Second Neoplasms Working Group

A Report from the Childhood Cancer Survivor Study

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University of Minnesota
June, 2021

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Scope of Research

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- The Second Neoplasm Working Group is charged with oversight of the complete and accurate ascertainment of subsequent malignant neoplasms and selected nonmalignant neoplasms in the CCSS survivor cohort, including details of the histology and tumor location, using submitted medical records.
- The Working Group:
  - Promotes, coordinates and facilitates research to establish the incidence of subsequent neoplasms (SNs)
  - Identifies populations at highest (and lowest) risk
  - Determines host and therapeutic risk factors for SNs
  - Characterizes temporal changes in patterns of SNs.
- The Working Group has had numerous collaborations with other CCSS Working Groups, including Genetics, Chronic Disease, Epidemiology/Biostatistics, and Cancer Control and Intervention

Working Group Membership

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- Joseph Neglia – Univ. of Minnesota
- Lucie Turcotte – Univ. of Minnesota
- Tara Henderson – Univ. of Chicago
- Rebecca Howell – M.D. Anderson
- Constance Owens – M.D. Anderson
- Chaya Moskowitz – Memorial Sloan Kettering
- Mike Arnold – Univ. of Colorado
- Miriam Conces – Nationwide Children's
- Sandy Constine – Univ. of Rochester
- James Edward Bates – Emory
- Greg Armstrong – St. Jude

Working Group Progress

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- Recently Published/In Press Manuscripts
  - Richard MA, et al: Genetic variation in POT1 and risk of thyroid subsequent malignant neoplasm: a report from the Childhood Cancer Survivor Study. PLOS ONE, 2020; 15(2):e0228887. (Genetics Lead)
  - Morton LM et al: Subsequent neoplasm risk associated with rare variants in DNA damage response and clinical radiation sensitivity syndrome genes in the Childhood Cancer Survivor Study, JCO Precis Oncol, 2020; 4(2020)926-936. (Genetics Lead)
  - Moskowitz C et al: Development and validation of a Personalized breast cancer risk prediction model for childhood cancer survivors treated with chest radiation: A report from the Childhood Cancer Survivor Study and the Dutch Hodgkin Late Effects and LATER cohorts. *In press, J Clin Oncol 2021*
- Manuscripts under review
  - Lung Cancer as a Subsequent Malignant Neoplasm in Survivors of Childhood Cancer, Ghosh et al. *under review: Cancer Epidemiology, Biomarkers & Prevention*
  - HPV associated malignancies. Henderson et al. *under review: CEBP 2021*

Working Group Progress - Analysis/Manuscript in Process (Approved Concepts)

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Concept	Author / Institution	Approval Year
Breast Cancer Risk in the Modern Treatment Era	Henderson / Chicago	2017
Late subsequent leukemia after childhood cancer.	Turcotte / Minnesota	2020
Body Mass Index and Risk of Subsequent Neoplasms	Joffe / Columbia	2020
Risk and Risk Factors for Colorectal Cancers in Childhood Cancer Survivors	Henderson / Chicago	2020
Updated epidemiology of secondary CNS malignancy following radiotherapy exposure in childhood cancer survivors	Galvin / Minnesota	2021
Evaluation of subsequent meningiomas in childhood cancer survivors.	Cooney / DFCI	2021
Mortality after Colorectal Cancer Among Survivors of Childhood Cancer	Major / Chicago	2021

New AOIs – Concepts in Development

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Concept	Author/Institution	AOI Submitted
Radiotherapy- and Chemotherapy-Related Risks of Thyroid Cancer	Morton / NCI	March 2021
Melanoma among Adult Survivors of Childhood Cancer	Rotz / Cleveland Clinic	March 2021
Nonmelanoma skin cancers	Boull / Minnesota	January 2021
Subsequent colorectal cancer after a childhood, adolescent or young adult cancer: An international pooled data analysis (Ancillary Study)	Moskowitz / MSKCC	September 2020
Breast Imaging Analysis Among Childhood Cancer Survivors Treated with Chest Radiation (Ancillary Study)	Moskowitz / MSKCC	April 2020

Highlights of Recently Completed Research

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- Henderson et al: Breast Cancer Update
- Wong et al: Cost benefit analysis of screening methods
- Moskowitz et al: Breast Cancer Prediction

Breast Cancer Risk by Treatment Era

A report from the Childhood Cancer Survivor Study

Tara O. Henderson, Qi Liu, Lucie M. Turcotte, Kevin C. Oeffinger, Joseph P. Neglia, Wendy Leisenring, David Hodgson, Lisa Diller, Lisa Kenney, Lindsay Morton, Amy Berrington de Gonzalez, Michael Arnold, Smita Bhatia, Rebecca Howell, Susan Smith, Leslie L. Robison, Gregory T. Armstrong, Yutaka Yasui, Chaya S. Moskowitz

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Results - Demographics

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Among 11,550 female survivors (median age 30.5 y, range 5.6-65.9 y), 361 females developed 428 breast cancers:

- 319 invasive (109 *in situ*)
- Median age at breast cancer diagnosis 39.5 y, range 19.9-58.8 y

Note: Lisa Kenny's Ann Int Med paper in 2004 reported on 95 women and 111 cases and we now have over 650 breast cancers in the cohort

Results: Primary Diagnoses of Women with Breast Cancer (N=361)

