Title
Occupational Cancer Risk in California Teachers and Risk Modification by Medication Use

Author
Haridass, Vikram

Publication Date
2019

UNIVERSITY OF CALIFORNIA,
IRVINE

Occupational Cancer Risk in California Teachers and Risk Modification by Medication Use

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Epidemiology

by

Vikram Haridass

Dissertation Committee:
Professor Hoda Anton-Culver, Chair
Professor Argyrios Ziogas
Associate Professor Luohua Jiang
Professor Christine McLaren
Professor Mahtab Jafari

2019

DEDICATION

To

My family and friends,
For showering me with complete love, care, and support

My Mentors,
For imparting wisdom and supporting me throughout my academic endeavors

And most of all,
My parents, Saraswathy and Shanmuganathan Haridass
For everything, I truly would not have made it this far without your unending love and support

Thank you, I am filled with so much gratitude.

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

Page

ACKNOWLEDGMENTS

First and foremost, I would like to thank my committee chair, Dr. Hoda Anton-Culver. Thank you for always setting aside time to provide me with guidance and wisdom as it pertained to my thesis research or the program in general. You have always held me to a standard of excellence and your guidance has helped nurtured my development throughout the Dissertation program, I am forever grateful for your influence throughout my graduate education.

Thank you to Dr. Argyrios Ziogas for spending countless hours with me discussing statistical methods and analytical approaches throughout my thesis research. The help you provided me with during my time in the Dissertation program is truly invaluable, and I want to express my appreciation for always welcoming me into your office and providing endless amounts of guidance. Thank you again for your patience and support throughout my thesis.

I would like to also express my appreciation for Dr. Luohua Jiang, your statistical expertise and guidance throughout my research was immensely integral and beneficial to my progress throughout my Dissertation research.

Lastly, and most importantly, the level of gratitude I have for my parents, Mr. and Mrs. Shan Haridass, cannot be articulated even in the most eloquent of phrasings. The constant hardships, and sacrifices made throughout your arduous journey to ultimately provide a better life for us in this country cannot ever be fully repaid. I promise to spend every moment of my life making you proud, and striving to reciprocate my appreciation for you and shower you with all my love for everything you have done for me.

Financial support was provided by Southern California NIOSH Education and Research Center (SCERC) Pilot Project Research Training Program Grant (#T42 OH008412).

CURRICULUM VITAE

Vikram Haridass

EDUCATION

B.S. in Molecular and Cell Biology,
Minor in Chemistry,
California State University, Long Beach 2013

M.S. in Epidemiology,
University of California, Irvine 2015

Ph.D. in Epidemiology,
University of California, Irvine 2019

RESEARCH EXPERIENCE

University of California, Irvine, Department of Epidemiology, Irvine, CA 2016-2019
Graduate Student Researcher
Advisor: Hoda Anton-Culver, Ph.D.
Examined the risk of developing breast cancer, endometrial cancer, ovarian cancer, malignant melanoma, non-Hodgkin's lymphoma, colorectal cancer, and lung cancer according to occupational characteristics and medication intakes using prospective data from 1995-2013 among 133,479 female teachers and school administrators enrolled in the California Teachers Study cohort

University of California, Irvine, Department of Epidemiology, Irvine, CA 2014-2015
Graduate Student Researcher
Advisor: Andrew Odegaard, Ph.D.
Conducted a prospective analysis using data from 1995-2013 examining the association between diet quality and incident invasive breast cancer risk among 133,479 pre- and postmenopausal female participants of the California Teacher Study cohort

California State University, Long Beach, Biological Sciences Department,
Long Beach, CA 2012-2013
Undergraduate Student Researcher
Principal Investigator: Huong-Wei Tsai, Ph.D.
Examined androgen receptor protein expression levels in key brain regions associated with the formation of sexually distinct behaviors among male and female mice ranging from prenatal to adult ages

PUBLCATIONS

Referred Journal Articles

1. **Haridass V.**, A. Ziogas, S.L. Neuhausen, H. Anton-Culver, A.O. Odegaard. Diet quality scores inversely associated with postmenopausal breast cancer risk are not associated with premenopausal breast cancer risk in the California Teachers Study. *J Nutr* 2018; **148**(11):1830-1837.

Referred Conference Proceedings

Haridass V., A. Ziogas, H. Anton-Culver. Occupational cancer risk in California teachers and risk modification by medication use. Presented at the 2018 Southern California NIOSH Education and Research Center Fall Interdisciplinary Workshop, September 2018, Los Angeles, California.

Haridass V., A. Ziogas, H. Anton-Culver. Occupational risk factors of teachers and the risk of melanoma breast, and endometrial cancers: a prospective analysis in the California Teachers Study. Presented at the University of California Irvine Chao Family Comprehensive Cancer Center Biostatistics Shared Resource Seminar Series, May 2018, Irvine, California,

AWARDS

Southern California Education and Research Center
National Institute Occupational Safety Health
Pilot Research Training Program Grant (NIH Award number: T42 OH008412) 2017

University of California, Irvine
School of Medicine Individual Fellowship Bonus Award 2017
School of Medicine Individual Fellowship Application Award 2017

California State University, Long Beach
California State University, Long Beach's Presidential Scholarship 2008

TEACHING EXPERIENCE

University of California, Irvine
Teaching Assistant
<u>Scientific Writing</u>
Dr. Maribel Alvarez Summer (Session I) 2017

<u>Drugs and the Brain</u>
Dr. Andrea Niocholas Fall 2016

CERTIFICATIONS

CITI Biomedical Investigator Human Research Protections Certificate 2018, 2013

ABSTRACT OF THE DISSERTATION

Occupational Cancer Risk in California Teachers and Risk Modification by Medication Use
By

Vikram Haridass

Doctor of Philosophy in Epidemiology

University of California, Irvine 2019

Professor Hoda Anton-Culver, Chair

Introduction: Teachers, as an occupational group, have been previously shown to have an elevated risk of breast, and endometrial cancers relative to the general population. However, no conclusive evidence regarding teacher-specific occupational risk factors driving this higher risk in cancer incidence have been established. Previous studies have found occupational physical activity levels to be inversely associated with risk of incident cancers, yet the conclusions regarding this association are not definitive.

The purpose of this dissertation is to assess cancer risk in participants of the California Teachers Study according to occupational characteristics and medication intake of school employees. The study will examine the association between various occupational characteristics and medication intakes among female school employees and cancer incidence of breast, endometrial, and malignant melanoma.

Methods: A prospective analysis of 133,479 female teachers and school administrators, aged 22-104 years, in the California Teachers Study cohort between 1995 and 2013 was conducted. Occupational characteristics and medication intakes were determined using participants' responses to the comprehensive questionnaire administered at baseline. Age-standardized incidence rates were calculated according to participants' occupational characteristics and compared to the incidence rates of California women, obtained from the California Cancer Registry. Multivariable Cox proportional hazard regression models were constructed to provide hazard ratios and corresponding 95% confidence intervals for estimates of cancer risk for breast, endometrial, and malignant melanoma according to occupational characteristics and medication intake of female teachers and school administrators.

Results: Throughout the eighteen years of follow-up in the California Teachers Study, there were 7,173, 1,351, and 1,919 teachers who developed breast cancer, endometrial cancer and malignant melanoma, respectively. There was an excess cancer incidence among California Teacher Study participants overall, and according to several occupational characteristics for breast, endometrial and malignant melanoma. Of note, lower levels of occupational physical activity was associated with an elevated risk across the three cancer types when compared to general female population of California and teachers with higher levels of occupational physical activity. Moreover, the elevated risk associated with minimal occupational physical activity levels was not mitigated by higher levels of recreational physical activity among participants of the study. Additionally, regular anti-inflammatory medication intake among study participants was associated with risk for breast cancer and malignant melanoma compared to non-regular users; there was no evidence for the difference in risk across the three cancer types according to statin use. **Conclusion:** This study showed that female teachers and school administrators are at an elevated risk of breast cancer, endometrial cancer, and malignant melanoma which was largely driven by a lack of occupational physical activity and regular anti-inflammatory medication intake.

CHAPTER 1

Introduction

Based on reports from the United States Bureau of Labor Statistics from 2016, there were 4,264,800 individuals actively employed in the teaching profession in preschool, primary, and secondary schools with an estimated annual growth in employment of approximately 8.0% [**1**]. Throughout the years in this growing occupation, teachers have been continually shown to be at an increased risk of developing breast cancer, endometrial cancer, and malignant melanoma relative to the general population- in studies conducted in the US [**2-5**] and worldwide [**6-12**]. Findings from these past studies show teachers, as an occupational group, have substantially elevated cancer risks, yet the overall evidence regarding teachers-specific occupational risk factors remains inconclusive.

Given the reported higher cancer incidence rates among teachers, developing a better understanding of preventive strategies in this occupational group may help improve recommendations, advocacy, and policy. Previous studies have found non-steroidal anti-inflammatory drug (NSAID), and cholesterol-lowering medication use to be inversely associated with risk of incident cancers [**13-16**]. However, the conclusions regarding this association are not definitive (with exception to NSAIDs and incident colorectal cancer). Therefore, further studies of these relationships among a cancer-susceptible group, such as teachers, may provide evidence for potential medication-specific preventive strategies.

Although teachers have been reported to have uniquely higher cancer incidence rates compared to the general population, it remains unclear whether teacher-specific occupational risk factors and exposures, such as medication intake, were the reasons that cause this higher risk in cancer incidence. Specifically, this dissertation will assess occupational characteristics, exposures, including medication intake, on the risk of developing three cancer types in female teachers from a large prospective California Teachers Study (CTS). To our knowledge, this is the first study to examine occupational associations to the risk of developing three common cancers in a prospective cohort of female teachers.

1.1. Occupational exposures and cancer risk

Teachers as an occupational group have been reported to have an increased risk of several common cancers including malignant melanoma, breast, and endometrial cancers. However, the evidence regarding the effects of occupational characteristics and types and level of exposures associated with cancer risk is sparse and inconsistent. Although a relatively understudied matter of significance, past studies examining teachers have provided crucial evidence linking causative factors of cancer (i.e. allostatic load, pro-inflammatory immune response, immune system depression) to this occupational group [**17-18**]. Specifically, teachers with greater occupational stress levels were shown to have suppressed immune systems (i.e. lower levels of Natural Killer and CD4+ T cells) [**17**], and an elevated pro-inflammatory immune response (i.e. higher levels of TNF-α, IL-6, IL-2, C-Reactive Protein) [**17-18**] compared to teachers with lower levels of occupational stress. This persistent dampening of the immune system and state of chronic tissue inflammation provide an optimal environment for tumorigenesis through lack of immunosurveillance (i.e. loss of cell death mechanisms from an immunosuppressive state) and increased oxidative stress (i.e. increased mutagenic activity to promote genomic instability), across all cancer types [**19-20**]. However, this induced pro-inflammatory immune response is not solely accounted to the stressful working conditions of teachers, but also sedentary occupational practices (i.e. low occupational physical activity levels) in which increased physical activity has been show to significantly reduce inflammation and allostatic load (i.e. serum IL-6, C-Reactive Protein, TNF-α, etc.) [**21-22**]. Yet, the evidence base regarding the association between occupational physical activity and incident MM, breast and endometrial cancer risk has not been conclusive with some studies observing no association [**23-26**] and others reporting an association [**27-32**]. Indeed, these results may be partially explained by the assessment of study populations consisting of heterogeneous occupational subgroups whose physical activity intensity levels largely differ from one another. Given inflammation's role as a "hallmark of cancer" [**33**], the prolonged exposure to occupational characteristics (i.e. occupational stress, sedentary occupational practices) associated with this pro-inflammatory immune response promote tumor formation across all cancer types, especially among inflammatory cancers such as breast and endometrial cancers [**34**], which may differ according to faculty position held in the educational services sector (i.e. more sedentary habits of administrators compared to teachers) and length of employment (i.e. ≥10 yrs. vs. <10 yrs.).

Although the literature regarding occupational risk factors of teachers and cancer risk is sparse, the few available studies provide evidence that the incidence of melanoma, breast, and endometrial cancers significantly differs according to employment position and the duration of employment. Findings from a previous prospective analysis examining incident cancer risk among teachers employed in CA from 1988-1992 found a relative excess incidence of MM, breast, and endometrial cancer when compared to the general population and was notably higher for teachers (i.e. preschool, elementary, junior high and senior high school) versus school employees in administrators/pupil services (incident breast cancer: 22% increase vs. 19% increase, incident endometrial cancer: 18% increase vs 3% increase, and incident malignant melanoma: 38% increase vs 29% increase) [**3**]. Additionally, duration of employment has been previously shown to increase the risk of MM, breast, and endometrial cancers (~5-fold) among a cohort of female junior high school teachers (SIR for ≥15 years of employment: 4.89, $P = 0.0034$) [**4**]. However, these findings are not conclusive given the sparse evidence base as previous studies have also shown no association between the incidence of premenopausal breast cancer and duration of employment as a teacher [**35**].

Malignant melanoma risk in teachers has also been linked to other more cancer-specific occupational exposures shared among teachers. One such exposure is high-voltage frequency transients, often referred to as "dirty power", emitted from the electrical wiring found throughout school facilities. Specifically, a previous investigation into teachers of a La Quinta, CA junior-high school provided evidence of substantially elevated incidence of malignant melanoma (9.8-fold higher) when compared to the general population (SIR 9.8, $P = 0.0008$), which became further exacerbated upon stratification according to classroom "dirty power" levels [**4**]. Additionally, ultraviolet radiation (UVR) exposures, solar and non-solar, among teachers have been previously shown to increase the risk of malignant melanoma. Particularly, non-solar UVR exposures among teachers result from exposure to school-facility lighting in which schools widely implement the use of fluorescent bulbs due to their cost-effectiveness, but have also been shown to emit the highest level of UV radiation (i.e. Effective irradiance = 4) relative to other lighting options [**36**] and therefore may be potentially carcinogenic after long periods of exposure. Past studies have shown an increased risk for skin cancer (75% increase) among teachers as an occupational group while accounting for all relevant risk factors, including skin type and solar-UVR exposures, therefore suggesting the importance of non-solar UVR sources in this cancer type [**37**]. Although the CTS does not directly measure occupational electromagnetic frequencies (from electrical wiring) and UVR (from fluorescent light exposures), our ability to examine the gradient across occupational characteristics in the CTS (i.e. years of employment, number of schools throughout employment, etc.) may serve as a qualitative measure of occupational EMF and UV radiation exposures, similar to the methodology of past studies which lack quantitative exposure levels [**38**].

The increase in cancer incidence among teachers has been reported to be associated with several lifestyle exposures (i.e. air pollution [**39**], BMI [**40**], recreational physical activity [**41**], diet [**42**], hormone replacement therapy [**43**], including the use of medications [**44**]. Previous studies have found non-steroidal anti-inflammatory, and cholesterol-lowering medication use had inverse association with risk of incident cancers [**13-16**]. Specifically, anti-inflammatory medications directly reduce the pro-inflammatory immune response, an established risk factor of cancer, through inhibition of the COX-2 enzyme and thus we expect this group to have wide-ranging effects across all cancer types [**34, 45-46**], especially among inflammatory cancer types such as breast [**13, 47**], endometrial [**14, 48**], and malignant melanoma [**16, 49**]. The use of cholesterol lowering medications (i.e. Statins) in relation to cancer risk have been of interest given their ability to interfere with the proto-oncogenic mevalonate pathway that has been shown to promote cellular proliferation, differentiation, and survival allowing for successful tumor formation [**50-51**]. Given this role of Statin's interference in oncogenic pathways, we anticipate regular Statin use to serve as a protective modifiable factor associated with melanoma, breast, and endometrial cancer risk among teachers.

1.2. Significance

A notable drawback in the majority of teacher-centered studies is the utilization of cross-sectional study designs [**52-63**]. Though economically practical, cross-sectional study designs offer a single snapshot into a teacher's occupational characteristics and exposures, typically consisting of teachers who have already developed adverse health outcomes. In turn, vastly limiting our understanding of the temporal relationship between occupational characteristics of teachers and the development of adverse health outcomes. Furthermore, carrying out randomized trials with comprehensive interventional approaches is not feasible, thus longitudinal cohort studies are the strongest line of evidence to inform this topic. To begin addressing this gap, the longitudinal California Teachers Study (CTS) has provided an ideal study population to examine associations among the educational services sector (i.e. female teachers) to the risk of developing adverse health outcomes, including cancer [**39-44, 58, 64**].

Though these past investigations into the CTS have been more focused on lifestyle exposures (i.e. diet, BMI, etc.) as opposed to the characteristics of teachers as an occupational group (i.e. occupational stress, teacher type, duration of employment, occupational physical activity, etc.), and typically examine the risk for a single cancer type.

Understanding the association between occupational characteristics, medication intake, and the risk of developing cancer is a necessary step to inform policy and recommendations that have the potential to lower the elevated cancer risks among teachers [**2-3**]. Yet, the evidence regarding teacher-specific occupational risk factors driving this increase in cancer incidence is relatively sparse as studies examining teachers are primarily interested in mental health outcomes, somatic conditions, and other chronic diseases (i.e. Type 2 Diabetes, Cardiovascular disease, etc.) [**17-18, 52-61**]. With help of the CTS, we were able to follow teachers throughout their employment and into retirement which may enable us to understand the association between occupational characteristics, modifying exposures (i.e. medication use), and incident cancer risk. Additionally, as a large number of these teachers have developed various incident cancers throughout the long period of follow-up (i.e. 20+ years), such studies may provide crucial evidence which links certain occupational characteristics and exposures with the risk for the three cancer types of interest.

Past epidemiological studies have begun to investigate the association of medication use on the risk of various incident cancers. Previous studies examining the association between NSAID use and incident cancer risk for breast [**13**], endometrial [**14**], and malignant melanoma [**15**] have reported an inverse relationship. However, the overall evidence is not conclusive as seen among other studies that have observed no association, although risk-adjusted estimates for regular NSAID use vs non-regular use were below one [**47-49**]. In addition, cholesterol-lowering medication use has been shown to lower the risk of breast cancer [**16**], endometrial cancer [**65**], and malignant melanoma [**15, 65**] in several earlier investigations. But these past findings regarding the protective role of cholesterol-lowering medication use have not been definitive [**66-70**]. Specifically, a study of 8,813 subjects conducted across three US hospitals found no association between statin use and risk of the ten most common cancers [**66**]. Similar results have also been observed in other cohort and case-controls studies [**67-70**].

Of note, these past studies investigating medication use have utilized study populations comprised of vastly different participants in terms of sociodemographic profiles which may introduce systematic errors (i.e. misclassification bias, confounding bias) that can potentially impact study results and hamper the ability to make statistical inferences. Additionally, the ability to detect significant differences in risk is limited when examining exposures with a proposed modest effect (i.e. anti-inflammatory and cholesterol lowering medications) in study populations that have low vulnerability for the outcome of interest and may also account for past inconsistent findings. Our investigation allowed us to examine the association between medication use and risk of incident cancers in a generally homogenous sociodemographic study population that has been shown to have an increased susceptibility for developing cancer compared to the general population [**2**]. Given the breadth of discordant findings, it is critically important to further examine the association of occupational characteristics and exposures of teachers (i.e. medication use) and the potential risk of cancers to ultimately lower the elevated incidence rates among teachers through improving guidelines, policy, and advocacy in this field.

1.3. Specific Aims and hypotheses

Aim 1: Compare incidence rates of breast cancer, endometrial cancer, and malignant melanoma from 1995-2013 among teachers in the CTS cohort to the cancer incidence rates of general California women.

We will also examine the cancer incidence rates according to occupational characteristics (i.e. teacher type, number of schools throughout employment, duration of employment, power lines near school, occupational stress and physical activity).

Hypothesis for Aim 1:

- Hypothesis 1.1: I hypothesize that teachers, as an occupational group, have uniquely higher **age-adjusted incidence rates** of breast cancer, endometrial cancer, and malignant melanoma than the rates among comparable California women.
- Hypothesis 1.2: I hypothesize that teachers and school administrators who report decreased occupational physical activity, have greater duration and number of schools throughout employment, and perceive greater occupational stress have higher **age-adjusted incidence rates** for breast cancer, endometrial cancer, and malignant melanoma than the general population of California women.

Aim 2: Examine the association between occupational characteristics among female teachers in the CTS cohort population and the risk for breast cancer, endometrial cancer, and malignant melanoma.

We will assess the same set of occupational characteristics as listed in Aim 1.

Hypotheses for Aim 2:

- Hypothesis 2.1: I hypothesize that female teachers, especially school administrators, who report higher levels of occupational stress, and lower occupational physical activity levels have an elevated risk of breast cancer, endometrial cancer, and malignant melanoma.
- Hypothesis 2.2: I hypothesize that teachers with greater durations and number of schools during employment have an elevated risk of breast cancer, endometrial cancer, and malignant melanoma.

Aim 3: Examine possible modifying effects of medication intake for anti-inflammatory and cholesterol-lowering medications on the risk of breast cancer, endometrial cancer, and malignant melanoma among teachers in the CTS.

We will examine the **frequency** and **duration of intake** for anti-inflammatory (i.e. aspirin, ibuprofen, and acetaminophen) and cholesterol-lowering (i.e. statins) medications.

Hypothesis for Aim 3:

- Hypothesis 3.1: I hypothesize that teachers reporting greater usage (i.e. greater duration and frequency) for anti-inflammatory and cholesterol-lowering medications have a lower risk of breast cancer, endometrial cancer, and malignant melanoma.

1.4. Chapter outline

Chapter 2: General methodology

Chapter 3: Rates of breast cancer, endometrial cancer, and malignant melanoma development among teachers and California Women

Chapter 4: The risk of incident breast cancer, endometrial cancer, and malignant melanoma according to the occupational characteristics of teachers

Chapter 5: The risk of incident breast cancer, endometrial cancer, and malignant melanoma according to the medication intake of teachers

Chapter 6: Conclusions

CHAPTER 2

Methods

2.1. Study population

The California Teachers Study (CTS) is an ongoing prospective cohort study that consists entirely of California female employees of the educational services sector (NAICS: 61). In order to be eligible for the CTS cohort, participants must have been active members of California Teachers Retirement System (STRS) in 1995 and at least actively employed in the CA school district for one full year. The STRS is a system established for public school teachers and administrators to receive retirement benefits and requires continual retirement contributions to remain actively enrolled with the program. Moreover, the STRS serves a representative sample of California school employees through its exhaustive coverage of educational institutions statewide. Specifically, members of the STRS are school employees found across 1,160 public school districts, community college districts, county offices of education, and statewide reporting agencies of California. In addition to active STRS membership and employment of at least one year, consent to participate in the CTS cohort further required completing the detailed 16-page mailed baseline questionnaire administered in 1995, which yielded the final CTS cohort consisting of 133,479 female public school teachers and administrators, aged 22-104 years old at enrollment. The establishment of the CTS cohort is as shown in **Figure 2.1**.

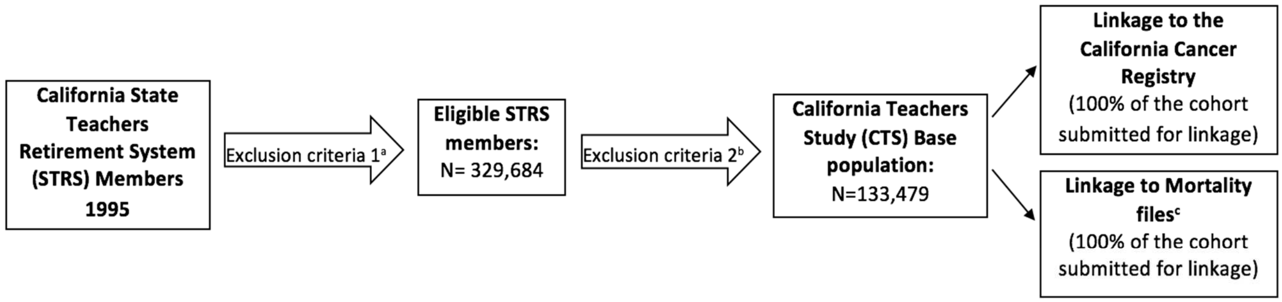


Figure 2.1: Flowchart of study selection process in the California Teachers Study cohort

[a] Teachers were excluded if they were not professional public school employees that were active members of STRS in 1995 with at least one full year of service in California schools, were not recently employed in the school system (within the past 72 months) or were not retired.

[b] Teachers were excluded if they did not complete the self-administered questionnaire mailed to the eligible STRS members in Fall 1995.

[c] Mortality and causes of death, including dates, were obtained through the California Department of Public Health Data Statistical Master Files (DSMF) and the National Death Index.

2.1.1. Occupational characteristics and medication intake

Occupational characteristics were determined from teachers' responses to the detailed questionnaire administered at study entry. Specifically, teacher type (i.e. preschool, elementary school, junior high school, senior high school, administrator, pupil services, other/multiple roles), number of schools throughout employment (i.e. 1, 2-3, 4-5, 6-8, 9-12, >12 schools), number of years in the school system (i.e. <1, 1-4, 5-9, 10-14, 15-19, ≥20 yrs.), occupational physical activity (i.e. walking or standing at work, 0-≥10 hrs./day), power lines near school (i.e. No power lines, power lines on poles, power lines on towers, power lines on poles and towers within 1 block of school property), and occupational stress levels (Likert scale, responses range from strongly agree to strongly disagree).

Moreover, the occupational stress measure was constructed according to the widely-used 'Effort-Reward Imbalance' (ERI) originally developed by Johannes Siegrist for investigating occupational psychosocial factors related to human-health outcomes. Briefly, the ERI defines occupational stress as an imbalance between perceived personal costs (“effort”) and personal gains (“reward”) in the workplace and thus is expressed as a ratio where values close to zero indicate relatively low effort and high reward, and values above 1 indicate relatively high effort and low reward. Per Siegrist J. and colleagues suggestions, this ratio was categorized into a binary variable in which individuals with an ERI ≤ 1 indicate low-risk stress, where as ERI values > 1 indicate high-risk stress to allow for comparability across different studies [**71**].

Medication intake behaviors in the CTS cohort were also recorded at study entry. This information included usage duration (i.e. Not regular, less than 1 year, 1 year, 2 years, 3-4 years 5-9 years, 10+ years) and frequency (i.e. None, 1-3 days/week, 4-6 days/week, everyday) to allow for a comprehensive analysis of medication use with the risk of three incident cancers. Specifically, we will be examining the use of NSAIDs (i.e. aspirin, ibuprofen, acetaminophen- although not classically considered a NSAID), and Anti-Cholesterols (i.e. Statins).

Of note, occupational stress and anti-cholesterol medication use were recorded in the third (i.e. Spring 2000) and fourth follow-up questionnaire (i.e. Fall 2005), respectively, and therefore the available information when examining these exposures was determined from those teachers who responded to those questionnaires and were cancer-free at the time of its completion.

2.1.2. Sociodemographic characteristics, and cancer risk factors

In addition to occupational characteristics recorded, there were also numerous lifestyle and non-lifestyle characteristics recorded at study entry. Specifically, the baseline questionnaire collected information on common risk factors for the three cancers of interest, along with other key demographic characteristics. Information included teacher's race (White, Black, Hispanic, Native American, Asian/Pacific Islander, Other/mixed), menopausal status (pre-, postmenopausal), hormone therapy (HRT) use (no HRT use, past HRT use, current estrogen therapy use, current estrogen progestin therapy use, other), parity status (non-parous, parous), oral contraceptive use (ever, never), age at menarche (y), age at menopause (y), family histories of breast cancer, endometrial cancer, malignant melanoma, and mole removal (no family history, at least one first degree relative, adopted/unknown). Additionally, information included personal histories of mole removal, breast cancer, and endometriosis (yes/no), as well as body mass index (BMI, kg/m^2), socioeconomic status (SES), smoking status (never, former, current), alcohol intake (g/day), vitamin D intake (IU/day), vitamin use (non-user, current single vitamin user, current multivitamin user, current single and multivitamin user), recreational physical activity levels (hrs./day), number of sun blisters (never, 1-2, 3-4, 5-9, 10+ times) age at first sun blister (years: 5 or less, 6-10, 11-15, 16-20, 21-25, 26+), skin sensitivity to sun exposure without protection (severe burn and blister, severe burn and no blister, mild burn and tan, no burn and tan only, no burn or tan), and tanning habits from repeated sun exposure (deep tan, moderate tan, light tan, no tan).

2.1.3. Ascertainment of cancer incidence, mortality, person-years of follow-up

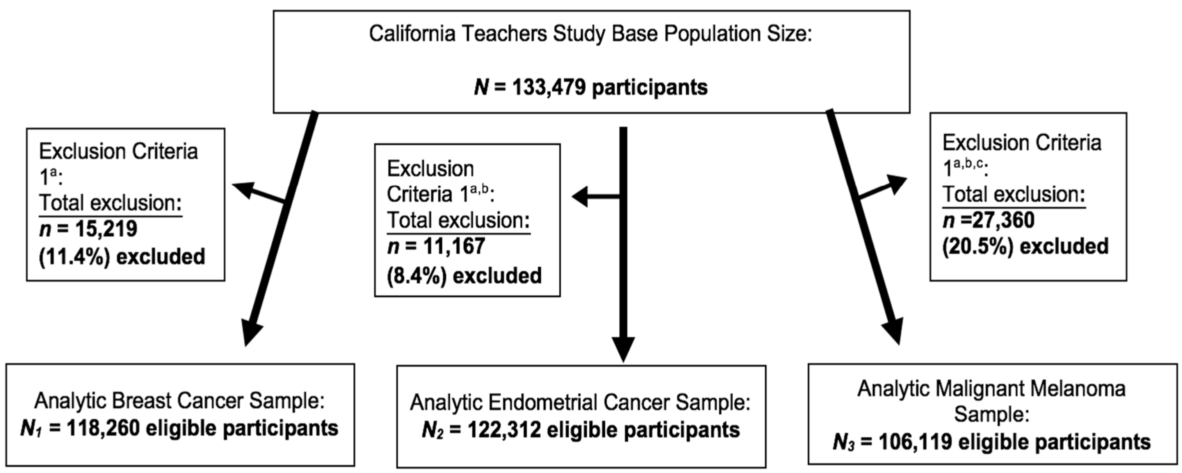
All Incident cases occurring in the CTS were identified through linkage with the California Cancer Registry (CCR) records, which is a population-based cancer registry for California residents. The state of California reports >99% of all cancer diagnoses to the CCR for current residents, so cohort members are actively followed for cancer outcomes without the need for further contact [**72**]. The incident cancer data captured all diagnoses for the cancers of interest among participants from 1995 to December 31, 2013. Cancers of interest were defined using ICD-10 codes: invasive breast (C50.0-50.9), in situ breast (D05.0-05.9), and invasive endometrial (C54.1), invasive malignant melanoma (C43.0-43.9), and in situ malignant melanoma (D03.0-03.9).

