



THE WOMEN'S
HEALTH INITIATIVE

The Long Life Study and LLS2: Overview, Design, Participants

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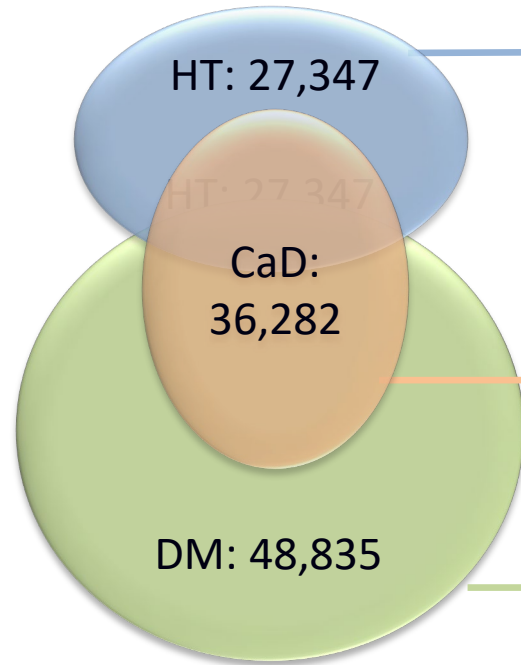
Professor, Bus Family Endowed Chair

Fred Hutchinson Cancer Center



Fred Hutch
Cancer Center

Partial factorial Clinical Trial



Hormone Therapy Trials Outcomes:

- Primary: Coronary Heart Disease
- Secondary: Hip Fracture
- Safety: Breast Cancer

Calcium/Vitamin D Trial Outcomes:

- Primary: Hip fractures
- Secondary: Colorectal Cancer

Dietary Modification Trial Outcomes:

- Primary: Breast Cancer and Colorectal Cancer
- Secondary: Coronary Heart Disease

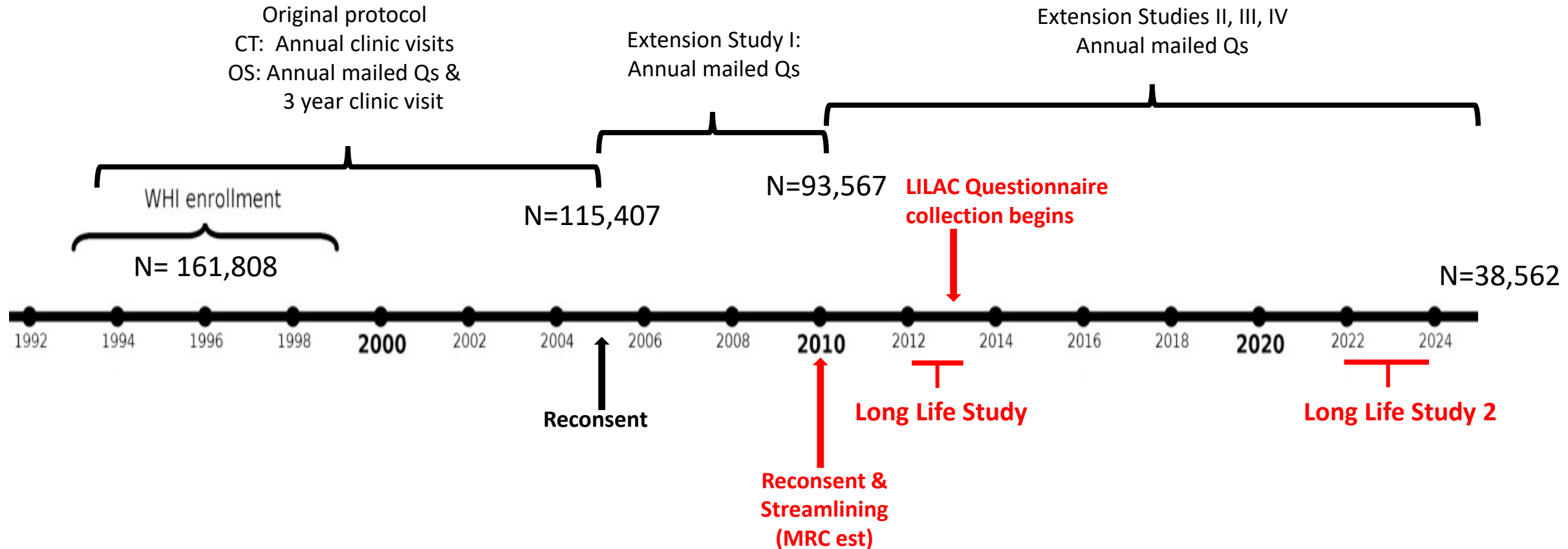
Observational Study



Observational Study

Total: 161,808 women

WHI Timeline

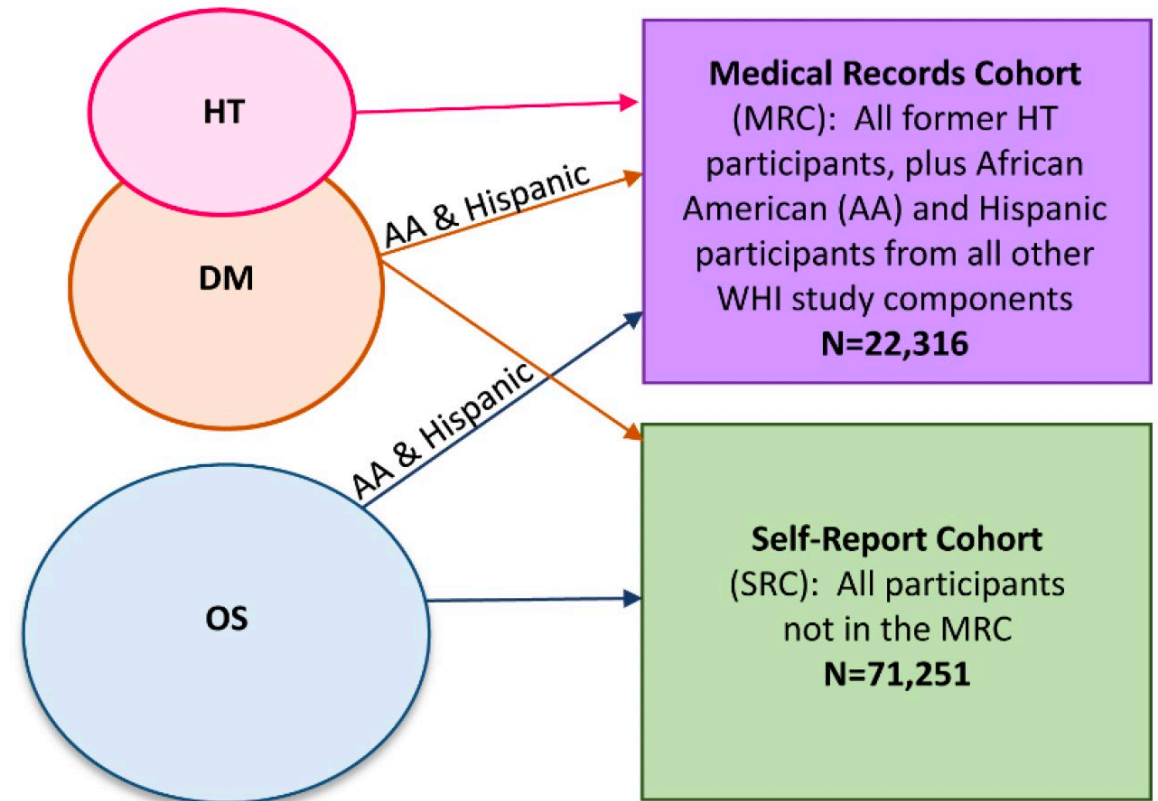


Long-Life Study (LLS)