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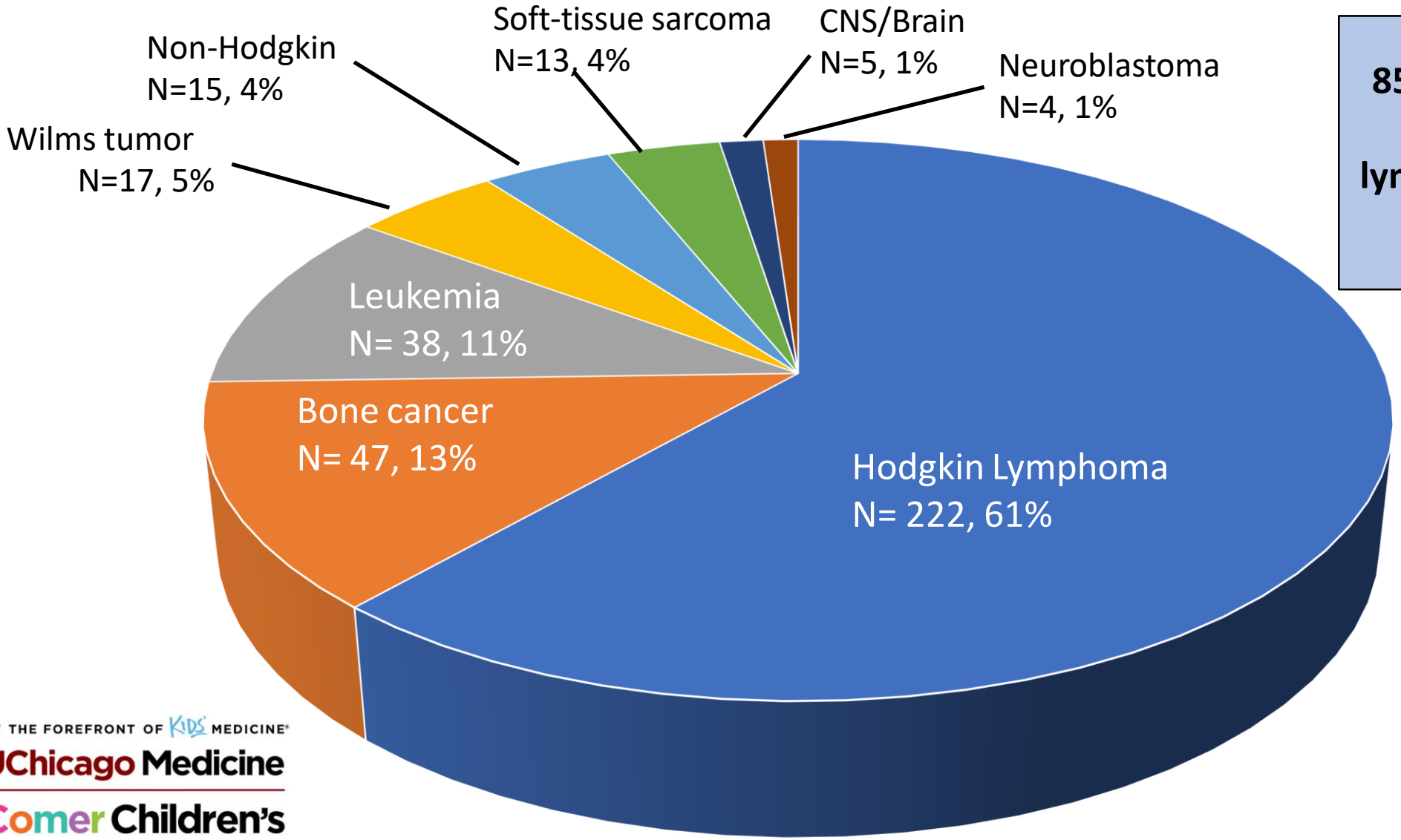

85% were survivors of Hodgkin lymphoma, leukemia or bone cancer

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Results: Survivors exposed to chest RT by treatment era (women only)

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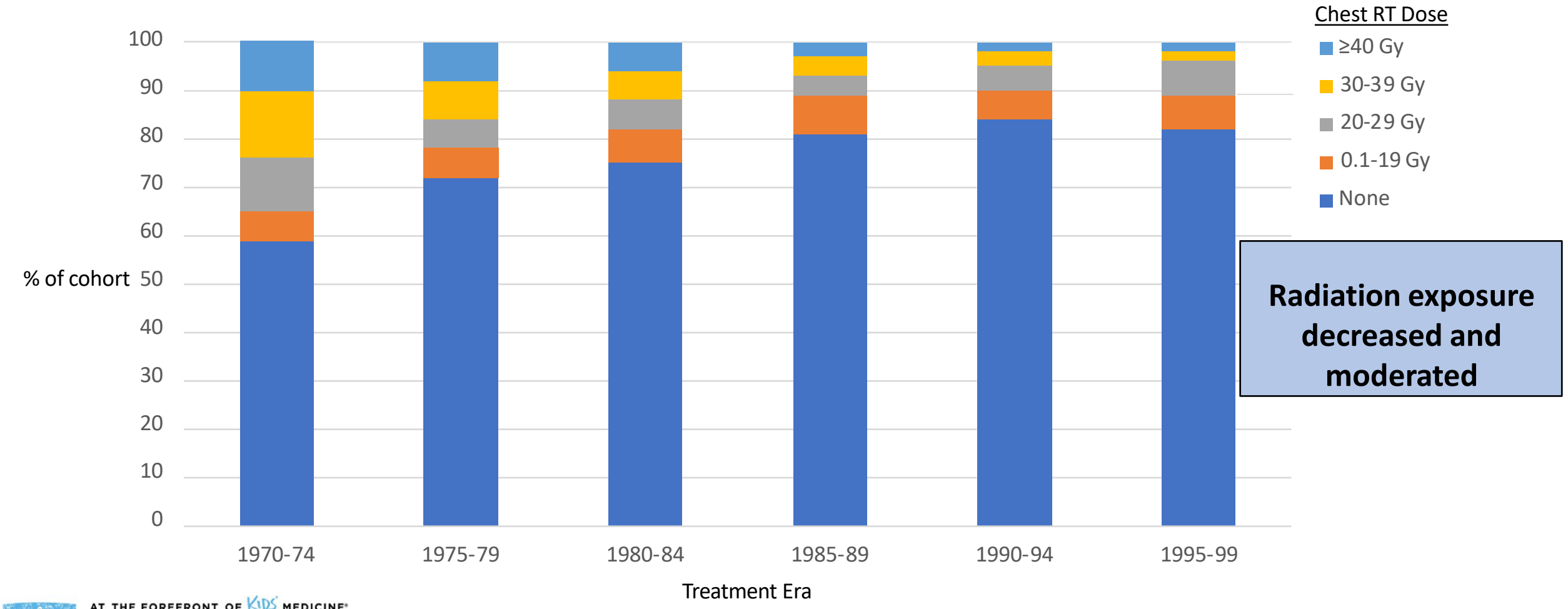