Mortality and causes of death, including dates, were obtained through the California Department of Public Health Data Statistical Master Files (DSMF) and the National Death Index. Similar to the CCR, the mortality data captured all deaths occurring among participants of the CTS from 1995 to 2013. In addition, participants who do not currently reside in California were identified through notification from participants, annual mailings, and linkage with other records. Teachers in the CTS cohort were censored if a death occurred or when they moved out of California. Furthermore, person-years of follow-up in the CTS begin from the date teachers completed the baseline questionnaire until diagnosis of cancer, death, a move out of California, or the end of follow-up (December 31, 2013), whichever occurred first.

2.2. Analytic cohort selection

Given our interest in the risk of multiple incident cancers, when we examined a given cancer all participants with a diagnosis of that cancer, those who had an unknown prior history of cancer, those who voluntarily withdrew from the CTS, those who did not reside in California at baseline, and those who consented to participate only in breast cancer research (*for endometrial cancer and malignant melanoma risk analyses only*) were excluded (n_{Breast} =15,219, and $n_{Endometrial}$ = 11,167, $n_{Melanoma}$ =11,627 excluded). Additionally, when we studied incident malignant melanoma, teachers who were not non-Hispanic white were further excluded (*n* = 15,733 excluded), as non-Hispanic whites comprise 87% of the CTS cohort. Based upon the above-mentioned exclusion criteria, of the 133,479 female teachers and school administrators in the CTS study population-base- we observed the analytic sample numbers for those truly at-risk for the cancers of interest to be as shown in **Figure 2.2**

FIGURE 2.2: Flowchart of the study selection process of Aim 1 analytic sample

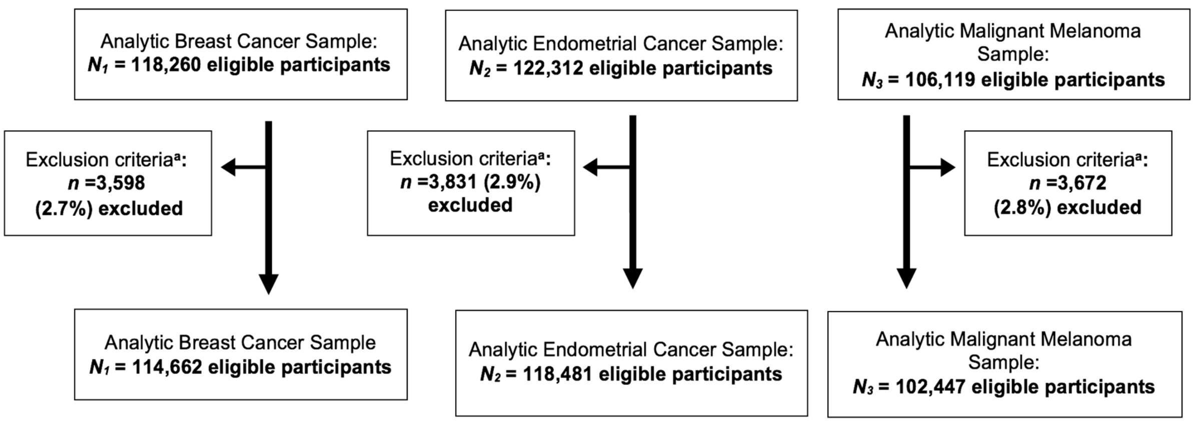


[a]Exclusion criteria 1 included participants who were diagnosed with the cancer of interest prior to baseline (breast cancer: 6,212 excluded; endometrial cancer: 1,619 excluded; malignant melanoma: 2,079 excluded), those who had an unknown prior history of cancer, those who voluntarily withdrew from the CTS (n=1 excluded), and those who did not reside in California prior to baseline (n=8,867 excluded)
[b]Further exclusion included those teachers who consented to participate only in breast cancer research (n=18 excluded).
[c]For malignant melanoma analyses, additional exclusions included CTS participants who were not non-Hispanic white (i.e. Hispanic, Black, Native American, Asian/Pacific Islander, Other) (n=15,733 excluded).

.

Given our interest in incident cancer risk among teachers according to their occupational characteristics, further exclusions for Aim 2 included CTS teachers who lacked complete data concerning the occupational characteristics of interest (i.e. teacher type, duration of employment, number of schools throughout employment, occupational stress, occupational physical activity, and power lines near school). Excluding those with missing information for the occupational exposures of interest helps to ensure the examination of cancer risk among teachers according to occupational characteristics is conducted among a uniform group of teachers which prevents the introduction of any additional biases due to missingness. Therefore, after implementing the necessary exclusion criteria for Aim 2- we observed the following number of teachers to be at-risk for the cancers of interest and have complete occupational characteristic data (**Figure 2.3**).

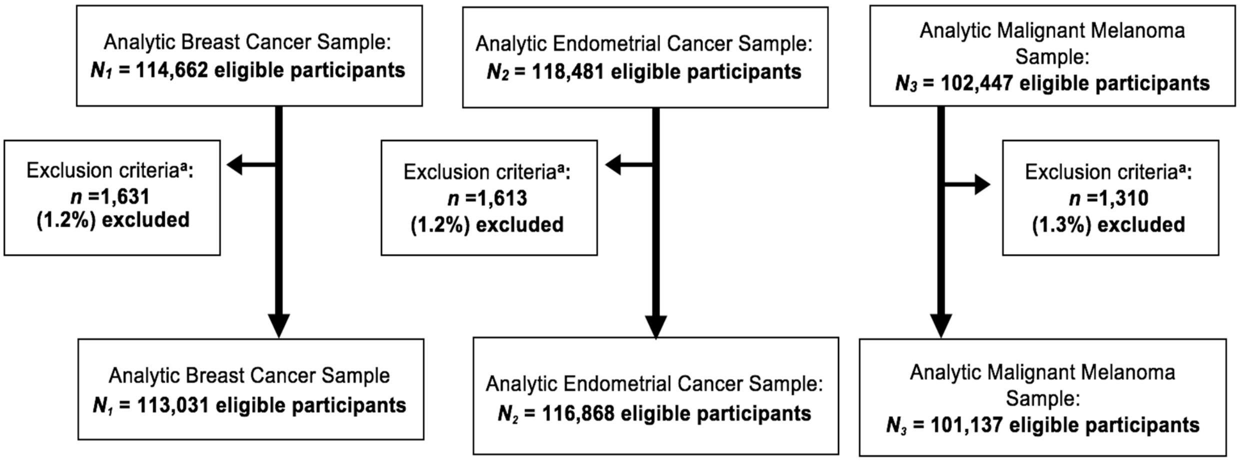
FIGURE 2.3: Flowchart of the study selection process of Aim 2 analytic sample



[a] Exclusion criteria for Aim 2 analyses included further exclusions of CTS teachers who lacked complete data regarding their occupational characteristic information.

For the third aim of our study, we further excluded those teachers who had missing information for the medication intakes of interest. Building upon the exclusions from Aim 1 and 2 analyses ensures the study examines the risk in the most uniform analytic cohort across the three specific aims of this study. Specifically, teachers who lacked complete data for the frequency and duration of aspirin, ibuprofen, acetaminophen, and statin use were further excluded from the Aim 3 analyses (**Figure 2.4**).

FIGURE 2.4: Flowchart of the study selection process of Aim 3 analytic sample



[a] Exclusion criteria for Aim 3 analyses included further exclusions of CTS teachers who lacked complete data regarding their medication intake characteristic information.

2.3. Summary of statistical analyses

2.3.1. Cancer Incidence Rates

Only primary tumors, as defined by ICD-10 codes, diagnosed from 1995-2013 were included in the analysis. Incidence rates were calculated using the first eighteen years of follow-up from date of entry through December 31, 2013. Cancer incidence rates were computed in the overall analytic samples and among occupational characteristic subgroups. Incidence rates were calculated for the following occupational characteristics. Additionally, *when applicable*, cancer incidence rates according to occupational characteristics were computed among prognostic subgroups of teachers in the CTS (i.e. recreational physical activity, etc.). In this analysis, cancer incidence rates are reported among the following age-specific subgroups: <50, 50-69, and ≥70 years old. Moreover, incidence rates were age-standardized (to the 2000 US population) and compared to the age-standardized statewide incidence rates of California women from 1995 to 2013 via the California Cancer Registry. Lastly, we calculated rate ratios (RR) comparing the age-adjusted incidence rates of teachers in the CTS to those for California women, and estimated the 95% confidence interval for the $\log_e$RR.

2.3.2. Incident cancer risk according to occupational characteristics and exposures

Multivariable Cox proportional hazards regression models, using age (in days) as the time metric and stratified by age at baseline (in years), were utilized to estimate hazard ratios (HRs) along with 95% confidence intervals (95% CIs) of breast cancer (in situ and invasive), endometrial cancer (invasive), and malignant melanoma (in situ and invasive) according to the occupational characteristics and medication intakes of teachers. The occupational characteristics we examined in relation to risk for these three cancer types were: teacher type, number of school throughout employment, years of employment in school system, occupational physical activity, power lines near school, and occupational stress. Furthermore, the medication intake exposures we examined were: aspirin, ibuprofen, acetaminophen, statins. As with the calculation of cancer incidence rates, all primary incident cases occurring after study entry and prior to the end of study follow-up (December 31, 2013) were included in this analysis. The proportional hazard assumption was assessed through modeling interaction terms of follow-up time with each of the occupational characteristics and medication intakes of interest. The cancer-specific cox regression models contained distinct adjustments in regards to specific confounders for each cancer type and all relevant potential confounders were determined *a priori*. The final multivariable models for each cancer type were constructed based on the evidence for parsimoniousness (i.e. lower AIC and

BIC values, Higher LRT and F-statistic values) as determined through a stepwise model-selection process (*critical value* (α) ≤ 0.05).

In addition, secondary effect modification analyses were conducted through modeling multiplicative interaction terms and models stratified by potential effect modifier (i.e. recreational physical activity, BMI, etc.) to better explain associations observed in the overall study population. When necessary, Wald's test for trend were carried out across the semi-quantitative occupational characteristics and medication intakes by using an ordinal variable coded as the median value of the characteristic category. All statistical tests were 2-sided and conducted with SAS software (version 9.4; SAS Institute). Each statistical method used for each specific aim will be further discussed in subsequent chapters: *Chapters 3, 4, & 5*.

CHAPTER 3

Rates of Breast Cancer, Endometrial Cancer, and Malignant Melanoma Development Among Teachers and California Women

3.1 INTRODUCTION

Teachers as an occupational group have been shown to be at an increased risk for developing the most common cancers, including breast and melanoma, relative to the general population [**2-5**]. Specifically, female teachers were shown to have an elevated risk of breast cancer (67% higher), endometrial cancer (72% higher), and malignant melanoma (59% higher) than the general population (based on US race-specific statewide incidence rates) [**2**]. Similar findings have been reported for teachers worldwide [**6-12**]. Moreover, past studies have reported female teachers to have notably higher rates of mortality from malignant melanoma (MM), breast, and endometrial cancers compared to the general population [**73-74**]. Although findings suggest teachers have uniquely higher risks of breast cancer, endometrial cancer, and malignant melanoma, no definitive evidence regarding teacher-specific occupational risk factors driving this higher risk in cancer incidence have been established.

The longitudinal California Teachers Study (CTS) has provided an ideal study population to examine associations among professional school employees (i.e. teachers, administrators.) to the risk of developing various cancers [**42-43, 75-76**]. Yet, these past investigations into cancer risk of teachers in the CTS have been more focused on lifestyle exposures (i.e. diet, BMI, etc.), and have not addressed the relative incidence of teachers as a group according to their occupational characteristics (i.e. teacher type, length of employment, occupational physical activity, etc.).

With the reported higher cancer incidence rates among teachers, research addressing occupational characteristics and risk of various incident cancers in teachers has the potential to lower this rate by improving recommendations, policy, and advocacy. Therefore, the purpose of this study is to compare the rate of breast cancer, endometrial cancer, and malignant melanoma development according to the occupational characteristics among teachers of the large prospective California Teachers Study to the rates observed in the general population of California women.

3.2 METHODS

A detailed description of the California Teachers Study (CTS) population, selection process of the analytic cohort, and assessment of teacher's occupational characteristics can be found in Chapter 2.

3.2.1 Cancer incidence rates

Of 133,479 female teachers and school administrators in the CTS study population, 118,260, 122,312, and 106,119 teachers were found to be truly at-risk of breast cancer, endometrial cancer, and malignant melanoma at study entry, respectively. Cancer diagnoses of interest among participants were identified through annual linkage with the CCR. Only primary tumors, as defined by ICD-10 codes, diagnosed from 1995-2013 were included in the analysis. Incidence rates were calculated using the first eighteen years of follow-up from date of entry through December 31, 2013. Person-months of follow-up were accrued from the date of receipt for the completed baseline questionnaire until the date of cancer diagnosis, death, move out of California, or end of study follow-up (i.e. December 31, 2013), whichever occurs first.

Cancer incidence rates were computed in the overall analytic samples and among occupational characteristic subgroups. Incidence rates were calculated for the following occupational characteristics: teacher type (multiple subjects, single subject, pupil services, administrator, multiple roles/other), number of school throughout employment (schools: 1, 2-3, ≥4), years of employment in school system (years: <10, 10-19, ≥20), occupational physical activity (hours/day: none, ≤1, 2-6, ≥7), power lines near school (no, yes, unsure), and occupational stress (stress level: low-risk, moderate-risk, high-risk). Additionally, *when applicable*, cancer incidence rates according to occupational characteristics were computed among prognostic subgroups of teachers in the CTS (i.e. recreational physical activity, BMI, etc.).

3.2.1.1 Age-Specific and age-standardized incidence rates

The above-mentioned CTS cancer incidence rates are reported as age-specific incidence rates (ASIR) among the following age-specific subgroups: <50, 50-69, and ≥70 years old. Moreover, incidence rates were age-standardized (to the 2000 US population) and compared to the age-standardized statewide incidence rates of California women from 1995 to 2013 via the California Cancer Registry. Lastly, we calculated rate ratios (RR) comparing the age-standardized incidence rates of teachers in the CTS to those for California women, and estimated the 95% confidence interval for the $\log_e$RR.

3.3 RESULTS

3.3.1 Age-standardized incidence rates in the CTS study cohort

Table 3.1 shows the average annual age-adjusted incidence rates (standardized to the 2000 US population) for invasive and in situ breast cancer among eligible CTS participants overall and according to their occupational characteristics. The maximum length of follow-up since study entry was 218 months (1995-2013). Throughout the entire study follow-up, 5,962 and 1,440 teachers were diagnosed with invasive and in situ breast cancer, respectively. These incidence rates were compared to those for women age 20 years or older in California for the years 1995 through 2013. We observed the age-standardized breast cancer incidence rates for teachers in the CTS to be 155.3 and 38.0 per 100,000 woman-years for invasive and in situ tumor types, respectively. The results align with findings from previous reports of high rates of breast cancer among teachers, with relative excess risk in the CTS of 23% and 40% for invasive and in situ cancer types, respectively, compared to the general female population of California. The age-adjusted invasive breast cancer incidence rate for CTS teachers sitting throughout the entire work day, 176.4 per 100,000 woman-years, was 40% higher than that of comparable California women. The rate of in situ breast cancer was substantially elevated for those working in pupil services (RR 1.67, 95% CI: 1.34-2.11) and multiple roles (RR 1.49, 95% CI: 1.30-1.74) relative to California women. Moreover, the relative excess incidence of in situ breast cancer was similarly large for those teachers employed for twenty years or more (59% higher), and those teachers standing or walking at work for one hour or less per day (64% higher).

Results from the secondary stratified analyses provided evidence the rate of invasive breast cancer development for decreased occupational physical activity levels was not attenuated by higher levels of recreational physical activity among teachers (recreational physical activity of <1.5 hrs./wk.: 41% higher, recreational physical activity of ≥1.5 hrs./wk.: 43% higher), nor lower levels of BMI of among the eligible CTS teachers (RR among BMI <25 kg/m^2 teachers: 1.43, 95% CI 1.32-1.55) (**Table 3.2**). As expected, the rate of invasive breast cancer among premenopausal teachers was not elevated by lower levels of occupational physical activity (RR 0.97, 95% CI: 0.71-1.32).

Table 3.1- Average annual age-adjusted breast cancer incidence rates among members of CTS cohort and CA women, 1995-2013 (*N*= 118,260)

	Invasive Breast Cancer AAIR (*n* cases)	In Situ Breast Cancer AAIR (*n* cases)	Invasive BrCa Rate Ratio (95% CI)	In Situ BrCa Rate Ratio (95% CI)
CA Women 1995-2013 (CCR)	126.3	27.2	*1.00 (ref.)*	*1.00 (ref.)*
CTS teachers overall:	155.3 (5,962)	38.0 (1,440)	1.23 (1.19-1.26)	1.40 (1.33-1.47)
Characteristic:				
Teacher type:				
Multiple subject teachers	154.7 (3,007)	36.7 (719)	1.22 (1.18-1.27)	1.35 (1.26-1.46)
Single subject teachers	156.5 (1,541)	38.7 (373)	1.24 (1.18-1.31)	1.42 (1.30-1.59)
Pupil services	142.1 (249)	45.4 (75)	1.12 (0.99-1.27)	1.67 (1.34-2.11)
Administrators	157.9 (201)	35.8 (43)	1.25 (1.08-1.44)	1.32 (0.99-1.80)
Multiple roles, other	151 (777)	40.4 (188)	1.20 (1.11-1.28)	1.49 (1.30-1.74)
Number of schools throughout employment:				
1 school	151.6 (854)	37.8 (214)	1.20 (1.12-1.28)	1.39 (1.22-1.59)
2-3 schools	153 (2,349)	36.7 (565)	1.21 (1.16-1.26)	1.35 (1.24-1.47)
≥4 schools	156.7 (2,572)	39.2 (619)	1.24 (1.20-1.29)	1.44 (1.33-1.56)
Years of employment in school system:				
< 10 yrs.	146.8 (938)	36.8 (265)	1.16 (1.10-1.25)	1.35 (1.20-1.53)
10-19 yrs.	155.2 (1,731)	36.0 (420)	1.23 (1.17-1.29)	1.32 (1.20-1.46)
≥20 yrs.	148.8 (3,106)	43.3 (713)	1.18 (1.14-1.22)	1.59 (1.48-1.72)
Occupational physical activity:				
none	176.4 (1,036)	41.4 (200)	1.40 (1.31-1.49)	1.52 (1.33-1.75)
≤1 hr./day	161.5 (796)	44.7 (197)	1.28 (1.19-1.37)	1.64 (1.43-1.89)
2-6 hrs./day	149 (3,254)	37.4 (827)	1.18 (1.14-1.22)	1.38 (1.29-1.47)
≥7 hrs./day	151.7 (689)	34.7 (174)	1.20 (1.11-1.29)	1.28 (1.10-1.48)
Power lines near school:				
No power lines present	157.1 (769)	37.1 (195)	1.24 (1.16-1.34)	1.37 (1.19-1.57)
Power lines present	153.8 (3,520)	37.7 (871)	1.22 (1.18-1.26)	1.39 (1.30-1.48)
Don't Know	157.6 (1,486)	39.5 (332)	1.25 (1.19-1.31)	1.45 (1.31-1.62)
Occupational stress[1]:				
Low Stress	154.8 (310)	45.4 (90)	1.23 (1.10-1.37)	1.67 (1.36-2.06)
Moderate Stress	156.9 (908)	39.0 (228)	1.24 (1.16-1.33)	1.43 (1.26-1.63)
High Stress	166.6 (2,573)	39.5 (627)	1.32 (1.27-1.37)	1.45 (1.34-1.57)

Rates calculated using the US 2000 Standard population age distribution, AAIR depicted as rate per 100,000 woman-years.

Age distribution for eligible CTS population ranges from 22-104 y.

[1] Rates computed only among those respondents of the third follow-up questionnaire (Spring 2000) who had no prior breast cancer diagnosis (*n*=67,934).

Table 3.2- Average annual age-adjusted invasive breast cancer incidence rates according to occupational physical activity among subgroups of CTS teachers (1995-2013) (*N*= 118,260)[1]

		Occupational physical activity		
		>1 hrs./day	**≤1 hr./day**	**none**
CTS teachers overall:	**AAIR (*n* cases)**	149.9 (3,943)	161.5 (796)	176.4 (1,036)
	RR (95% CI)	1.19 (1.15-1.22)	1.28 (1.19-1.37)	1.40 (1.31-1.49)
Recreational physical activity:				
<1.5 hrs./wk.	**AAIR (*n* cases)**	150.1 (1,827)	170.5 (404)	178 (471)
	RR (95% CI)	1.19 (1.14-1.24)	1.35 (1.22-1.49)	1.41 (1.29-1.54)
≥ 1.5 hrs./wk.	**AAIR (*n* cases)**	149.8 (2,116)	150.4 (392)	180.8 (565)
	RR (95% CI)	1.19 (1.14-1.24)	1.19 (1.08-1.31)	1.43 (1.32-1.55)
BMI[2]:				
< Overweight	**AAIR (*n* cases)**	147.3 (2,359)	159.2 (456)	181.1 (597)
	RR (95% CI)	1.17 (1.12-1.21)	1.26 (1.15-1.38)	1.43 (1.32-1.55)
≥ Overweight	**AAIR (*n* cases)**	153.1 (1,584)	165.6 (340)	159.3 (439)
	RR (95% CI)	1.21 (1.15-1.27)	1.31 (1.18-1.46)	1.26 (1.15-1.38)
Menopausal status:				
Premenopausal	**AAIR (*n* cases)**	114.0 (1,220)	124.6 (220)	122.1 (39)
	RR (95% CI)	0.90 (0.85-0.95)	0.99 (0.86-1.13)	0.97 (0.71-1.32)
Postmenopausal	**AAIR (*n* cases)**	150.7 (2,723)	127.4 (576)	158.8 (997)
	RR (95% CI)	1.19 (1.15-1.24)	1.01 (0.92-1.09)	1.26 (1.18-1.34)

[1] Rates calculated using the US 2000 Standard population age distribution, age-adjusted incidence rates (AAIR) depicted as rate per 100,000. Rate ratio (RR) compares the age-adjusted incidence rate of CTS teachers to the rate of California women from 1995-2013 (AAIR-California Women= 126.3 per 100,000 woman-years).

[2] Overweight as defined by clinical BMI cutpoints, < Overweight: <25 kg/m^2 and ≥ Overweight: ≥25 kg/m^2.

Table 3.3 shows the comparison between average annual incidence rates for endometrial cancer among CTS teachers and California women. Throughout the follow-up period, 1,400 incident endometrial cancer cases were identified among teachers in the study cohort. The average annual incidence rate of endometrial cancer among teachers was observed to be 27.3 per 100,000 woman-years. In relation of teacher's risk to the general population, we found the rate of endometrial cancer development among teachers to be 21% higher than that of comparable California women (RR 1.21, 95% CI: 1.15-1.27). This relative excess in endometrial cancer was not limited to teachers overall, but was notably higher when examining their risk according to occupational characteristics. The age-adjusted incidence rate of those CTS teachers standing or walking at work for one hour or less per day, 29.7 per 100,000 woman-years, was substantially elevated than expected based on the statewide rate after eighteen years of follow-up (RR 1.32, 95% CI: 1.20-1.45). Additionally, the endometrial cancer incidence rate for teachers in the CTS with multiple roles was 31% greater than that of California women (RR 1.31, 95% CI: 1.14-1.50).

Table 3.4 shows the average annual incidence rates for invasive endometrial cancer according to occupational physical activity levels among teacher subgroups of the CTS. In the overall analytic sample, we observed the age-adjusted incidence rate for teachers with ≤1 hr./day of occupational physical activity to be 32% higher than the average-annual rate among general California women (RR 1.32, 95% CI: 1.20-1.45). Upon further analyses, the relative excess incidence for minimal occupational physical activity was notably exacerbated among teachers with greater recreational physical activity levels (i.e. ≥1.5 hrs./wk.). Specifically, the age-adjusted incidence rate among teachers of the CTS with greater recreational physical activity levels and ≤1 hr./day of occupational physical activity, 32.1 per 100,000 woman-years, was 42% higher than that of comparable California women (RR 1.42, 95% 1.25-1.62). Conversely, the rate according to occupational physical activity levels was not monotonically inverse among teachers with lower levels of recreational physical activity (occupational physical activity: >1 hr./day: 28% higher vs. ≤1 hr./day: 23% higher). Additionally, this elevated rate of invasive endometrial cancer for sedentary occupational practices of teachers compared to the general population was limited to teachers with BMIs ≥ 25 kg/m^2 (i.e. overweight and obese) (RR among ≥ overweight teachers: 1.75, 95%: 1.53-2.00). While the risk among normal and underweight teachers did not significantly differ from the general female population of California according to their occupational physical activity levels (RR among < overweight teachers: 1.07, 95% CI: 0.94-1.22).

Table 3.3- Average annual age-adjusted endometrial cancer incidence rates among members of CTS cohort and CA women, 1995-2013 (*N*= 122,312)		
	Invasive Endometrial Cancer	
	AAIR (*n* Cases)	**Rate Ratio (95% CI)**
CA Women 1995-2013 (CCR)	22.6	*1.00 (ref.)*
CTS teachers overall:	27.3 (1,400)	1.21 (1.15-1.27)
Characteristic:		
Teacher type:		
Multiple subject teachers	26.7 (688)	1.18 (1.09-1.27)
Single subject teachers	28.4 (368)	1.26 (1.14-1.40)
Pupil services	24.7 (57)	1.10 (0.84-1.42)
Administrators	16.2 (30)	0.72 (0.51-1.03)
Multiple roles, other	29.6 (208)	1.31 (1.14-1.50)
Number of schools throughout employment:		
1 school	28.1 (204)	1.25 (1.08-1.43)
2-3 schools	28.1 (568)	1.25 (1.15-1.35)
≥4 schools	26.1 (579)	1.16 (1.07-1.25)
Years of employment in school system:		
< 10 yrs.	25.6 (189)	1.14 (0.98-1.31)
10-19 yrs.	26.0 (389)	1.15 (1.04-1.27)
≥20 yrs.	26.7 (773)	1.19 (1.11-1.27)
Occupational physical activity:		
≤1 hr./day	29.7 (439)	1.32 (1.20-1.45)
2-6 hrs./day	27.5 (788)	1.22 (1.14-1.31)
≥7 hrs./day	21.0 (124)	0.93 (0.78-1.11)
Power lines near school:		
No power lines present	29.9 (193)	1.33 (1.15-1.53)
Power lines present	27.1 (820)	1.20 (1.12-1.29)
Don't Know	25.4 (338)	1.13 (1.01-1.25)
Occupational stress[1]:		
Low Stress	32.5 (86)	1.44 (1.17-1.78)
Moderate Stress	25.7 (211)	1.14 (0.99-1.30)
High Stress	26.5 (557)	1.17 (1.08-1.28)

Rates calculated using the US 2000 Standard population age distribution, AAIR depicted as rate per 100,000 woman-years.
Age distribution for eligible CTS population ranges from 22-104 y.
[1] Rate computed for those respondents of the third follow-up questionnaire (Spring 2000) who had no prior endometrial cancer diagnosis (*n*=70,284).

Table 3.4- Average annual age-adjusted invasive endometrial cancer incidence rates according to occupational physical activity among subgroups of CTS teachers (1995-2013) (*N*= 122,312)[1]

		Occupational physical activity	
		>1 hrs./day	**≤1 hr./day**
CTS teachers overall:	**AAIR (*n* cases)**	26.3 (912)	29.7 (439)
	RR (95% CI)	1.17 (1.09-1.24)	1.32 (1.20-1.45)
Recreational physical activity:			
<1.5 hrs./wk.	**AAIR (*n* cases)**	28.9 (454)	27.7 (204)
	RR (95% CI)	1.28 (1.17-1.41)	1.23 (1.07-1.41)
≥ 1.5 hrs./wk.	**AAIR (*n* cases)**	24.1 (458)	32.1 (235)
	RR (95% CI)	1.07 (0.98-1.17)	1.42 (1.25-1.62)
BMI[2]:			
< Overweight	**AAIR (*n* cases)**	20.7 (437)	24.2 (226)
	RR (95% CI)	0.92 (0.83-1.01)	1.07 (0.94-1.22)
≥ Overweight	**AAIR (*n* cases)**	35.8 (475)	39.4 (213)
	RR (95% CI)	1.59 (1.45-1.74)	1.75 (1.53-2.00)

[1] Rates calculated using the US 2000 Standard population age distribution, age-adjusted incidence rates (AAIR) depicted as rate per 100,000. Rate ratio (RR) compares the age-adjusted incidence rate of CTS teachers to the rate of California women from 1995-2013 (AAIR-California Women= 126.3 per 100,000 woman-years).

[2] Overweight as defined by clinical BMI cutpoints, < Overweight: <25 kg/m^2 and ≥ Overweight: ≥25 kg/m^2.

The average annual incidence rate of malignant melanoma in CTS teachers and California women are shown in **Table 3.5**. In total, 1,015 and 904 teachers developed invasive and in situ melanoma throughout follow-up, respectively. The age-adjusted incidence rate of malignant melanoma (MM) in teachers of the CTS was observed to be 33.6 and 26.1 per 100,000 woman-years for invasive and in situ tumor types, respectively. These rates of MM in the CTS show teachers as having substantially higher risk of MM (invasive: 44% higher; in situ: 82% higher) when compared to average annual rates of non-Hispanic white California women. Most notably, the rate of invasive MM among CTS teachers who stand or walk at work for one hour or less per day was double that of comparable California women (RR 2.00, 95% CI: 1.79-2.23) and monotonic in trend. Moreover, we observed substantially elevated invasive MM risk among teachers in the CTS with multiple roles (2.05-fold higher), and two to three schools throughout employment (1.65-fold higher) relative to the risk of comparable California women. The rates of in situ MM in single-subject teachers (i.e. junior high, high school) were 96% higher than would be expected based on the statewide rate after eighteen years of follow-up.

The examination of the rate of invasive MM among teachers according to subgroups defined by recreational physical activity and BMI levels are shown in **Table 3.6**. In the overall analytic sample, minimal occupational physical activity (i.e. ≤1 hr./day) was observed to elevate the risk of invasive MM development by 2-fold than would be expected based on race-specific statewide incidence rates after eighteen years of follow-up. Notably, the relative excess of invasive malignant melanoma for minimal occupational physical activity was substantially exacerbated among teachers of the CTS with lower levels of recreational physical activity (2.44-fold higher). Additionally, we observed lesser but still elevated rates of malignant melanoma development for minimal occupational physical activity among teachers with greater levels of recreational physical activity (RR for occupational physical activity of ≤1 hr./day: 1.53, 95% CI: 1.32-1.77). Moreover, the rate of invasive malignant melanoma for decreased occupational physical activity levels was more pronounced among teachers who are not overweight (i.e. <25 kg/m^2) in which the age-standardized incidence rate for ≤1 hr./day of occupational physical activity corresponded with a 2.14-fold increase when compared to general California women (RR 2.14, 95% CI: 1.86-2.46). The rate of invasive malignant melanoma development among overweight and obese teachers was observed to be lesser but still elevated than comparable California women (RR for occupational physical activity of ≤1 hr./day among normal and underweight teachers: 1.72, 95% CI: 1.44-2.04).

