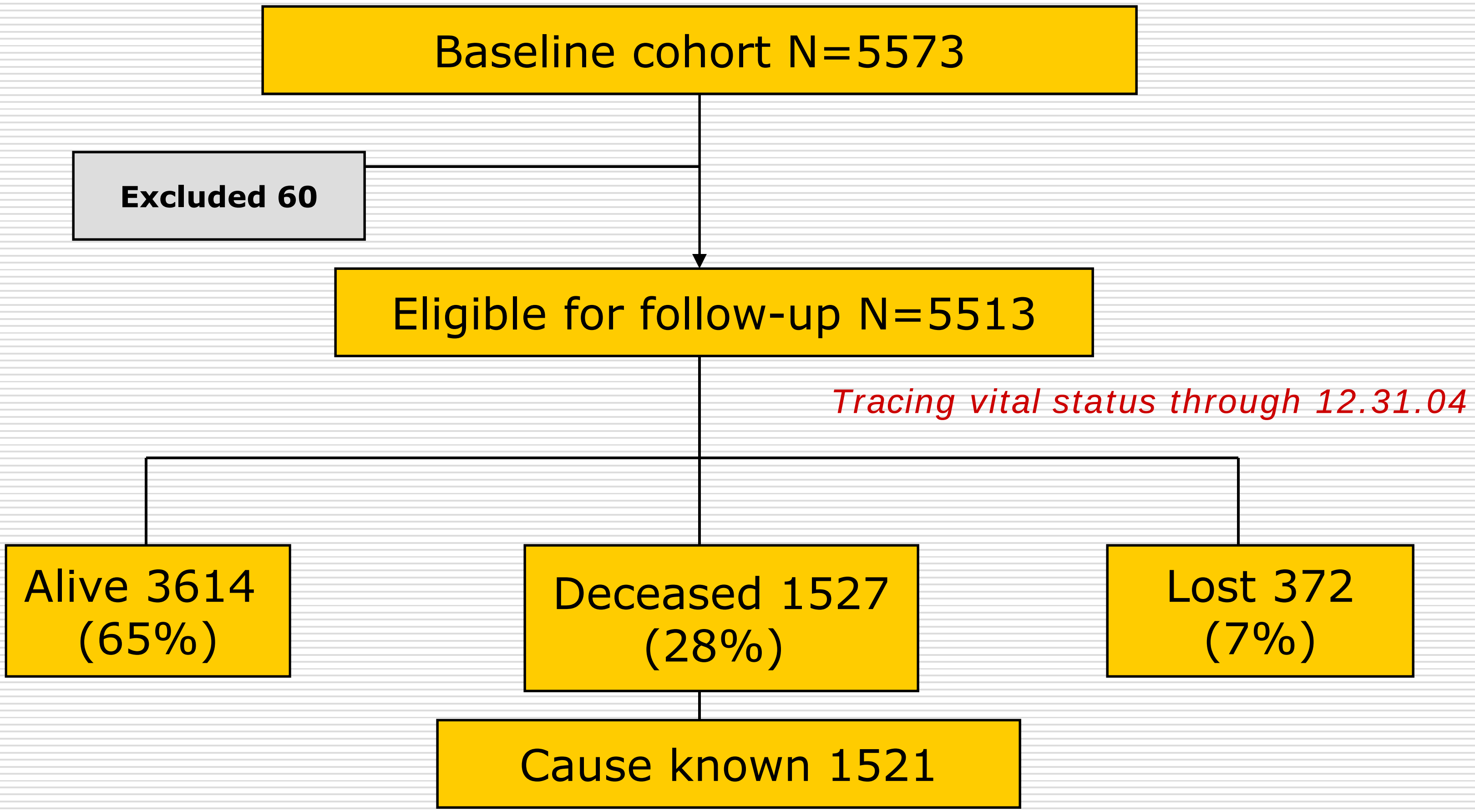
- Individual dose estimates for diagnostic exposures in large group of individuals
- Provides *direct* risk estimates for breast cancer in low-dose range
- Availability of cancer risk factor information
- Radiation exposure at vulnerable age for breast cancer risk

Limitations

- Clustering of dose around growth spurt
- Information on cancer risk factors and breast cancer conditional upon survival until 1992
- 19% of original cohort lost to follow-up for incidence analyses

Cancer mortality - update

Study Population



Data Analysis

- Outcome: cause-specific deaths
- Observed/Expected ratio (SMR)
- Expected number of deaths based on mortality rates of female US population, adjusted for calendar period and attained age

Conclusions

- Scoliosis patients who had frequent X-ray exposures in childhood/adolescence were at two-fold increased risk of breast cancer cf. patients who had few X-ray exposures

- A linear dose response was observed, ERR/Gy = 2.9

- No stat. significant differences in dose response were observed by breast development stage at the time of exposure