Radiation exposure decreased and moderated

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Results: Survivors exposed to anthracyclines by treatment era

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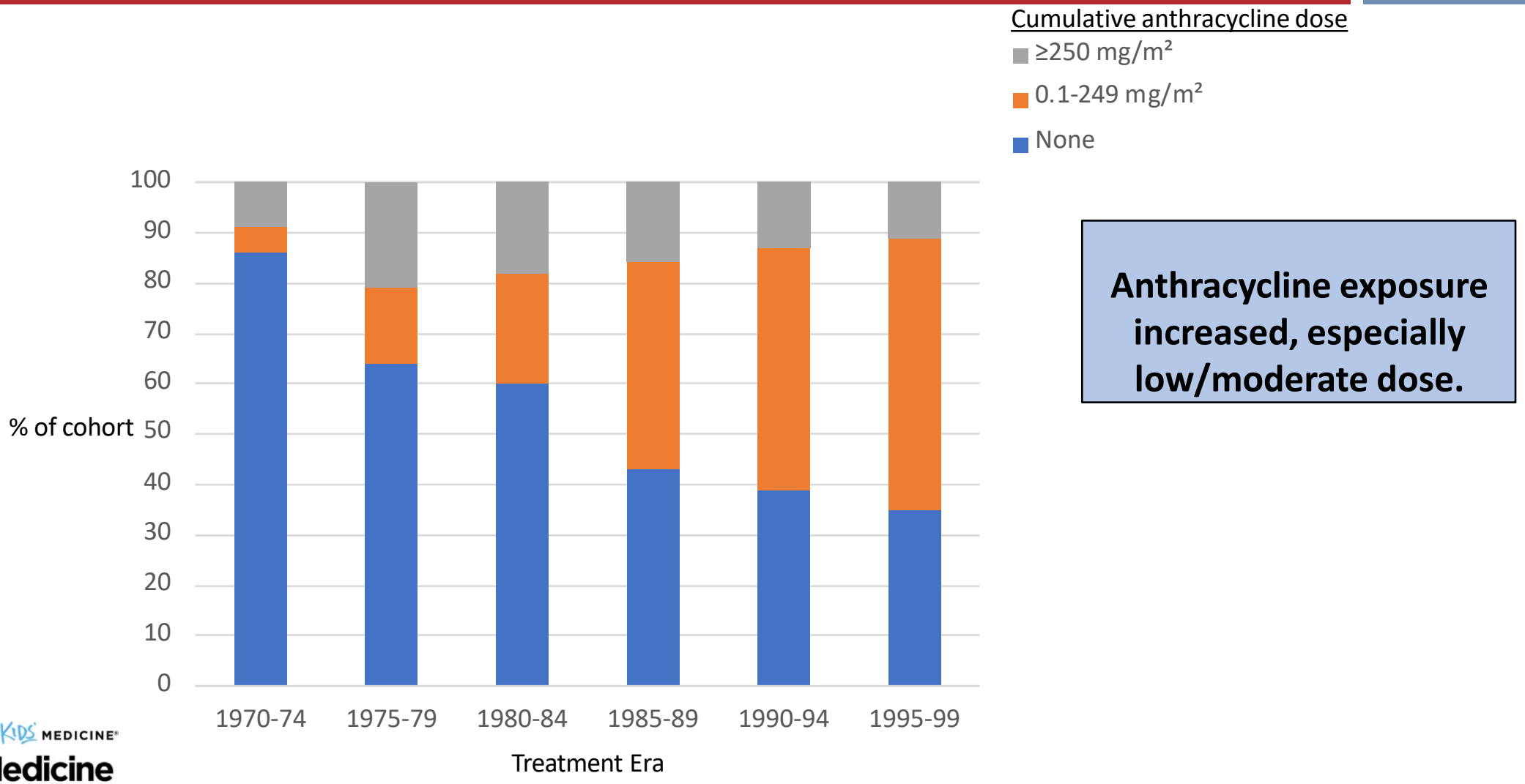

Anthracycline exposure increased, especially low/moderate dose.

