Area-level socioeconomic status and cancer outcomes: Is there an association and can it be explained by behavior?

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Abstract

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Increasingly, area-level socioeconomic status (SES) is recognized as an important predictor of health outcomes and health behaviors independent of individual-level socioeconomic characteristics; however, associations between area-level SES and cancer outcomes are not well understood. Ecologic evidence suggests a relationship between area-level socioeconomic status and cancer incidence and mortality; however, fewer studies have included measures of individual socioeconomic status to assess whether observed associations are due to the compositional effect of the individuals living within the areas of interest. Little is known about individual-level behaviors or risk factors that may explain the pathways through which area-level socioeconomic factors could affect cancer risk.

In an effort to summarize risk behaviors that affect cancer risk, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) published eight

recommendations related to body weight, physical activity and dietary behaviors aimed at reducing cancer incidence worldwide, based on a comprehensive review of the literature related to common cancers. However, the reduction in total and site-specific cancer risk and cancer mortality associated with adhering to these guidelines is unknown.

Using data from the VITamins And Lifestyle (VITAL) cohort study, including 77,719 adults aged 50-76 at baseline in 2000-2002 and living in the 13 counties of the Western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry, we examined whether meeting the WCRF/AICR cancer prevention recommendations related to body fatness, physical activity, energy density of the diet, fruit and vegetable intake, consumption of red and processed meats and alcohol use was associated with reductions in total cancer mortality. We further used data from the 2000 U.S. Census to develop an area-level SES index for the block group of residence of each VITAL participant to examine whether area-level SES is associated with total and site-specific cancer incidence and cancer mortality. Finally, we examined whether and to what extent individual modifiable risk factors including the WCRF/AICR recommendations examined plus cancer screening and pack-years of smoking explained the observed association between area-level SES and cancer mortality.

Each additional WCRF/AICR recommendation met was associated with a 9% reduction in total cancer mortality (hazard ratio (HR): 0.91, 95% confidence interval (CI): 0.87, 0.96) among participants with no history of cancer at baseline. Meeting at least five recommendations was associated with a 60% reduction in cancer mortality compared with meeting no recommendations (HR: 0.40, 95% CI: 0.25, 0.62). These associations were similar among men and women and among participants older and younger than 65 years at baseline, but the

association was somewhat stronger among non-smokers (HR per recommendation: 0.85, 95% CI: 0.78, 0.93) than among ever-smokers (HR: 0.94, 95% CI: 0.88, 1.00; $P_{trend} = 0.091$).

After controlling for age, sex, race/ethnicity, and marital status, living in areas in the lowest quintile of area-level SES was associated with increased lung cancer incidence (HR: 2.21, 95% CI: 1.69, 2.90) and colorectal cancer incidence among men (HR: 1.75, 95% CI: 1.14, 2.70) and total cancer mortality (HR: 1.68, 95% CI: 1.47, 1.93) compared with living in areas in the highest quintile of area-level SES. Further controlling for compositional factors including individual education and household income weakened but did not eliminate these associations (HR for lung cancer: 1.43, 95% CI: 1.07, 1.91; HR for colorectal cancer: 1.53, 95% CI: 0.99, 2.38; HR for cancer mortality: 1.28, 95% CI: 1.11, 1.48).

Among participants with no history of cancer at baseline, living in areas in the lowest quintile of area-level SES was associated with 77% higher cancer mortality than living in areas in the highest quintile of area-level SES (HR: 1.77, 95% CI: 1.50, 2.11). Adding individual-level modifiable risk factors into the models reduced the observed association by 45% (95% CI: -72%, -15%). In models further controlling for individual education and income, area-level SES remained associated with cancer mortality (HR for highest- vs. lowest-SES areas: 1.37, 95% CI: 1.14, 1.65) and adding modifiable risk factors reduced the association by 37% (95% CI: -93%, 22%). Smoking, screening and physical activity explained the largest proportion of the association in both models.

Adherence to the WCRF/AICR cancer prevention recommendations developed to reduce incidence of common cancers could substantially reduce cancer mortality. Living in low-SES areas is associated with increased lung cancer incidence, increased colorectal cancer incidence among men, and higher total cancer mortality. These associations are largely, but not completely,

explained by individual education and income. The association between area-level SES and cancer mortality is also partially explained by behavior, particularly smoking, physical activity, and screening; but area-level SES remains associated with cancer mortality after accounting for individual SES and behaviors, suggesting a possible contextual effect of area-level SES independent of these factors.