- **Goal:** Develop a resource to support studies of healthy aging and examining changing levels of intermediate markers of CVD risk on subsequent clinical events

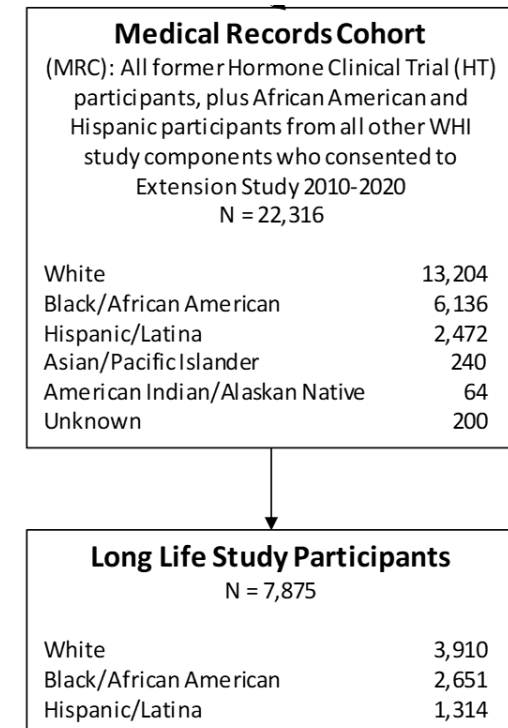
Medical Records Cohort (MRC)

- Established in 2010 with the WHI 2010-2015 Extension Study II
- Included:
 - Former HT trial participants
 - All African American and Hispanic participants from other study components
- Full outcomes ascertainment: adjudicated outcomes (primarily cardiovascular events, hip fracture, deaths)



Long-Life Study (LLS)

- **Goal:** Develop a resource to support studies of healthy aging and examining changing levels of intermediate markers of CVD risk on subsequent clinical events
- **Eligibility:** Medical Record Cohort (MRC) members
 - GWAS data
 - CVD biomarker data from study baseline
 - Oversampled older women



LLS Home Visit Data Collection

- Physical measurements: height, weight, blood pressure, pulse, waist circumference
- Grip strength
- Short Performance Physical Battery (SBBP) components:
 - Balance tests
 - Timed walk
 - Chair stand
- Fasting blood draw
 - CVD biomarkers (n=7325, 93%): glucose, insulin, creatinine, CRP, HDL, LDL, triglyceride, cholesterol
 - CBC (n=7406, 94%): 26 variables including hematocrit, hemoglobin, WBC/RBC/platelets, WBC differential
- Stored Blood: Serum, EDTA plasma, RBC, extracted DNA and RNA

LLS Participant Characteristics and Outcomes (n=7875)

Participant characteristics

Age at visit

63-69	724	9.2%
70-79	3050	38.7%
80-89	3689	46.8%
≥90	412	5.2%

Race

White	4877	61.9%
Black	2517	32.0%

Ethnicity

Hispanic	1277	16.2%
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Study component

Clinical trial	5956	75.6%
Observational Study	1919	24.4%

Vital Status/Participation

	N	%
Deceased	4293	54.5%
Alive: Current/Recent Participation	3156	40.1%
Alive: Past/Unknown	1	<0.1%
Stopped or Lost to Follow-up	425	5.4%

Selected Verified Outcomes after LLS Visit

	N
CHD	802
Total CVD	2779
Breast Cancer	317
Total Cancer	1171
Hip Fracture	490



Life & Longevity After Cancer (LILAC)

• Goals:

- Obtain cancer treatment information and long-term cancer outcomes for women diagnosed with 1 of 8 selected cancers
- Obtain fixed tumor tissue for cancers diagnosed since 2002

• Case Eligibility

- No cancer prior to WHI enrollment
- Confirmed first adjudicated invasive breast, endometrial, ovarian/fallopian/peritoneal, lung, colorectal, melanoma, lymphoma, or leukemia during study follow-up

• Case Exclusion criteria:

- Cancer other than the selected types
- Cancer prior to WHI baseline

LILAC cancer cases (N=17,128)

<u>Diagnosis year</u>		
<2000	1828	11.1%
2000-2004	5076	29.6%
2005-2009	4120	24.1%
2010-2014	3298	19.2%
2015-2019	2185	12.8%
2020-2022	621	3.6%
<u>Enrollment type</u>		
Consent	9835	57.4%
Partial waiver	7293	42.6%



Life & Longevity After Cancer (LILAC)

- Treatment data
 - Medical record abstraction and Medicare claims data
- Questionnaire data
 - Baseline questionnaire (Form 340)
 - One-year annual survey (Form 370)
 - Annual follow-up survey (Form 371)
- Cancer free controls (up to 5 per case)
 - Alive and free of cancer at time of cancer diagnosis (risk-set sampling)
 - Matched on:
 - Age (+/- 1 year)
 - WHI enrollment date
 - CT/OS
 - HT enrollment
 - LLS1 enrollment

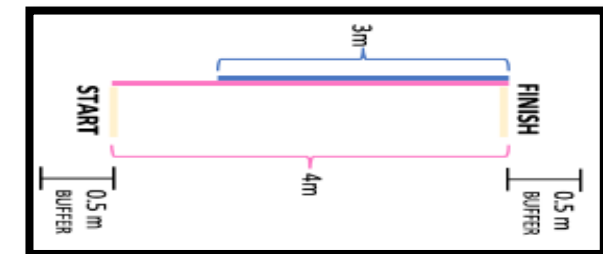
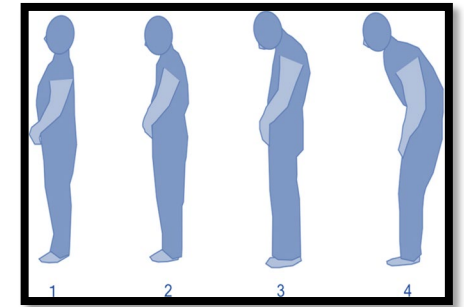
Cancer type		
Breast	7813	45.5%
Colorectal	2015	11.7%
Endometrial	1260	7.3%
Ovarian/FT/PP	945	5.5%
Lung	2383	13.9%
Melanoma	889	5.2%
NHL/MF	1187	6.9%
Leukemia	659	3.8%

Long-Life Study 2 (LLS2)