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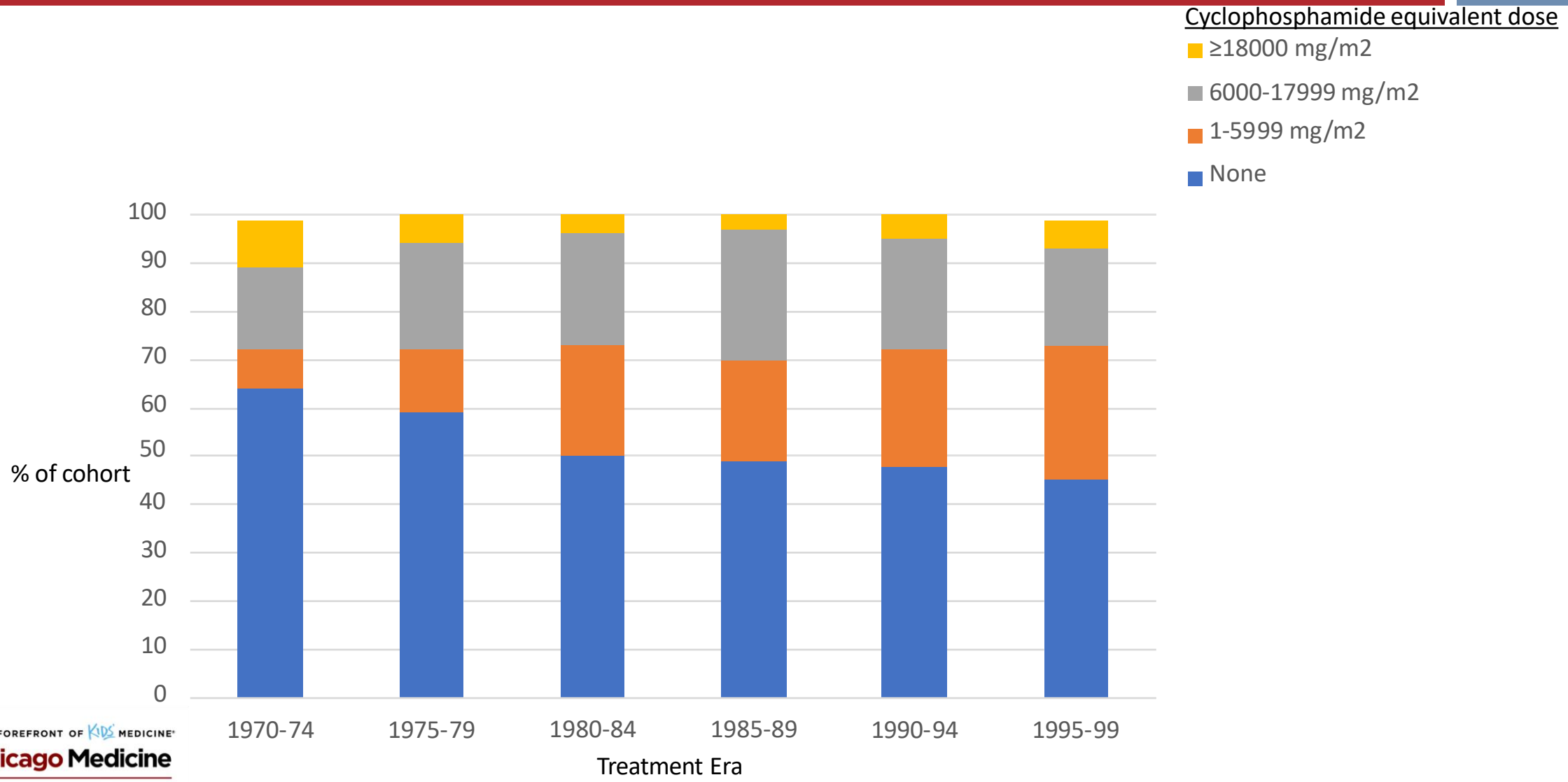
Results: Survivors exposed to alkylators by treatment era



Cumulative Incidence (CI) of Breast Cancer by Treatment Decade (All Primary Cancers)

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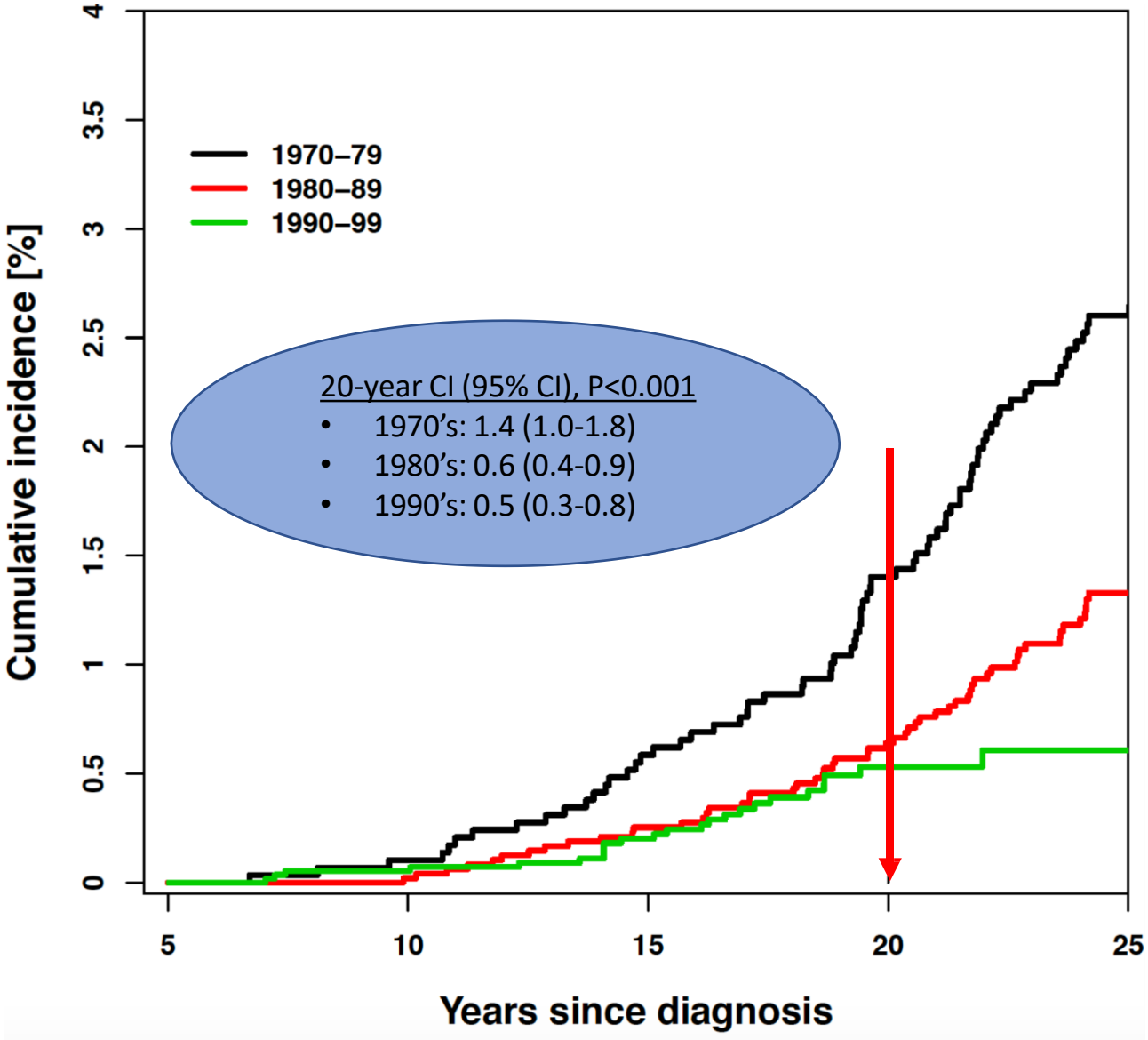