TABLE OF CONTENTS

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INTRODUCTION

Increasingly, area-level socioeconomic status (SES) is recognized as an important predictor of health outcomes and health behaviors independent of individual-level socioeconomic characteristics.[1] Measures of area-level SES, including incomes, home values, and employment characteristics and educational attainment of area residents, have been associated with several health outcomes[2-9] including cancer incidence and mortality[10-18] and with health behaviors and modifiable risk factors including diet,[19] body weight,[20] and smoking.[21]

Although research into area-level effects on health is becoming more common, less is known about which features of areas affect health and how.[22,23] Observed associations between area-level SES and cancer risk could be due to compositional effects, such that individuals living in low-SES areas are themselves of low socioeconomic status or have other individual risk factors that influence their cancer risk, and those risks would be the same regardless of where they lived. On the other hand, living in a low-SES area could directly impact cancer risk through some contextual effect of place that operates via the physical or social characteristics of the area and independently of individual demographic characteristics. The most likely explanation is that there is some combination of compositional and contextual effects at work and that while individuals who live in lower-SES areas almost certainly have lower incomes and lower educational attainment than residents of higher-SES areas, they also face greater exposure to physical and/or social characteristics that in turn affect cancer risk either directly or by influencing behaviors related to cancer risk, regardless of individual socioeconomic status.

As indicated in Figure 1.1, features of the local environment that could affect health behaviors include physical characteristics such as environmental hazards, air pollution, noise, characteristics of the built environment including urbanization, land use and green spaces, and the presence of advertising; neighborhood services including transportation, policing, education and health facilities; other neighborhood resources such as food and retail outlets, recreation facilities and employment opportunities; and social features including social cohesion and social networks, cultural norms and values, and local policies.[1,20,22]

The associations between individual and area-level factors on cancer risk are likely complex, and thus far little work has been done to disentangle the relative contributions of individual and area-level factors on cancer risk or to identify likely pathways through which area-level SES affects cancer outcomes; however, identifying such pathways could lead to effective interventions aimed at decreasing socioeconomic disparities in cancer risk and mortality. Even in studies of area-level SES and cancer outcomes that include data at the individual level, little attention has been paid to identifying pathways through which area-level SES could influence cancer risk. In an examination of potential behavioral pathways between area-level SES and cancer risk in women, multivitamin use and BMI were identified as potential modifiable risk factors on the pathway between low-SES areas and rectal cancer;[14] however, little else is known about specific behaviors that could explain observed associations between area-level SES and cancer outcomes.

One potentially important pathway between area-level SES and cancer outcomes is through behaviors that are related to cancer incidence and mortality. It is estimated that the majority of human cancers can be attributed to modifiable risk factors including diet, physical activity and tobacco use.[24] In 2007 the World Cancer Research Fund (WCRF) and American

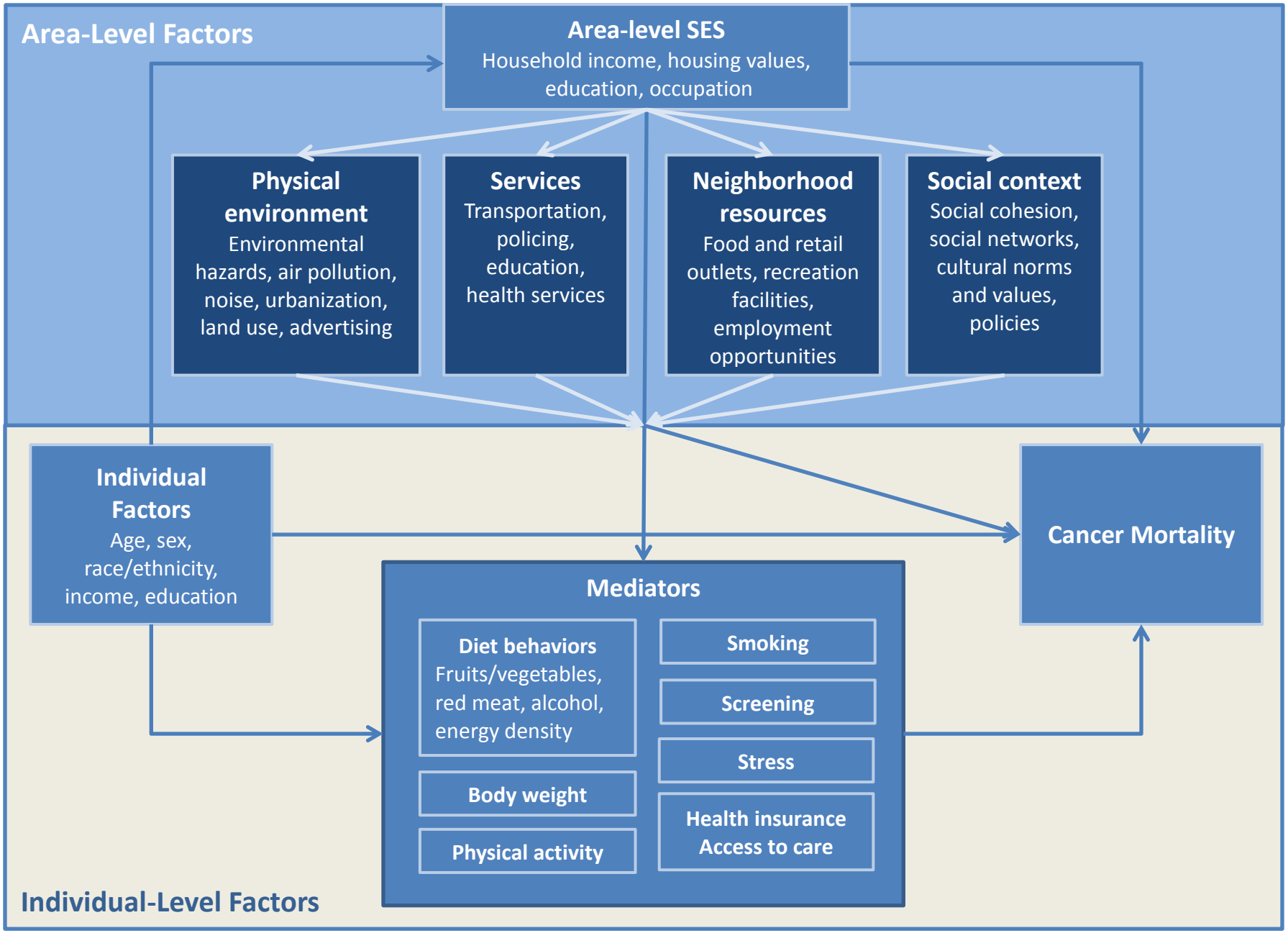
Institute for Cancer Research (AICR) published 8 recommendations related to body weight, diet and physical activity aimed at preventing the most common cancers worldwide.[25] Their recommendations include maintaining normal body weight; getting regular physical activity; reducing dietary energy density; eating mostly plant foods; limiting consumption of red meat, alcohol and salt; and getting required nutrients through food rather than supplements.[25] Although these guidelines were based on a comprehensive review of the literature, the reduction in cancer mortality associated with meeting these guidelines is not known.