Table 3.5- Average annual age-adjusted malignant melanoma incidence rates among members of CTS cohort and CA women, 1995-2013 (*N*=106,119)				
	Invasive Melanoma AAIR (*n* cases)	**In Situ Melanoma AAIR (*n* cases)**	**Invasive Melanoma Rate Ratio (95%CI)**	**In Situ Melanoma Rate Ratio (95%CI)**
CA Women 1995-2013 (CCR)	23.3	14.3	*1.00 (ref.)*	*1.00 (ref.)*
CTS teachers overall:	33.6 (1,048)	26.1 (932)	1.44 (1.35-1.53)	1.82 (1.71-1.95)
Characteristic:				
Teacher type:				
Multiple subject teachers	34.0 (560)	24.8 (464)	1.46 (1.34-1.58)	1.73 (1.58-1.90)
Single subject teachers	30.9 (257)	28.1 (236)	1.33 (1.17-1.50)	1.96 (1.73-2.23)
Pupil services	29.4 (42)	24.3 (45)	1.26 (0.93-1.71)	1.69 (1.27-2.27)
Administrators	28.3 (40)	24.5 (29)	1.21 (0.89-1.65)	1.71 (1.19-2.46)
Multiple roles, other	47.8 (116)	26.0 (130)	2.05 (1.71-2.46)	1.82 (1.53-2.16)
Number of schools throughout employment:				
1 school	29.7 (152)	27.7 (144)	1.27 (1.09-1.49)	1.93 (1.64-2.28)
2-3 schools	38.5 (449)	26.0 (394)	1.65 (1.50-1.81)	1.82 (1.64-2.01)
≥4 schools	26.4 (414)	25.4 (366)	1.13 (1.03-1.25)	1.77 (1.60-1.97)
Years of employment in school system:				
< 10 yrs.	34.5 (225)	25.5 (173)	1.48 (1.30-1.69)	1.78 (1.53-2.07)
10-19 yrs.	33.1 (292)	23.7 (280)	1.42 (1.27-1.59)	1.66 (1.47-1.86)
≥20 yrs.	21.6 (498)	24.4 (451)	0.93 (0.85-1.01)	1.70 (1.55-1.87)
Occupational physical activity:				
≤1 hr./day	46.6 (328)	21.7 (241)	2.00 (1.79-2.23)	1.52 (1.33-1.72)
2-6 hrs./day	33.1 (589)	26.8 (558)	1.42 (1.31-1.54)	1.87 (1.72-2.04)
≥7 hrs./day	26.1 (98)	26.4 (105)	1.12 (0.92-1.36)	1.84 (1.52-2.23)
Power lines near school:				
No power lines present	32.4 (150)	25.3 (130)	1.39 (1.18-1.63)	1.77 (1.49-2.10)
Power lines present	33.3 (625)	25.9 (548)	1.43 (1.32-1.55)	1.81 (1.66-1.97)
Don't Know	34.9 (240)	25.8 (226)	1.50 (1.32-1.70)	1.80 (1.58-2.05)
Occupational stress[1]:				
High-risk	22.8 (373)	20.4 (139)	0.98 (0.88-1.08)	1.42 (1.21-1.68)
Low-risk	21.8 (173)	16.4 (370)	0.93 (0.81-1.09)	1.15 (1.03-1.27)

Rates calculated using the US 2000 Standard population age distribution, AAIR depicted as rate per 100,000 woman-years.
Age distribution for eligible CTS population ranges from 22-104 y.
[1] Rate computed for those respondents of the third follow-up questionnaire (Spring 2000) who had no prior malignant melanoma diagnosis (*n*=62,328).

Table 3.6- Average annual invasive malignant melanoma incidence rates according to occupational physical activity among subgroups of CTS teachers (1995-2013) (*N*=106,119)[1]

		Occupational physical activity		
		≥ 7 hrs./day	**2-6 hrs./day**	**≤1 hr./day**
CTS teachers overall	**AAIR (*n* cases)**	26.1 (98)	33.1 (589)	46.6 (328)
	RR (95% CI)	1.12 (0.92-1.36)	1.42 (1.31-1.54)	2.00 (1.79-2.23)
Recreational physical activity:				
< 1.5 hrs./wk.	**AAIR (*n* cases)**	22.9 (40)	27.7 (226)	57.0 (151)
	RR (95% CI)	0.98 (0.72-1.34)	1.19 (1.04-1.35)	2.44 (2.08-2.87)
≥ 1.5 hrs./wk.	**AAIR (*n* cases)**	28.2 (58)	37.6 (363)	35.7 (177)
	RR (95% CI)	1.21 (0.93-1.56)	1.61 (1.45-1.79)	1.53 (1.32-1.77)
BMI[2]:				
< Overweight	**AAIR (*n* cases)**	28.4 (65)	34.4 (375)	49.9 (197)
	RR (95% CI)	1.22 (0.95-1.55)	1.48 (1.33-1.63)	2.14 (1.86-2.46)
≥ Overweight	**AAIR (*n* cases)**	20.0 (33)	29.9 (214)	40.0 (131)
	RR (95% CI)	0.86 (0.61-1.21)	1.28 (1.12-1.47)	1.72 (1.44-2.04)

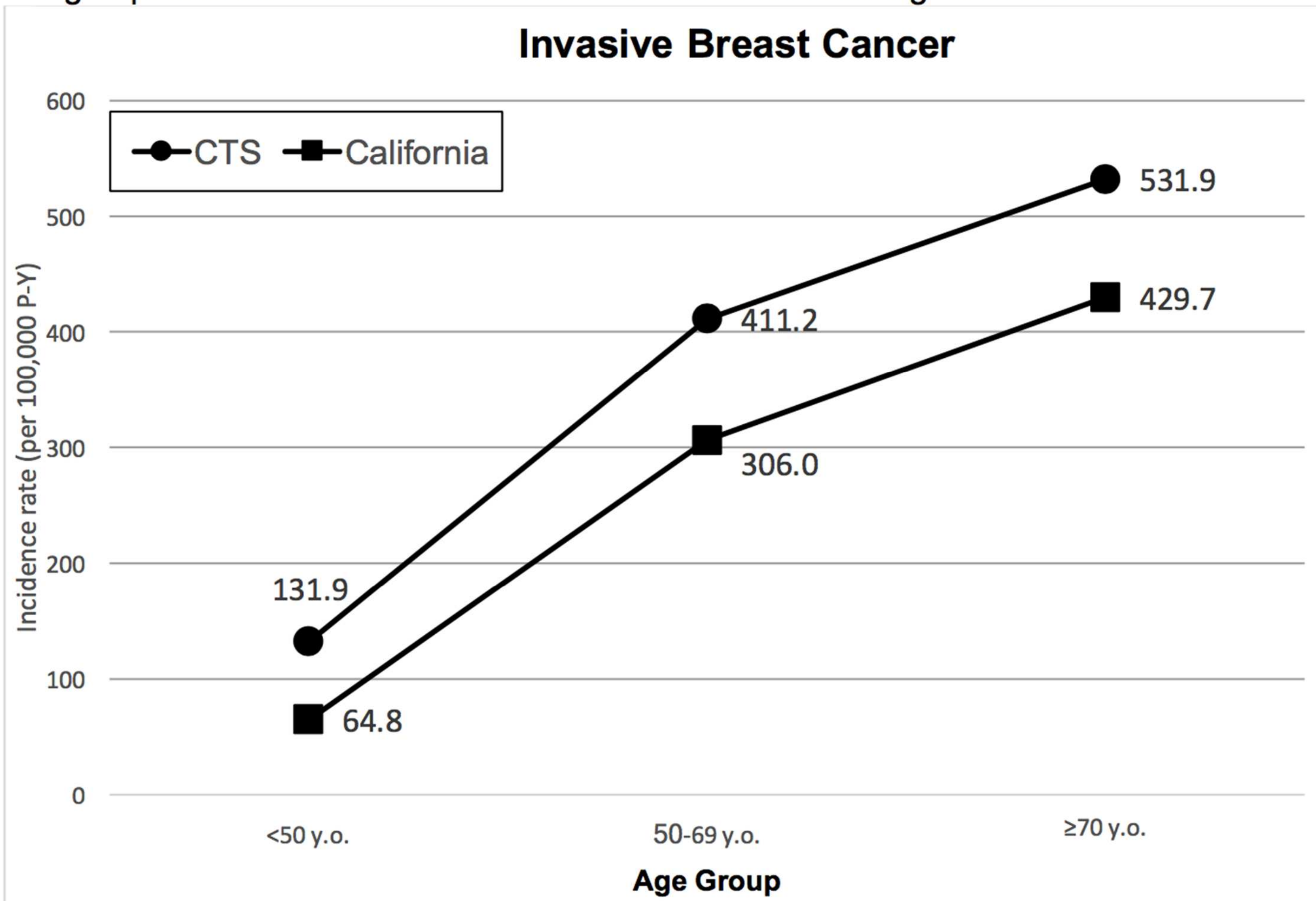
[1] Rates calculated using the US 2000 Standard population age distribution, age-adjusted incidence rates (AAIR) depicted as rate per 100,000 woman-years. Rate ratio (RR) compares the age-adjusted incidence rate of CTS teachers to the rate of California women from 1995-2013 (AAIR Invasive = 23.3, AAIR In Situ = 14.3).

[2] Overweight as defined by clinical BMI cut-points, < Overweight: <25 kg/m^2 and ≥ Overweight: ≥25 kg/m^2.

3.3.2 Overall age-specific incidence rates in the CTS study cohort

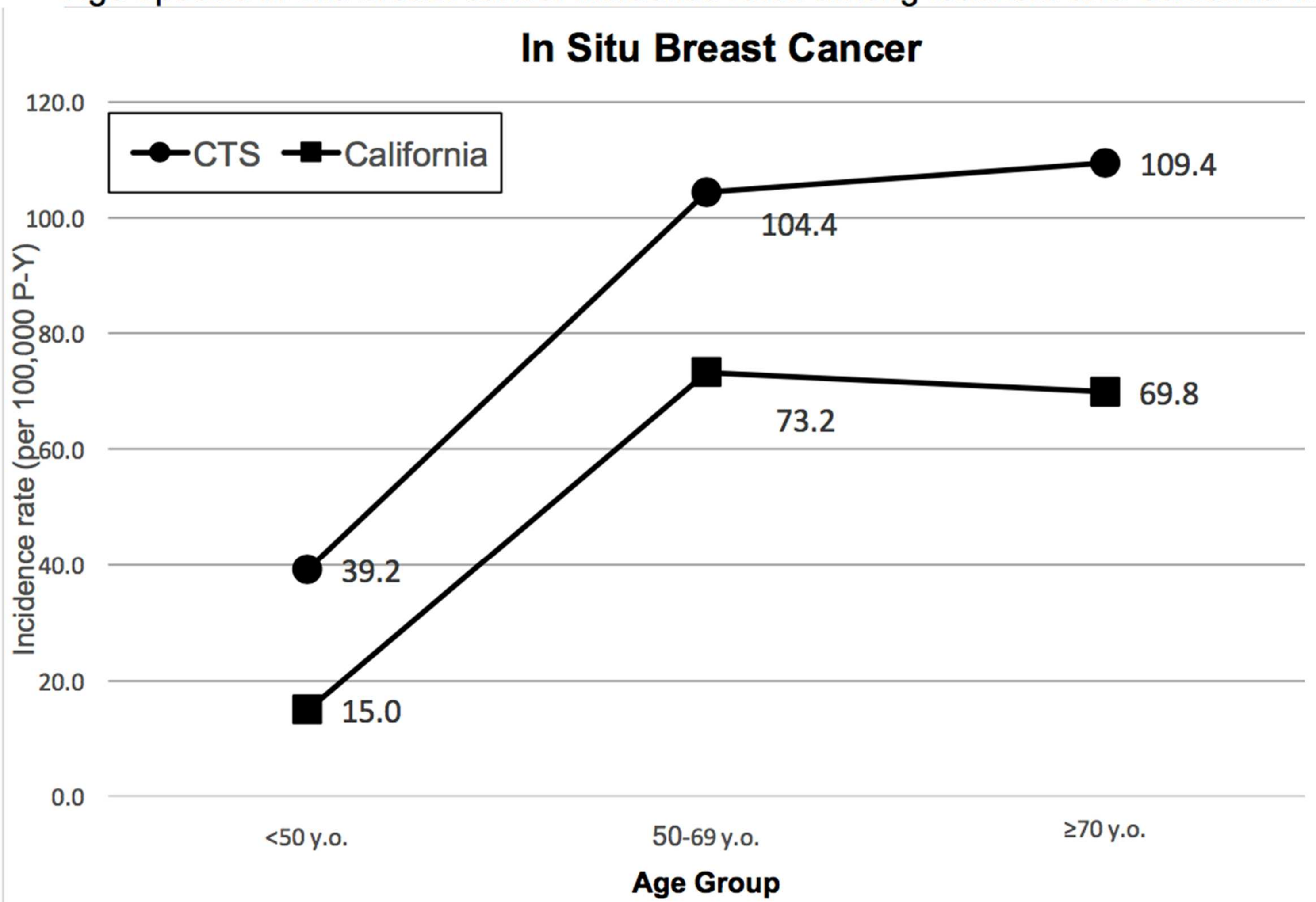
The relative excess cancer incidence among CTS teachers compared to the general female population of California can be seen across all age groups in **Figures 3.1A-E**. The age-specific incidence rate of invasive breast cancer was observed to be 131.9, 411.2, and 531.9 cases per 100,000 woman-years for teachers aged <50 y, 50-69 y, and ≥70 y; respectively. These observed rates were higher than the rates of comparable California women across all age groups (**Figure 3.1A**). Similarly, in situ breast cancer risk was notably higher among teachers of the CTS when compared to the age-specific incidence rates of general California women (CTS vs. CA ASIRs per 100,000 w-y, <50 y: 39.2 vs. 15.0; 50-69 y: 104.4 vs. 73.2; ≥70 y: 109.4 vs. 69.8) (**Figure 3.1B**). Moreover, the rate of endometrial cancers among teachers across the various age groups was observed to be higher than the rates among comparable CA women (CTS vs. CA ASIRs per 100,000 w-y, <50 y:10.2 vs. 7.6; 50-69 y: 82.0 vs. 65.5; ≥70 y: 115.4 vs. 76.6) (**Figure 3.1C**). Lastly, we observed a similar relative excess incidence of malignant melanoma (invasive and in situ tumor types) among teachers of the CTS when compared to the statewide age-specific incidence rates from 1995-2013 (**Figures 3.1D-E**).

Figure 3.1A: Age-specific invasive breast cancer incidence rates among teachers and California women



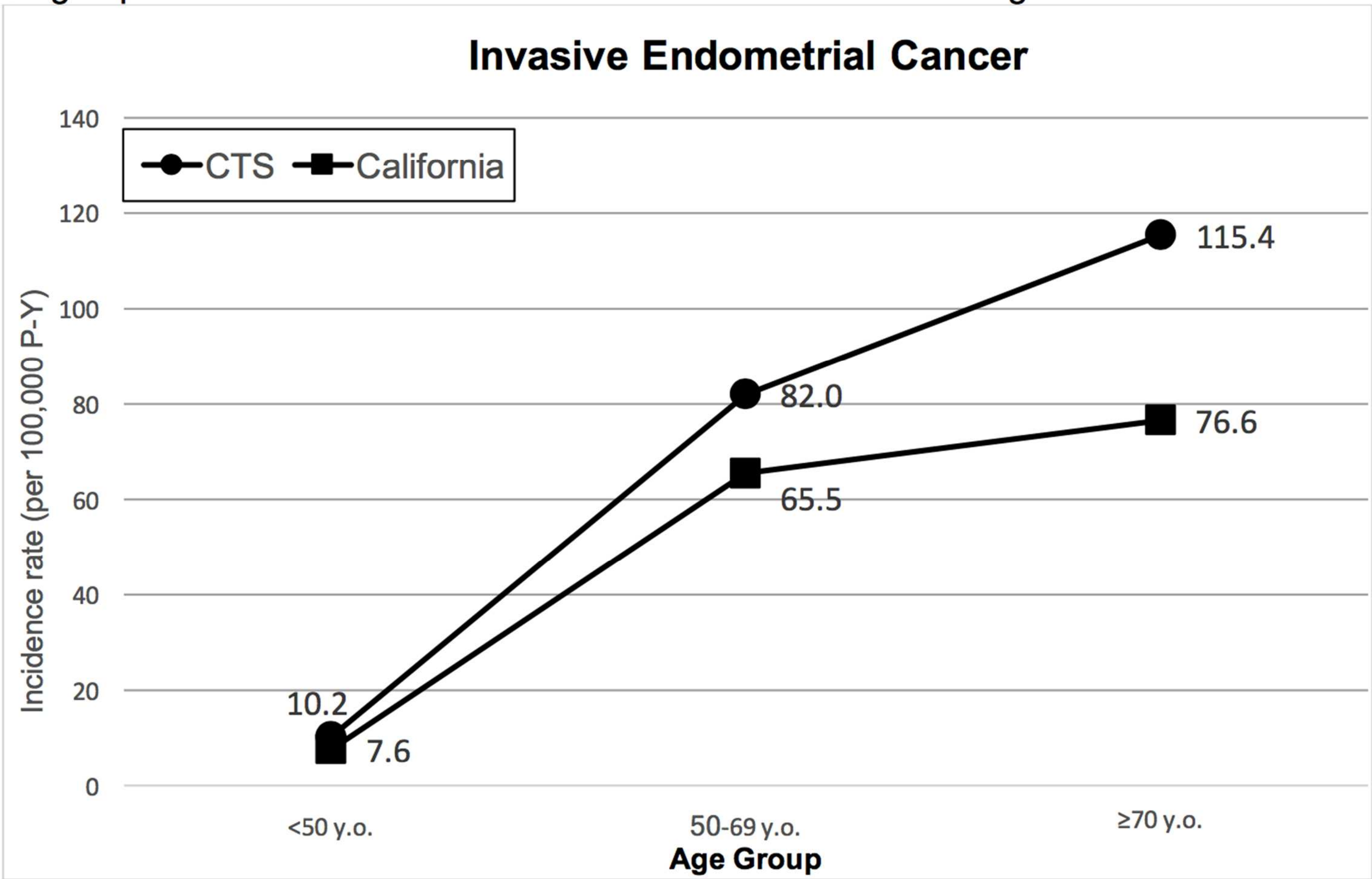
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.1B: Age-specific in situ breast cancer incidence rates among teachers and California women



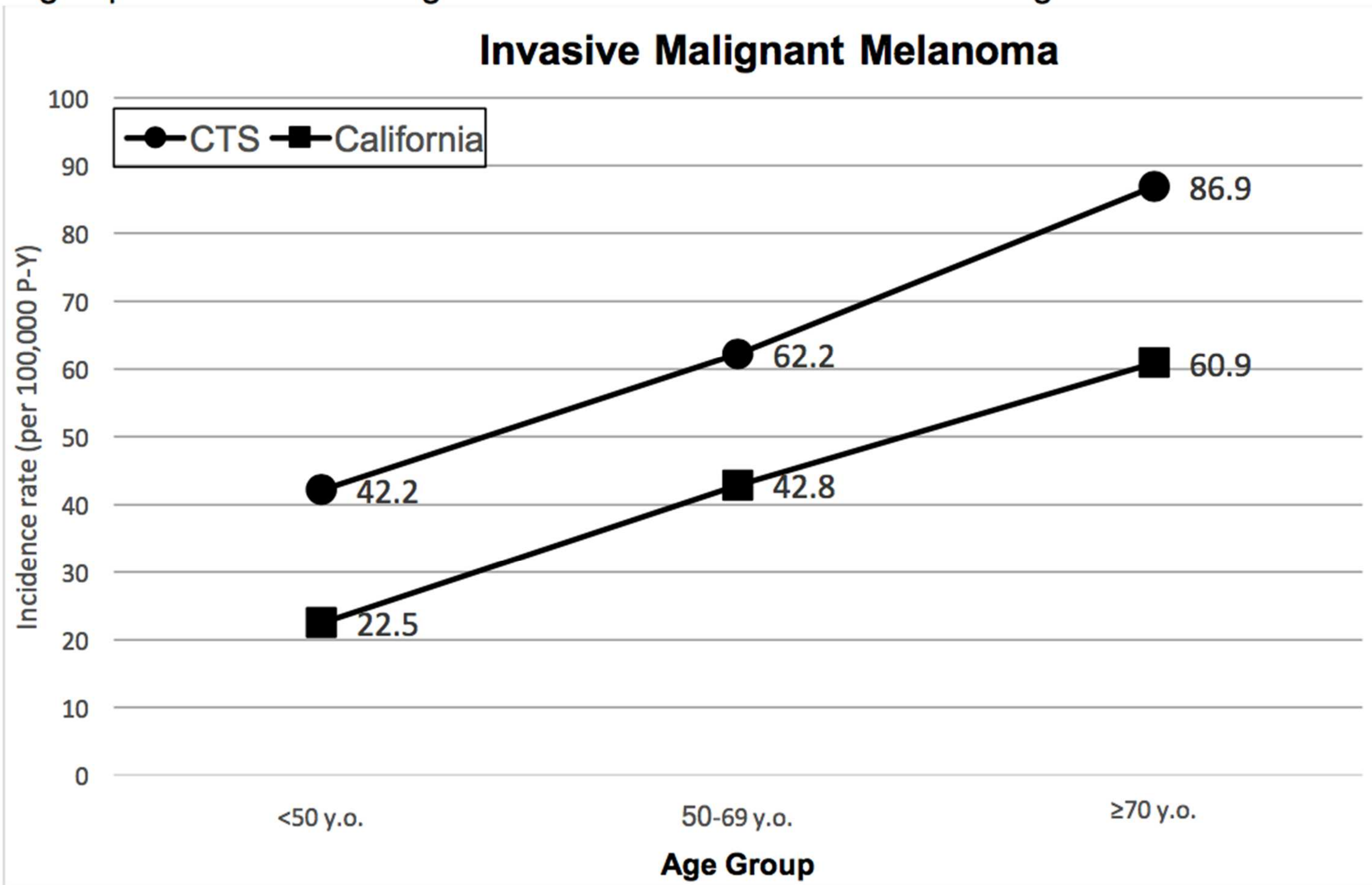
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.1C: Age-specific invasive endometrial cancer incidence rates among teachers and California women



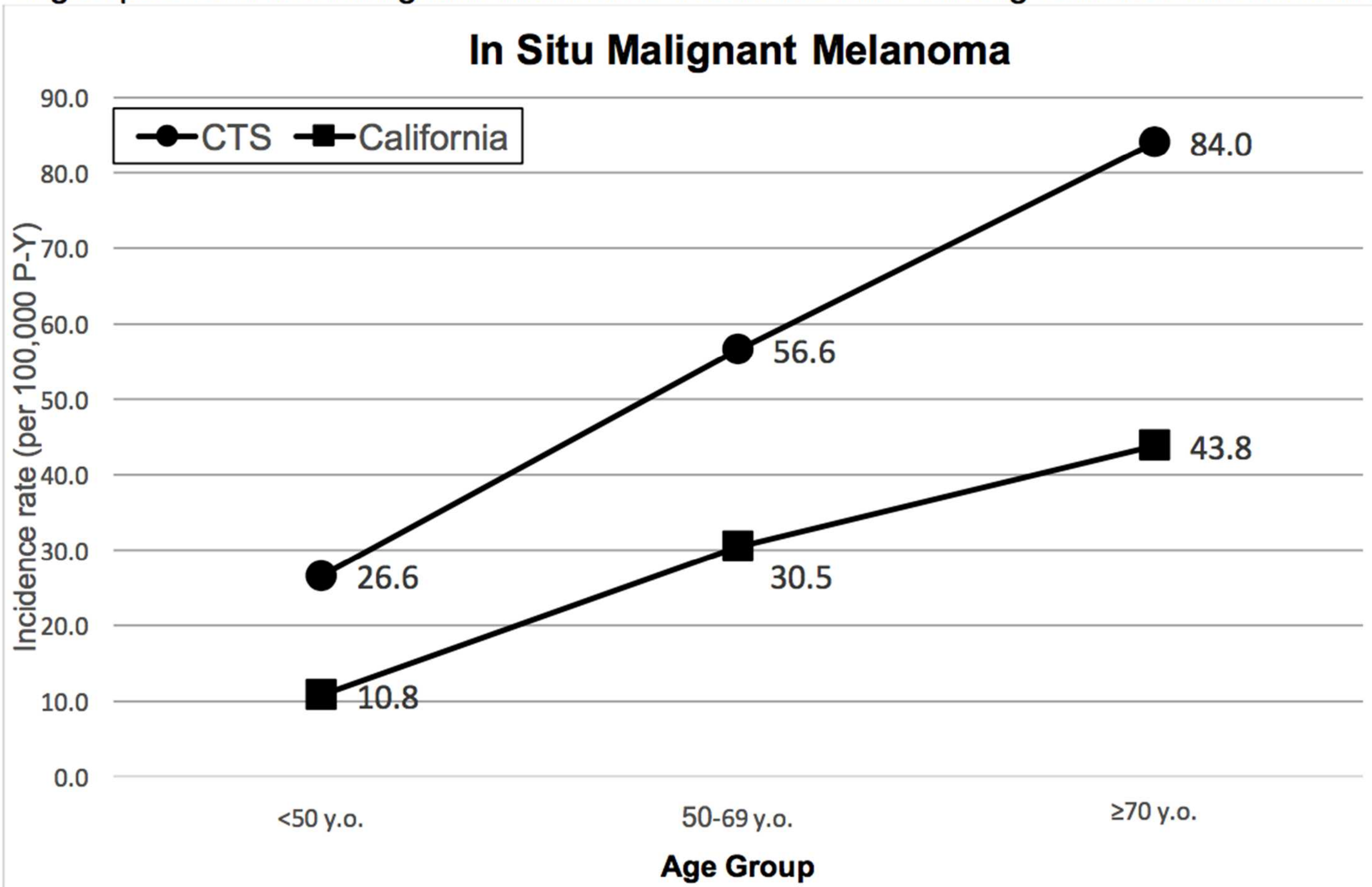
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.1D: Age-specific invasive malignant melanoma incidence rates among teachers and California women



Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.1E: Age-specific in situ malignant melanoma incidence rates among teachers and California women

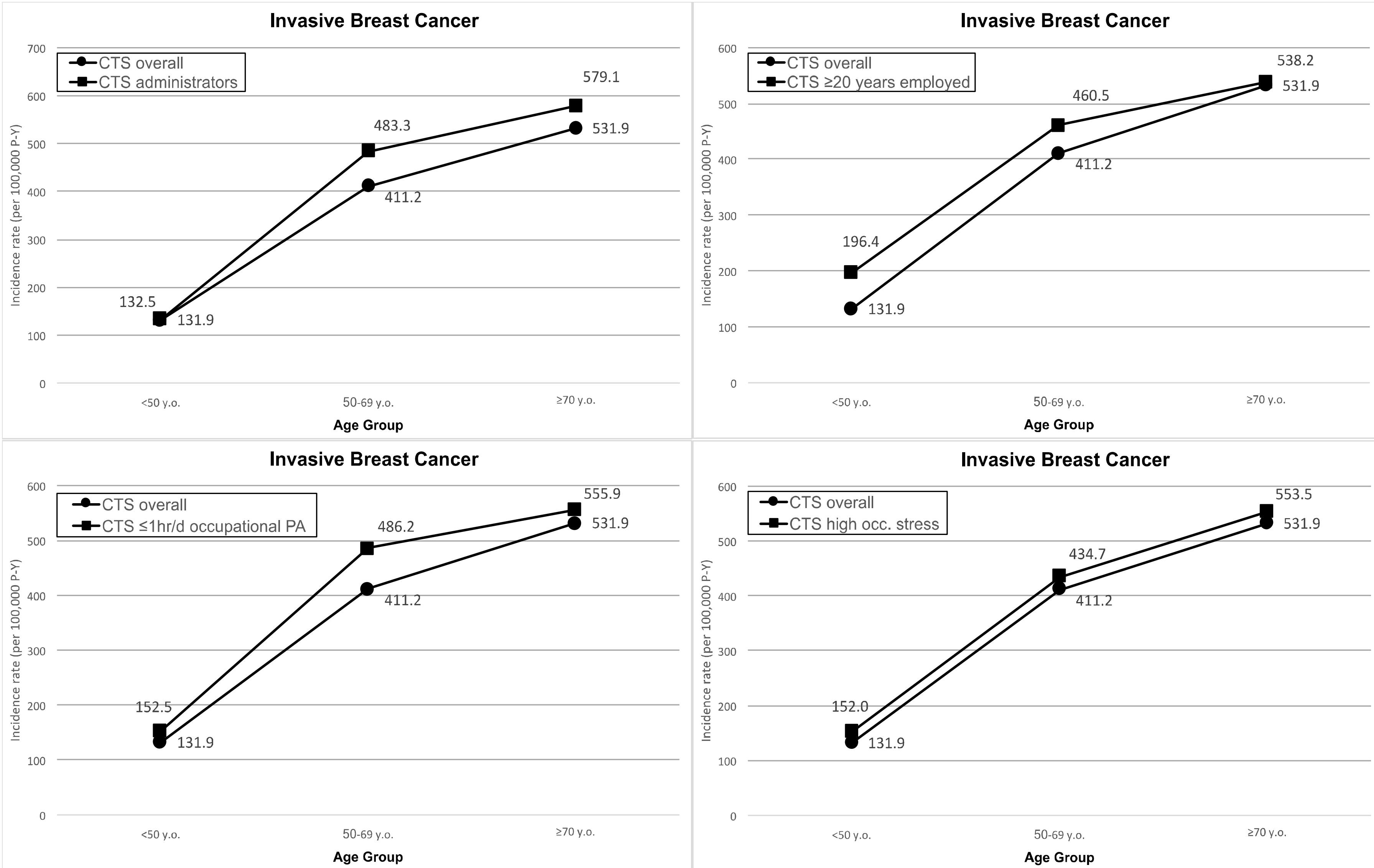


Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

3.3.3 Age-specific incidence rates of CTS teachers according to occupational characteristics

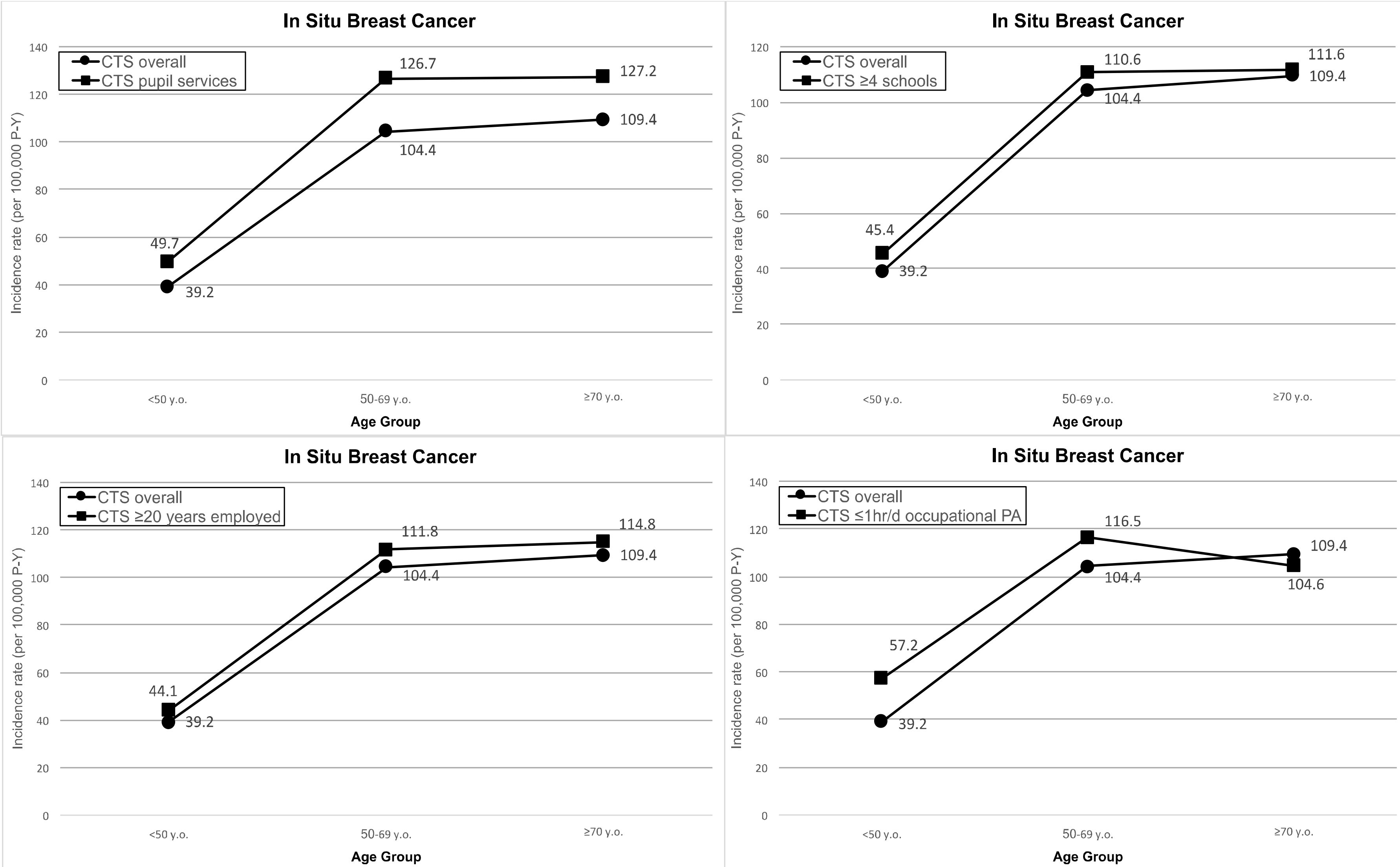
We observed notable differences in the age-specific cancer incidence rates among teachers who have certain distinct occupational characteristics. The relative cancer incidence of teachers with these occupational characteristics are shown in **Figures 3.2A-E.** The relative excess incidence of invasive breast cancer among administrators, teachers employed ≥20 y, teachers with ≤1 hr./day of occupational physical activity, and teachers with high occupational stress compared to the overall CTS study population is apparent across all age groups. Similarly, the rate of in situ breast cancer among teachers in the CTS was subtly elevated for those working in pupil services, ≥4 schools throughout employment, ≥20 years throughout employment, and ≤1 hr./day of occupational physical activity when compared to rates observed in the overall study population. Moreover, teachers in the CTS with multiple roles, ≥20 y of employment, and ≤1 hr./day of occupational physical activity had higher rates of endometrial cancer development across all age groups compared to all CTS teachers. The risk of malignant melanoma among teachers was also observed to notably differ according to their occupational characteristics. Specifically, CTS teachers with ≤1 hr./day of occupational physical activity, and administrators had an excess rate of invasive MM compared to the rate of all CTS teachers. The relative excess risk of in situ MM tumor types in the CTS was similarly observed for administrators, and multiple role teachers as well. Conversely, we observed a decreased rate of in situ MM among those teachers with minimal occupational physical activity and low occupational stress compared the overall CTS population.