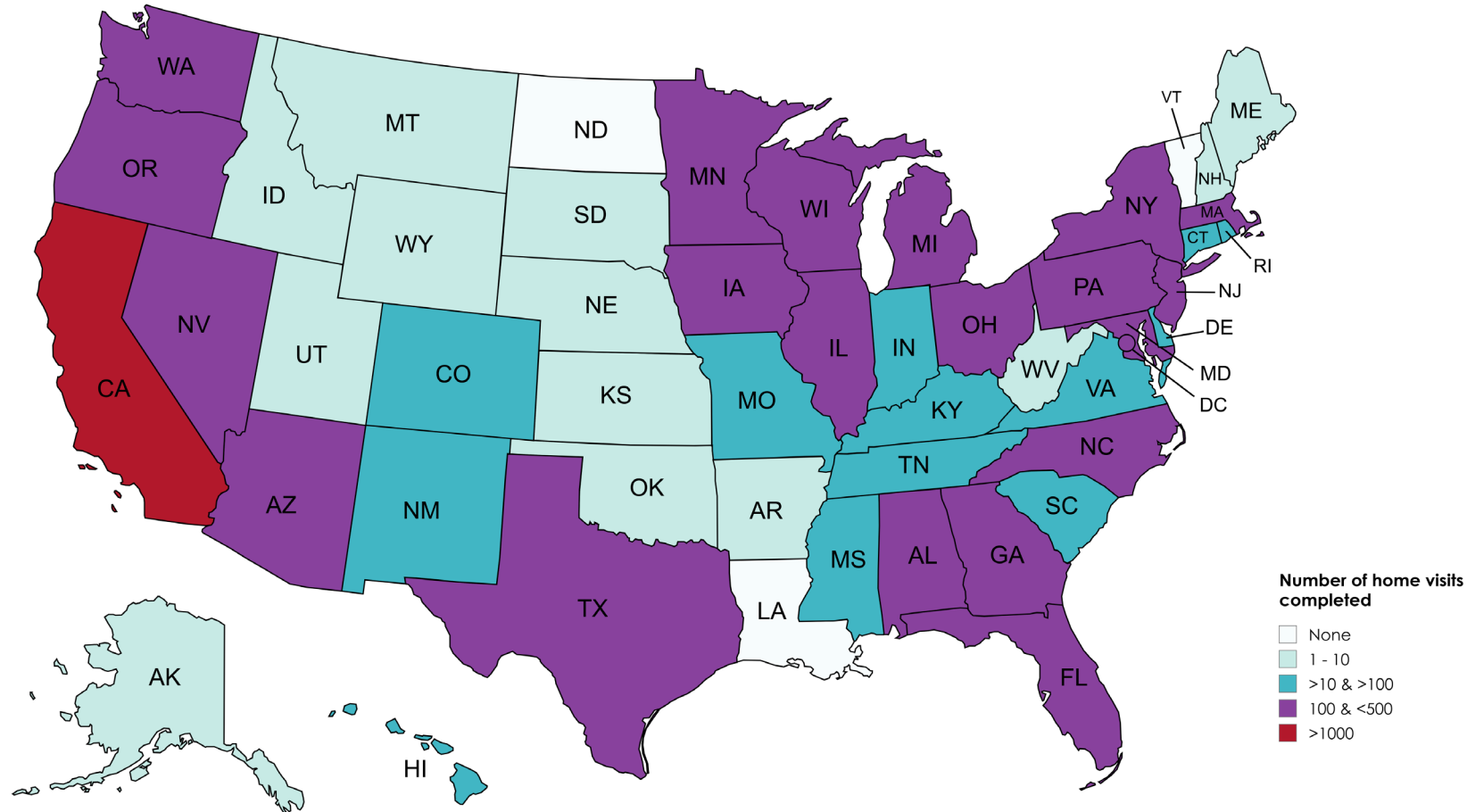
- Designed to repeat the LLS protocol (home visits conducted by ExamOne)
- Eligibility (n=15,885 → 7508 consented → 5905 completed home visit)
 - All living LLS participants (4172 → 2214 consented → 1837 completed visit)
 - Expanded to all MRC participants (6579 → 2214 consented → 2039 completed visit)
 - LILAC participants (5104 → 2655 consented → 2029 completed visit) (LILAC-LLS)
- Exclusion criteria:
 - Unable to provide informed consent
 - Residing in an institution

Long-Life Study (LLS2)

- Home visit protocol
 - Physical measurements: height, weight, blood pressure, pulse, waist circumference, kyphosis
 - Physical functional measurements: balance, gait speed (timed walk), chair stand, grip strength (SPPB)
 - Vision exam (n=3699, 99.2%)
 - Fasting blood draw (n=5541, 94%)
 - CVD biomarkers (n=5438): glucose, insulin, creatinine, CRP, HDL, LDL, triglyceride, total cholesterol
 - CBC (n=5173): variables including hematocrit, hemoglobin, WBC/RBC/platelets, WBC differential
- Stored LLS Blood: Serum, EDTA plasma, extracted DNA and RNA



Home Visits Completed by State



LLS2 Participant Characteristics and Outcomes (n=5905)

Participant characteristics (n=5905)

<u>Age at visit</u>		
75-79	722	12.2%
80-89	3997	67.9%
90-99	1156	19.6%
≥100	30	0.5%
<u>Race</u>		
White	4581	77.6%
Black	1053	17.8%
<u>Ethnicity</u>		
Hispanic	492	8.3%
<u>Study component</u>		
Clinical trial	3958	67.0%
Observational Study	1947	33.0%

<u>Vital Status/Participation</u>	<u>N</u>	<u>%</u>
Deceased	447	7.6%
Alive: Current/Recent Participation	5344	90.5%
Alive: Past/Unknown	2	<0.1%
Stopped or Lost to Follow-up	112	1.9%

<u>Selected Verified Outcomes after LLS2 Visit</u>	<u>N</u>
CHD	56
Total CVD	225
Breast Cancer	33
Total Cancer	133
Hip Fracture	49

Cancer cases in LLS2

Prevalent cancer	Number (%)
Colorectal Cancer	191 (9.4%)
Endometrial Cancer	223 (11.0%)
Breast Cancer (invasive)	1266 (62.4%)
Leukemia Cancer	1 (4.7%)
Lung Cancer	96 (4.7%)
Lymphoma (non-Hodgkins)	58 (2.9%)
Melanoma of the Skin	165 (8.1%)
Ovarian Cancer/FT/PP	22 (1.3%)
Sezary (T-cell Lymphoma)	1 (0.0%)

Incident cancer	Number
Colorectal Cancer	11
Breast Cancer (invasive)	28
Total Cancer	133