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Multivariable analysis: anthracyclines are associated with higher breast cancer rates

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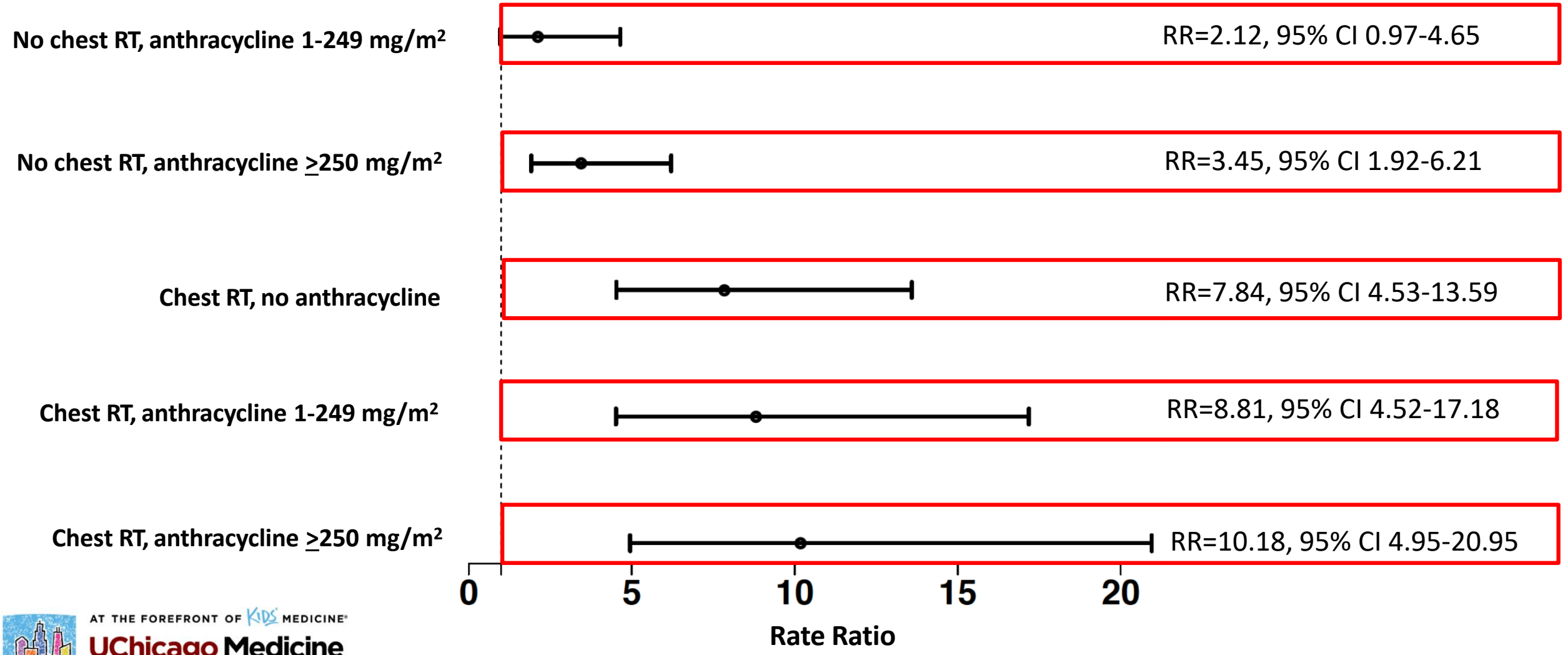

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* Ref: No chest RT and no anthracyclines

** Model adjusted for: attained age, age at dx, year of dx (5-year interval), CED dose, pelvic RT Y/N

Modeling of Breast Cancer Trends with Time

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	No treatment adjustment	Adjusted for chest RT	Adjusted for all treatment*
RR every 5 years (95% CI)	0.79 (0.70-0.90)	0.88 (0.77-1.00)	0.84 (0.73-0.97)
p-value	<0.001	0.06	0.01

***Treatment includes chest RT, pelvic RT, anthracyclines, alkylating agents**

After adjusting for treatment exposures, we still observe a decrease in breast cancer risk over time.

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Conclusions

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- Breast cancer rates in more recently treated childhood cancer survivors are lower
  - Largely due to the reduced use of chest RT
  - Tempered by the concurrent increased use of anthracycline chemotherapy
- Future work should focus on the breast cancer rate decline unexplained by these changes in treatment exposures.