Figure 3.2A- Age-specific invasive breast cancer incidence rates according to the occupational characteristics of CTS teachers



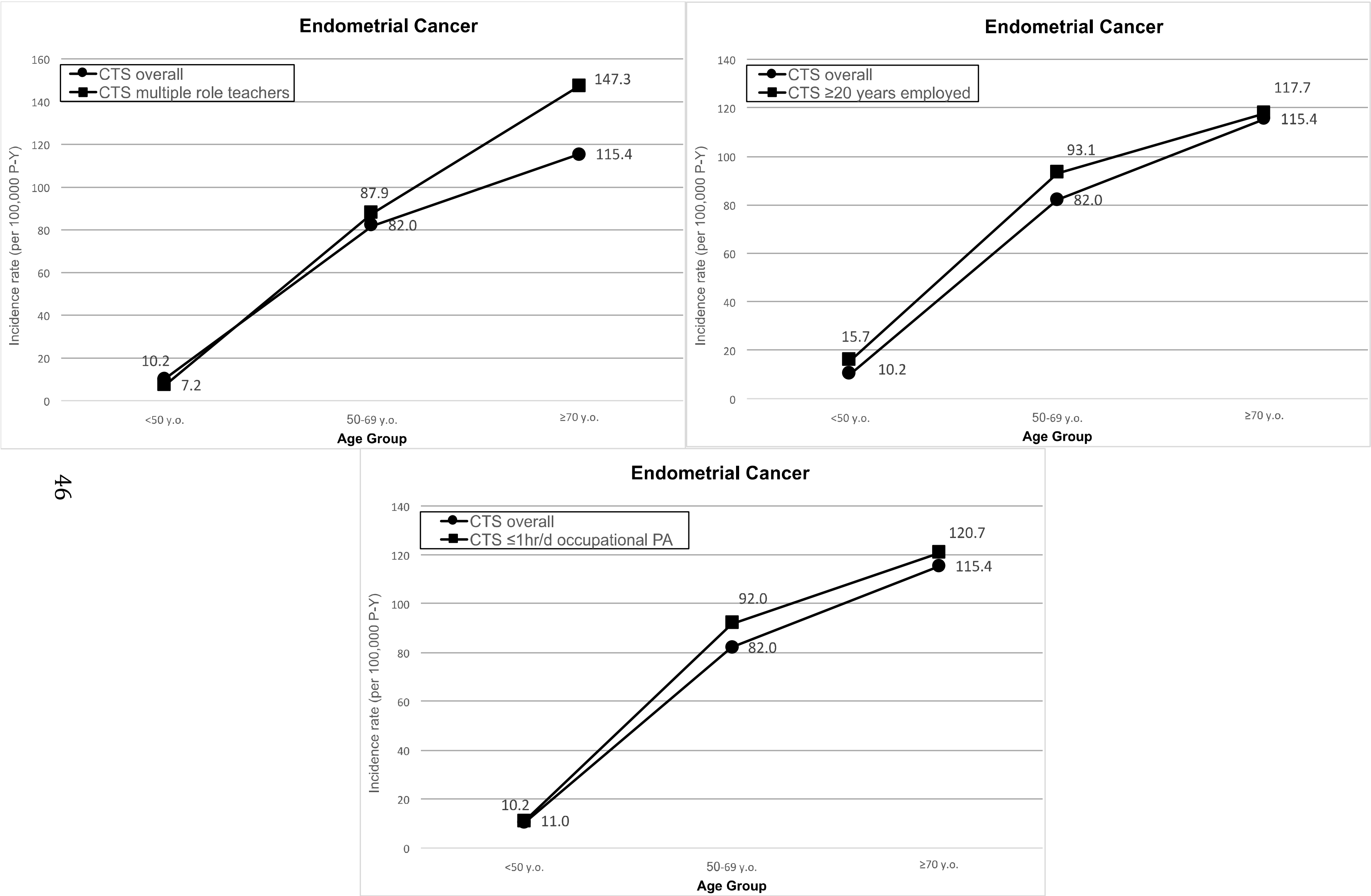
Occupational PA: Occupational Physical activity, hours per day standing or walking at work.
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.2B- Age-specific in situ breast cancer incidence rates according to the occupational characteristics of CTS teachers



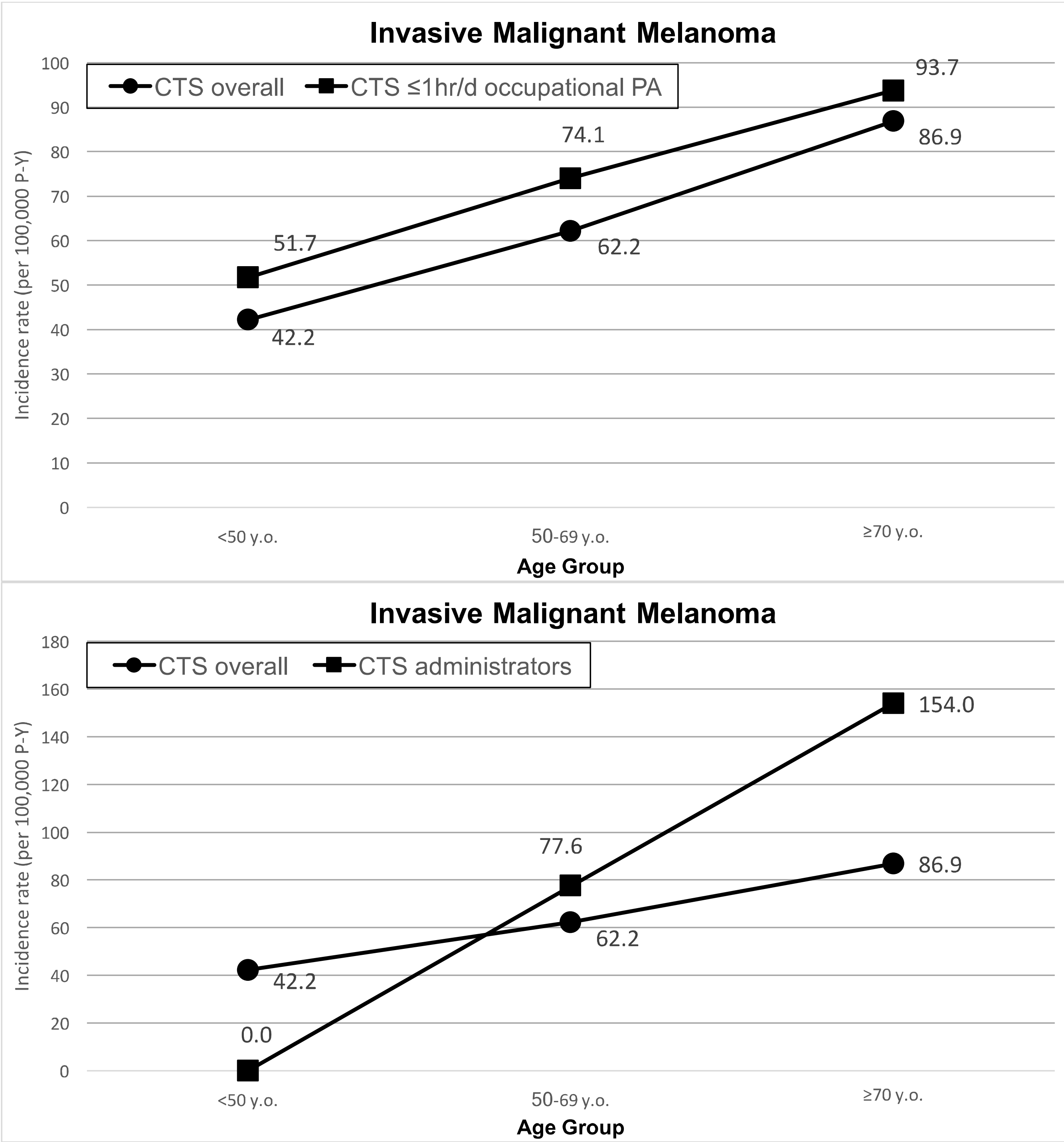
Occupational PA: Occupational Physical activity, hours per day standing or walking at work
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.2C- Age-specific endometrial cancer incidence rates according to the occupational characteristics of CTS teachers



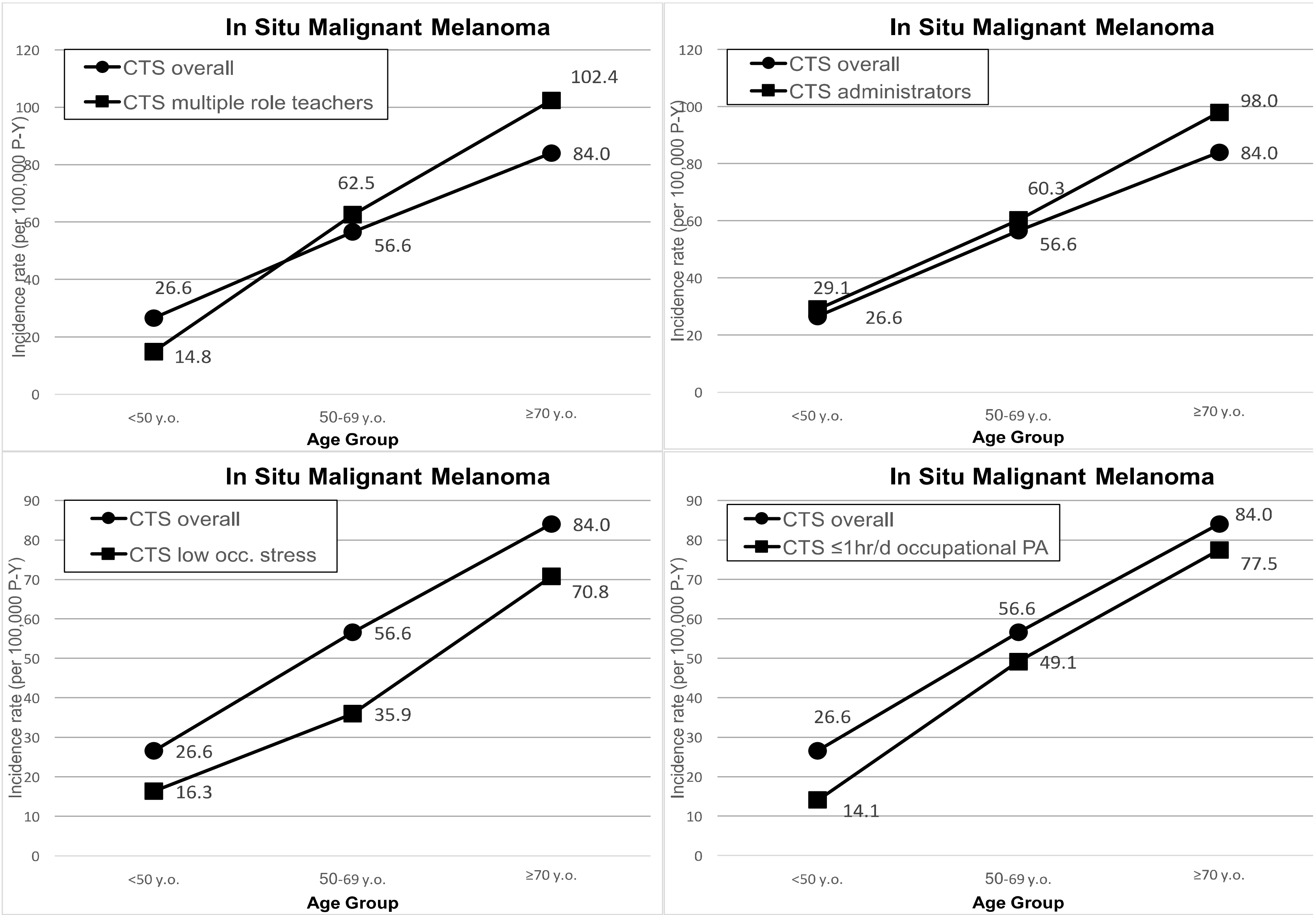
Occupational PA: Occupational Physical activity, hours per day standing or walking at work.
Rates calculated among those women ≥20 y in the CTS and California for the 1995 through 2013.

Figure 3.2D- Age-specific invasive malignant melanoma incidence rates according to the occupational characteristics of CTS teachers



Occupational PA: Occupational Physical activity, hours per day standing or walking at work.
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

Figure 3.2E- Age-specific in situ malignant melanoma incidence rates according to the occupational characteristics of CTS teachers



Occupational PA: Occupational Physical activity, hours per day standing or walking at work.
Rates calculated among those women ≥20 y in the CTS and California for the years 1995 through 2013.

3.4 DISCUSSION

Throughout eighteen years of follow-up in the CTS, we observed California female teachers to have uniquely higher risks for incident breast cancer, endometrial cancer, and malignant melanoma when compared to the general female population of California. Specifically, we observed the greatest relative excess risk for malignant melanoma, followed by breast and endometrial cancers among teachers. Additionally, the excess rates of cancer incidence were notably higher among teachers in the CTS who exhibit several distinct occupational characteristics.

These results regarding the cancer risk of teachers in this study align with previous research that examined cancer incidence of teachers in the United States [**2-5**] and worldwide [**6-12**]. An earlier investigation into the CTS found the rate of breast cancer, endometrial cancer, and malignant melanoma to be substantially elevated than would be expected based on the statewide rate after three years of follow-up (1995-1998). Specifically, Bernstein, et al. observed a significantly elevated rate of breast cancer (invasive: 51% higher, in situ: 67% higher), endometrial cancer (72%), and malignant melanoma (59%) among teachers compared to California women [**2**]. Additionally, a study of cancer incidence consisting of 15 million people from five Nordic countries found substantially elevated risks of breast cancer (SIR 1.22, 95% CI 1.20-1.24), endometrial cancer (SIR 1.11, 95%CI: 1.07-1.15), and malignant melanoma (SIR 1.35, 95%CI: 1.29-1.41) among teachers compared to the general population [**6**]. Furthermore, studies into women of Shanghai, China have continually shown elevated rates of breast cancer associated with the occupation of teaching, although non-significant which may be partly accounted to the limited number cases thus precluding strong statistical inference [**8-9**]. The overall trend in results from these past studies are consistent with the excess risk of cancer among teachers observed in this study.

The excess cancer risk was not solely observed in the overall study population of teachers in the CTS, but we also identified several distinct occupational characteristics associated with notably higher rates of cancer development when compared to California women. In brief, the occupational characteristics related to notably higher rates of cancer development among teachers in this study were employment position, duration of employment, and occupational physical activity levels. We observed teachers in the CTS with a multiple role employment position to have substantially higher rates of invasive malignant melanoma and endometrial cancer. Additionally, administrators and multiple role teachers had notably higher rates of in situ malignant melanoma and pupil service workers had an elevated rate of in situ breast cancer. Although findings pertaining this topic are sparse [**3, 9, 77**] a previous study examining cancer incidence rates of teachers according to employment position found teachers to have significantly higher rates of malignant melanoma, breast, and endometrial cancers. Moreover, "non-teachers" (i.e. administrators and pupil services) were shown to be at a lesser but still elevated risk of breast cancer, and malignant melanoma although non-significant which may be accounted to the low number in observed cases [**3**]. The rate of in situ breast cancer in this study was notably higher among teachers with ≥20 years of employment, while rates among the remaining cancer types did not increase notably according to duration of employment. The overall evidence regarding duration of employment as a teacher and cancer risk is inconsistent due in part to the sparse evidence base [**4-5, 8, 11**]. Milham and Morgan identified an excess risk of cancer (i.e.

breast cancer, endometrial cancer, and malignant melanoma) among teachers with a greater duration of employment compared to risk in the general population [**4**]. Another investigation into occupational breast cancer risk among French participants found elevated risk estimates among teachers with greater durations of employment (≥10 years) compared to teachers with shorter durations, however the limited number of cases in this study precludes strong statistical inference [**11**]. While these previous studies align more closely with our findings, others have not observed elevated rates of breast cancer with greater durations of employment as a teacher [**5, 8**].

The strongest consistent relationship we observed between cancer incidence and occupational characteristics in the CTS was with occupational physical activity (PA) levels. Specifically, we observed substantially elevated rates of breast cancer (invasive and in situ), endometrial cancer, and malignant melanoma (invasive only) among teachers with lower levels of occupational physical activity, regardless of recreational physical activity levels. As stated earlier, studies examining cancer risk in teachers according to their occupational PA levels are sparse. However, previous studies have examined this relationship among study populations consisting of heterogeneous occupational titles. Specifically, previous studies have reported an inverse association between occupational physical activity and various incident cancer risks, but the evidence informing this topic is inconsistent. Some studies report an inverse association between occupational physical activity and incident MM, breast and endometrial cancer risk [**27-30, 32, 78**], and others observed no association [**23-26, 31**]. Although past findings are mixed, higher physical activity levels has a large body of evidence from observational and experimental studies supporting the beneficial effects on pathways such as oxidative stress and inflammation which are established “hallmarks of cancer” [**21-22, 33**]. Moreover, this notion is further supported by previous findings regarding the inverse association between incident cancer risk and recreational physical activity [**79**].

There are several strengths of this study. This is the first study to examine the cancer risk of teachers according to multiple occupational characteristics. Having the ability to identify occupational characteristics linked to notably higher rates of cancer development among teachers is a novel contribution to the evidence base informing this topic. Additionally, the CTS is the largest cohort study of female teachers and school administrators and provides a large active workforce which serves optimally to address the research question in this study. Another strength of this study can be accounted to our ability to calculate incidence rates adjusted for sex and age which allows for comparison the rates observed in a population-base of ~20 million female California residents. Lastly, given the large sample size and number of cases observed throughout the extensive follow-up period (i.e. 18 years) we were able to generate precise estimates of cancer incidence which improves our ability to make strong statistical inferences.

Limitations in this study include the slight non-representativeness of the CTS study population which consists of 87% white teachers and 45% high SES teachers. However, the increased rate of cancer development among teachers has been observed worldwide, regardless of race, and previous studies examining the relationship between SES and cancer risk have not provided any definitive conclusions regarding this matter. Additionally, information beyond race and gender is not available in the California Cancer Registry and thus findings in this study may be partly accounted for by disparities of health insurance coverage in the state of California. Lastly, the self-report of occupational characteristic among teachers in the CTS introduces some level of misclassification bias, however this is likely non-differential with respect to disease status and thus would push estimates towards the null.

In conclusion, the analyses of cancer risk among teachers in this study have provided evidence for the uniquely higher risk of developing breast cancer, endometrial cancer, and malignant melanoma among teachers compared to the general population. Additionally, the rate across the three cancer types was observed to significantly differ, non-uniformly, according to the distinct occupational characteristics of teachers such as employment position, duration of employment, and number of schools throughout employment. Of note, lower levels of occupational physical activity was associated with elevated incidence rate for the cancers of interest in this study.

CHAPTER 4

The Risk of Incident Breast Cancer, Endometrial Cancer, and Malignant Melanoma According to the Occupational Characteristics of Teachers

4.1 INTRODUCTION

The incidence of breast cancer, endometrial cancer, and malignant melanoma among teachers has been previously shown to differ according to their occupational characteristics [**3-4, 9, 77**]. These past findings align with the growing body of evidence regarding uniquely higher risks of various incident cancers among teachers, as an occupational group, in the United States [**2-5**] and worldwide [**6-12, 77**]. The occupational characteristic information available in these past studies was limited in comparison to the information provided by those participants of the California Teachers Study (CTS), the largest cohort study comprised of female school teachers and administrators. Additionally, previous studies have not examined whether the incidence of breast cancer, endometrial cancer, malignant melanoma among teachers differs according to their occupational characteristics. Thus, the investigation of cancer risk among teachers according to their occupational characteristics is warranted in this population.

Indeed, the lack of evidence regarding occupational factors and cancer risk among teachers is partly due to the lack of daily exposures to chemical and mutagenic compounds as seen among industrial and factory workers. However, a study examining cancer incidence rates among teachers compared to the general population found notably higher rates of cancer among teachers with greater durations of employment

[**4**], and particular teacher types [**3, 9, 77]**. Additionally, past studies have provided crucial evidence linking occupational stress and physical activity levels to an elevated pro-inflammatory immune response and oxidative stress levels [**17, 21**], which are established “hallmarks of cancer” [**19, 33, 80**]. Currently, the studies examining the association between occupational characteristics and incident breast cancer, endometrial cancer, and malignant melanoma among teachers are lacking in the literature. Therefore, no definitive conclusions have been established regarding the occupational characteristics driving the higher risks for several incident cancers among those employed in the educational services sector (i.e. teachers).

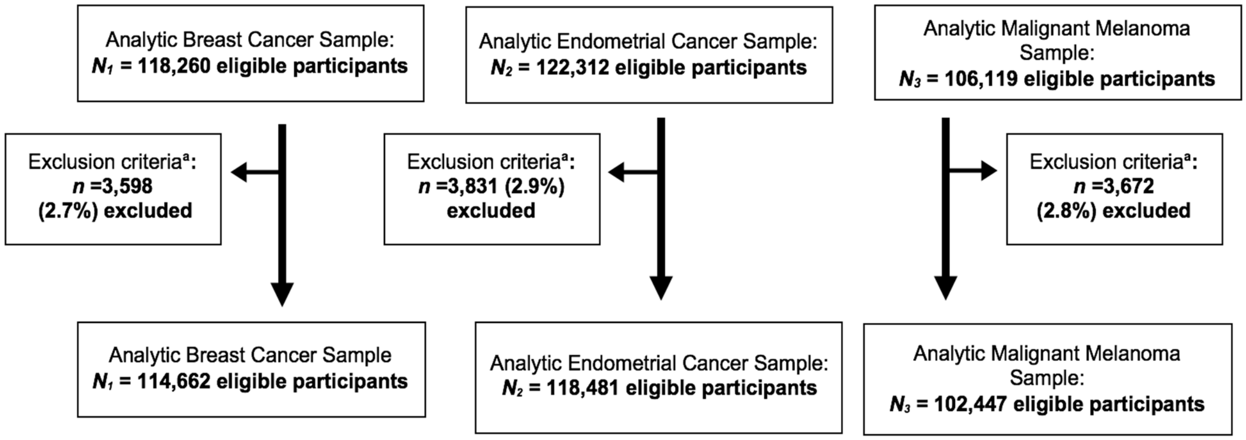
Given the growing evidence base regarding the uniquely higher risk for various incident cancers among teachers compared to the general population, developing a better understanding of the distinct occupational characteristics associated with higher cancer risk has the potential to improve cancer prevention practices among teachers. To do so, we examined various occupational characteristics in relation to incident breast cancer, endometrial cancer, and malignant melanoma risk in female teachers from the large prospective California Teachers Study (CTS).

4.2 METHODS

Chapter 2 contains the detailed description of the California Teachers Study (CTS) population, as well as the assessment of teacher’s occupational and cancer risk factor characteristics.

Given our interest in incident cancer risk among teachers according to their occupational characteristics, teachers who lacked complete data concerning the occupational characteristics of interest were further excluded from the Aim 1 analytic samples (**Figure 4.1**).

FIGURE 4.1: Flowchart of the study selection process of Aim 2 analytic sample



[a] Exclusion criteria for Aim 2 analyses included further exclusions of CTS teachers who lacked complete data regarding their occupational characteristic information.

4.2.1 Incident cancer risk according to occupational characteristics

Multivariable Cox proportional hazards regression models, using age (in days) as the time metric and stratified by age at baseline (in years), were utilized to estimate hazard ratios (HRs) along with 95% confidence intervals (95% CIs) of breast cancer (in situ and invasive), endometrial cancer (invasive), and malignant melanoma (in situ and invasive) according to the occupational characteristics of teachers. The occupational characteristics we examined in relation to risk for these three cancer types were: teacher type (multiple subjects, single subject, pupil services, administrator, multiple roles/other), number of school throughout employment (schools: 1, 2-3, ≥4), years of employment in school system (years: <10, 10-19, ≥20), occupational physical activity (hours per day standing or walking at work: none/ ≤1, 2-6, ≥7), power lines near school (no, yes, unsure), occupational stress (stress level: low-risk , moderate-risk stress, high-risk stress). Teachers were followed from the date they completed the baseline questionnaire until diagnosis with the given cancer type, death, a move out of California, or the end of follow-up (December 31, 2013), whichever occurred first. There was no evidence the proportional hazard assumption was violated through modeling interaction terms of follow-up time with each of the occupational characteristics of interest.

Considering our interest in multiple cancer types, distinct adjustments were made in regards to specific confounders for each cancer type (to increase the precision of estimates for occupational associations with incident cancer risk). Thus, each cancer type-specific multivariable model differed but there was also overlap in adjustments across models due to the strong confounding role played by lifestyle factors in various cancer types (i.e. BMI, socioeconomic status (SES)). Potential confounders for the multivariable regression analyses were determined *a-priori*, and only adjusted for if its inclusion contributed to the predictive ability of the final model for a given cancer type as determined through statistical model-selection processes (i.e. automatic forward-selection and backwards-elimination methodology). For the hormone-dependent cancers (i.e. breast, endometrial) we adjusted for race, BMI, physical activity level, SES, parity status, hormone replacement therapy use, age at menarche, menopausal status, age at menopause, family history of the particular cancer type, smoking status, alcohol intake, and personal history of breast cancer and endometriosis (*endometrial cancer models only*) [**81-82**]. Lastly, we adjusted for recreational physical activity, number of sun blisters, age at first sun blister, skin tendency to sun exposure without protection, skin tanning behaviors, family history of melanoma, family history of mole removal, and personal history of mole removal to assess occupational associations with malignant melanoma risk [**83**]. Additionally, secondary analyses in which the outcome was stratified upon an established prognostic characteristic for the given cancer type were conducted to better explain associations observed in the overall study population. When necessary, Wald's test for trend were carried out across the semi-quantitative occupational characteristics by using an ordinal variable coded as the median value of the occupational characteristic category. All statistical tests were 2-sided and conducted with SAS software (version 9.4; SAS Institute).

4.3 RESULTS

4.3.1 Incident breast cancer risk among teachers in the CTS

4.3.1.1 Breast cancer risk factors and occupational characteristics

Of the 118,260 teachers who were truly at-risk for invasive and in situ breast cancer at baseline, 114,662 teachers were found to have complete occupational characteristic data and thus eligible for this study. Of the eligible participants, 5,775 and 1,398 teachers were diagnosed with invasive and in situ breast cancer, respectively, throughout the eighteen-year follow-up period (1995-2013). The sociodemographic and lifestyle characteristics for the overall CTS cohort and according to incident cancer status are shown in **Table 4.1.** Female teachers of the CTS were primarily non-Hispanic white (87%), postmenopausal (58%), non-smokers (67%), moderate drinkers (60%), of high SES (45%), parous (80%), and had no family history of breast cancer (85%). The teachers diagnosed with incident invasive and in situ breast cancer were more often older, current users of estrogen and progestin therapy (EPT), had higher smoking rates, alcohol intake, later ages of menopause, and at least one first degree relative diagnosed with breast cancer.