Ancillary Studies to LLS and LLS2

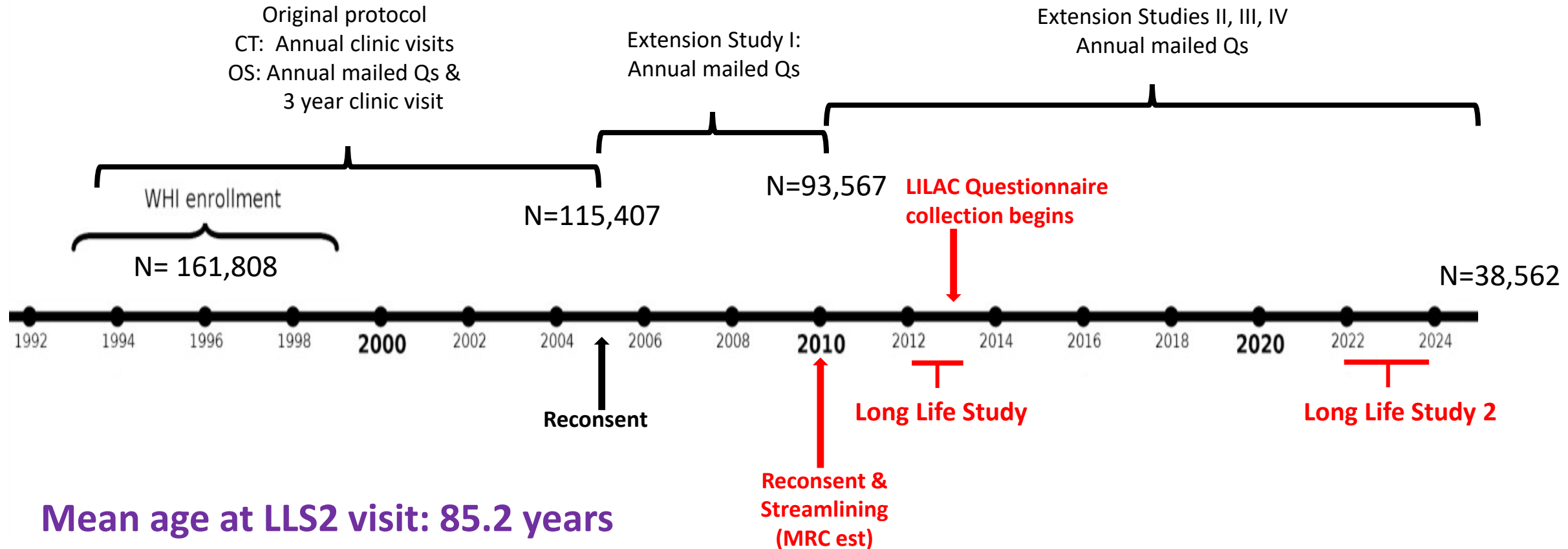
LLS

- Objective Physical Activity & Cardiovascular Health in Women (OPACH) (LaCroix) - Data collected included 1-week accelerometer data and sleep log, physical activity questionnaire, and falls calendar form every month for a year
- WHI-Food Intake Study (WHI-FI) (Beasley) - 6094 FFQs

LLS2

- OPACH2 (LaCroix, LaMonte) - Second accelerometer measurement, plus heart rate, $VO_{2\max}$
- Ms. LILAC (Banack) - Characterized muscle mass (D3-method) in cancer survivors and non-cancer controls
- WHISH trial (Kooperberg, Stefanick, LaCroix)
- WHI Vision Impairment Project (VIP Study) (Gower)

LLS and LLS2 are a unique resource to study aging



Mean age at LLS2 visit: 85.2 years
24+ years of longitudinal data

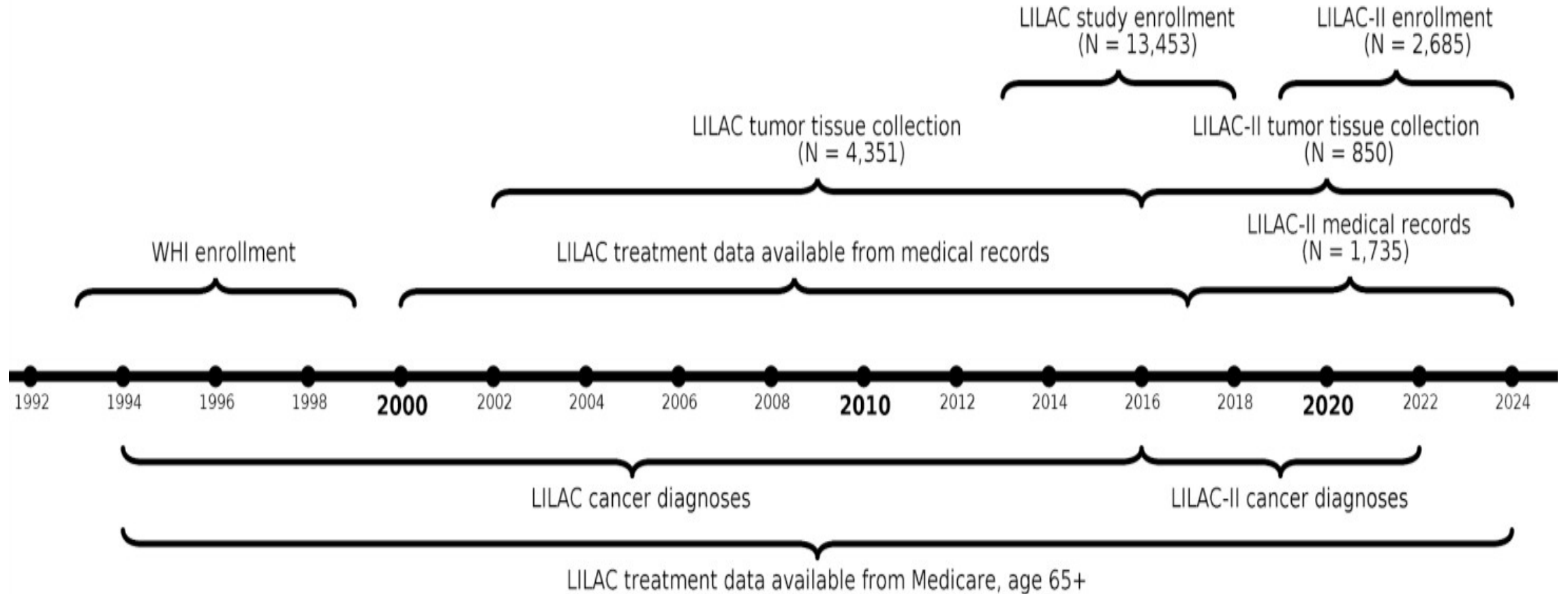
Funding

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- LLS HHSN268201100046C
- LILAC (LILAC1 UM1CA173642 NCI and LILAC2 U01CA173642 NCI)
- LLS2 75N9201R0030

Thank you



LILAC timeline



Comparison of Metabolic Syndrome Scores between Older Women with and without a Cancer History in the WHI Long Life Study 2

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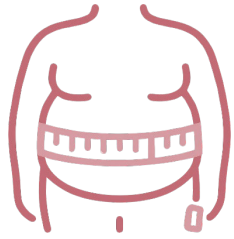
Department of Internal Medicine

The Ohio State University

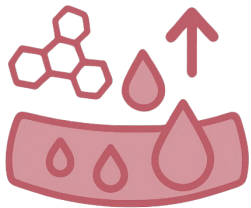
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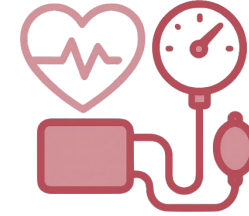
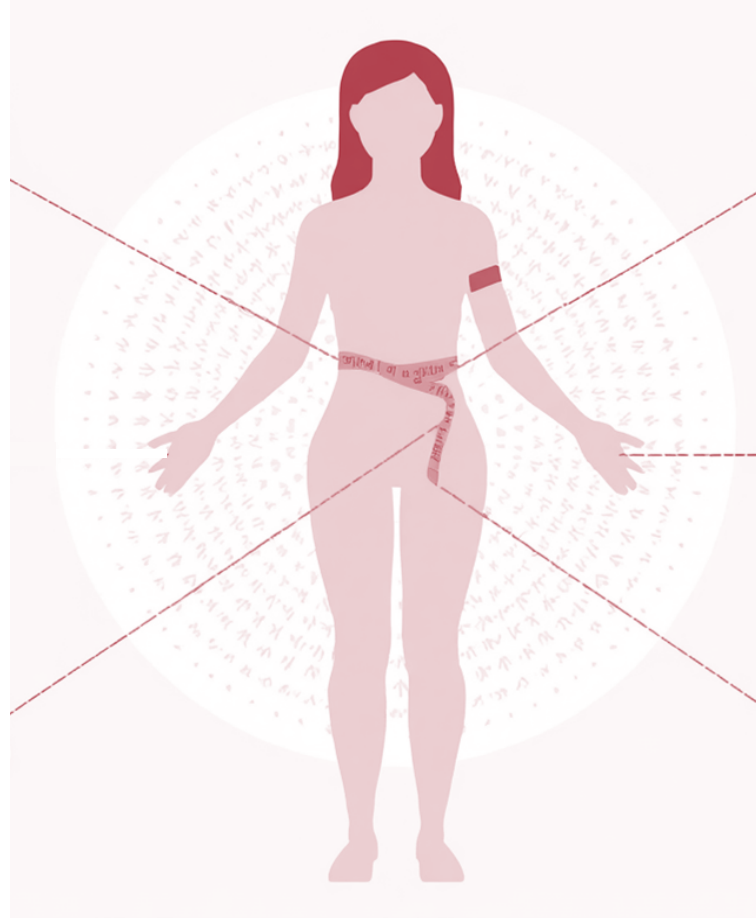
Metabolic Syndrome (MetS) ≥ 3 factors