Next steps

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Although breast cancer risk has lessened we still must screen and counsel or long-term survivors:

- *Cost effective screening strategies (Lennie Wong)*
- *Individual counseling (Chaya Moskowitz)*

Efficacy and cost-effectiveness of annual breast cancer screening. *Wong et al.(ASCO 2021)*

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- Investigating efficacy and cost effectiveness of COG's image-based screening recommendations
- Estimated from simulated lifetimes of 5M chest irradiated HL survivors who were screened by:
  - Annual digital mammogram
  - Annual Digital breast tomosynthesis (DBT)
  - MRI
  - DBT + MRI
  - Mammogram + MRI
- Treatment related breast cancer risk and non breast ca mortality were estimated from Hodgkin Lymphoma Survivors in the CCSS

Efficacy and cost-effectiveness of annual breast cancer screening (ASCO 2021)

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Screening strategy	LY gained	BC mortality reduced (%)	Cost (2017 US$)	QALYs	ICER (*vs* no screening)	ICER (*vs* comparator £)
No screening	REF	REF	95,073	16.576	NA	NA
MAM	0.35	7.0	99,477	16.651	58,726	58,726 !
MRI	0.34	6.7	107,035	16.652	157,625	Dominated ¥
DBT	0.38	8.1	100,393	16.659	65,686	65,686 !
MAM+MRI	0.46	9.7	109,726	16.678	144,222	385,285 *
DBT+MRI	0.47	9.8	112,699	16.680	170,646	551,843 #

£Comparator: ! No screening, * MAM, # DBT. ¥ More expensive and less effective than DBT

ICER: Incremental Cost Effectiveness Ratio (cost per QALY gained)

Efficacy and cost-effectiveness of annual breast cancer screening (ASCO 2021)

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- Conclusions:
  - Annual screening is beneficial as measured by life-years gained and breast cancer deaths reduced
  - Annual mammogram or digital breast tomosynthesis (DBT) are most cost effective compared to no screening, both with Incremental Cost Effectiveness Ratio of < $100,000
  - Addition of MRI to mammogram or DBT was not cost-effective

Predicting breast cancer risk in childhood cancer survivors treated with chest radiation

A Report from the Childhood Cancer Survivor Study (CCSS) and the Dutch Hodgkin Late Effects and LATER Cohorts

Chaya S. Moskowitz, Joanne F. Chou, Cecile M. Ronckers, Susan A. Smith, Danielle Friedman, Dana Barnea, Simone de Vries, Judith Kok, Suzanne L. Wolden, Tara O. Henderson, Helena J. H. van der Pal, Leontien C.M. Kremer, Joseph P. Neglia, Lucie M. Turcotte, Rebecca M. Howell, Michael A. Arnold, Michael Schaapveld , Berthe Aleman , Cecile Janus, Birgitta Versluys, Wendy Leisenring, Charles A. Sklar, Colin B. Begg, Leslie L. Robison, Malcolm C. Pike, Gregory T. Armstrong, Flora E. van Leeuwen, Kevin C. Oeffinger on behalf of the CCSS, Dutch LATER and Dutch Hodgkin Lymphoma Late Effects Groups

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Childhood Cancer Survivor Study

Memorial Sloan Kettering Cancer Center

Supported by the National Cancer Institute (R01CA136783; U24CA55727), the Meg Berté Owen Fund, and the American Lebanese Syrian Association Charities

Individual Probability of Breast Cancer

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- There are risk factors known to modify breast cancer risk
  - e.g. chest RT field (size) and chest RT dose to the breast tumor site estimated from dosimetry
- Probability of an individual developing breast cancer is **unknown**
- Variation in probability across childhood cancer survivors **unknown**

Goal

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- Develop a breast cancer risk prediction model applicable to childhood cancer survivors treated with chest RT
- Incorporate treatment exposures, reproductive factors, and other potential risk factors

Model Validation Data

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- Diagnosed 1987-1999
- 600 females with chest RT, 23 with breast cancer

Dutch LATER cohort

- 5-year survivors diagnosed 1963-2001 before age 21
- 238 females with chest RT, 22 with breast cancer

Dutch Hodgkin Late Effects Cohort

- 5-year survivors of HL diagnosed 1965-2000 before age 21
- 226 females with chest RT, 61 with breast cancer

Risk Factors Evaluated

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Treatment-related factors

- Chest RT prescribed dose
- Chest RT fields (field size)
- Ovarian RT
- Alkylating agent chemotherapy
- Anthracycline chemotherapy
- Age at diagnosis
- Childhood cancer diagnosis

Gail Model factors

- Age
- Age at menarche
- Age at first live-birth
- Family history of breast cancer
- Biopsy with atypical hyperplasia

Other factors

- Race
- Age at menopause
- Years of intact ovarian function
- Hormone therapy
- BMI
- Chest RT near menarche

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	
Chest RT field (dose):	
Menopausal status:	
Anthracyclines:	
Chest RT within 1 year of menarche:	
Family history:	

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	
Menopausal status:	
Anthracyclines:	
Chest RT within 1 year of menarche:	
Family history:	

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	
Anthracyclines:	
Chest RT within 1 year of menarche:	
Family history:	

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	
Chest RT within 1 year of menarche:	
Family history:	

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	No
Chest RT within 1 year of menarche:	
Family history:	

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	No
Chest RT within 1 year of menarche:	No
Family history:	

Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	No
Chest RT within 1 year of menarche:	No
Family history:	No

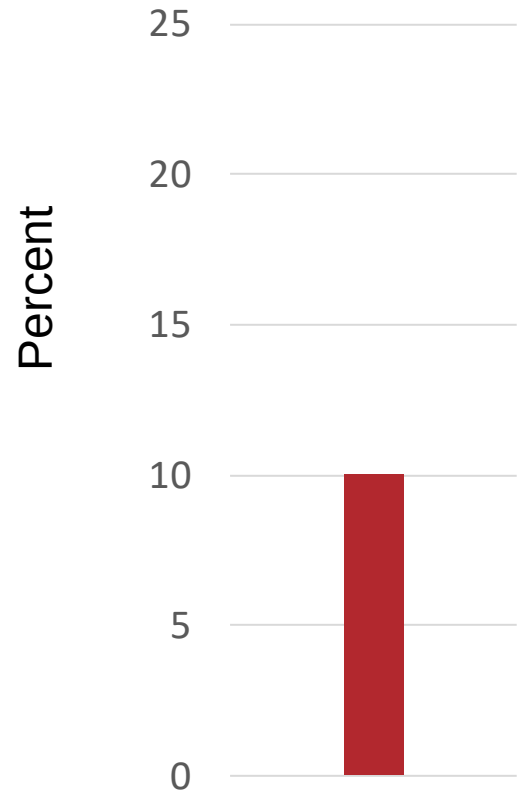
Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	No
Chest RT within 1 year of menarche:	No
Family history:	No