Table 4.2 shows the occupational characteristics of CTS teachers overall and according to incident breast cancer status. Teachers in the CTS were primarily multiple-subject teachers (i.e. pre-school and elementary) (53%), with two to three schools throughout employment (43%), twenty or more years throughout employment (42%), moderately active throughout the workday (60%), teaching at schools with power lines present (62%), and had high-risk stress levels (62%). The teachers diagnosed with invasive breast cancer during follow-up were more often administrators, with four or more schools throughout employment, twenty or more years of employment, and had lower levels of occupational physical activity. Teachers who developed in situ breast cancer during the study were more likely to be working in pupil services, with greater years of employment and lower occupational physical activity levels.

Table 4.1- Descriptive characteristics according to incident breast cancer status (*N*= 114,662)				
	Non-Cases (*n*=107,489)	**Invasive Cases (*n*=5,775)**	**In Situ Cases (*n*=1,398)**	**Overall (*N*=114,662)**
Characteristic:	N (%)*	N (%)*	N (%)*	N (%)
Age (y)	52 ± 14	57 ± 12	55 ± 11	53 ± 14
BMI (kg/m^2)	24.8 ± 5.1	25.1 ± 4.8	24.6 ± 4.9	24.8 ± 5.0
Recreational physical activity (hrs./wk.)	2.2 ± 2.6	2.3 ± 2.7	2.3 ± 2.7	2.3 ± 2.6
Age at first pregnancy (y)	25.5 ± 4.2	25.8 ± 4.3	25.9 ± 4.4	26 ± 4
Age at menarche (y)	5.5 ± 1.4	5.5 ± 1.4	5.5 ± 1.5	6 ± 1
Race:				
White	14,551 (94.9)	606 (4.0)	170 (1.1)	99,335 (86.6)
Non-white	92,938 (93.6)	5,169 (5.2)	1,228 (1.2)	15,327 (13.4)
Total:	107,489	5,775	1,398	114,662
Menopausal and HRT status:				
Premenopausal	46,094 (95.9)	1,479 (3.1)	471 (1.0)	48,044 (41.9)
Post, no HRT use	25,563 (93.3)	1,550 (5.7)	289 (1.1)	27,402 (23.9)
Post, past HRT use	7,273 (93.4)	413 (5.3)	98 (1.3)	7,784 (6.8)
Post, current ET use	14,016 (92.5)	945 (6.2)	199 (1.3)	15,160 (13.2)
Post, current EPT use	14,543 (89.4)	1,388 (8.5)	341 (2.1)	16,272 (14.2)
Total:	107,489	5,775	1,398	114,662
Smoking status:				
Never	72,326 (94.3)	3,453 (4.5)	905 (1.2)	76,684 (66.9)
Former	29,787 (92.5)	1,961 (6.1)	443 (1.4)	32,191 (28.1)
Current	5,376 (92.9)	361 (6.2)	50 (0.9)	5,787 (5.1)
Total:	107,489	5,775	1,398	114,662
Second-hand smoke exposure:				
No exposure	21,059 (94.9)	904 (4.1)	231 (1.0)	22,194 (19.4)
Childhood only	29,047 (94.1)	1,462 (4.7)	372 (1.2)	30,881 (26.9)
Adulthood only	23,909 (93.4)	1,396 (5.5)	290 (1.1)	25,595 (22.3)
Both child/adulthood	33,474 (93.0)	2,013 (5.6)	505 (1.4)	35,992 (31.4)
Total:	107,489	5,775	1,398	114,662
Alcohol intake:				
None	34,634 (94.3)	1,710 (4.7)	397 (1.1)	36,741 (32.0)
< 20 g/day	64,696 (93.7)	3,460 (5.0)	861 (1.2)	69,017 (60.2)
≥20 g/day	8,159 (91.6)	605 (6.8)	140 (1.6)	8,904 (7.8)
Total:	107,489	5,775	1,398	114,662
Vitamin use:				
Non-user	37,671 (94.2)	1,842 (4.6)	493 (1.2)	40,006 (34.9)
Current single vitamin Use	13,215 (93.1)	820 (5.8)	166 (1.2)	14,201 (12.4)
Current multivitamin Use	23,791 (94.2)	1,200 (4.8)	262 (1.0)	25,253 (22.0)
Current single and multivitamin use	32,812 (93.2)	1,913 (5.4)	477 (1.4)	35,202 (30.7)
Total:	107,489	5,775	1,398	114,662

SES:				
Low	4,796 (94.6)	229 (4.5)	45 (0.9)	5,070 (4.4)
Medium-low	18,771 (94.5)	888 (4.5)	214 (1.1)	19,873 (17.3)
Medium-high	36,420 (94.1)	1,823 (4.7)	460 (1.2)	38,703 (33.8)
High	47,502 (93.1)	2,835 (5.6)	679 (1.3)	51,016 (44.5)
Total:	107,489	5,775	1,398	114,662
Parity status:				
Nulliparous	22,149 (94.3)	1,069 (4.6)	274 (1.2)	23,492 (20.5)
Parous	85,340 (93.6)	4,706 (5.2)	1,124 (1.2)	91,170 (79.5)
Total:	107,489	5,775	1,398	114,662
Age at menopause:				
Periods haven't stopped	51,848 (95.4)	1,946 (3.6)	561 (1.0)	54,355 (47.4)
<50 y	31,903 (93.1)	1,935 (5.6)	439 (1.3)	34,277 (29.9)
≥50 y	23,738 (91.2)	1,894 (7.3)	398 (1.5)	26,030 (22.7)
Total:	107,489	5,775	1,398	114,662
Family history of breast cancer:				
No 1st degree relative	91,364 (94.2)	4,593 (4.7)	1,079 (1.1)	97,036 (84.6)
At least one 1st degree relative	12,192 (90.6)	978 (7.3)	280 (2.1)	13,450 (11.7)
Adopted, unknown	3,933 (94.2)	204 (4.9)	39 (0.9)	4,176 (3.6)
Total:	107,489	5,775	1,398	114,662

Continuous characteristics presented as mean value ± standard deviation.
*Proportions depict percent of cancer cases according to sociodemographic and women's health characteristics.

Table 4.2- Occupational characteristics according to incident breast cancer status (*N*= 114,662)				
	Non-Cases (*n*=107,489)	**Invasive Cases (*n*=5,775)**	**In Situ Cases (*n*=1,398)**	**Overall (*N*=114,662)**
Characteristic:	N (%)*	N (%)*	N (%)*	N (%)
Teacher type:				
Multiple subject teachers	57,345 (93.9)	3,007 (4.9)	719 (1.2)	61,071 (53.3)
Single subject teachers	29,039 (93.8)	1,541 (5.0)	373 (1.2)	30,953 (27.0)
Pupil services	4,583 (93.4)	249 (5.1)	75 (1.5)	4,907 (4.3)
Administrator	2,892 (92.2)	201 (6.4)	43 (1.4)	3,136 (2.7)
Multiple roles, other	13,630 (93.4)	777 (5.3)	188 (1.3)	14,595 (12.7)
Total:	107,489	5,775	1,398	114,662
Number of schools throughout employment:				
1 school	19,403 (94.8)	854 (4.2)	214 (1.0)	20,471 (17.9)
2-3 schools	45,758 (94.0)	2,349 (4.8)	565 (1.2)	48,672 (42.5)
≥4 schools	42,328 (93.0)	2,572 (5.7)	619 (1.4)	45,519 (39.7)
Total:	107,489	5,775	1,398	114,662
Years of employment in school system:				
< 10 yrs.	29,590 (96.1)	938 (3.0)	265 (0.9)	30,793 (26.9)
10-19 yrs.	33,268 (93.9)	1,731 (4.9)	420 (1.2)	35,419 (30.9)
≥20 yrs.	44,631 (92.1)	3,106 (6.4)	713 (1.5)	48,450 (42.3)
Total:	107,489	5,775	1,398	114,662
Occupational physical activity:				
none	14,425 (92.1)	1,036 (6.6)	200 (1.3)	15,661 (13.7)
≤1 hr./day	13,671 (93.2)	796 (5.4)	197 (1.3)	14,664 (12.8)
2-6 hrs./day	64,365 (94.0)	3,254 (4.8)	827 (1.2)	68,446 (59.7)
≥7 hrs./day	15,028 (94.6)	689 (4.3)	174 (1.1)	15,891 (13.9)
Total:	107,489	5,775	1,398	114,662
Power lines near school:				
No power lines present	14,626 (93.8)	769 (4.9)	195 (1.3)	15,590 (13.6)
Power lines present	66,179 (93.8)	3,520 (5.0)	871 (1.2)	70,570 (61.6)
Don't know	26,684 (93.6)	1,486 (5.2)	332 (1.2)	28,502 (24.9)
Total:	107,489	5,775	1,398	114,662
Occupational stress[1]:				
High-risk	42,273 (93.0)	2,573 (5.7)	627 (1.3)	45,473 (62.4)
Moderate-risk	15,713 (93.2)	908 (5.4)	228 (1.4)	16,849 (23.1)
Low-risk	5,212 (92.9)	310 (5.5)	90 (1.6)	5,612 (7.7)
Total:	63,198	3,791	945	67,934

*Proportions depict percent of cancer cases according to occupational characteristics.

[1] Computed only among those respondents of the third follow-up questionnaire (Spring 2000) who had no prior breast cancer diagnosis (*n*=67,934).

4.3.1.2 Associations between occupational characteristics and incident breast cancer risk

Table 4.3 displays the hazard ratios for incidence of invasive pre- and postmenopausal breast cancer according to the occupational characteristics of teachers. Throughout the eighteen years of follow-up in the CTS, we observed significantly elevated risks of post- and premenopausal invasive breast cancer among teachers with decreased occupational physical activity levels when compared to highly-active teachers (HR for none vs ≥7 hrs./day: 1.13, 95% CI 1.01-1.28, HR for ≤1 hr. vs ≥7 hrs./day: 1.19, 95% CI: 1.00-1.41, respectively). Lastly, we observed no difference in the risk for invasive breast cancer among pre- and postmenopausal teachers according to the remaining occupational characteristics of interest.

The hazard ratios for the incidence of pre- and postmenopausal in situ breast cancer according to the various occupational characteristics of CTS teachers can be found in **Table 4.4**. Overall, there was no association between the occupational characteristics and incident in situ breast cancer among pre- and postmenopausal teachers.

Notably, the association between occupational physical activity and invasive breast cancer risk was observed to differ according to several prognostic factors of teachers (**Table 4.5**). Specifically, the elevated risk observed among teachers with no daily occupational physical activity was greater among pre- and postmenopausal teachers with BMI levels ≥30 kg/m^2 (23% and 42% higher, respectively); whereas estimates for normal and overweight teachers more closely resembled those of the overall analytic sample. Additionally, the elevated risk was subtly higher among pre- and postmenopausal teachers with a family history of breast cancer. Interestingly, greater levels of recreational physical activity did not attenuate the elevated risk among sedentary teachers (i.e. none, ≤1 hr./day occupational physical activity).

Table 4.3- Association between occupational characteristics and invasive breast cancer risk (*N*= 114,662)[1]				
	Postmenopausal (*N*=66,618/4,296 Cases)		**Premenopausal (*N*=48,044/1,479 Cases)**	
	N* Cases/*N	**HR (95% CI)**	***N* Cases/*N***	**HR (95% CI)**
Characteristic:				
Teacher Type:				
Multiple subject teachers	2,206/34,439	1.00 (Ref.)	801/26,632	1.00 (Ref.)
Single subject teachers	1,124/17,441	1.00 (0.93-1.08)	417/13,512	1.00 (0.89-1.12)
Pupil services	188/3,094	0.89 (0.77-1.04)	61/1,813	1.01 (0.82-1.25*)
Administrators	167/2,358	1.07 (0.91-1.25)	34/778	
Multiple roles, other	611/9,286	1.04 (0.95-1.13)	166/5,309	0.91 (0.77-1.08)
Number of schools throughout employment:				
1 school	582/8,962	1.00 (Ref.)	272/11,509	1.00 (Ref.)
2-3 schools	1,672/26,529	0.96 (0.87-1.05)	677/22,143	1.11 (0.97-1.28)
≥4 schools	2,042/31,127	0.98 (0.90-1.08)	530/14,392	1.11 (0.96-1.29)
Years of employment in school system:				
< 10 yrs.	420/7,317	1.00 (Ref.)	518/23,476	1.00 (Ref.)
10-19 yrs.	1,127/18,274	1.00 (0.90-1.12)	604/17,145	1.06 (0.94-1.20)
≥20 yrs.	2,749/41,027	1.01 (0.91-1.12)	357/7,423	1.04 (0.89-1.21)
Occupational physical activity:				
≥7 hrs./day	435/6,998	1.00 (Ref.)	254/8,893	1.00 (Ref.)
2-6 hrs./day	2,288/35,927	1.01 (0.91-1.12)	966/32,519	0.96 (0.83-1.10)
≤1 hr./day	576/9,158	1.00 (0.88-1.13)	220/5,506	1.19 (1.00-1.41**)
none	997/14,535	1.13 (1.01-1.28)	39/1,126	
Power Lines near school:				
No power lines present	546/8,664	1.00 (Ref.)	223/6,926	1.00 (Ref.)
Power lines present	2,563/39,460	1.01 (0.92-1.10)	957/31,110	1.03 (0.89-1.19)
Don't Know	1,187/18,494	1.03 (0.93-1.15)	299/10,008	1.03 (0.87-1.23)
Occupational Stress[2]:				
High-risk	1,880/25,777	1.00 (Ref)	693/19,696	1.00 (Ref.)
Moderate-risk	663/9,708	0.93 (0.86-1.02)	245/7,141	0.99 (0.85-1.14)
Low-risk	246/3,476	0.98 (0.86-1.12)	64/2,136	0.82 (0.64-1.06)

[1] Cox proportional hazards regression models for postmenopausal invasive breast cancer risk adjusted for: age, hormone therapy use, family history of breast cancer, age at menopause, age at menarche, smoking status, alcohol intake (g/day), BMI (kg/m^2), and SES. Premenopausal models adjusted for: age, family history of breast cancer, parity status, and physical activity (hrs./wk.).

[2] Estimates computed only among those respondents of the third follow-up questionnaire (Spring 2000) who had no prior breast cancer diagnosis (*n*=67,934).

* Estimate for combined group of administrators and pupil services.

**Estimate for combined group of teachers with ≤1 hr./day and no daily occupation physical activity.

Table 4.4- Association between occupational characteristics and in situ breast cancer risk (*N*= 114,662)[1]				
	Postmenopausal (*N*=66,618/927 Cases)		**Premenopausal (*N*=48,044/471 Cases)**	
	N* Cases/*N	**HR (95% CI)**	***N* Cases/*N***	**HR (95% CI)**
Characteristic:				
Teacher type:				
Multiple subject teachers	486/34,439	1.00 (Ref.)	233/26,632	1.00 (Ref.)
Single subject teachers	235/17,441	0.95 (0.81-1.11)	138/13,512	1.14 (0.92-1.41)
Administrators and Pupil services	85/5,452	1.06 (0.84-1.34)	33/2,591	1.17 (0.81-1.70)
Multiple roles, other	121/9,286	0.94 (0.77-1.14)	67/5,309	1.25 (0.95-1.64)
Number of schools throughout employment:				
1 school	119/8,962	1.00 (Ref.)	95/11,509	1.00 (Ref.)
2-3 schools	362/26,529	1.00 (0.81-1.23)	203/22,143	0.95 (0.74-1.21)
≥4 schools	446/31,127	1.03 (0.84-1.26)	173/14,392	1.02 (0.79-1.32)
Years of employment in school system:				
< 10 yrs.	89/7,317	1.00 (Ref.)	176/23,476	1.00 (Ref.)
10-19 yrs.	239/18,274	1.05 (0.82-1.34)	181/17,145	0.90 (0.73-1.12)
≥20 yrs.	599/41,027	1.08 (0.86-1.36)	114/7,423	1.07 (0.82-1.40)
Occupational physical activity:				
≥5 hrs./day	300/21,345	1.00 (Ref.)	238/25,498	1.00 (Ref.)
2-4 hrs./day	313/21,580	1.07 (0.91-1.25)	150/15,914	0.92 (0.75-1.13)
≤1 hr./day	314/23,693	1.09 (0.92-1.30)	83/6,632	1.20 (0.94-1.55)
Power lines near school:				
No power lines present	131/8,664	1.00 (Ref.)	64/6,926	1.00 (Ref.)
Power lines present	567/39,460	0.93 (0.77-1.12)	304/31,110	1.16 (0.89-1.52)
Don't Know	229/18,494	0.89 (0.72-1.11)	103/10,008	1.24 (0.91-1.69)
Occupational stress[2]:				
High-risk	415/25,777	1.00 (Ref)	212/19,696	1.00 (Ref.)
Moderate-risk	151/9,708	0.97 (0.81-1.17)	77/7,141	1.05 (0.83-1.33*)
Low-risk	64/3,476	1.18 (0.91-1.54)	26/2,136	

[1] Cox proportional hazards regression models for postmenopausal in situ breast cancer risk adjusted for: age, family history of breast cancer, hormone therapy use, parity status, smoking status, and alcohol intake (g/day). Premenopausal models adjusted for: age, family history of breast cancer, age at menarche, and BMI (kg/m^2).

[2] Estimates computed only among those respondents of the third follow-up questionnaire (Spring 2000) who had no prior breast cancer diagnosis (*n*=67,934).

*HR estimate for combined group of low-risk stress and moderate-risk stress teachers.

Table 4.5-Association between occupational physical activity and invasive breast cancer risk according to prognostic factors (*N*=114,662)[1]

		Postmenopausal Invasive Breast Cancer (*n*=66,618)			
	Occupational PA[2]:	≥ 7 hrs./day	2-6 hrs./day	≤1 hr./day	none
BMI:					
≤24.9 kg/m^2	**HR (95% CI)**	1.00 (Ref.)	1.00 (0.88-1.15)	0.97 (0.82-1.15)	1.12 (0.95-1.31)
	n* cases/*n	254/4,165	1,310/21,260	310/5,221	572/8,871
25.0 –29.9 kg/m^2	**HR (95% CI)**	1.00 (Ref.)	0.98 (0.81-1.18)	0.96 (0.76-1.21)	1.09 (0.87-1.36)
	n* cases/*n	131/1,875	660/9,496	163/2,416	289/3,858
≥30.0 kg/m^2	**HR (95% CI)**	1.00 (Ref.)	1.15 (0.85-1.56)	1.27 (0.90-1.79)	1.42 (1.00-2.02)
	n* cases/*n	50/976	318/5,171	103/1,521	136/1,806
Breast cancer family history[3]:					
No family history	**HR (95% CI)**	1.00 (Ref.)	0.98 (0.87-1.09)	0.97 (0.85-1.12)	1.12 (0.98-1.29)
	n* cases/*n	355/5,879	1,808/30,050	454/7,556	793/11,799
At least one first degree relative	**HR (95% CI)**	1.00 (Ref.)	1.26 (0.96-1.65)	1.19 (0.87-1.64)	1.19 (0.87-1.63)
	n* cases/*n	62/877	411/4,675	104/1,268	160/2,033
Recreational physical activity:					
< 1.5 hrs./wk.	**HR (95% CI)**	1.00 (Ref.)	0.92 (0.80-1.07)	0.95 (0.79-1.13)	1.14 (0.95-1.37)
	n* cases/*n	211/3,197	1,016/16,474	288/4,689	448/6,885
≥ 1.5 hrs./wk.	**HR (95% CI)**	1.00 (Ref.)	1.09 (0.95-1.26)	1.05 (0.88-1.26)	1.15 (0.98-1.36)
	n* cases/*n	224/3,801	1,272/19,453	288/4,469	549/7,650
		Premenopausal Invasive Breast Cancer (*n*=48,044)			
	Occupational PA[2]:	**≥ 7 hrs./day**	**2-6 hrs./day**	**≤1 hr./day[4]**	
BMI:					
≤24.9 kg/m^2	**HR (95% CI)**	1.00 (Ref.)	0.94 (0.79-1.12)	1.19 (0.96-1.47)	
	n* cases/*n	169/6,135	626/21,951	171/4,448	
25.0 –29.9 kg/m^2	**HR (95% CI)**	1.00 (Ref.)	1.14 (0.83-1.57)	1.13 (0.75-1.71)	
	n* cases/*n	46/1,733	207/6,464	45/1,360	
≥30.0 kg/m^2	**HR (95% CI)**	1.00 (Ref.)	0.78 (0.55-1.12)	1.23 (0.80-1.91)	
	n* cases/*n	39/1,025	133/4,104	43/824	
Breast cancer family history[3]:					
No family history	**HR (95% CI)**	1.00 (Ref.)	0.89 (0.77-1.04)	1.19 (0.98-1.44)	
	n* cases/*n	213/7,742	753/28,249	217/5,761	
At least one first degree relative	**HR (95% CI)**	1.00 (Ref.)	1.21 (0.84-1.75)	1.28 (0.81-2.04)	
	n* cases/*n	34/810	168/3,123	39/664	
Recreational physical activity:					
< 1.5 hrs./wk.	**HR (95% CI)**	1.00 (Ref.)	0.91 (0.75-1.10)	1.14 (0.90-1.45)	
	n* cases/*n	128/4,051	472/15,649	139/3,546	
≥ 1.5 hrs./wk.	**HR (95% CI)**	1.00 (Ref.)	1.00 (0.82-1.22)	1.23 (0.96-1.58)	
	n* cases/*n	126/4,842	494/16,870	120/3,086	

[1] Cox proportional hazards regression models for postmenopausal invasive breast cancer risk adjusted for: age, hormone therapy use, family history of breast cancer, age at menopause, age at menarche, smoking status, alcohol intake (g/day), BMI (kg/m^2), and SES. Premenopausal models adjusted for: age, family history of breast cancer, parity status, and recreational physical activity (hrs./wk.) when the outcome is not stratified among the particular covariable.

[2] Occupational PA: Occupational Physical activity, hours/day for standing and/or walking at work.

[3] Estimates not shown for teachers with unknown family history and/or are adopted (*n* =4,176).

[4] Estimates for none and ≤1 hr./day category combined due to a low number cases.

4.3.2 Incident endometrial cancer risk among teachers in the CTS

4.3.2.1 Endometrial cancer risk factors and occupational characteristics

Of the 122,312 teachers that had no diagnosis of endometrial cancer prior to baseline, 118,481 were observed to have complete data regarding the occupational characteristics of interest and thus were eligible for this study. Of the eligible participants, 1,351 teachers developed invasive endometrial cancer throughout the eighteen-year follow-up period. The baseline descriptive characteristics among these teachers who developed invasive endometrial cancer and those who were cancer-free throughout follow-up are shown in **Table 4.6**. In the overall analytic sample, teachers were primarily non-Hispanic white (87%), postmenopausal (59%), non-smokers (67%), moderate drinkers (60%), of high SES (45%), parous (80%), had no family history of endometrial cancer (94%) and no personal histories of breast cancer (95%) and endometriosis (91%). Additionally, teachers who developed invasive endometrial cancer were more often current EPT users, former smokers, nulliparous, older at menopause, and had a previous breast cancer diagnosis.

The occupational characteristics of CTS teachers according to incident endometrial cancer status are presented in **Table 4.7**. Teachers in the CTS were primarily multiple-subject teachers (i.e. pre-school and elementary) (53%), with two to three schools throughout employment (42%), twenty or more years throughout employment (43%), moderately active throughout the workday (60%), teaching at schools with power lines present (61%), and had high-risk stress levels (67%). The teachers diagnosed with invasive endometrial cancer during follow-up were more often multiple role teachers, with twenty or more years of employment, and had lower levels of occupational physical activity.

Table 4.6- Descriptive characteristics according to incident endometrial cancer status (*N*= 118,481)			
	Non-Cases (*n*=117,130)	**Invasive Cases (*n*=1,351)**	**Overall (*N*=118,481)**
Characteristic:	N (%)*	N (%)*	N(%)
Age (y)	53 ± 14	58 ± 11	53 ± 14
BMI (kg/m^2)	24.8 ± 5.0	27.0 ± 6.6	24.8 ± 5.0
Recreational physical activity (hrs./wk.)	2.3 ± 2.6	2.2 ± 2.6	2.3 ± 2.6
Age at first pregnancy (y)	26 ± 4	25 ± 4	26 ± 4
Age at menarche (y)	6 ± 1	5 ± 1	6 ± 1
Race:			
White	101,584 (98.8)	1,205 (1.2)	102,789 (86.8)
Non-white	15,546 (99.1)	146 (0.9)	15,692 (13.2)
Total:	117,130	1,351	118,481
Menopausal and HRT status:			
Premenopausal	47,931 (99.2)	371 (0.8)	48,302 (40.8)
Post, no HRT use	29,281 (98.6)	423 (1.4)	29,704 (25.1)
Post, past HRT use	9,171 (98.5)	136 (1.5)	9,307 (7.9)
Post, current ET use	14,776 (99.6)	57 (0.4)	14,833 (12.5)
Post, current EPT use	15,971 (97.8)	364 (2.2)	16,335 (13.8)
Total:	117,130	1,351	118,481
Smoking status:			
Never	77,980 (98.9)	862 (1.1)	78,842 (66.5)
Former	33,241 (98.7)	426 (1.3)	33,667 (28.4)
Current	5,909 (98.9)	63 (1.1)	5,972 (5.0)
Total:	117,130	1,351	118,481
Second-hand smoke exposure:			
No exposure	22,474 (99.1)	210 (0.9)	22,684 (19.2)
Childhood only	31,355 (99.0)	320 (1.0)	31,675 (26.7)
Adulthood only	26,375 (98.8)	328 (1.2)	26,703 (22.5)
Both child/adulthood	36,926 (98.7)	493 (1.3)	37,419 (31.6)
Total:	117,130	1,351	118,481
Alcohol intake:			
None	37,500 (98.8)	468 (1.2)	37,968 (32.1)
< 20 g/day	70,439 (98.9)	770 (1.1)	71,209 (60.1)
≥20 g/day	9,191 (98.8)	113 (1.2)	9,304 (7.9)
Total:	117,130	1,351	118,481
Vitamin use:			
Non-user	40,539 (99.0)	404 (1.0)	40,943 (34.6)
Current single vitamin use	14,684 (98.7)	189 (1.3)	14,873 (12.6)
Current multivitamin use	25,637 (99.0)	272 (1.0)	25,909 (21.9)
Current single and multivitamin use	36,270 (98.7)	486 (1.3)	36,756 (31.0)
Total:	117,130	1,351	118,481

SES:			
Low	5,166 (99.1)	48 (0.9)	5,214 (4.4)
Medium-low	20,184 (98.9)	228 (1.1)	20,412 (17.2)
Medium-high	39,421 (98.8)	463 (1.2)	39,884 (33.7)
High	52,359 (98.8)	612 (1.2)	52,971 (44.7)
Total:	117,130	1,351	118,481
Parity status:			
Nulliparous	23,822 (98.7)	322 (1.3)	24,144 (20.4)
Parous	93,308 (98.9)	1,029 (1.1)	94,337 (79.6)
Total:	117,130	1,351	118,481
Age at menopause:			
Periods haven't stopped	54,227 (99.1)	492 (0.9)	54,719 (46.2)
<50 y	35,933 (99.3)	261 (0.7)	36,194 (30.6)
≥50 y	26,970 (97.8)	598 (2.2)	27,568 (23.3)
Total:	117,130	1,351	118,481
Family history of endometrial cancer:			
No 1st degree relative	109,857 (98.9)	1,260 (1.1)	111,117 (93.8)
At least one 1st degree relative	3,524 (98.5)	54 (1.5)	3,578 (3.0)
Adopted, unknown	3,749 (99.0)	37 (1.0)	3,786 (3.2)
Total:	117,130	1,351	118,481
Personal history of breast cancer:			
No	113,641 (98.9)	1,292 (1.1)	112,925 (95.3)
Yes	3,489 (98.3)	59 (1.7)	5,556 (4.7)
Total:	117,130	1,351	118,481
Personal history of endometriosis:			
No	106,484 (98.8)	1,285 (1.2)	107,769 (91.0)
Yes	10,646 (99.4)	66 (0.6)	10,712 (9.0)
Total:	117,130	1,351	118,481

Continuous characteristics presented as mean value ± standard deviation.
*Proportions depict percent of cancer cases according to sociodemographic and women's health characteristics.

Table 4.7- Occupational characteristics according to incident endometrial cancer status (*N*= 118,481)

	Non-Cases (*n*=117,130)	Invasive Cases (*n*=1,351)	Overall (*N*=118,481)
Characteristic:	N (%)*	N (%)*	N (%)
Teacher type:			
Multiple subject teachers	62,351 (98.9)	688 (1.1)	63,039 (53.2)
Single subject teachers	31,645 (98.9)	368 (1.1)	32,013 (27.0)
Administrator and Pupil services	8,288 (99.0)	87 (1.0)	8,375 (7.1)
Multiple roles, other	14,846 (98.6)	208 (1.4)	15,054 (12.7)
Total:	117,130	1,351	118,481
Number of schools throughout employment:			
1 school	20,809 (99.0)	204 (1.0)	21,013 (17.7)
2-3 schools	49,595 (98.9)	568 (1.1)	50,163 (42.3)
≥4 schools	46,726 (98.8)	579 (1.2)	47,305 (39.9)
Total:	117,130	1,351	118,481
Years of employment in school system:			
< 10 yrs.	30,942 (99.4)	189 (0.6)	31,131 (26.3)
10-19 yrs.	36,093 (98.9)	389 (1.1)	36,482 (30.8)
≥20 yrs.	50,095 (98.5)	773 (1.5)	50,868 (42.9)
Total:	117,130	1,351	118,481
Occupational physical activity:			
≤1 hr./ day	31,429 (98.6)	439 (1.4)	31,868 (26.9)
2-6 hrs./day	69,610 (98.9)	788 (1.1)	70,398 (59.4)
≥7 hrs./day	16,091 (99.2)	124 (0.8)	16,215 (13.7)
Total:	117,130	1,351	118,481
Power lines near school:			
No power lines present	15,848 (98.8)	193 (1.2)	16,041 (13.5)
Power lines present	71,963 (98.9)	820 (1.1)	72,783 (61.4)
Don't Know	29,319 (98.9)	338 (1.1)	29,657 (25.0)
Total:	117,130	1,351	118,481
Occupational stress[1]:			
High-risk	46,495 (98.8)	552 (1.2)	47,047 (66.9)
Moderate-risk	17,220 (98.8)	205 (1.2)	17,425 (24.8)
Low-risk	5,728 (98.6)	84 (1.4)	5,812 (8.3)
Total:	69,443	841	70,284

*Proportions depict percent of cancer cases according to occupational characteristics.
[1] Computed for those respondents of the third follow-up questionnaire (Spring 2000) who had no prior endometrial cancer diagnosis (*n*=70,284).