Abdominal obesity



High triglyceride



High blood pressure



High fasting glucose



High HDL



MetS and Cancer

- Cancer treatment increases risk of MetS:



Chemo



Radiation



Endocrine
therapy



Weight gain
Insulin resistance
Dyslipidemia

- MetS increases the risk of cancer recurrence and mortality:

- Breast cancer recurrence: ↑ 50-200%
- Breast cancer mortality : ↑ 19-207%
- Colorectal cancer mortality: ↑ 50-248%
- Endometrial cancer mortality: ↑ 28-98%
- All cancer mortality: ↑ 22-33%

Cancer Survivors: A Growing Population with Age

Cancer survivors represent:

14.5% of women aged 65-74 years

19.7% of women aged 75-84 years

36.4% of women aged 85+ years



MetS and Aging

- Prevalence of MetS increases with aging
 - By age ≥ 60 , 40-60% women have MetS
- Among older women, MetS increases risk of:
 - Cardiovascular disease
 - Functional decline and frailty
 - Cognitive impairment
- Among older cancer survivors, MetS may accelerate aging phenotypes

Research Gap

- Most studies on metabolic syndrome in female cancer survivors have focused on *a single cancer site* and included *younger* survivors
- There is a need to clarify whether specific cancer sites or treatments are differentially associated with poor metabolic health among older women



Objectives

- Examine differences in ***MetS composite score*** and ***individual components*** between women with and without a history of cancer
- Identify whether specific ***cancer sites*** or ***treatments*** have greater associations with MetS composite score and individual components among women with a cancer history



Inclusion criteria

The LILAC Study
Life and Longevity after Cancer



- Women who participated in WHI LLS2 study
- Completed blood draws
- Cases: LILAC participants in LLS2 who completed form 340 and have treatment information from medical record abstraction **n=1574**
- Controls: LILAC matched controls without cancer **n=1863**

***Note:** Selection process for cancer matched controls: Women diagnosed with cancer were matched with up to 5 cancer-free WHI participants. Matching factors included: age at enrollment, WHI enrollment date, CT/OS enrollment, Hormone Therapy (HT) enrollment, and Long Life Study (LLS) enrollment. All the controls matched exactly on CT/OS, HT Trial, LLS enrollment with their corresponding cases and age was matched within one year. WHI enrollment data matched within 30 days for most participants but relaxed to 90 days to match an additional 45 participants.*

Outcome: MetS

- **MetS (Y/N):** ≥ 3 of the 5 components obtained from LLS2 (Form 301)
 - waist circumference ≥ 88 cm
 - triglycerides ≥ 150 mg/dL
 - HDL cholesterol < 50 mg/dL
 - blood pressure: systolic ≥ 130 mmHg, or diastolic ≥ 85 mmHg, or use of antihypertensive medications, or hypertension history
 - fasting blood glucose ≥ 100 mg/dL
- **MetS score:** total number of MetS components



Statistical Analysis

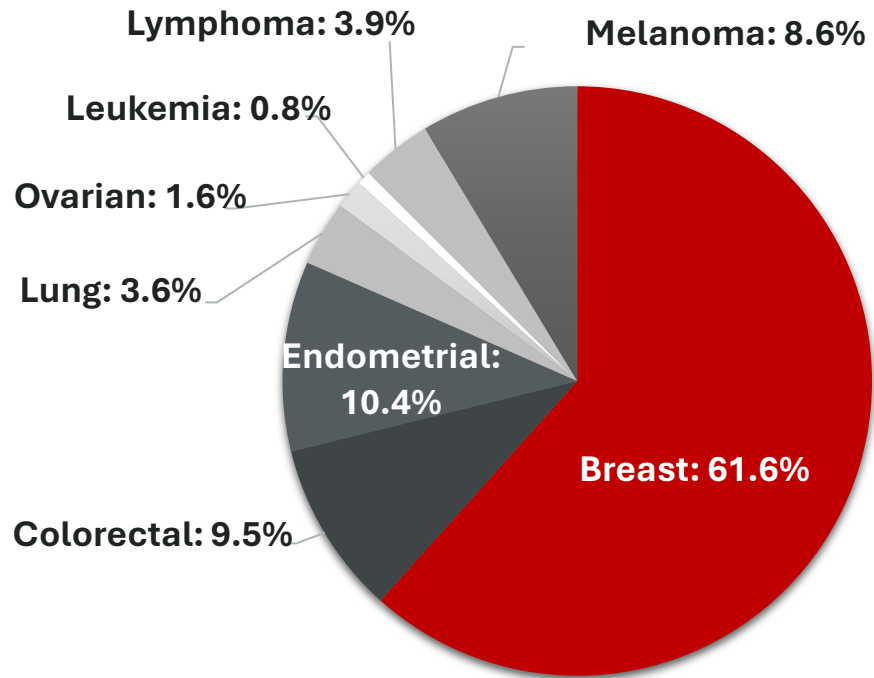
- **Exposure:** cancer history (adjudicated cancer outcomes)
- **Covariates:** age, race/ethnicity, education, marital status, income, insurance
- **Analysis:**
 - Description of study sample and compare between women with and without a cancer history
 - Linear regression: MetS composite score
 - Logistic regression: Individual components and MetS (Y/N)
 - Adjusted for random effects for matched subsets, to account for correlation and lack of independence of subjects within each matched set

Participant characteristics

Parameter	Women without cancer history (n=1863)	Women with cancer history (n=1574)	P-value
Age at LLS2, median [IQR]	85.2 [81.8-88.8]	85.2 [81.9-88.5]	0.77
Race, n (%)			
American Indian/Alaskan	3 (0.2)	--	<0.001
Asian	19 (1.1)	15 (1.0)	
Native Hawaiian/PI	1 (0.1)	--	
Black	363 (20.1)	66 (4.2)	
White	1392 (77.1)	1468 (93.8)	
More than one	28 (1.6)	16 (1.0)	
Education, n (%)			
College/Assoc. Degree	1416 (76.5)	1353 (86.3)	<0.001
≤High school	435 (23.5)	215 (13.7)	
Marital status, n (%)			
Married/ living as married	1271 (68.3)	1122 (71.3)	0.002
Widowed	187 (10.1)	108 (6.9)	
Divorced/separated	327 (17.6)	258 (16.4)	
Never married	75 (4.0)	85 (5.4)	
Insurance, n (%)			
No Insurance	121 (6.6)	42 (2.7)	<0.001
Private	1458 (79.2)	1321 (84.4)	
Public	63 (3.4)	49 (3.1)	
Public+Private	200 (10.9)	153 (9.8)	

Women with a cancer history (N=1574)