Acknowledgements

Michele Doody, Charles Land

National Cancer Institute, NIH, DHHS, Bethesda MD

Marilyn Stovall, Susan Smith, Rita Weathers

The University of Texas MD Anderson Cancer Center, Houston TX

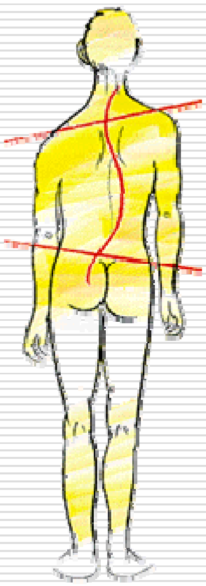
John Lonstein

Twin Cities Spine Center, Minneapolis MN

Jeremy Miller

Information Management Services (IMS), Rockville MD

14 participating orthopedic medical centers:
Twin cities Spine Center Minneapolis MN, Dupont Institute Wilmington DE, Children's Hospital Boston MA, University Hospital Hershey PA, and the respective Shriner's hospitals of Chicago IL, Greenville SC, Philadelphia PA, Portland OR, San Francisco CA, Springfield MA, St Louis MO, and Tampa FL



Current treatment guidelines

- General guidelines for management of AIS at the time of presentation
- Patients with angles of trunk rotation of <7º (as measured by the scoliometer, show picture 3) are followed clinically (every 3-6 months in premenarchal females, every four to six months in males and postmenarchal females). Radiographs (standing, full-length PA) spinal views should be obtained if the angle of trunk rotation increases to ≥7º.
- Patients with Cobb angles of <20º at the time of presentation may be observed.
- Skeletally immature patients with Cobb angles of 20º to 29º are followed closely and are braced if they exhibit progression (an increase in Cobb angle of ≥5º over a three- to six-month time period).
- Skeletally immature patients with Cobb angles of 30º to 40º are usually braced.
- Skeletally immature patients with Cobb angles of >50º at the time of diagnosis usually require surgical intervention. Such patients with Cobb angles between 40º and 50º may be managed with bracing or surgery.

Etiologic classification

- Neuromuscular scoliosis occurs in patients with neurologic or musculoskeletal problems such as cerebral palsy, myelomeningocele, muscular dystrophy, or leg length discrepancy. It is the result of muscle imbalance and lack of trunk control.
- Neuromuscular scoliosis may be structural or nonstructural. Nonstructural scoliosis has no rotational component; it may be related to postural abnormalities, leg length discrepancy, or pain (eg, splinting in patients with pneumonia or empyema). Most patients with neuromuscular scoliosis have additional findings related to the underlying disorder that help in making the diagnosis.
- Congenital scoliosis results from asymmetry in the vertebrae secondary to congenital anomalies (eg, hemivertebrae, failure of segmentation). Congenital scoliosis usually manifests before adolescence.
- Idiopathic scoliosis is scoliosis for which there is no definite etiology; it is therefore a diagnosis of exclusion. Idiopathic scoliosis is divided into three subcategories based upon the patient's age at presentation:
- - Infantile: 0 to 3 years
  - Juvenile: 4 to 9 years
  - Adolescent: ≥10 years

Cause of Death (ICD-9th Revision)	O†	SMR†	95% CI	EAR/10,000 Woman-yrs
All Causes‡	1527	1.46*	1.39-1.54	
All Malignant Neoplasms	354	1.08	0.97-1.20	
Oral Cavity (140-149)	7	1.93	0.77-3.98	
Esophagus (150)	4	1.42	0.38-3.63	
Stomach (151)	2	0.35	0.04-1.26	
Colon (153, 1590)	26	0.99	0.65-1.45	
Rectum (1540-1542; 1544-149)	3	0.66	0.13-1.93	
Liver (1550-1551; 1553-1569)	1	0.17*	0.00-0.94	
Pancreas (1570-1579)	17	1.17	0.68-1.87	
Lung (162)	56	0.76*	0.57-0.99	
Bone (170)	2	1.91	0.21-6.90	
Melanoma of Skin (172)	6	1.29	0.47-2.82	
Connective and Soft Tissue (171)	2	0.87	0.10-3.12	
Breast (174)	112	1.68*	1.38-2.02	
Uterine Cervix (180)	3	0.31*	0.06-0.92	
Uterine Corpus (179, 181-182)	8	1.02	0.44-2.00	
Ovary (183)	21	0.99	0.61-1.52	
Kidney (189, 1887)	3	0.55	0.11-1.62	
Bladder (1880-6; 1888-1889)	4	1.34	0.36-3.42	
Eye (190)	0	0.00	0.0-19.31	
Brain and CNS (191-192)	14	1.48	0.81-2.48	
Thyroid (193)	0	0.00	0.00-4.58	
All Lymphoid Malignancies (200-204; 2384)	14	0.66	0.36-1.10	
Hodgkin Disease (201)	2	0.91	0.10-3.29	
Non-Hodgkin Lymphoma (200; 202)	7	0.59	0.24-1.22	
Multiple Myeloma (2030, 2386)	4	0.84	0.23-2.16	
Leukemia and Aleukemia (204-208; 2024, 2031)	10	0.87	0.42-1.60	
CLL§ (2041)	1	0.70	0.01-3.90	
Non-CLL (2040, 2042-2089; 2024, 2031)	9	0.88	0.40-1.67	