4.3.2.2 Associations between occupational characteristics and incident endometrial cancer risk

The hazard ratios for incident endometrial cancer according to the occupational characteristics of CTS teacher are depicted in **Table 4.8.** Throughout the eighteen years of follow-up in the CTS, we observed significantly elevated risks of invasive endometrial cancer among teachers of the CTS with decreased occupation physical activity levels when compared to highly-active teachers (HR for ≤1 hr. vs. ≥7 hrs./day: 1.25, 95% CI 1.02-1.54). Moreover, we observed significantly elevated risk of endometrial cancer among multiple role teachers when compared to multiple subject teachers (HR 1.17, 95% CI: 1.00-1.37). Notably, the association among administrators and pupil service workers was marginally insignificant which may be due to opposing effect sizes among these occupational subgroups. Upon analyzing the association in these occupational subgroups separately (**Table 4.9**), the risk of endometrial cancer among administrators was significantly reduced, while the risk among pupil service teachers did not differ significantly from those multiple subject teachers (HR for administrator vs multiple subject teachers: 0.66, 95% CI: 0.46-0.95; HR for pupil services vs multiple subject teachers: 0.93, 95% CI: 0.71-1.22).

There were apparent differences in the estimates of effect for occupational physical activity (PA) and endometrial cancer risk after conducting several sensitivity analyses (**Table 4.10**). Results from the univariate age-adjusted model provide significant evidence for the inverse monotonic relationship between occupational physical activity and incident endometrial cancer among teachers (*P*-trend= 0.007).

Additionally, the elevated risk associated with no daily occupational physical activity in the overall analytic cohort was most notably exacerbated among teachers in the CTS who were never parous (HR for ≤1 hr. vs. ≥7 hr./day: 1.57, 95% CI: 1.00-2.44, *P*-trend= 0.048). Moreover, we observed a similar strengthening of the inverse relationship between occupational physical activity and endometrial cancer risk among teachers who are only postmenopausal, not overweight (i.e. BMI < 25 kg/m^2) (*P*-trend= 0.053), and those with higher recreational PA levels (*P*-trend= 0.005).

Table 4.8- Association between occupational characteristics and invasive endometrial cancer risk (*N*= 118,481)[1]		
Characteristic:	***N* Cases/ *N***	**HR (95% CI)**
Teacher type:		
Multiple subject teachers	688/63,039	1.00 (Ref.)
Single subject teachers	368/32,013	1.03 (0.91-1.17)
Administrators and Pupil services	87/8,375	0.82 (0.65-1.02)
Multiple roles, other	208/15,054	1.17 (1.00-1.37)
Number of schools throughout employment:		
1 school	204/21,013	1.00 (Ref.)
2-3 schools	568/50,163	1.01 (0.86-1.18)
≥4 schools	579/47,305	0.92 (0.79-1.08)
Years of employment in school system:		
< 10 yrs.	189/31,131	1.00 (Ref.)
10-19 yrs.	389/36,482	1.02 (0.85-1.22)
≥20 yrs.	773/50,868	1.02 (0.85-1.21)
Occupational physical activity:		
≥7 hrs./day	124/16,215	1.00 (Ref.)
2-6 hrs./day	788/70,398	1.25 (1.04-1.52)
≤1 hr./day	439/31,868	1.25 (1.02-1.54)
Power lines near school:		
No power lines present	193/16,041	1.00 (Ref.)
Power lines present	820/72,783	0.91 (0.77-1.06)
Don't Know	338/29,657	0.90 (0.76-1.08)
Occupational stress[2]:		
High-risk	552/47,047	1.00 (Ref)
Moderate-risk	205/17,425	0.99 (0.84-1.16)
Low-risk	84/5,812	1.18 (0.94-1.49)

[1] Cox proportional hazards regression models for invasive endometrial cancer risk adjusted for: age, menopausal status, hormone therapy use, personal history of endometriosis, age at menopause, BMI, parity status, and age at menarche.
[2] Estimates computed for those respondents of the third follow-up questionnaire (Spring 2000) who had no prior endometrial cancer diagnosis (*n*=70,284).

Table 4.9- Association between employment position and invasive endometrial cancer risk (*N*= 118,481)[1]

Characteristic:	*N* Cases/ *N*	HR (95% CI)
Teacher Type:		
Multiple subject teachers	688/63,039	1.00 (Ref.)
Single subject teachers	368/32,013	1.03 (0.91-1.17)
Pupil services	57/5,079	0.93 (0.71-1.22)
Administrators	30/3,296	0.66 (0.46-0.95)
Multiple roles, other	208/15,054	1.17 (1.00-1.37)

[1] Cox proportional hazards regression models for invasive endometrial cancer risk adjusted for: age, menopausal status, hormone therapy status, personal history of endometriosis, age at menopause, BMI, parity status, and age at menarche.

Table 4.10- Association between occupational physical activity and invasive endometrial cancer risk among prognostic subgroups of teachers (*N*= 118,481)[1]

		Occupational physical activity			
		≥ 7 hrs./day	**2-6 hrs./day**	**≤1 hr./day**	***P*-trend[2]**
Age adjusted only	**HR (95%CI)**	1.00 (ref).	1.30 (1.08-1.58)	1.34 (1.09-1.65)	0.0074
	n* cases/*n	124/16,215	788/70,398	439/31,868	
Parity status:					
Never parous	**HR (95%CI)**	1.00 (ref).	1.39 (0.92-2.10)	1.57 (1.00-2.44)	0.0482
	n* cases/*n	26/3,744	181/14,314	115/6,086	
Ever parous	**HR (95%CI)**	1.00 (ref).	1.22 (0.99-1.51)	1.17 (0.92-1.48)	
	n* cases/*n	98/12,471	607/56,084	324/25,782	
Menopausal status:					
Premenopausal	**HR (95%CI)**	1.00 (ref).	1.16 (0.86-1.56)	1.12 (0.77-1.62)	
	n* cases/*n	53/8,926	261/32,679	57/6,679	
Postmenopausal	**HR (95%CI)**	1.00 (ref).	1.32 (1.03-1.69)	1.33 (1.03-1.74)	
	n* cases/*n	71/7,289	527/37,719	382/25,171	
BMI:					
< Overweight (< 25 kg/m^2)	**HR (95%CI)**	1.00 (ref).	1.29 (0.98-1.69)	1.35 (1.00-1.83)	0.0527
	n* cases/*n	59/10,478	378/44,378	226/19,503	
≥ Overweight (≥ 25 kg/m^2)	**HR (95%CI)**	1.00 (ref).	1.26 (0.97-1.64)	1.22 (0.92-1.64)	
	n* cases/*n	65/5,737	410/26,020	213/12,365	
Recreational physical activity:					
< 1.5 hrs./wk.	**HR (95% CI)**	1.00 (ref).	1.07 (0.83-1.39)	1.00 (0.75-1.33)	
	n* cases/*n	69/7,410	385/32,966	204/15,878	
≥ 1.5 hrs./wk.	**HR (95% CI)**	1.00 (ref).	1.48 (1.11-1.96)	1.57 (1.16-2.13)	0.005
	n* cases/*n	55/8,805	403/37,432	235/15,990	

[1] Cox proportional hazards regression models for invasive endometrial cancer risk adjusted for: age, menopausal status, hormone therapy status, personal history of endometriosis, age at menopause, BMI, parity status, and age at menarche when outcome not stratified on particular covariable.

[2-] Wald's test for trend across occupational physical activity levels by using an ordinal variable coded as the median value of the occupational physical activity category.

4.3.3 Incident malignant melanoma risk among teachers in the CTS

4.3.3.1 Malignant melanoma risk factors and occupational characteristics

Of the 106,119 teachers in the CTS who had no diagnosis of malignant melanoma prior to baseline and are non-Hispanic white, 102,447 teachers were observed to have complete information regarding the occupational characteristics of interest and thus were eligible for this study. **Table 4.11** shows key demographic and lifestyle characteristics of teachers overall and according to incident malignant melanoma (MM) status. Female teachers of the CTS were primarily postmenopausal (62%), and of high SES (46%). In terms of skin health history, teachers in the CTS were more likely to have at least one sun blister (72%), first sun blister at 11-20 years (46%), mild skin burns from sun exposure without protection (48%), moderately tan skin after repeated sun exposure (48%), no personal history of mole removal (82%), and no family histories of mole removal (80%) and melanoma (91%). Throughout follow-up, 1,015 and 904 teachers were diagnosed with invasive and in situ MM, respectively. The demographic profile for those teachers who developed invasive and in situ MM was more often older, postmenopausal, current users of hormone replacement therapy, had lower Vitamin D intakes, age ten or younger at first sun blister occurrence, had more sun blister occurrences, more severe burns from sun exposure without protection, no tan after repeated sun exposure, greater personal history of mole removal, and family histories of mole removal and melanoma.

The occupational characteristics of CTS teachers according to incident MM status are presented in **Table 4.12**. Teachers in the CTS were primarily multiple-subject teachers (i.e. pre-school and elementary) (53%), with two to three schools throughout employment (42%), twenty or more years throughout employment (44%), moderately active throughout the workday (59%), teaching at schools with power lines present (61%), and had high-risk stress (67%).The teachers diagnosed with invasive MM during follow-up were more often administrators, with a greater number of schools and years throughout employment, and had lower levels of occupational physical activity. Teachers who developed in situ MM during the study had a greater number of schools and years throughout employment, and perceived greater levels of stress.

Table 4.11- Descriptive characteristics according to incident melanoma status (*N*=102,447)				
	Non-Cases (*n*=100,528)	**Invasive Cases (*n*=1,015)**	**In Situ Cases (*n*=904)**	**Overall (*N*=102,447)**
Characteristic:	N (%)*	N (%)*	N (%)*	N (%)
Age (y)	54 ± 14	55 ± 13	55 ± 12	54 ± 14
Recreational physical activity (hrs./wk.)	2.3 ± 2.7	2.4 ± 2.5	2.7 ± 2.8	2.3 ± 2.7
BMI (kg/m^2)	24.8 ± 5.0	24.7 ± 5.0	24.4 ± 4.5	24.8 ± 5.0
Menopausal and HRT status:				
Premenopausal	38,141 (98.4)	324 (0.8)	284 (0.7)	38,749 (37.8)
Post, no HRT use	12,833 (98.1)	134 (1.0)	112 (0.9)	13,079 (12.8)
Post, past HRT use	8,384 (98.0)	84 (1.0)	83 (1.0)	8,551 (8.3)
Post, current ET use	13,241 (97.8)	155 (1.1)	143 (1.1)	13,539 (13.2)
Post, current EPT use	14,495 (97.7)	165 (1.1)	169 (1.1)	14,829 (14.5)
Other	13,434 (98.1)	153 (1.1)	113 (0.8)	13,700 (13.4)
Total:	100,528	1,015	904	102,447
Vitamin use:				
Non-user	33,676 (98.4)	311 (0.9)	252 (0.7)	34,239 (33.4)
Current single vitamin use	12,706 (97.7)	151 (1.2)	148 (1.1)	13,005 (12.7)
Current multivitamin use	22,086 (98.2)	221 (1.0)	193 (0.9)	22,500 (22.0)
Current single and multivitamin use	32,060 (98.0)	332 (1.0)	311 (1.0)	32,703 (31.9)
Total:	100,528	1,015	904	102,447
Vitamin D intake:				
Low (≤143.11 IU)	25,643 (98.1)	277 (1.1)	223 (0.9)	26,143 (25.5)
High (>143.11 IU)	67,056 (98.1)	672 (1.0)	620 (0.9)	68,348 (66.7)
Unknown, other	7,829 (98.4)	66 (0.8)	61 (0.8)	7,956 (7.8)
Total:	100,528	1,015	904	102,447
SES:				
Low	3,748 (98.4)	35 (0.9)	25 (0.7)	3,808 (3.7)
Medium-low	16,998 (98.5)	141 (0.8)	121 (0.7)	17,260 (16.8)
Medium-high	33,962 (98.2)	330 (1.0)	283 (0.8)	34,575 (33.7)
High	45,820 (97.9)	509 (1.1)	475 (1.0)	46,804 (45.7)
Total:	100,528	1,015	904	102,447
Sun blister status:				
No	28,688 (98.7)	205 (0.7)	185 (0.6)	29,078 (28.4)
Yes	71,840 (97.9)	810 (1.1)	719 (1.0)	73,369 (71.6)
Total:	100,528	1,015	904	102,447
Age at first sun blister:				
Never	28,688 (98.7)	205 (0.7)	185 (0.6)	29,078 (28.4)
0-10 y	17,043 (97.4)	242 (1.4)	207 (1.2)	17,492 (17.1)
11-20 y	45,652 (98.0)	495 (1.1)	459 (1.0)	46,606 (45.5)
21+ y	9,145 (98.6)	73 (0.8)	53 (0.6)	9,271 (9.1)
Total:	100,528	1,015	904	102,447
Number of sun blister occurrences:				
Never	28,688 (98.7)	205 (0.7)	185 (0.6)	29,078 (28.4)
1-2 times	32,699 (98.2)	312 (0.9)	286 (0.9)	33,297 (32.5)
3-4 times	19,785 (97.8)	239 (1.2)	206 (1.0)	20,230 (19.7)
≥5 times	19,356 (97.6)	259 (1.3)	227 (1.1)	19,842 (19.4)
Total:	100,528	1,015	904	102,447

Tendency of skin in sun without protection:				
No burn, tan only	15,389 (98.9)	74 (0.5)	98 (0.6)	15,561 (15.2)
Mild burn, with tan	48,492 (98.3)	455 (0.9)	401 (0.8)	49,348 (48.2)
Severe burn, no blister	22,297 (97.6)	294 (1.3)	254 (1.1)	22,845 (22.3)
Severe burn, with blister	14,350 (97.7)	192 (1.3)	151 (1.0)	14,693 (14.3)
Total:	100,528	1,015	904	102,447
Tanning habits from repeated sun exposure:				
No tan	4,432 (97.4)	68 (1.5)	52 (1.1)	4,552 (4.4)
Light tan	28,100 (97.6)	370 (1.3)	308 (1.1)	28,778 (28.1)
Moderate tan	48,050 (98.2)	465 (1.0)	408 (0.8)	48,923 (47.8)
Deep tan	19,946 (98.8)	112 (0.6)	136 (0.7)	20,194 (19.7)
Total:	100,528	1,015	904	102,447
Personal history of mole removal:				
No	82,696 (98.3)	721 (0.9)	675 (0.8)	84,092 (82.1)
Yes	17,832 (97.2)	294 (1.6)	229 (1.2)	18,355 (17.9)
Total:	100,528	1,015	904	102,447
Family history of mole removal:				
No	80,006 (98.2)	758 (0.9)	696 (0.9)	81,460 (79.5)
Yes	20,522 (97.8)	257 (1.2)	208 (1.0)	20,987 (20.5)
Total:	100,528	1,015	904	102,447
Family history of melanoma:				
No 1st degree relative	91,815 (98.2)	901 (1.0)	817 (0.9)	93,533 (91.3)
At least one 1st degree relative	5,821 (97.5)	89 (1.5)	60 (1.0)	5,970 (5.8)
Adopted, unknown	2,892 (98.2)	25 (0.8)	27 (0.9)	2,944 (2.9)
Total:	100,528	1,015	904	102,447

Continuous characteristics presented as mean value ± standard deviation.
*Proportions depict percent of cancer cases according to sociodemographic and skin health characteristics.

Table 4.12- Occupational characteristics according to incident melanoma status (*N*= 102,447)				
	Non-Cases (*n*=100,528)	**Invasive Cases (*n*=1,015)**	**In Situ Cases (*n*=904)**	**Overall (*N*=102,447)**
Characteristic:	N (%)*	N (%)*	N (%)*	N (%)
Teacher type:				
Multiple subject teachers	53,194 (98.1)	560 (1.0)	464 (0.9)	54,218 (52.9)
Single subject teachers	27,701 (98.3)	257 (0.9)	236 (0.8)	28,194 (27.5)
Pupil services	4,346 (98.0)	42 (0.9)	45 (1.0)	4,433 (4.3)
Administrator	2,663 (97.5)	40 (1.5)	29 (1.1)	2,732 (2.7)
Multiple roles, other	12,624 (98.1)	116 (0.9)	130 (1.0)	12,870 (12.6)
Total:	100,528	1,015	904	102,447
Number of schools throughout employment:				
1 school	17,420 (98.3)	152 (0.9)	144 (0.8)	17,716 (17.3)
2-3 schools	42,358 (98.0)	449 (1.0)	394 (0.9)	43,201 (42.2)
≥4 schools	40,750 (98.1)	414 (1.0)	366 (0.9)	41,530 (40.5)
Total:	100,528	1,015	904	102,447
Years of employment in school system:				
< 10 yrs.	25,818 (98.5)	225 (0.9)	173 (0.7)	26,216 (25.6)
10-19 yrs.	30,923 (98.2)	292 (0.9)	280 (0.9)	31,495 (30.7)
≥20 yrs.	43,787 (97.9)	498 (1.1)	451 (1.0)	44,736 (43.7)
Total:	100,528	1,015	904	102,447
Occupational physical activity:				
≤1 hr./day	27,801 (98.0)	328 (1.2)	241 (0.8)	28,370 (27.7)
2-6 hrs./day	59,206 (98.1)	589 (1.0)	558 (0.9)	60,353 (58.9)
≥7 hrs./day	13,521 (98.5)	98 (0.7)	105 (0.8)	13,724 (13.4)
Total:	100,528	1,015	904	102,447
Power lines near school:				
No power lines present	13,843 (98.0)	150 (1.1)	130 (0.9)	14,123 (13.8)
Power lines present	61,656 (98.1)	625 (1.0)	548 (0.9)	62,829 (61.3)
Don't know	25,029 (98.2)	240 (0.9)	226 (0.9)	25,495 (24.9)
Total:	100,528	1,015	904	102,447
Occupational stress[1]:				
High-risk	41,411 (98.2)	373 (0.9)	370 (0.9)	42,154 (66.9)
Low-risk	19,862 (98.5)	173 (0.9)	139 (0.7)	20,174 (33.1)
Total:	61,273	546	509	62,328

*Proportions depict percent of cancer cases according to occupational characteristics.
[1] Computed for those respondents of the third follow-up questionnaire (Spring 2000) who had no prior malignant melanoma diagnosis (*n*=62,328).

4.3.3.2 Associations between occupational characteristics and incident malignant melanoma risk

Table 4.13 displays the hazard ratios for incident malignant melanoma according to the occupational characteristics of teachers. There was an elevated risk of invasive malignant melanoma among administrators when compared to multiple subject teachers of the CTS (HR 1.38, 95% CI: 1.00-1.91). Notably, the risk of invasive malignant melanoma was strongly associated with the occupational physical activity levels of CTS teachers. Specifically, we observed a strong inverse dose-response relationship across the levels of occupational physical activity and invasive melanoma risk in the CTS cohort (2-6 hr./day: 33% increase, ≤1 hr./day: 59% increase; *P*-trend= 0.0001). In situ MM risk among teachers was not observed to differ widely across the occupational characteristics of interest, however there was a significant positive association between occupational stress and in situ melanoma risk in the CTS cohort (HR for low-risk stress vs high-risk: 0.80, 95% CI: 0.66-0.97).

Of note, results from the secondary stratified analyses provided evidence that the association between occupational physical activity and invasive melanoma risk differs according to various prognostic factors of teachers (**Table 4.14**). Specifically, the increased incidence of invasive MM related to lower occupational physical activity levels was substantially higher among teachers with lower recreational physical activity levels (HR=1.78), higher BMIs (HR=1.76), family history of melanoma (HR=2.89), no family history of mole removal (HR=1.73), and those with skin complexions that more readily burn (HR for light/no tan= 2.01). Additionally, we observed lesser but still elevated risk associated with decreased occupational physical activity among teachers with greater recreational physical activity levels (*P*-trend= 0.02), lower BMIs (*P*-trend= 0.006), no family history of melanoma (*P*-trend= 0.002), and skin types prone to medium tans (*P*-trend= 0.05). Conversely, the association was no longer significant for teachers with skin types that deeply tan and those with a family history of mole removal.

Table 4.13- Association between occupational characteristics and incident malignant melanoma risk (*N*= 102,447)[1]

	Invasive Melanoma (*N*= 1,015 cases)		In Situ Melanoma (*N*=904 cases)	
	N Cases/ *N*	HR (95% CI)	*N* Cases/ *N*	HR (95% CI)
Characteristic:				
Teacher type:				
Multiple subject teachers	560/54,218	1.00 (Ref.)	464/54,218	1.00 (Ref.)
Single subject teachers	257/28,194	0.92 (0.79-1.07)	236/28,194	1.00 (0.86-1.17)
Pupil services	42/4,433	0.88 (0.64-1.21)	45/4,433	1.12 (0.88-1.44)
Administrators	40/2,732	1.38 (1.00-1.91)	29/2,732	
Multiple roles, other	116/12,870	0.88 (0.72-1.08)	130/12,870	1.15 (0.94-1.39)
Number of schools throughout employment:				
1 school	152/17,716	1.00 (Ref.)	144/17,716	1.00 (Ref.)
2-3 schools	449/43,201	1.16 (0.96-1.40)	394/43,201	1.03 (0.85-1.25)
≥4 schools	414/41,530	1.04 (0.86-1.26)	366/41,530	0.91 (0.75-1.11)
Years of employment in school system:				
< 10 yrs.	225/26,216	1.00 (Ref.)	173/26,216	1.00 (Ref.)
10-19 yrs.	292/31,495	0.94 (0.78-1.14)	280/31,495	1.03 (0.85-1.25)
≥20 yrs.	498/44,736	1.01 (0.83-1.23)	451/44,736	0.91 (0.75-1.11)
Occupational physical activity:				
≥7 hrs./day	98/13,724	1.00 (Ref.)	105/13,724	1.00 (Ref.)
2-6 hrs./day	589/60,353	1.33 (1.08-1.65)	558/60,353	1.14 (0.92-1.40)
≤1 hr./day	328/28,370	1.59 (1.25-2.02)	241/28,370	1.00 (0.78-1.27)
	***P*-trend**[2]:	0.0001		
Power lines near school:				
No power lines present	150/14,123	1.00 (Ref.)	130/14,123	1.00 (Ref.)
Power lines present	625/62,829	0.91 (0.76-1.08)	548/62,829	0.93 (0.77-1.12)
Don't Know	240/25,495	0.89 (0.72-1.09)	226/25,495	1.00 (0.80-1.24)
Occupational stress[3]**:**				
High-risk	373/42,154	1.00 (Ref)	370/42,154	1.00 (Ref)
Low-risk	173/20,174	0.97 (0.81-1.16)	139/20,174	0.80 (0.66-0.97)

[1] Cox proportional hazards regression models for invasive malignant melanoma risk adjusted for: age, recreational physical activity, family history of melanoma, age at first sun blister, personal history of mole removal, tendency of skin in sun without protection, and tanning habits from repeated sun exposure. In Situ melanoma models adjusted for age, recreational physical activity, age at first sun blister, personal history of mole removal, tendency of skin in sun without protection, and tanning habits from repeated sun exposure.
[2-] Wald's test for trend across occupational physical activity levels by using an ordinal variable coded as the median value of the occupational physical activity category.

[3] Estimates computed for those respondents of the third follow-up questionnaire (Spring 2000) who had no prior malignant melanoma diagnosis (*n*=62,328).

Table 4.14- Association between occupational physical activity and invasive melanoma risk among prognostic subgroups of teachers (*N*= 102,447)

		Occupational physical activity			
		≥ 7 hrs./day	2-6 hrs./day	≤1 hr./day	*P*-trend[1]
Recreational physical activity:					
< 1.5 hrs./wk.	**HR (95%CI)**	1.00 (ref).	1.25 (0.89-1.75)	1.78 (1.23-2.56)	0.002
	n* cases/*n	40/6,046	226/27,197	151/13,737	
≥ 1.5 hrs./wk.	**HR (95%CI)**	1.00 (ref).	1.40 (1.06-1.85)	1.47 (1.08-2.00)	0.02
	n* cases/*n	58/7,678	363/33,156	177/14,633	
BMI[2]:					
< Overweight	**HR (95%CI)**	1.00 (ref).	1.31 (1.01-1.71)	1.51 (1.12-2.03)	0.007
	n* cases/*n	65/8,913	375/38,275	197/17,449	
≥ Overweight	**HR (95%CI)**	1.00 (ref).	1.38 (0.96-1.99)	1.76 (1.18-2.63)	0.005
	n* cases/*n	33/4,811	214/22,078	131/10,921	
Melanoma family history[3]:					
No family history	**HR (95%CI)**	1.00 (ref).	1.28 (1.02-1.61)	1.47 (1.15-1.89)	0.002
	n* cases/*n	89/12,392	523/55,075	289/26,066	
At least one first degree relative	**HR (95%CI)**	1.00 (ref).	1.79 (0.81-3.97)	2.89 (1.22-6.83)	0.01
	n* cases/*n	7/925	51/3,643	31/1,402	
Mole removal family history:					
No	**HR (95%CI)**	1.00 (ref).	1.45 (1.11-1.90)	1.73 (1.30-2.32)	0.0001
	n* cases/*n	62/10,356	428/47,123	268/23,981	
Yes	**HR (95%CI)**	1.00 (ref).	1.12 (0.78-1.61)	1.29 (0.83-1.99)	0.28
	n* cases/*n	36/3,368	161/13,320	60/4,389	
Skin tan levels from repeated sun exposure:					
Light or no tan	**HR (95%CI)**	1.00 (ref).	1.57 (1.10-2.25)	2.01 (1.37-2.97)	0.0003
	n* cases/*n	34/4370	248/19,529	156/9,431	
Medium tan	**HR (95%CI)**	1.00 (ref).	1.23 (0.91-1.68)	1.40 (1.00-1.98)	0.05
	n* cases/*n	49/6,356	274/28,868	142/13,699	
Deep tan	**HR (95%CI)**	1.00 (ref).	1.14 (0.65-2.01)	1.12 (0.57-2.18)	
	n* cases/*n	15/2,998	67/11,956	30/5,240	

[1-] Wald's test for trend across occupational physical activity levels by using an ordinal variable coded as the median value of the occupational physical activity category.

[2] Overweight as defined by clinical BMI cut-points, < Overweight: <25 kg/m^2 and ≥ Overweight: ≥25 kg/m^2.

[3] Estimates not shown for teachers with unknown family history and/or are adopted (*n*= 2,944).

4.4 DISCUSSION

In a population of female teachers in the CTS, after eighteen years of follow-up, we observed uniquely higher risk for endometrial cancers among teachers with multiple roles, and an elevated risk of invasive malignant melanoma among administrators. As with the comparison of cancer incidence rates among teachers and the female population of California reported in *Chapter 3*, occupational physical activity levels were continually shown to be associated with incidence of cancer among teachers. Specifically, we observed the risk of developing invasive breast cancer, endometrial cancer, and malignant melanoma to be significantly elevated among teachers of the CTS with lower levels of occupational physical activity (i.e. none, ≤1 hr./day) when compared to teachers with greater occupational physical activity levels (i.e. ≥7 hrs./day). The elevated cancer incidence of invasive breast, endometrial, and malignant melanoma among teachers with decreased occupational physical activity compared to teachers with greater occupational physical activity was not dissipated by greater levels of recreational physical activity in this study. The risk adjusted estimates among teachers with minimal occupational (i.e. none, ≤1 hr./day) and greater recreational physical activity levels remained above one, and were observed to be higher than the estimates among teachers with both minimal occupational and recreational physical activity levels for invasive breast and endometrial cancers.

The overall evidence regarding the risk of developing breast cancer, endometrial cancer and malignant melanoma among teachers according to their occupational characteristics is sparse. Fortunately, previous studies have compared the cancer incidence rates among teachers to the general population according to several occupational characteristics. Findings from a study conducted by Reynolds et al. provided intriguing evidence for notably higher rates of cancer development among “teachers” when compared to general California women, while lesser but still elevated rates for breast and malignant melanoma among “administrators and pupil service workers” [**3**]. Additional studies have also observed differences in cancer incidence among teachers according to employment position [**9, 77**]. Moreover, the estimates of cancer risk in our study among teachers with greater durations of employment were subtly elevated when compared to teachers with lower durations. Although, reports regarding the risk of developing cancer among teachers according to their durations of employment are sparse, results in this study align with findings from previous case-control studies [**5, 8**].

The strongest consistent relationship we observed between cancer risk and occupational characteristics in the CTS was with occupational physical activity (PA) levels. The elevated risk of invasive breast cancer, endometrial cancer and malignant melanoma among teachers who are sedentary throughout the workday is a novel finding that has not been previously examined in a population of female teachers. However, previous studies have examined this relationship among study populations consisting of heterogeneous occupational titles. Specifically, previous studies have reported an inverse association between occupational physical activity and incident cancer risk, but the evidence informing this topic is inconsistent. Occupational physical activity was inversely associated with invasive breast cancer risk among postmenopausal participants of the NIH-AARP cohort (HR for ≥9 hrs. vs. <3 hrs./day sitting at work: 1.19, 95% CI: 1.02-1.39) [**27**]. Similar findings regarding the inverse association between occupational physical activity and invasive breast and endometrial cancer risk have been previously reported [**23, 28-29, 32, 78**]. Additionally, the risk for incident melanoma has been previously shown to be inversely associated to occupational physical activity levels among Canadian and Turkish study populations [**30-31**]. Although findings from these past studies are generally similar to the results of this study, the overall evidence regarding occupational physical activity and incident cancer risk is not definitive, as seen among other studies that did not observe an inverse association [**24-26, 31, 84]**. Nonetheless, higher physical activity levels has a large body of evidence from observational and experimental studies supporting the beneficial effects on pathways such as oxidative stress and inflammation which are well-established "hallmarks of cancer" [**19, 33, 80**].

Greater recreational physical activity levels was not observed to mitigate the elevated risk of invasive breast cancer, endometrial cancer, and malignant melanoma associated with lower levels of occupational physical activity (i.e. none, ≤1 hr./day). Past studies examining the association between physical activity and the incidence of breast cancer have provided evidence for the inverse association, especially among postmenopausal women [**26, 32**]. Similar findings have been shown for endometrial cancer risk, which aligns with cancer biology for the shared risk factors among hormone-dependent cancer types [**29, 85**]. Malignant melanoma risk has not been previously shown to be inversely associated with recreational physical activity levels in which past studies have hypothesized greater levels of recreational physical activity increase exposure to solar ultraviolet radiation exposures thus serving to increase the risk [**79**]. Although increased recreational physical activity has been previously shown to reduce the risk of invasive breast and endometrial cancer, the risk-adjusted estimates remained above one for the three cancer types of interest among those teachers with increased recreational physical activity levels thus suggesting the importance of physical activity levels in the workplace where teachers spend majority of their time.

There are several strengths of this study. It is the first study to examine the relationship between occupational characteristics and risk for three common cancers in a study population consisting entirely of female teachers. Moreover, this investigation utilized participants from the largest cohort study of female teachers and school administrators, the California Teachers Study (*N*= 133,479). Another strength can be found in our ability to examine a broad range of occupational characteristics among teachers and school administrators which was not available in past studies that examined the cancer risk of teachers. Furthermore, many teachers with distinct occupational characteristics developed the cancers of interest throughout the long period of follow-up (1995-2013) to provide crucial evidence for occupational factors related to teachers' cancer risk.