Cancer Type



Cancer Treatment Received

Chemotherapy

27%

Radiation

50%

Hormonal

76%



MetS individual components and composite score

Variables	Women without cancer history (n=1863) median [IQR]	Women with cancer history (n=1574) median [IQR]	P-value
Waist circumference ←	91.4 [81.3-99.1]	88.9 [81.3-98.8]	0.002
Triglycerides ←	96 [73-126]	99 [77-133]	0.001
HDL cholesterol	64 [53-75]	64 [54-77]	0.21
Systolic blood pressure	126 [119-138]	125 [118-137]	0.14
Diastolic blood pressure	73 [67-79]	73 [67-79]	0.56
Any HTN component* ←	1483 (79.6)	1198 (76.1)	0.01
Fasting blood glucose	94 [87-103]	94 [87-102]	0.31
MetS Score	2 [1-3]	2 [1-3]	0.11
0, n (%)	161 (8.6)	177 (11.3)	0.03
1-2, n (%)	1176 (63.1)	978 (62.1)	
3-5, n (%)	526 (28.2)	419 (26.6)	
Metabolic Syndrome, n (%)	526 (28.2)	419 (26.6)	0.29

*SBP≥130, DBP≥85, used anti-HTN meds, HTN diagnosis history

Association between MetS score and individual components and cancer history

	No cancer history	With cancer history	Adjusted	
	median [IQR]	median [IQR]	LS Means (95% CI)	P
MetS Score	2 [1-3]	2 [1-3]	-0.02 (-0.09, 0.05)	0.61



No interaction by age

Take home messages

- 26.6-28.2% women had metabolic syndrome in LLS2
 - No differences between women with and without a cancer history
 - Survival bias (women who completed LLS2 may be healthier than general pop)
- Women with a cancer history are:
 - Less likely to have abdominal obesity
 - More likely to have high triglycerides
- No interaction by age was found in the association between MetS and cancer

Next steps

- Complete analysis among women with a cancer history to identify whether certain cancer types or treatments increased the risk of MetS
- Consider interaction of rural/urban residency with MetS and cancer

Future directions

- Examine other cohorts with diverse populations: wider range of age (35-80 yrs), various racial/ethnic groups, etc.
- Look at longitudinal changes in MetS individual components (perhaps using WHI baseline data) comparing women with and without a cancer history

Thank you

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Association between CRP and cognitive decline among those with and without a history of cancer in the WHI LLS2

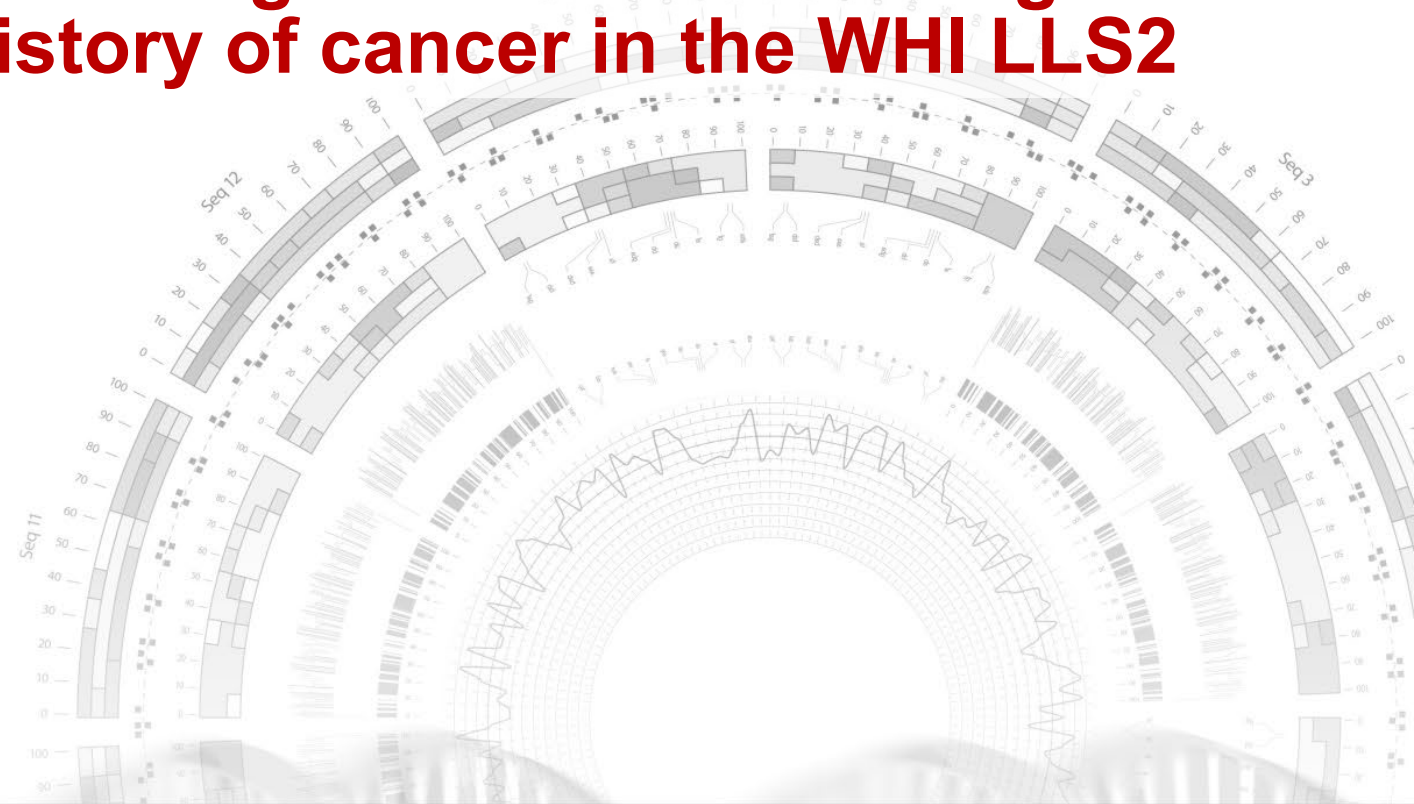
Chloe Hery, PhD

Postdoctoral Researcher
The Ohio State University
Thursday, May 7th 2026

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Cognitive Decline

- Aging and history of cancer can both increase the risk of cognitive decline in older adults
- Cognitive changes after a cancer diagnosis is an impactful side effect of certain cancer treatments
 - Some cognitive changes may be short term, but others have shown may persist for 10-20 years post-treatment
- Many different aspects of cancer and cancer treatment may affect cognition, inflammation may play a role through cellular damage

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(Ahles et al Ann Clin Psychology 2018; Mandelblatt et al. J Clin Oncol 2014; Schilder et al. J Clin Oncol 2010; de Ruiter et al Human Brain Mapping 2011)

Cognitive Decline & CRP

- C-Reactive Protein (CRP) is a commonly measured inflammation marker (blood-based)
- Higher CRP levels can reflect acute and chronic systemic inflammation
- Systemic inflammation may contribute to neuroinflammation
 - Blood-brain barrier permeability; vascular dysfunction
- Neuroinflammatory and vascular changes may impair neuronal function and accelerate cognitive decline



CRP, Cognitive Decline & Cancer

- Inflammation, often measured by CRP, tends to be higher in those diagnosed with cancer
 - Pre-treatment (tumor microenvironment)
 - During treatment (induces inflammatory responses)
 - Post-treatment (low-level chronic inflammation)
- Higher CRP is associated with future cognitive decline in both those with a history of cancer and those without
- Few have examined this in older postmenopausal women and considered cancer history, including multiple cancer sites