Risk of breast cancer by age 40: **10%**



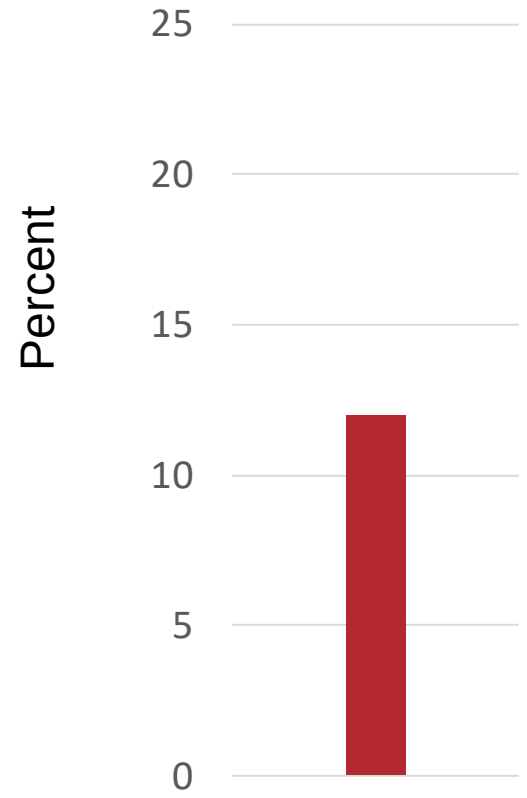
Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	Yes
Chest RT within 1 year of menarche:	No
Family history:	No

Risk of breast cancer by age 40: **12%**



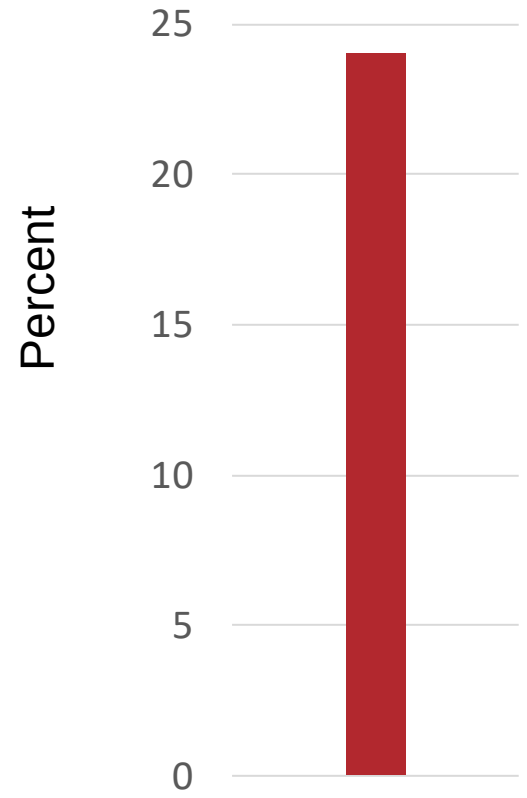
Risk Profiles

CCSS

Female childhood cancer survivor presenting to her physician with the following history:

Current age:	30
Chest RT field (dose):	Mantle (36 Gy)
Menopausal status:	Still menstruating
Anthracyclines:	Yes
Chest RT within 1 year of menarche:	Yes
Family history:	Yes

Risk of breast cancer by age 40: **24%**



Conclusions

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- Risk of breast cancer tends to be very high in childhood cancer survivors treated with chest RT
- There is variation in this risk with some childhood cancer survivors having lower risk
- Model performance is in-line with model performance of other breast cancer prediction models used in practice with other populations

Ancillary Studies

CCSS

- Lucie Turcotte: Treatment Modifications and Provider Decision Making in the Management of Subsequent Breast Cancers Among Survivors (K08 Award)
  - Cases assembled from CCSS N=432
    - 90% of cases with complete data at this time
  - Control selection underway at U of MN and will include U Chicago & Duke
  - Case data abstracted

Ancillary Studies

CCSS

- Principal Investigator: Cecile Ronckers (Princess Maxima Center for Pediatric Oncology, Utrecht): Title: Risk Factors for Female Breast Cancer After Treatment for Childhood and Adolescent Cancer: An Individual Patient Data Analysis
  - Dates of Funding: 7/18-6/21, Funding Source: Kika Foundation
  - Study Aims: 1) Establish an internationally pooled and harmonized database for breast cancer outcomes, 2) Answer three questions identified by the International Harmonization Guidelines:
    - Risk for subsequent breast cancer including risk <20Gy
    - Risk associated with anthracycline exposure
    - Aattained age >50 years.

Ancillary Studies – Proposed

CCSS

- Chaya Moskowitz (Memorial Sloan Kettering), Kevin Oeffinger (Duke University) - Title: Evaluation of Breast Imaging of Childhood, Adolescent, and Young Adult Survivors Treated with Chest Radiation
  - Study Aims: 1) Characterize qualitative and quantitative imaging features and radiologists' performance on mammography and breast MRI in women with a history of chest radiation therapy for a childhood, adolescent, or young adult cancer, and 2) Develop models to predict breast cancer risk among women with a history of chest radiation therapy for a childhood, adolescent, or young adult cancer.
  - Status: Submitted October 2020, unscored; Resubmission planned for July 2021.
- Chaya Moskowitz (Memorial Sloan Kettering) & Tara Henderson (University of Chicago): Title: International Study of Subsequent Colorectal Cancer Among Survivors of Childhood, Adolescent, and Young Adult Cancers (I-SCRY)
  - Study Aims: Evaluate the risk and risk factors for colorectal cancer.
  - Status: Submitted March 2021

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for second neoplasms based on temporal changes in primary therapy
- Identify genetic susceptibility for specific subsequent neoplasms that modifies risk conferred by therapeutic exposure
- Utilize the large CCSS cohort to identify high-risk populations among aging survivors
- Describe SN treatment and treatment toxicities.