Limitations include some level of misclassification bias with the self-reported occupational characteristics, although this is likely non-differential with respect to disease status thus pushing estimates toward the null. We also had to exclude ~3% of the study population due to incomplete occupational characteristic data, although they did not differ in any material way from the analytic population with ascertained cancer status. The self-report of other lifestyle-related data may also result in non-differential misclassification and residual confounding in our models. The California Teachers Study population is comprised of ~87% non-Hispanic white teachers and thus can potentially be considered slightly non-representative, however a good understanding of the biological mechanism between occupational characteristics and incident cancer risk can overcome any issues with generalizability. Lastly, changes in occupational characteristics of teachers occurring after baseline would further inform the study results, but were not available.

In conclusion, across the occupational characteristics of interest, the risk for incident cancer was most consistently elevated among teachers with lower occupational physical activity levels among the three cancer types examined in this study. Additionally, the risk remained elevated among teachers who had greater exercise levels (i.e. recreational physical activity). Therefore, with the previous reports of uniquely higher risk for incident cancer among teachers, as an occupational group, inadequate occupational physical activity should be a topic of interest to inform future research, policy, and recommendations to potentially reduce the elevated rate of cancer development among teachers.

CHAPTER 5

The Risk of Incident Breast Cancer, Endometrial Cancer, and Malignant Melanoma According to the Medication Intake of Teachers

5.1 INTRODUCTION

Gaining a better understanding of preventive factors related to cancer risk has the potential of reducing the reported elevated breast, endometrial, and malignant melanoma risk among teachers as an occupational group [**2**]. Specifically, nonsteroidal anti-inflammatory drugs (NSAIDs) and cholesterol-lowering medication use has been a topic of interest in the scientific literature given their ability to interfere with tumorigenic pathways necessary for aggressive tumor formation [**34, 45-46, 50-51**]. The findings regarding NSAIDs use and risk of incident melanoma [**49**], breast [**47**], and endometrial cancers [**48**] were suggestively inverse but inconsistent thus precluding any definitive conclusions regarding this topic. Moreover, the overall findings from past studies examining Statin use on the risk of various incident cancers (i.e. breast, endometrial, and malignant melanoma) are shaky and inconsistent [**65-66**]

Indeed, the inconsistent findings across studies may be partially accounted to difference in measurement methods (i.e. regular use vs. long-term use) and the lack of assessment into cancer-susceptible populations, which suggests the need to further examine these relationships among the susceptible occupational cohort of the CTS [**2**]. Specifically, the ability to detect significant differences in risk is limited when examining exposures with a proposed modest effect (i.e. NSAIDs and Statins) in study populations that have a low vulnerability for the outcome of interest and may account for past inconsistent findings. Lastly, the assessment of study populations comprised of vastly different participants in terms of sociodemographic profiles may introduce systematic errors (i.e. confounding bias) thus potentially hampering the ability to make statistical inferences regarding the association medication intake and incident cancer risk.

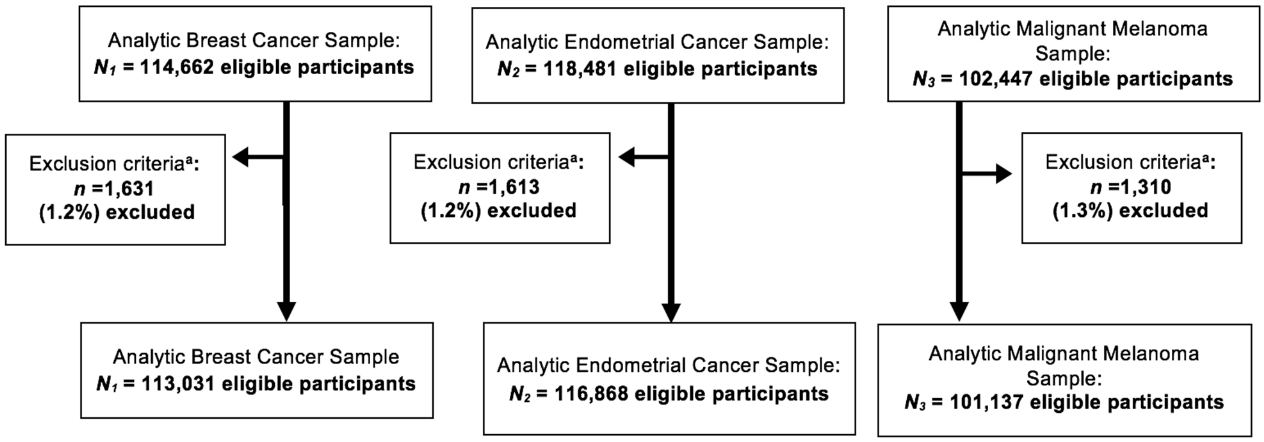
Therefore, this investigation examined the association between medication use and risk of three incident cancers (i.e. breast, endometrial, malignant melanoma) in a homogenous sociodemographic study population that has been shown to have an increased cancer vulnerability compared to the general population [**2**]. Due to the breadth of discordant findings regarding this topic, it is critically important to further examine the association of medication use and risk of various cancers to potentially lower the elevated incidence rate among teachers through improving guidelines, policy, and advocacy in this field.

5.2 METHODS

Chapter 2 contains the detailed description of the California Teachers Study (CTS) population, as well as the assessment of teacher's medication intake and cancer risk factor characteristics.

Given our interest in incident cancer risk among teachers according to their medication intakes, teachers who lacked complete data concerning the medication intakes of interest were further excluded from the Aim 2 analytic samples (**Figure 5.1**).

FIGURE 5.1: Flowchart of the study selection process of Aim 3 analytic sample



[a] Exclusion criteria for Aim 3 analyses included further exclusions of CTS teachers who lacked complete data regarding their medication intake characteristic information.

5.2.1 Incident cancer risk according to medication intake

Multivariable Cox proportional hazards regression models, using age (in days) as the time metric and stratified by age at baseline (in years), were utilized to estimate hazard ratios (HRs) along with 95% confidence intervals (95% CIs) of breast cancer (in situ and invasive), endometrial cancer (invasive), and malignant melanoma (in situ and invasive) according to the medication intake of teachers. For the medication intake of interest (i.e. aspirin, ibuprofen, acetaminophen, statins), frequency of use was categorized into no use and regular use (i.e. 1-3 days/ week, 4-6 days/week, every day), and duration of use was assessed as not regular, less than 5 years, and greater than 5 years- similar to past studies [**86**]. Teachers were followed from the date they completed the baseline questionnaire until diagnosis with the given cancer type, death, a move out of California, or the end of follow-up (December 31, 2013), whichever occurred first. There was no evidence the proportional hazard assumption was violated through modeling interaction terms of follow-up time with each of the medication intakes of interest. All statistical tests were 2-sided and conducted with SAS software (version 9.4; SAS Institute).

Chapter 4 contains a detailed description of the various adjustments for the cancer-specific multivariable cox proportional hazard regression models

5.3 RESULTS

5.3.1 Incident breast cancer risk among teachers in the CTS

5.3.1.1 Medication intake of teachers according to incident breast cancer case status

Of the 114,662 teachers that were included in the Aim 2 analyses, 113,031 teachers were found to have complete medication intake data and thus eligible for this study. Of the eligible participants, 5,698 and 1,388 teachers were diagnosed with invasive and in situ breast cancer, respectively, throughout the eighteen-year follow-up period (1995-2013). **Table 5.1** shows the medication intake of CTS teachers overall and according to incident breast cancer status. Teachers in the CTS were primarily non-regular users of aspirin (78%), acetaminophen (87%), ibuprofen (80%), and statins (76%). Among those in the CTS with regular medication intake, teacher more often exhibited aspirin intake of ≥5 years (14%), acetaminophen intake of ≥ 5 years (8%), and ibuprofen intake of <5 years (13%). The teachers diagnosed with invasive breast cancer during follow-up more often exhibited regular aspirin use with greater durations of use (i.e. ≥5 years), non-regular acetaminophen use, regular ibuprofen use, and regular statin use. Teachers who developed in situ breast cancer during the study were more likely to be aspirin users with greater durations of use, acetaminophen and ibuprofen users with shorter durations of use (i.e. <5 years), and statin users.

Table 5.1- Medication intake according to incident breast cancer status (*N*= 113,031)				
	Non-Cases (*n*=105,945)	**Invasive Cases (*n*=5,698)**	**In Situ Cases (*n*=1,388)**	**Overall (*N*=113,031)**
Characteristic:	N (%)*	N (%)*	N (%)*	N (%)
Aspirin				
Frequency of use:				
Not regular	82,846 (94.0)	4,247 (4.8)	1,061 (1.2)	88,154 (78.0)
Regular use	23,099 (92.9)	1,451 (5.8)	327 (1.3)	24,877 (22.0)
Total:	105,945	5,698	1,388	113,031
Duration of use (y):				
Not regular	82,846 (94.0)	4,247 (4.8)	1,061 (1.2)	88,154 (78.0)
Less than 5 years	8,848 (93.4)	515 (5.4)	112 (1.2)	9,475 (8.4)
≥5 years	14,251 (92.5)	936 (6.1)	215 (1.4)	15,402 (13.6)
Total:	105,945	5,698	1,388	113,031
Acetaminophen				
Frequency of use:				
Not regular	92,003 (93.7)	5,013 (5.1)	1,196 (1.2)	98,212 (86.9)
Regular use:	13,942 (94.1)	685 (4.6)	192 (1.3)	14,819 (13.1)
Total:	105,945	5,698	1,388	113,031
Duration of use (y):				
Not regular	92,003 (93.7)	5,013 (5.1)	1,196 (1.2)	98,212 (86.9)
Less than 5 years	5,194 (94.1)	241 (4.4)	83 (1.5)	5,518 (4.9)
≥5 years	8,748 (94.1)	444 (4.8)	109 (1.2)	9,301 (8.2)
Total:	105,945	5,698	1,388	113,031
Ibuprofen				
Frequency of use:				
Not regular	85,038 (93.8)	4,506 (5.0)	1,092 (1.2)	90,636 (80.2)
Regular use:	20,907 (93.4)	1,192 (5.3)	296 (1.3)	22,395 (19.8)
Total:	105,945	5,698	1,388	113,031
Duration of use (y):				
Not regular	85,038 (93.8)	4,506 (5.0)	1,092 (1.2)	90,636 (80.2)
Less than 5 years	13,719 (93.3)	782 (5.3)	203 (1.4)	14,704 (13.0)
≥5 years	7,188 (93.5)	410 (5.3)	93 (1.2)	7,691 (6.8)
Total:	105,945	5,698	1,388	113,031
Statin use[1]:				
Not regular	39,403 (92.6)	2,492 (5.9)	629 (1.5)	45,524 (76.1)
Regular use	12,166 (91.2)	916 (6.9)	250 (1.9)	13,332 (23.9)
Total:	51,569	3,408	879	55,856

* Proportions depict percent of cancer cases according to medication intake.

[1] Computed only among those respondents of the fourth follow-up questionnaire who had no prior breast cancer diagnosis (*n*=55,856).

5.3.1.2 Associations between medication intake and incident breast cancer risk

Table 5.2 displays the hazard ratios for incidence of invasive pre- and postmenopausal breast cancer according to the medication intake of teachers. Throughout the eighteen years of follow-up in the CTS, we observed significantly elevated risks of pre- and postmenopausal invasive breast cancer among various medication intakes. Specifically, the risk of breast cancer among postmenopausal teachers was significantly elevated among regular users of ibuprofen when compared to non-regular users in the CTS (HR 1.10, 95% CI: 1.02-1.19). Moreover, the risk was observed to be greater among those teachers with longer durations of use (HR for ≥5 years vs no regular use: 1.14, 95% CI: 1.01-1.28, *P*-trend= 0.01). There was evidence for a modest positive association between aspirin use and postmenopausal invasive breast cancer risk (HR for ≥5 years vs no regular use: 1.08, 95% CI: 1.00-1.17). Conversely, premenopausal breast cancer risk was not observed to significantly differ according to the medication intake of teachers in the CTS cohort.

The hazard ratios for the incidence of pre- and postmenopausal *in situ* breast cancer according to the various medication intake of CTS teachers can be found in **Table 5.3**. Among postmenopausal teachers, we observed the incidence of in situ breast cancer to be moderately elevated among those who regularly use acetaminophen for less than 5 years when compared to non-regular users (HR 1.44, 95% CI: 1.09-1.89). For premenopausal teachers, regular ibuprofen use for less than 5 years was associated with 28% higher risk when compared non-regular users (HR 1.28, 95% CI: 1.00–1.63). For the remaining medication intakes, we did not detect any significant associations to in situ breast cancer risk among pre- and postmenopausal teachers. However, there were several marginally insignificant associations that suggest regular intake is related to the development of in situ breast cancer among teachers. Specifically, there was suggestive evidence for the elevated incidence of postmenopausal in situ breast cancer among regular statin users when compared to non-regular users (HR 1.14, 95% CI: 0.96-1.35). Lastly, in situ breast cancer risk among premenopausal teachers was suggestively associated to greater durations of aspirin intake (24% higher), and regular acetaminophen use (19% higher).

Table 5.2- Association between medication intake and invasive breast cancer risk (*N*=113,031)[1,2]

	Postmenopausal (*N*=65,615/4,240 Cases)		Premenopausal (*N*=47,416/1,458 Cases)	
	N* Cases/*N	**HR (95% CI)**	***N* Cases/*N***	**HR (95% CI)**
Characteristic:				
Aspirin				
Frequency of use:				
Not regular	3,038/47,690	1.00 (Ref.)	1,209/40,464	1.00 (Ref.)
Regular use	1,202/17,925	1.05 (0.98-1.12)	249/6,952	1.03 (0.90-1.18)
Duration of use (y):				
Not regular	3,038/47,690	1.00 (Ref.)	1,209/40,464	1.00 (Ref.)
Less than 5 years	435/6,850	0.99 (0.90-1.10)	80/2,625	0.92 (0.73-1.15)
≥5 years	767/11,075	1.08 (1.00-1.17*)	169/4,327	1.10 (0.93-1.29)
	***P*-trend**:	0.0776		
Acetaminophen				
Frequency of use:				
Not regular	3,761/57,721	1.00 (Ref.)	1,252/40,491	1.00 (Ref.)
Regular use	479/7,894	0.99 (0.90-1.09)	206/6,925	0.99 (0.86-1.15)
Duration of use (y):				
Not regular	3761/57,721	1.00 (Ref.)	1252/40,941	1.00 (Ref.)
Less than 5 years	169/2,974	0.93 (0.80-1.08)	72/2,544	0.98 (0.77-1.24)
≥5 years	310/4,920	1.03 (0.91-1.15)	134/4,381	1.00 (0.84-1.20)
Ibuprofen				
Frequency of use:				
Not regular	3376/53,238	1.00 (Ref.)	1130/37,398	1.00 (Ref.)
Regular use	864/12,377	1.10 (1.02-1.19)	328/10,018	1.06 (0.93-1.19)
Duration of use (y):				
Not regular	3376/53,238	1.00 (Ref.)	1130/37,398	1.00 (Ref.)
Less than 5 years	569/8,278	1.08 (0.99-1.18)	213/6,426	1.06 (0.92-1.23)
≥5 years	295/4,099	1.14 (1.01-1.28)	115/3,592	1.05 (0.86-1.27)
	***P*-trend**:	0.01		
Statin use[3]:				
Not regular	1711/22,027	1.00 (Ref.)	781/20,497	1.00 (Ref.)
Regular use	794/10,508	0.93 (0.85-1.01)	122/2,824	0.89 (0.73-1.08)

[1] Cox proportional hazards regression models for postmenopausal invasive breast cancer risk adjusted for: age, hormone therapy status, family history of breast cancer, age at menopause, age at menarche, smoking status, alcohol intake (g/day), BMI (kg/m^2), and SES. Premenopausal models adjusted for: age, family history of breast cancer, parity status, and recreational physical activity (hrs./wk.).

[2] Wald's test for trend across medication intake levels by using an ordinal variable coded as the median value of the medication intake category.

[3] Estimates computed only among those respondents of the fourth follow-up questionnaire who had no prior breast cancer diagnosis (*n*=55,856).

Table 5.3- Association between medication intake and in situ breast cancer risk (*N*=113,031)[1]

	Postmenopausal (*N*=65,615/921 Cases)		Premenopausal (*N*=47,416/467 Cases)	
	N Cases/*N*	HR (95% CI)	*N* Cases/*N*	HR (95% CI)
Characteristic:				
Aspirin				
Frequency of use:				
Not regular	676/47,690	1.00 (Ref.)	385/40,464	1.00 (Ref.)
Regular use	245/17,925	0.98 (0.85-1.13)	82/6,952	1.09 (0.86-1.39)
Duration of use (y):				
Not regular	676/47,690	1.00 (Ref.)	385/40,464	1.00 (Ref.)
Less than 5 years	89/6,850	0.95 (0.76-1.19)	23/2,625	0.84 (0.55-1.28)
≥5 years	156/11,075	1.00 (0.84-1.19)	59/4,327	1.24 (0.94-1.63)
Acetaminophen				
Frequency of use:				
Not regular	806/57,721	1.00 (Ref.)	390/40,491	1.00 (Ref.)
Regular use	115/7,894	1.11 (0.91-1.35)	77/6,925	1.19 (0.93-1.53)
Duration of use (y):				
Not regular	806/57,721	1.00 (Ref.)	390/40,491	1.00 (Ref.)
Less than 5 years	55/2,974	1.44 (1.09-1.89)	28/2,544	1.23 (0.84-1.81)
≥5 years	60/4,920	0.92 (0.70-1.19)	49/4,381	1.17 (0.87-1.58)
Ibuprofen				
Frequency of use:				
Not regular	740/53,238	1.00 (Ref.)	352/37,398	1.00 (Ref.)
Regular use	181/12,377	1.04 (0.88-1.23)	115/10,018	1.21 (0.98-1.49)
Duration of use (y):				
Not regular	740/53,238	1.00 (Ref.)	352/37,398	1.00 (Ref.)
Less than 5 years	124/8,278	1.07 (0.88-1.29)	79/6,426	1.28 (1.00-1.63)
≥5 years	57/4,099	0.98 (0.75-1.29)	36/3,592	1.08 (0.76-1.52)
Statin use[2]:				
Not regular	383/22,027	1.00 (Ref.)	246/20,497	1.00 (Ref.)
Regular use	209/10,508	1.14 (0.96-1.35)	41/2,824	1.05 (0.75-1.48)

[1] Cox proportional hazards regression models for Postmenopausal in situ breast cancer risk adjusted for: age, family history of breast cancer, hormone therapy status, parity status, smoking status, and alcohol intake (g/day). Premenopausal models adjusted for: age, family history of breast cancer, age at menarche, and BMI (kg/m^2).

[2] Estimates computed only among those respondents of the fourth follow-up questionnaire who had no prior breast cancer diagnosis (*n*=55,856).

5.3.2 Incident endometrial cancer risk among teachers in the CTS

5.3.2.1 Medication intake of teachers according to incident endometrial cancer case status

Of the 118,481 teachers that were included in the Aim 2 analyses, 116,868 teachers were found to have complete medication intake data and thus eligible for this study. Of the eligible participants, 1,332 teachers were diagnosed with invasive endometrial cancer throughout the eighteen-year follow-up period (1995-2013). The medication intake of CTS teachers according to incident endometrial cancer status are presented in **Table 5.4**. Teachers in the CTS were primarily non-regular users of aspirin (78%), acetaminophen (87%), ibuprofen (80%), and statins (76%). Among those in the CTS with regular medication intake, teachers more often exhibited aspirin intake of ≥5 years (14%), acetaminophen intake of ≥ 5 years (8%), and ibuprofen intake of <5 years (13%). The teachers diagnosed with invasive endometrial cancer during follow-up were more often regular users of aspirin with lower durations of use (i.e. <5 years), non-regular users of acetaminophen, regular users of ibuprofen with lower durations of use, and regular users of statins.

Table 5.4- Medication intake according to incident endometrial cancer status (*N*= 116,868)				
		Non-Cases (*n*=115,536)	**Invasive Cases (*n*=1,332)**	**Overall (*N*=116,868)**
Characteristic:		N (%)*	N (%)*	N (%)
Aspirin				
Frequency of use:				
Not regular		90,069 (98.9)	1,015 (1.1)	91,084 (77.9)
Regular use		25,467 (98.8)	317 (1.2)	25,784 (22.1)
	Total:	115,536	1,332	116,868
Duration of use (y):				
Not regular		90,069 (98.9)	1,015 (1.1)	91,084 (77.9)
Less than 5 years		9,725 (98.7)	131 (1.3)	9,856 (8.4)
≥5 years		15,742 (98.8)	186 (1.2)	15,928 (13.6)
	Total:	115,536	1,332	116,868
Acetaminophen				
Frequency of use:				
Not regular		100,419 (98.8)	1,194 (1.2)	101,613 (87.0)
Regular use		15,117 (99.1)	138 (0.9)	15,255 (13.1)
	Total:	115,536	1,332	116,868
Duration of use (y):				
Not regular		100,419 (98.8)	1,194 (1.2)	101,613 (87.0)
Less than 5 years		5,635 (99.0)	56 (1.0)	5,691 (4.9)
≥5 years		9,482 (99.1)	82 (0.9)	9,564 (8.2)
	Total:	115,536	1,332	116,868
Ibuprofen				
Frequency of use:				
Not regular		92,734 (98.9)	1,064 (1.1)	93,798 (80.3)
Regular use		22,802 (98.8)	268 (1.2)	23,070 (19.7)
	Total:	115,536	1,332	116,868
Duration of use (y):				
Not regular		92,734 (98.9)	1,064 (1.1)	93,798 (80.3)
Less than 5 years		14,979 (98.8)	182 (1.2)	15,161 (13.0)
≥5 years		7,823 (98.9)	86 (1.1)	7,909 (6.8)
	Total:	115,536	1,332	116,868
Statin Use[1]:				
Not regular		43,201 (98.8)	507 (1.2)	43,708 (75.8)
Regular use		13,710 (98.3)	242 (1.7)	13,952 (24.2)
	Total:	56,911	749	57,660

* Proportions depict percent of cancer cases according to medication intake.
[1] Computed only among those respondents of the fourth follow-up questionnaire who had no prior endometrial cancer diagnosis (*n*=57,660).

5.3.2.2 Associations between medication intake and incident endometrial cancer risk

The hazard ratios for incident endometrial cancer according to the medication intake of CTS teachers are depicted in **Table 5.5.** Throughout the eighteen years of follow-up in the CTS, we observed no statistically significant association between any of the medications and invasive endometrial cancer risk. However, there were several marginally insignificant inverse associations among the medication intakes of interest. Specifically, the strongest evidence for association was observed among regular users of acetaminophen (HR regular use vs. non-regular use: 0.86, 95% CI: 0.72-1.03) which became stronger with greater durations of use (HR for ≥5 years vs. non-regular use: 0.83, 95% CI: 0.66-1.04). Additionally, the risk was suggestively lower among regular aspirin users with greater durations of use (HR for ≥5 years vs. non-regular use: 0.91, 95% CI: 0.78-1.07).

Table 5.5- Association between medication intake and invasive endometrial cancer risk (*N*= 116,868) [1,2]		
Characteristic:	*N* Cases/ *N*	HR (95% CI)
Aspirin		
Frequency of use:		
Not regular	1,015/91,084	1.00 (Ref.)
Regular use	317/25,784	0.95 (0.83-1.08)
Duration of use (y):		
Not regular	1,015/91,084	1.00 (Ref.)
Less than 5 years	131/9,856	1.00 (0.83-1.20)
≥5 years	186/15,928	0.91 (0.78-1.07)
Acetaminophen		
Frequency of use:		
Not regular	1,194/101,613	1.00 (Ref.)
Regular use	138/15,255	0.86 (0.72-1.03)
Duration of use (y):		
Not regular	1,194/101,613	1.00 (Ref.)
Less than 5 years	56/5,691	0.91 (0.69-1.19)
≥5 years	82/9,564	0.83 (0.66-1.04)
	***P*-trend**:	0.0872
Ibuprofen		
Frequency of use:		
Not regular	1,064/93,798	1.00 (Ref.)
Regular use	268/23,070	1.02 (0.89-1.17)
Duration of use (y):		
Not regular	1,064/93,798	1.00 (Ref.)
Less than 5 years	182/15,161	1.05 (0.89-1.23)
≥5 years	86/7,909	0.98 (0.79-1.22)
Statin use [3]:		
Not regular:	507/43,708	1.00 (Ref.)
Regular use:	242/13,952	1.06 (0.91-1.24)

[1] Cox proportional hazards regression models for invasive endometrial cancer risk adjusted for: age, menopausal status, hormone therapy status, personal history of endometriosis, age at menopause, BMI, parity status, and age at menarche.
[2]- Wald's test for trend across medication intake levels by using an ordinal variable coded as the median value of the medication intake category.
[3] Estimates computed only among those respondents of the fourth follow-up questionnaire who had no prior endometrial cancer diagnosis (*n*=57,660).

5.3.3 Incident malignant melanoma risk among teachers in the CTS

5.3.3.1 Medication intake of teachers according to incident malignant melanoma case status

Of the 102,447 teachers that were included in the Aim 2 analyses, 101,137 teachers were found to have complete medication intake data and thus eligible for this study. Of the eligible participants, 1,007 and 891 teachers were diagnosed with invasive and in situ malignant melanoma, respectively, throughout the eighteen-year follow-up period (1995-2013). The medication intake of CTS teachers according to incident MM status are presented in **Table 5.6**. Teachers in the CTS were primarily non-regular users of aspirin (77%), acetaminophen (87%), ibuprofen (80%), and statins (76%). Among those in the CTS with regular medication intake, teacher more often exhibited aspirin intake of ≥5 years (14%), acetaminophen intake of ≥ 5 years (8%), and ibuprofen intake of <5 years (13%). The teachers diagnosed with invasive MM cancer during follow-up were more often non-regular users of aspirin and acetaminophen, regular users of ibuprofen with greater durations of use (i.e. ≥5 years), and regular statin users. Teachers who developed in situ MM during the study were more often non-regular users of aspirin, acetaminophen, and were equally likely to exhibit non-regular or regular intake for ibuprofen, and statins.

Table 5.6- Medication intake according to incident malignant melanoma status (*N*= 101,737)				
	Non-Cases (*n*=99,239)	**Invasive Cases (*n*=1,007)**	**In Situ Cases (*n*=891)**	**Overall (*N*=101,137)**
Characteristic:	N (%)*	N (%)*	N (%)*	N (%)
Aspirin				
Frequency of use:				
Not regular	76,366 (98.1)	793 (1.0)	696 (0.9)	77,855 (77.0)
Regular use	22,873 (98.2)	214 (0.9)	195 (0.8)	23,282 (23.0)
Total:	99,239	1,007	891	101,137
Duration of use (y):				
Not Regular	76,366 (98.1)	793 (1.0)	696 (0.9)	77,855 (77.0)
Less than 5 years	8,636 (98.2)	77 (0.9)	77 (0.9)	8,790 (8.7)
≥5 years	14,237 (98.2)	137 (0.9)	118 (0.8)	14,492 (14.3)
Total:	99,239	1,007	891	101,137
Acetaminophen				
Frequency of use:				
Not regular	86,244 (98.1)	880 (1.0)	791 (0.9)	87,915 (86.9)
Regular use	12,995 (98.3)	127 (1.0)	100 (0.8)	13,222 (13.1)
Total:	99,239	1,007	891	101,137
Duration of use (y):				
Not regular	86,244 (98.1)	880 (1.0)	791 (0.9)	87,915 (86.9)
Less than 5 years	4,812 (98.0)	54 (1.1)	42 (0.9)	4,908 (4.9)
≥5 years	8,183 (98.4)	73 (0.9)	58 (0.7)	8,314 (8.2)
Total:	99,239	1,007	891	101,137
Ibuprofen				
Frequency of use:				
Not regular	79,226 (98.1)	796 (1.0)	717 (0.9)	80,739 (79.8)
Regular use	20,013 (98.1)	211 (1.0)	174 (0.9)	20,398 (20.2)
Total:	99,239	1,007	891	101,137
Duration of use (y):				
Not regular	79,226 (98.1)	796 (1.0)	717 (0.9)	80,739 (79.8)
Less than 5 years	13,087 (98.2)	134 (1.0)	104 (0.8)	13,325 (13.2)
≥5 years	6,926 (97.9)	77 (1.1)	70 (1.0)	7,073 (7.0)
Total:	99,239	1,007	891	101,137
Statin use[1]:				
Not regular	38,315 (98.8)	242 (0.6)	242 (0.6)	38,799 (75.5)
Regular use	12,412 (98.6)	94 (0.8)	78 (0.6)	12,584 (24.5)
Total:	50,727	336	320	51,383

[*] Proportions depict percent of cancer cases according to medication intake.
[1] Computed only among those respondents of the fourth follow-up questionnaire who had no prior malignant melanoma diagnosis (*n*=51,383).

5.3.3.2 Associations between medication intake and incident malignant melanoma risk

The multivariable hazard ratios for malignant melanoma risk according to medication intake of teachers are shown in **Table 5.7**. Overall, we observed a reduced risk of incident malignant melanoma among teachers who regularly use anti-inflammatory medications. Specifically, regular aspirin use was moderately associated with a lower risk of invasive malignant melanoma (HR for regular vs non-regular use: 0.83, 95% CI: 0.71-0.97). Additionally, teachers with aspirin use of less than 5 years experienced a greater reduction in the risk of invasive MM (20% lower) when compared to non-regular users (HR 0.80, 95% CI: 0.63-1.01). Moreover, the risk of in situ tumor types was significantly lower among teachers who regularly use aspirin (15% lower), and those with greater durations of usage (18% lower) (*P*-trend for duration of use= 0.04). Additionally, we observed suggestive evidence for the inverse relationship between in situ MM risk and greater durations of acetaminophen use among teachers in the CTS cohort (HR for ≥5 years vs. non-regular: 0.78, 95% CI: 0.60-1.02).