Objective

- To examine whether history of cancer modifies the relationship between CRP and Cognitive Change Index (CCI) scores among participants from the WHI LLS2
 - CRP from LLS2 Exam
 - CCI scores from Form 151A, after LLS2 Exam
- Hypotheses:
 1. Higher CRP levels will be associated with worse CCI scores
 2. Effect of higher CRP levels on CCI scores will be stronger in those with a history of cancer compared to those without a history of cancer.
 - 2a. Those with a history of cancer will have higher CRP levels

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Methods - Measures

- **CRP Values:** high sensitivity, mg/L (LLS2 Exam)
 - **Low** (0 to <1 mg/L)
 - **Moderate** (1 to <3 mg/L)
 - **High** (≥ 3 mg/L)
- **Cognitive Change Index (CCI)** (Form 151A):
 - 20-question index, assesses self-reported perception of cognitive decline
 - Participants answer questions about their current ability compared to 5 years ago
 - Score range: 20-100 (higher score indicates more memory concerns)
 - Minimal memory concerns (<35)
 - Low memory concerns (35 to <50)
 - Moderate memory concerns (50 to <65)
 - Severe memory concerns (≥ 65)

Methods - Cognitive Change Index (CCI)

This next set of questions asks you to rate any change in your abilities, daily functioning and activities. Fill in the circle for each question that best fits your current ability level compared to 5 years ago.

	No change	Minimal change	Some change	Clearly noticeable change	Much worse
32. Recalling information when I really try	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
33. Remembering names and faces of new people I meet	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
34. Remembering things that have happened recently	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
35. Recalling conversations a few days later	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
36. Remembering where things are usually kept	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5

Methods – Sample

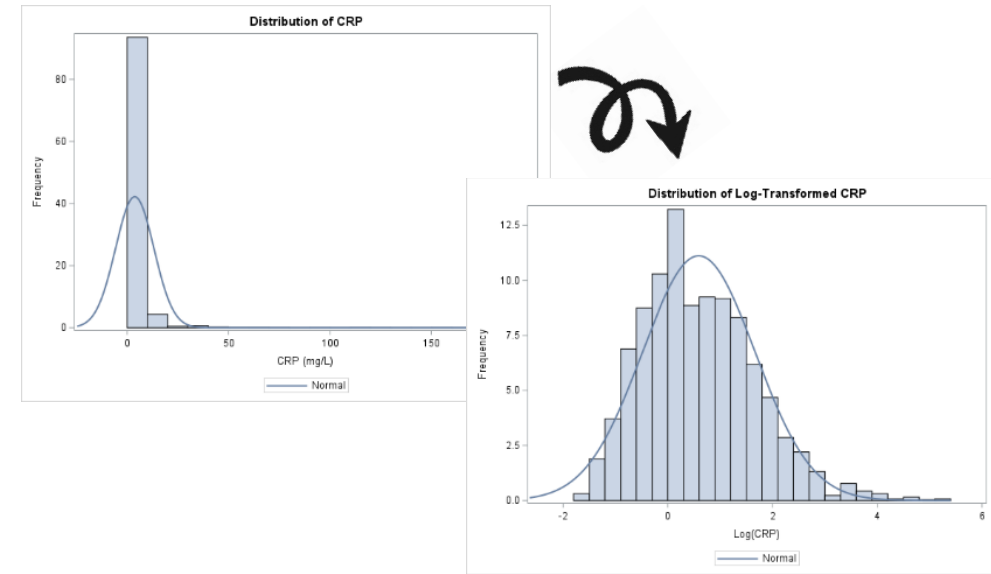
■ WHI Study Sample

- LLS2 participants with completed blood draw and F151A after LLS2 Exam (N=2,585)
- N = 2,290 had complete CCI scores
 - History of Cancer (LILAC) n=1,066
 - No Cancer History n=1,224

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Methods – Statistical Analysis

- Description of study sample
- Log transformed CRP values
- CCI Score as a continuous outcome
 - Also examined CCI cut points
- General Linear Model (GLM)
 - Unadjusted Analyses
 - Log(CRP)
 - Various sociodemographics (age, race, ethnicity, education, income, marital status, region of residence)
 - History of Cancer (yes/no)
 - Adjusted Analysis
 - $CCI = \log CRP + \text{significant factors from univariate analyses}$
 - $CCI = \log CRP + Ca Hx + \text{significant factors}$



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Results – Demographics & Cancer Clinical Factors

■ Overall Sample:

- Average age at LLS2: 84.8 years old (± 4.7 years)
- 85.4% White, 93.6% non-Hispanic
 - Those with no Ca Hx were more likely to be Black (16.8% vs. 3%, $p < 0.0001$) and Hispanic (9.9% vs 2.3%, $p < 0.0001$) likely reflecting recruitment efforts in MRC
- 55.8% with \geq College degree
- 70.2% were married
- Average F151A completion 10 months ($\pm 5m$) after LLS2

■ Those with a History of Cancer:

- Age at Dx: 69.5 years old (± 7.4 years)
- Site: 62% breast cancer
- Stage: 75% localized
- Treatments: 89% surgery, 27% chemo, 50% radiation, 76% ET

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Results – CCI & CRP Overall, and by History of Cancer

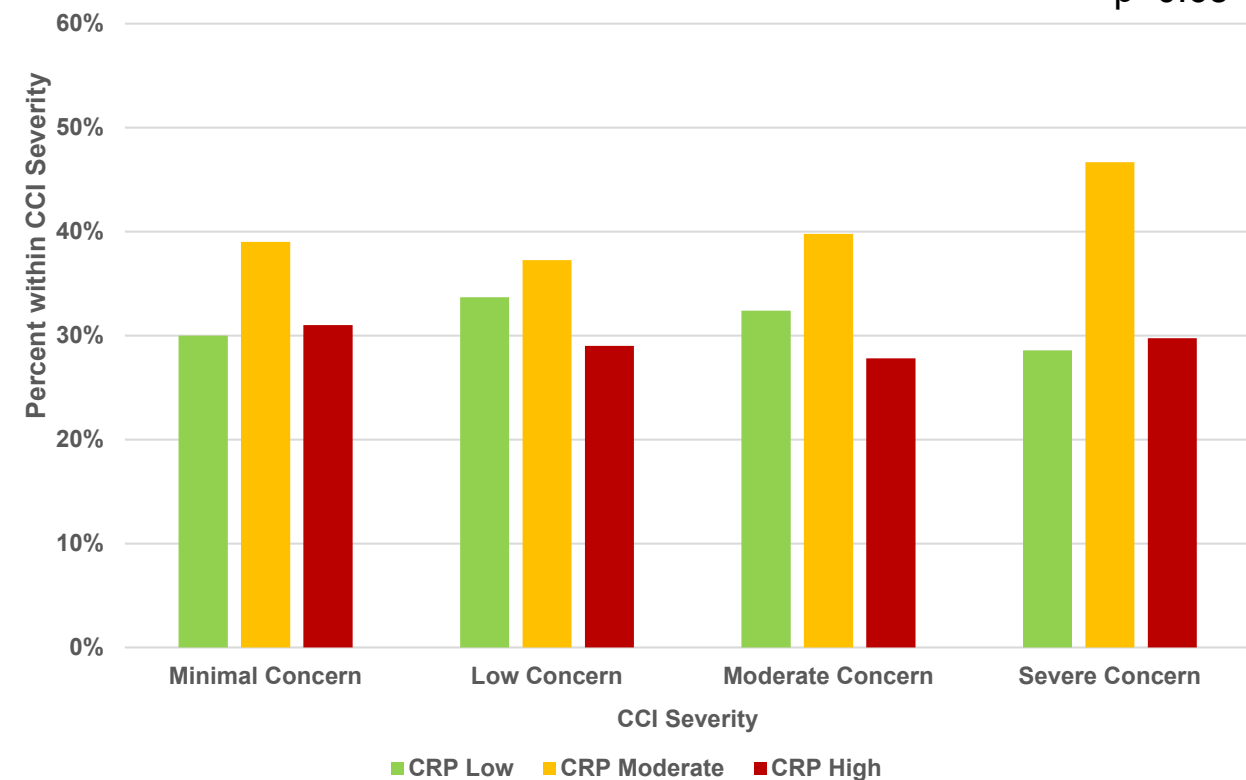
	Overall Sample (n=2290)	History of Cancer (n=1066)	No History of Cancer (n=1224)	P- value*
CCI Score, Mean (SD)	35.8 (13.4)	35.9 (13.3)	35.7 (13.4)	0.72
CCI Severity				0.49
Minimal Concerns (<35)	1268 (55.4)	684 (54.8)	584 (55.9)	
Low Concerns (35 to <50)	679 (29.7)	313 (29.4)	366 (29.9)	
Moderate Concerns (50 to <65)	259 (11.3)	132 (12.4)	127 (10.4)	
Severe Concerns (65+)	84 (3.6)	37 (3.5)	47 (3.8)	
CRP, Median (IQR)	1.61 (0.83-3.58)	1.58 (0.85-3.38)	1.63 (0.82-3.75)	0.69
CRP Cutpoints				0.12
Low (0 to <1 mg/L)	718 (31.4)	334 (31.3)	384 (31.4)	
Moderate (1 to <3 mg/L)	884 (38.6)	432 (40.5)	452 (36.9)	
High (≥3 mg/L)	688 (30.0)	300 (28.2)	388 (31.7)	