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for second neoplasms based on temporal changes in primary therapy
- Identify genetic susceptibility for specific subsequent neoplasms that modifies risk conferred by therapeutic exposure
- Utilize the large CCSS cohort to identify high-risk populations among aging survivors
- Describe SN treatment and treatment toxicities.

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for second neoplasms based on temporal changes in primary therapy
  - Concept: Body Mass Index and Risk of Subsequent Neoplasms approved and work is underway (Lenat Joffe, Lucie Turcotte, et al)
  - Updates / variations on prior reports are progressing
    - Breast Cancer
    - CNS Malignant Tumors
    - Meningioma
    - Melanoma
    - NMSC
    - Colon cancer
    - Thyroid cancer
  - International Collaboration with Dutch
  - Proposal for collaborative chemo-only analysis with European groups

Five Year Plan: Progress Update

CCSS

- Identify genetic susceptibility for specific subsequent neoplasms that modifies risk conferred by therapeutic exposure
  - Work is led by genetics working group
  - SMN group available for path reviews, study design and interpretation

Five Year Plan: Progress Update

CCSS

- Utilize the large CCSS cohort to identify high-risk populations among aging survivors
  - Concept under discussion (Turcotte / Neglia)

- Describe SN treatment and treatment toxicities.
  - Turcotte K08 ancillary study previously discussed

SN Reviews

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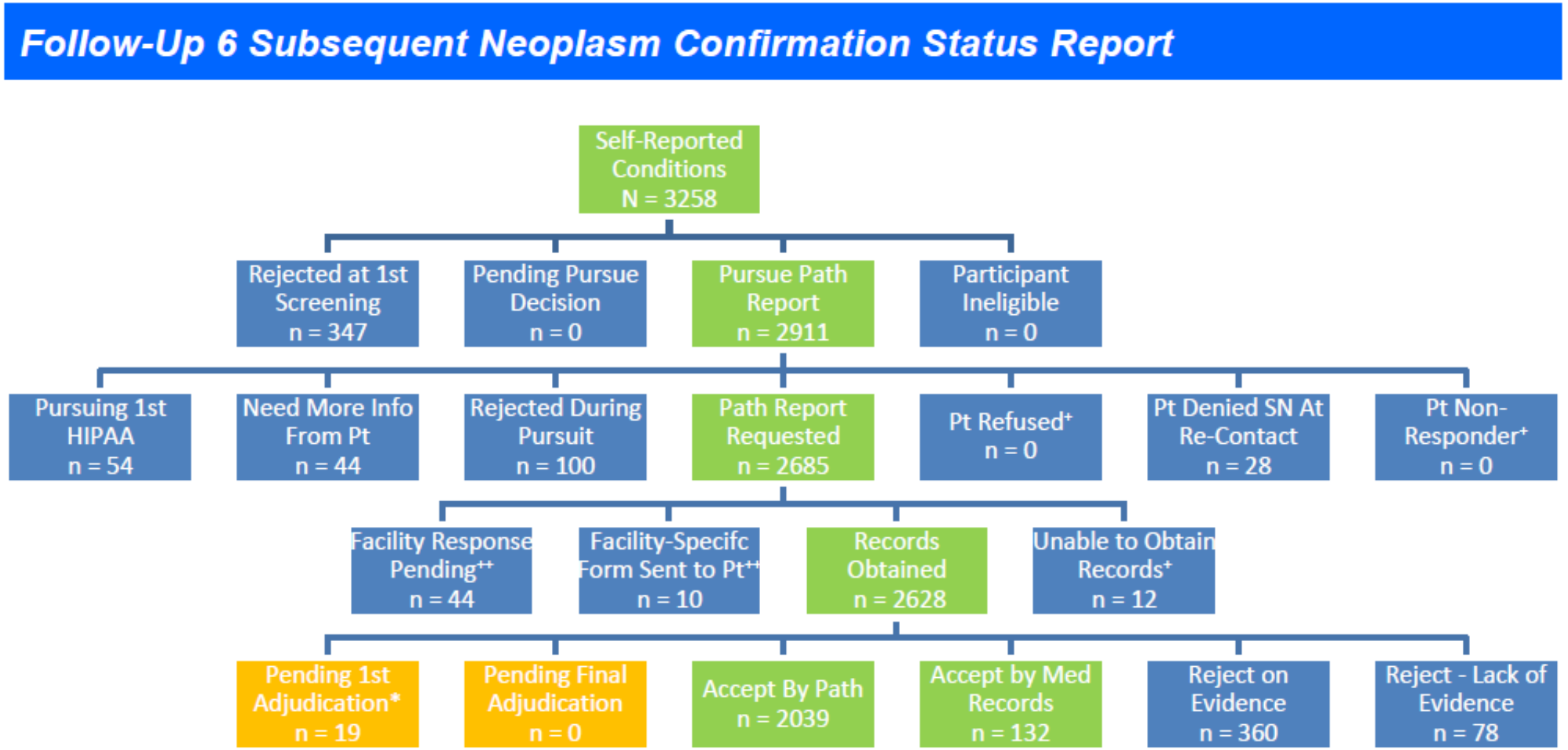

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Discussion: Opportunities and Threats

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- Major Threat or Challenge:
  - Time intensive case review process
  - Limited number of "classic" questions reduces appeal to young investigators – involvement with genetics group critical

- Major Opportunity:
  - VPR
  - International Collaborations

Discussion

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