Table 5.7- Association between medication intake and incident malignant melanoma risk (*N*= 101,137)[1,2]

	Invasive Melanoma (*N*= 1,007 cases)		In Situ Melanoma (*N*=891 cases)	
	N Cases/ *N*	HR (95% CI)	*N* Cases/ *N*	HR (95% CI)
Characteristic:				
Aspirin				
Frequency of use:				
Not regular	793/77,855	1.00 (Ref.)	696/77,855	1.00 (Ref.)
Regular use	214/23,282	0.83 (0.71-0.97)	195/23,282	0.85 (0.73-1.00)
Duration of use (y):				
Not regular	793/77,855	1.00 (Ref.)	696/77,855	1.00 (Ref.)
Less than 5 years	77/8,790	0.80 (0.63-1.01)	77/8,790	0.90 (0.71-1.14)
≥5 years	137/14,492	0.85 (0.71-1.02)	118/14,492	0.82 (0.68-1.00)
			***P*-trend:**	0.04
Acetaminophen:				
Frequency of use:				
Not regular	880/87,915	1.00 (Ref.)	791/87,915	1.00 (Ref.)
Regular use	127/13,222	0.95 (0.79-1.15)	100/13,222	0.86 (0.70-1.06)
Duration of use (y):				
Not regular	880/87,915	1.00 (Ref.)	791/87,915	1.00 (Ref.)
Less than 5 years	54/4,908	1.10 (0.83-1.45)	42/4,908	0.98 (0.72-1.34)
≥5 years	73/8,314	0.87 (0.68-1.11)	58/8,314	0.78 (0.60-1.02)
Ibuprofen				
Frequency of use:				
Not regular	796/80,739	1.00 (Ref.)	717/80,739	1.00 (Ref.)
Regular use	211/20,398	1.03 (0.88-1.20)	174/20,398	0.95 (0.80-1.12)
Duration of use (y):				
Not regular	796/80,739	1.00 (Ref.)	717/80,739	1.00 (Ref.)
Less than 5 years	134/13,325	0.99 (0.83-1.19)	104/13,325	0.85 (0.70-1.05)
≥5 years	77/7,073	1.10 (0.87-1.39)	70/7,073	1.13 (0.88-1.44)
Statin Use[3]:				
Not regular	242/38,799	1.00 (Ref.)	242/38,799	1.00 (Ref.)
Regular use	94/12,584	1.05 (0.82-1.34)	78/12,584	0.83 (0.64-1.07)

[1] Cox proportional hazards regression models for invasive malignant melanoma risk adjusted for: age, family history of melanoma, age at first sun blister, personal history of mole removal, tendency of skin in sun without protection, and tendency of skin to repeated sun exposure. In Situ melanoma models adjusted for age, age at first sun blister, personal history of mole removal, tendency of skin in sun without protection, and tendency of skin to repeated sun exposure.
[2-]Wald's test for trend across medication intake levels by using an ordinal variable coded as the median value of the medication intake category.
[3] Estimates computed only among those respondents of the fourth follow-up questionnaire who had no prior malignant melanoma diagnosis (*n*=51,383).

5.4 DISCUSSION

After eighteen years of follow-up in the CTS (1995-2013), we identified several medication intake behaviors of teachers associated with incident cancer risk. Specifically, regular use of aspirin was moderately associated with lower risk for malignant melanoma and suggestive evidence for the modestly reduced risk of in situ malignant melanoma among regular acetaminophen and ibuprofen users. Moreover, there was an inverse association between aspirin, and acetaminophen and endometrial cancer risk, albeit marginally nonsignificant. Conversely, regular use of NSAIDs was observed to be positively associated with risk for postmenopausal breast cancer. In terms of Statin use, we observed mixed results across the three cancer types of interest. The association between statin use and risk of invasive breast cancer, and in situ malignant melanoma was suggestively inverse, while effect sizes for regular statin use were above one for invasive endometrial cancer and postmenopausal in situ breast cancer, although marginally nonsignificant.

Although past studies investigating cancer risk among teachers according to their medication intake are sparse, the relationship between medication intake and cancer risk has been a topic of interest in research and our findings generally align with the published reports. Specifically, regular aspirin use has been previously shown to increase the risk for incident breast cancer [**46-47**], and decrease the risk for endometrial cancer [**14, 87**] and malignant melanoma [**46, 49, 88-89**]. Furthermore, regular ibuprofen use has been previously shown to be positively associated with invasive breast cancer risk [**90-92**]. The results regarding acetaminophen use in this cohort were somewhat consistent with past investigations in which previous studies observed suggestive evidence for lower endometrial cancer [**14**] and malignant melanoma risk [**93-94**], and suggestive evidence for the positive association with in situ postmenopausal breast cancer risk [**95**]. The studies examining Statin use on the risk of various incident cancers have provided more confusion than clarity regarding this matter. Specifically, a study conducted across three US hospitals found no association between statin use and risk of breast cancer, endometrial cancer, and malignant melanoma [**66**]. While other studies report mixed results as current statin use was associated with lower risks of incident malignant melanoma (21% decrease), and endometrial cancer (35% decrease), but was not observed with breast cancer (11% increase) [**65**].

This study has several strengths. This is the first study to examine the risk of breast cancer, endometrial cancer, and malignant melanoma according to medication intake among female teachers, an occupational group that has been previously shown to have an increased susceptibility for the cancers of interest [**2**]. Additional strengths include the extensive period of follow-up (i.e. 1995-2013) in which many teachers with distinct medication intake behaviors developed the cancers of interest thus providing crucial evidence for medications related to cancer risk. Moreover, the large number of events across the three cancer types in this study coupled with the long follow-up period increases the precision of risk-adjusted estimates thus improving our ability to make strong statistical inferences. The detailed information regarding medication intake in the CTS is another strength of this study that allowed for a more comprehensive assessment of the association between medications and cancer risk.

Limitations included some level of misclassification bias with the self-reported medication intake, although this is likely non-differential with respect to disease status and thus may have pushed estimates towards the null. Additionally, we excluded ~1% of the study population due to incomplete medication intake information, although they did not materially differ from the participants included in the analytic population. Information regarding changes in medication intake occurring after baseline and before the end of follow-up would further inform the study results, but were not available. Lastly, the self-report of other lifestyle-related data may also result in non-differential misclassification and residual confounding in our models.

In conclusion, across the medications of interest, the most notable and consistent association to incident cancer risk was with anti-inflammatory medication intake in this study. Specifically, regular use of aspirin was associated with a lower risk of incident malignant melanoma. There was suggestive evidence, albeit non-significant, for a reduced risk of endometrial cancer among regular anti-inflammatory medication users. Furthermore, regular anti-inflammatory medication use in the CTS was associated with an elevated risk of invasive and in situ breast cancer. Conversely, the association between regular statin use and risk for the cancers of interest in this study was overall null, however the evidence for a reduced risk of invasive breast cancer and in situ malignant melanoma was marginally insignificant thus implying the need for future research. Therefore, given the scientific literature regarding the elevated risk of breast cancer, endometrial cancer, and malignant melanoma among teachers, anti-inflammatory medication use should be a topic of interest to inform future research, policy, and recommendation to potentially reduce the elevated risk of cancer.

CHAPTER 6

Summary and Conclusions

6.1 OVERALL SUMMARY

In summary, we observed female teachers of the CTS to have excess cancer incidences of breast, endometrial, and malignant melanoma than would be expected based on statewide incidence data after eighteen years of follow-up. Upon further investigation of cancer incidence according to the teachers' occupational characteristics, there were distinct occupational factors associated with each cancer type. Most notably, the strong evidence observed for the inverse relationship between occupational physical activity and cancer risk across the three cancer types of interest, which was not attenuated by greater levels of recreational physical activity. In addition, regular use of anti-inflammatory medications was associated with a reduced risk of malignant melanoma and a suggestively inverse association to endometrial cancer risk, whereas the risk of breast cancer was significantly elevated among teachers who regularly used these medications- consistent with previous findings. In our present analysis, the relationship between malignant melanoma, breast, and endometrial cancer risk and statin use is unclear.

6.2 STRENGTHS AND LIMITATIONS

The California Teachers Study is an ongoing prospective cohort study, currently in its 24th year of follow-up, and is the largest occupational cohort consisting entirely of female teachers (*N*=133,479) thus providing an ideal study population for this current investigation. Additionally, participants of the CTS were 22-104 years old at study enrollment and thus is not limited in its ability to help inform recommendation, policy, and advocacy across all age groups unlike other existing study populations.

All participants of the CTS are followed from the date they completed the baseline questionnaire until cancer diagnosis, death, the end of follow-up, or lost to follow up (e.g. move out of California without further follow-up), whichever occurs first. Furthermore, all incident cases are identified through linkage with the California Cancer Registry (CCR) records, a population-based cancer registry for California residents. The state of California reports >99% of all cancer diagnoses to the CCR for current residents, so cohort members are actively followed for cancer outcomes without the need for further contact [**72**] and thus devoid of issues such as outcome misclassification bias that are inherent in study populations with self-reported health outcome status. Moreover, all participants of the CTS completed a comprehensive 16-page baseline questionnaire that collected a wide range of information including occupational, familial, lifestyle and demographic characteristics, which bolsters the efficiency of statistical analyses by allowing for the calculation of more precise risk-adjusted estimates that account for well-known risk factors and various confounders.

Previous investigations into cancer risk among teachers have been limited to examining the risk among teachers overall, due to their lack of information regarding occupational characteristics. This present study improves upon these earlier investigations by examining cancer incidence among teachers according to a broad range of occupational characteristics thus providing more insight into teacher-specific occupational risk factors associated with various cancer types. Furthermore, these earlier investigations relate the cancer risk of teachers to the general population through calculating Standardized Incidence Ratios (SIRs) whereas this present study improved upon this through calculating age-adjusted incidence rates using the US 2000 Standard population which is a more stringent methodology to account for the age distribution of the general population and allows for direct comparison with other published age-adjusted cancer incidence rates. In addition, it is not feasible to carry out randomized trials relating occupational characteristics to cancer risk, therefore longitudinal cohort studies are the strongest line of evidence to inform this topic. Specifically, there was a large number of teachers who developed the cancers of interest throughout the long period of follow-up (i.e. 18 years) thus providing crucial evidence linking certain occupational characteristics with the risk of various incident cancers.

Limitations of this study include the composition of the CTS study population in which teachers tended to be non-Hispanic white (87%), of high SES (~45%), and the majority of teachers have private medical insurance, which may contribute to various differences such as access to healthcare, and diet from the general population-therefore potentially impacting the generalizability of results. Moreover, the comparison of cancer risk among teachers to the general female population of California may be partly explained by disparities of health insurance coverage in the state of California, as information beyond race and gender is not available in the California Cancer Registry. The self-reported occupational and medication intake introduces some level of misclassification bias, although this is likely non-differential with respect to disease status thus might have pushed HR estimates toward the null. Furthermore, as with all epidemiological studies it is not feasible to collect information regarding every prognostic factor and thus unmeasured factors introduces residual confounding in our statistical models. Lastly, the repeated assessment of occupational and medication intake would have allowed us to examine the changes in exposure levels in relation to the risk of various incident cancers, but was not available.

6.3 CONCLUSION

Teachers have been continually shown to be at an elevated risk of breast cancer, endometrial cancer, and malignant melanoma in studies conducted in the United States and worldwide [**2-12**]. However, findings from past studies provided little evidence regarding the specific occupational characteristics driving this higher risk in cancer incidence among teachers.

The California Teachers Study has provided an intriguing study population to investigate occupational associations to cancer risk, although past investigations into this matter were non-existent thus findings from this present study provide integral evidence regarding the elevated cancer risk (i.e. breast cancer, endometrial cancer, malignant melanoma) among teachers according to their occupational characteristics and therefore has the potential to lower these risks by improving recommendations, policy, and advocacy

Occupational physical activity among teachers has not been widely investigated but findings from this present study provide evidence for the notably higher cancer incidence among teachers who are not physically active (i.e. standing, walking at work) throughout the workday thus suggesting the importance of reducing sedentary behaviors among teachers. Moreover, higher levels of recreational physical activity did not attenuate the elevated risk of cancer across the three cancer types, a novel finding that suggests the importance of workplace physical activity levels among teachers. As teachers spend most of their day in the classroom, the lack of physical activity has been previously shown to elevate levels of inflammatory cytokines [**21-22**] which have been shown to increase the carcinogenic potential across all cancer types [**33, 96**]. Moreover, with the previous reports of uniquely higher cancer risks among teachers there remains little evidence for preventive strategies in which results from this present study suggest the importance of anti-inflammatory medication intake. Specifically, findings support the elevated risk of breast cancer, the reduced risk of malignant melanoma and suggestive evidence for the reduced risk of endometrial cancer among regular anti-inflammatory medication users in the CTS thus informing future research, policies, and recommendations regarding an additional modifiable factor to lower the elevated rates of cancer among teachers as an occupational group.

References:

1. Employment by detailed occupation. 2016. Massachusetts Ave NE (DC): U.S. Bureau of Labor Statistics; [accessed 2018 Nov 11]. https://www.bls.gov/emp/tables/emp-by-detailed-occupation.htm/.
2. Bernstein L, Allen M, Anton-Culver H, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). *Cancer Causes and Control* 2002; **13**: 625-35.
3. Reynolds P, Elkin EP, Layefsky ME, Lee GM. Cancer in California school employees, 1988-1992. *Am J Ind Med* 1999; **36**: 271-8.
4. Milham S, Morgan LL. A new electromagnetic exposure metric: high frequency voltage transients associated with increased cancer incidence in teachers in a California school. *Am J Ind Med* 2008; **51**: 579-86.
5. Petralia SA, Vena JE, Freudenheim JL, et al. Breast cancer risk and lifetime occupational history: employment in professional and managerial occupations. *Occupational and environmental medicine* 1998; **55**: 43-8.
6. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer–follow-up of 15 million people in five Nordic countries. *Acta Onco* 2009; **48**: 646-790.
7. Pukkala E,I. Cancer risk by social class and occupation: a survey of 109,000 cancer cases among Finns of working age. *Karger Medical and Scientific Publishers* 1995; Vol. 7.
8. Gardner KM, Ou Shu X, Jin F, et al. Occupations and breast cancer risk among Chinese women in urban Shanghai. *Am J Ind Med* 2002; **42**: 296-308.
9. Ji B, Blair A, Shu XO, et al. Occupation and Breast Cancer Risk Among Shanghai Women in a Population-Based Cohort Study. *Am J Ind Med* 2008; **51**: 100–10.
10. Pollán M, Gustavsson P. High-risk occupations for breast cancer in the Swedish female working population. *Am J Public Health* 1999; **89**: 875-81.
11. Villeneuve S, Févotte J, Anger A, et al. Breast cancer risk by occupation and industry: Analysis of the CECILE study, a population-based case–control study in France. *Am J Ind Med* 2011; **54**: 499-509.
12. Vågerö D, Swerdlow AJ, Beral V. Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. *Occup Environ Med* 1990; **47**(5): 317-24.
13. Sharpe CR, Collet JP, McNutt M, Belzile E, Boivin JF, Hanley J a. Nested case-control study of the effects of non-steroidal anti-inflammatory drugs on breast cancer risk and stage. *Br J Cancer* 2000; **83**(2): 112–20.
14. Viswanathan AN, Feskanich D, Schernhammer ES, Hankinson SE. Aspirin, NSAID, and acetaminophen use and the risk of endometrial cancer. *Cancer Res* 2008; **68**(7): 2507–13.
15. Kaae J, Boyd HA, Hansen AV, Wulf HC, Wohlfahrt J, Melbye M. Photosensitizing Medication Use and Risk of Skin Cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**(11): 2942–9.
16. Kochhar R, Khurana V, Bejjanki H, Caldito G, Fort C. Statins to reduce breast cancer risk: A case control study in US female veterans. *Journal of Clinical Oncology* 2005; **23**(16_suppl): 514.

17. Bellingrath S, Rohleder N, Kudielka BM. Healthy Working School Teachers with High Effort-Reward-Imbalance and Overcommitment Show Increased pro-Inflammatory Immune Activity and a Dampened Innate Immune Defence. *Brain, Behavior, and Immunity* 2010; **24**(8): 1332–9.
18. Bellingrath S, Weigl T, Kudielka BM. Chronic Work Stress and Exhaustion Is Associated with Higher Allostatic Load in Female School Teachers. *Stress* 2009; **12**(March): 37–48.
19. Wang D, DuBois RN. Prostaglandins and cancer. *Gut* 2006; **55**(1): 115-22.
20. Thanan R, Oikawa S, Hiraku Y, et al. Oxidative stress and its significant roles in neurodegenerative diseases and cancer. *International journal of molecular sciences* 2014; **16**(1): 193-217.
21. Gay JL, Salinas JJ, Buchner DM, et al. Meeting Physical Activity Guidelines Is Associated with Lower Allostatic Load and Inflammation in Mexican Americans. *Journal of Immigrant and Minority Health* 2015; **17**: 574–81.
22. Jarvie JL, Whooley MA, Regan MC, Sin NL, Cohen BE. Effect of Physical Activity Level on Biomarkers of Inflammation and Insulin Resistance over 5 Years in Outpatients with Coronary Heart Disease (from the Heart and Soul Study*). American Journal of Cardiology* 2014; **114**(8): 1192–7.
23. Shu XO, Hatch MC, Zheng W, Gao YT, Brinton LA. Physical activity and risk of endometrial cancer*. Epidemiology* 1993; **1**: 342-9.
24. Lahmann PH, Friedenreich C, Schuit AJ, et al. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 2007; **16**(1): 36–42.
25. Friberg E, Mantzoros CS, Wolk A. Physical activity and risk of endometrial cancer: a population-based prospective cohort study. *Cancer Epidemiol Biomarkers Prev* 2006; **15**(11): 2136–40.
26. Sprague BL, Trentham-Dietz A, Newcomb PA, Titus-Ernstoff L, Hampton JM, Egan KM. Lifetime recreational and occupational physical activity and risk of in situ and invasive breast cancer. *Cancer Epidemiology and Prevention Biomarkers* 2007; **16**(2): 236-43.
27. George SM, Irwin ML, Matthews CE, et al. Beyond recreational physical activity: examining occupational and household activity, transportation activity, and sedentary behavior in relation to postmenopausal breast cancer risk*. American journal of public health* 2010; **100**(11): 2288-95.
28. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. *N Engl J Med* 1997; **336**(18): 1269–75
29. Friedenreich CM, Cook LS, Magliocco AM, Duggan MA, Courneya KS. Case-control study of lifetime total physical activity and endometrial cancer risk. *Cancer Causes Control* 2010; **21**: 1105–16.
30. Lee TK, MacArthur AC, Gallagher RP, Elwood MJ. Occupational physical activity and risk of malignant melanoma: the Western Canada Melanoma Study. *Melanoma Res* 2009; **19**(4): 260-6.
31. Dosemeci M, Hayes RB, Vetter R, et al. Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes & Control* 1993; **4**(4): 313-21.

32. Matthews CE, Shu XO, Jin F, et al. Lifetime physical activity and breast cancer risk in the Shanghai Breast Cancer Study. *British journal of cancer* 2001; **84**(7): 994.
33. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-Related Inflammation, the Seventh Hallmark of Cancer: Links to Genetic Instability. *Carcinogenesis* 2009; **30**(7): 1073–8.
34. Shebl FM, Hsing AW, Park Y, et al. Non-steroidal anti-inflammatory drugs use is associated with reduced risk of inflammation-associated cancers: NIH-AARP study. *PloS one* 2014; **9**(12): e114633.
35. Petralia SA, Vena JE, Freudenheim JL, et al. Risk of premenopausal breast cancer and patterns of established breast cancer risk factors among teachers and nurses*. American journal of industrial medicine* 1999; **35**(2):137-41.
36. Fenton L, Moseley H. UV emissions from low energy artificial light sources. *Photodermatology, photoimmunology & photomedicine* 2014; **30**(2-3): 153-9.
37. Suárez B, López-Abente G, Martínez C, et al. Occupation and Skin Cancer: The Results of the HELIOS-I Multicenter Case-Control Study. *BMC Public Health* 2007; **7**: 180.
38. Fabbro-Peray P, Daures JP, Rossi JF. Environmental risk factors for non-Hodgkin's lymphoma: a population-based case–control study in Languedoc-Roussillon, France. *Cancer Causes and Control* 2001; **12**(3): 201-12.
39. Lipsett MJ, Ostro BD, Reynolds P, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *American journal of respiratory and critical care medicine* 2011; **184**(7): 828-35.
40. Bessonova L, Marshall SF, Ziogas A, et al. The Association of Body Mass Index with Mortality in the California Teachers Study. *International Journal of Cancer* 2011; **129**: 2492–501.
41. Mai PL, Sullivan-Halley J, Ursin G, et al. Physical Activity and Colon Cancer Risk among Women in the California Teachers Study. *Cancer Epidemiology Biomarkers and Prevention* 2007; **16**(March): 517–25.
42. Link LB, Canchola AJ, Bernstein L, et al. Dietary Patterns and Breast Cancer Risk in the California Teachers. *American Journal of Clinical Nutrition* 2013; **98**: 1524–32.
43. DeLellis Henderson K, Duan L, Sullivan-Halley J, et al. Menopausal Hormone Therapy Use and Risk of Invasive Colon Cancer: The California Teachers Study. *Am J Epidemiol* 2010; **171**(4): 415–25.
44. Zell JA, Ziogas A, Bernstein L, et al. Meat Consumption, Nonsteroidal Anti-Inflammatory Drug Use, and Mortality among Colorectal Cancer Patients in the California Teachers Study. *Cancer Prevention Research* 2010; **3**: 865–75.
45. Cao Y, Nishihara R, Wu K, et al. Population-Wide Impact of Long-Term Use of Aspirin and the Risk for Cancer. *JAMA Oncology* 2016; **2**(6): 762–9.
46. Brasky TM, Liu J, White E, et al. Non-Steroidal Anti-Inflammatory Drugs and Cancer Risk in Women: Results from the Women's Health Initiative. *International Journal of Cancer* 2014. **135**: 1869–83.
47. Kim S, Shore DL, Wilson LE, et al. Lifetime use of nonsteroidal anti-inflammatory drugs and breast cancer risk: results from a prospective study of women with a sister with breast cancer. *BMC cancer* 2015; **15**(1): 960.

48. Verdoodt F, Kjaer SK, Friis S. Influence of aspirin and non-aspirin NSAID use on ovarian and endometrial cancer. *Maturitas* 2017; **100**: 1-7.
49. Gamba CA, Swetter SM, Stefanick ML, et al. Aspirin Is Associated with Lower Melanoma Risk among Postmenopausal Caucasian Women: The Women's Health Initiative. *Cancer* 2013; **119**: 1562–9.
50. Boudreau DM, Yu O, Johnson J. Statin Use and Cancer Risk: A Comprehensive Review. *Expert opinion on drug safety* 2010; **9**(4): 603–21.
51. Zeiser R, Maas K, Youssef S, Dürr C, Steinman L, Negrin RS. Regulation of Different Inflammatory Diseases by Impacting the Mevalonate Pathway. *Immunology* 2009; **127**: 18–25.
52. Yang X, Ge C, Hu B, Chi T, Wang L. Relationship between Quality of Life and Occupational Stress among Teachers. *Public Health* 2009; **123**(11): 750–5.
53. Bellingrath S, Weigl T, Kudielka BM. Cortisol Dysregulation in School Teachers in Relation to Burnout, Vital Exhaustion, and Effort-Reward-Imbalance. *Biological Psychology* 2008; **78**: 104–13.
54. Bellingrath S, Kudielka BM. Effort-Reward-Imbalance and Overcommitment Are Associated with Hypothalamus-Pituitary-Adrenal (HPA) Axis Responses to Acute Psychosocial Stress in Healthy Working Schoolteachers. *Psychoneuroendocrinology* 2008; **33**: 1335–43.
55. Nurul I, Haslinda A, Saidi M, Shamsul B, Zailina H. Prevalence of Low Back Pain and Its Risk Factors among School Teachers. *American Journal of Applied Sciences* 2010; **7**(5): 634–39.
56. Nerrière E, Vercambre MN, Gilbert F, Kovess-Masféty V. Voice Disorders and Mental Health in Teachers: A Cross-Sectional Nationwide Study. *BMC Public Health* 2009; **9**: 370.
57. Tak S, Groenewold M, Alterman T, Park RM, Calvert GM. Excess Risk of Head and Chest Colds among Teachers and Other School Workers. *Journal of School Health* 2011; **81**(9): 560–5.
58. Von Behren J, Lipsett M, Horn-Ross PL, et al. Obesity, Waist Size and Prevalence of Current Asthma in the California Teachers Study Cohort. *Thorax* 2009; **64**: 889–93.
59. Melamed S, Kushnir T, Shirom A. Burnout and Risk Factors for Cardiovascular Diseases. *Behavioral Medicine* 1992; **18**(2): 53–60.
60. Khosropanah SH, Tahmasebi J, Zibaeenezhad MJ, et al. Prevalence of Coronary Artery Disease Risk Factors in Teachers Residing in Shiraz-Iran 2009. *Iran Cardiovasc Res J* 2010; **4**: 50–4.
61. Abtahi F, Naghshzan A, Zibaeenezhad MJ, et al. The Relationship between Body Mass Index and Pre-Diabetes in Teachers Residing in Shiraz-Iran 2009. *Iran Cardiovasc Res J* 2010; **4**(3): 112–7.
62. Tsui JK, Calne DB, Wang Y, Schulzer M, Marion SA. Occupational risk factors in Parkinson's disease. *Canadian journal of public health* 1999; **90**(5): 334-7.
63. Sobel E, Davanipour Z, Sulkava R, et al. Occupations with Exposure to Electromagnetic Fields: A Possible Risk Factor for Alzheimer's Disease. *American Journal of Epidemiology* 1995; **142**(5): 515–24.
64. Ostro B, Hu J, Goldberg D, et al. Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the

California Teachers Study Cohort. *Environmental Health Perspectives* 2015; **123**(6): 549–56.
65. Jacobs EJ, Newton CC, Thun MJ, Gapstur SM. Long-Term Use of Cholesterol-Lowering Drugs and Cancer Incidence in a Large United States Cohort. *Cancer Research* 2011; **71**: 1763–71.
66. Coogan PF, Rosenberg L, Strom BL. Statin use and the risk of 10 cancers. *Epidemiology* 2007; **18**(2): 213-9.
67. Boudreau DM, Yu O, Miglioretti DL, Buist DSM, Heckbert SR, Daling JR. Statin Use and Breast Cancer Risk in a Large Population-Based Setting. *Cancer Epidemiol Biomarkers Prev* 2007; **16**(3): 416–21.
68. Kaye J a., Jick H. Statin use and cancer risk in the General Practice Research Database. *Br J Cancer* 2004; **90**: 635–7.
69. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: A series of nested case-control studies. *BMC Cancer* 2011; **11**(1): 409.
70. Li X, Wu XB, Chen Q. Statin use is not associated with reduced risk of skin cancer: a meta-analysis. *Br J Cancer* 2014. **110**(10): 802–7.
71. Siegrist J, Starke D, Chandola T, et al. The Measurement of Effort-Reward Imbalance at Work: European Comparisons. *Social Science and Medicine* 2004; **58**: 1483–99.
72. Kwong SL, Perkins CI, Morris CR, Cohen R, Allen M, Wright WE. Cancer in California: 1988–1999. *California Department of Health Services, Cancer Surveillance Section* 2001.
73. Milham S. Occupational mortality in Washington state 1950-1989. *NIOSH Pub* 1997; **83**: 116.
74. King AS, Threlfall WJ, Band PR, Gallagher RP. Mortality among female registered nurses and school teachers in British Columbia. *American journal of industrial medicine* 1994; **26**: 125-32.
75. Chang ET, Lee VS, Canchola AJ, et al. Dietary Patterns and Risk of Ovarian Cancer in the California Teachers Study Cohort. *Nutrition and Cancer* 2008; **60**: 285–91.
76. Cash SW, Ma H, Horn-Ross PL, et al. Recreational physical activity and risk of papillary thyroid cancer among women in the California Teachers Study. *Cancer epidemiology* 2013; **37**: 46-53.
77. Pukkala E, Poskiparta M, Apter D, Vihko V. Life-long physical activity and cancer risk among Finnish female teachers. *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP)* 1993; **2**(5): 369-76.
78. Levi F, Pasche C, Lucchini F, La Vecchia C. Occupational and leisure time physical activity and the risk of breast cancer. *European Journal of Cancer* 1999; **35**(5): 775-8.
79. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA internal medicine* 2016; **176**(6): 816-25.

80. Hung RJ, Ulrich CM, Goode EL, et al. Cross Cancer Genomic Investigation of Inflammation Pathway for Five Common Cancers: Lung, Ovary, Prostate, Breast, and Colorectal Cancer. *Journal of the National Cancer Institute* 2015; **107**: 1–10.
81. Autier P. Risk factors for breast cancer for women aged 40 to 49 years. *Ann Intern Med* 2012. **157**(7): 529-.
82. Savelli L, De Iaco P, Santini D, et al. Histopathologic Features and Risk Factors for Benignity, Hyperplasia, and Cancer in Endometrial Polyps. *American Journal of Obstetrics and Gynecology* 2003; **188**: 927–31.
83. Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. *Mayo Clinic Proceedings* 2007; **82**(3): 364-80.
84. Vågerö D, Ringbäck G, Kiviranta H. Melanoma and other tumors of the skin among office, other indoor and outdoor workers in Sweden 1961-1979. *British journal of cancer* 1986; **53(**4): 507.
85. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Physical activity and endometrial cancer risk, a systematic review of current evidence. *Cancer Epidemiology and Prevention Biomarkers* 2007; **16**(4): 639-48.
86. Zell JA, Ziogas A, Bernstein L, et al. Nonsteroidal Anti-Inflammatory Drugs: Effects on Mortality after Colorectal Cancer Diagnosis. *Cancer* 2009. **115**: 5662–71.
87. Brøns N, Baandrup L, Dehlendorff C, Kjaer SK. Use of nonsteroidal anti-inflammatory drugs and risk of endometrial cancer: a nationwide case–control study. *Cancer Causes & Control* 2015; **26**(7): 973-81.
88. Curiel-Lewandrowski C, Nijsten T, Gomez ML, Hollestein LM, Atkins MB, Stern RS. Long-Term Use of Nonsteroidal Anti-Inflammatory Drugs Decreases the Risk of Cutaneous Melanoma: Results of a United States Case-Control Study. *J Invest Dermatol* 2011; **131** (7): 1460–8.
89. Joosse A, Koomen ER, Casparie MK, Herings RM, Guchelaar HJ, Nijsten T. Non-steroidal anti-inflammatory drugs and melanoma risk: large Dutch population-based case–control study. *Journal of Investigative Dermatology* 2009; **129**(11): 2620-7.
90. Marshall SF, Bernstein L, Anton-Culver H, et al. Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status. *Journal of the National Cancer Institute* 2005; **97**(11): 805-12.
91. Ready A, Velicer CM, McTiernan A, White E. NSAID use and breast cancer risk in the VITAL cohort. *Breast cancer research and treatment* 2008; **109**(3): 533-43.
92. Zhang X, Smith-Warner SA, Collins LC, Rosner B, Willett WC, Hankinson SE. Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and postmenopausal breast cancer incidence. *Journal of Clinical Oncology* 2012; **30**(28): 3468.
93. Johannesdottir SA, Chang ET, Mehnert F, Schmidt M, Olesen AB, Sørensen HT. Nonsteroidal Anti-Inflammatory Drugs and the Risk of Skin Cancer: A Population-Based Case-Control Study. *Cancer* 2012; **118**: 4768–76.
94. Jeter JM, Han J, Martinez ME, Alberts DS, Qureshi AA, Feskanich D. Non-Steroidal Anti-Inflammatory Drugs, Acetaminophen, and Risk of Skin Cancer in the Nurses' Health Study. *Cancer Causes & Control* 2012; **23**(9): 1451-61.

95. Johnson TW, Anderson KE, Lazovich D, Folsom AR. Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer. *Cancer Epidemiology and Prevention Biomarkers* 2002; **11**(12): 1586-91.
96. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nature Reviews Cancer* 2013; **13**(11): 759.