*T-test for continuous variable; Chi square test for categorical variable; Wilcoxon rank-sum for skewed data; IQR: Interquartile Range (Column percents)

Results – CCI, CRP, & History of Cancer

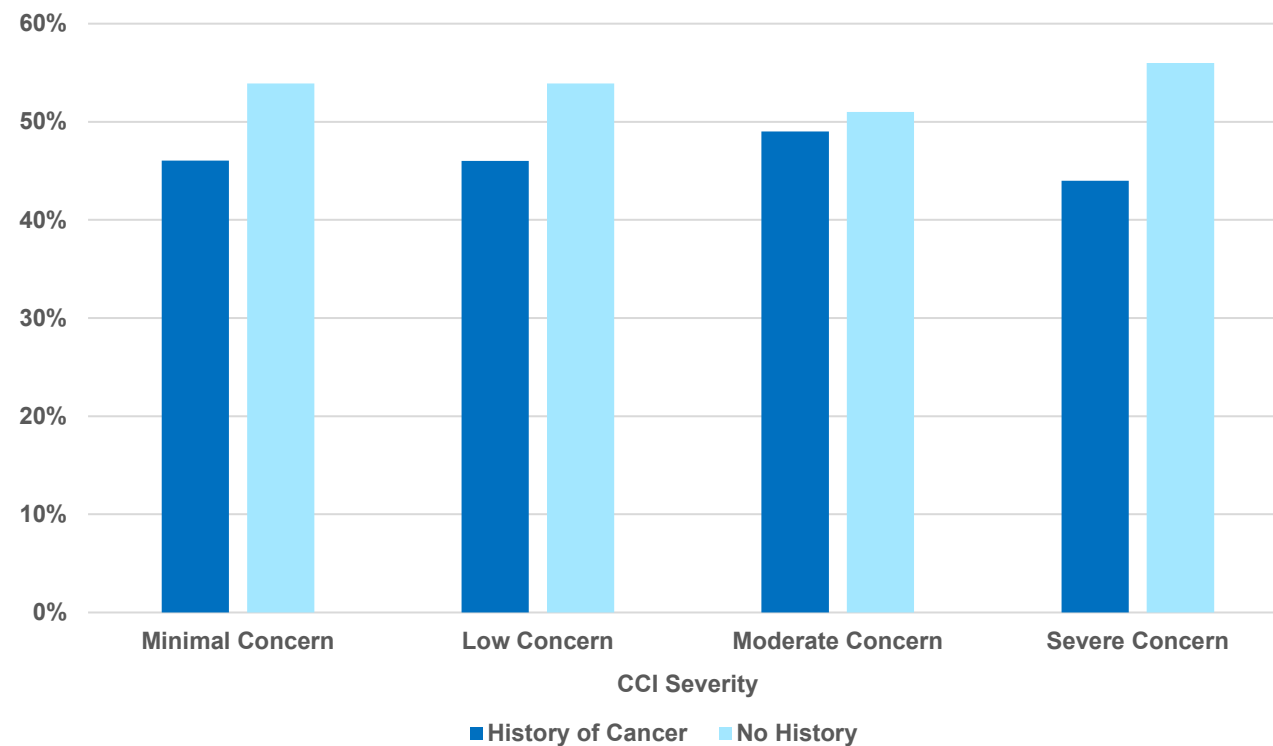
CCI Severity by CRP Value

p=0.68



CCI Severity by History of Cancer

p=0.49



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Results – Multivariable* Linear Regression of CCI Score

Variable	Estimate, β (SE)	p-value
logCRP	-0.35 (0.26)	0.18
Age (years)	0.55 (0.06)	<0.001
Income		0.31
<\$20,000	1.33 (1.30)	0.31
\$20-35,000	1.73 (0.92)	0.06
\$35-50,000	0.13 (0.81)	0.87
\$50-75,000	0.04 (0.75)	0.95
\$75,000+ (Ref)	—	—
Marital status		0.09
Never Married	-2.75 (1.39)	0.048
Divorced/Separated	-0.74 (0.80)	0.36
Widowed	1.23 (1.06)	0.25
Married (Ref)	—	—

*Unadjusted analyses of sociodemographic factors included if $p < 0.2$;
(N=2,207)

CRP:

- In unadjusted models, logCRP was not a significant predictor of CCI
- When added to the multivariable model, it remained non-significant

History of cancer (not shown):

- In unadjusted models, Ca Hx was not a significant predictor of CCI
- When added to the multivariable model, it remained non-significant
- Effect modification:
 - Interaction of LogCRP* Cancer
 - $p = 0.75$

Discussion

- CCI score was not associated with CRP or History of Cancer
- Age, as expected, was a strong predictor of CCI score
- With an average age of 85 during LLS2, most participants had minimal self-reported memory change compared to 5 years prior
- Additional data to be examined:
 - Comorbidities
 - BMI
 - Depression, psychosocial factors
 - Cancer subgroup analyses (by site, stage, treatment types)

Limitations

- CCI and CRP only at one time point
- Self-reported memory concerns
- CRP can fluctuate in response to acute factors (illness, injury, etc)
- Cancer survivors were 10+ years post-diagnosis on average, may be a healthier population than other cancer survivors

Future Research & Implications

- Inflammation may contribute to cognitive decline, and continuing to explore if this relationship differs by cancer history will have important clinical and survivorship implications

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Thank you! Questions?

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