In addition to body weight, diet and physical activity, several other modifiable risk factors are associated with cancer risk and mortality. Tobacco use is the single largest cause of cancer in Western countries, and smoking alone accounts for approximately 30% of cancer deaths in the United States and approximately 16% of cancers worldwide.[24,26-28] Screening can detect cancers in earlier stages and lead to lower cancer mortality.[29-31]

Area-level socioeconomic factors are associated with several individual-level behaviors and modifiable risk factors for cancer, including diet, alcohol consumption, obesity, sedentary behaviors, smoking and screening, independent of individual-level SES.[19,32-37] If area-level SES influences these behaviors (e.g. through differences in the physical characteristics, services, resources, or the social context) they could at least partially explain observed associations between area-level SES and cancer outcomes. This study proposes to examine the association between area-level SES and total and site-specific cancer incidence and total cancer mortality, controlling for individual-level demographic and socioeconomic characteristics, and then to examine whether and to what extent several individual-level behaviors and modifiable risk

factors (BMI, physical activity, energy density, fruit and vegetable intake, consumption of red and processed meats, alcohol intake, smoking and cancer screening) explain any observed association between area-level SES and the cancer mortality.

Figure 1. Conceptual model of the association between area-level socioeconomic status and cancer outcomes



CHAPTER 1: Adherence to the WCRF/AICR cancer prevention recommendations and cancer mortality

Abstract

Background: In 2007 the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) released eight recommendations related to body fatness, physical activity and diet aimed at preventing the most common cancers worldwide. The association between meeting these recommendations and cancer mortality is not known.

Methods: We operationalized six recommendations (related to body fatness; physical activity; and consumption of foods that promote weight gain, plant foods, red and processed meat, and alcohol) and examined their association with cancer mortality over 7.7 years of follow-up in the VITamins And Lifestyle (VITAL) study cohort. Participants included 57,841 men and women ages 50-76 years at baseline in 2000-2002 who had never been diagnosed with cancer. Cancer deaths (n = 1,595) were tracked through the Washington State death file.

Results: Cancer mortality was reduced by 60% in respondents who met at least five recommendations compared to those who met none (HR: 0.40, 95% CI: 0.25, 0.62). Each additional recommendation met was associated with a 9% reduction (HR: 0.91, 95% CI: 0.87, 0.96; $P_{trend} < 0.001$). This association did not differ by sex or age but was stronger in non-smokers (HR: 0.85, 95% CI: 0.78, 0.93) than in smokers (HR: 0.94, 95% CI: 0.88, 1.00; $P_{interaction} = 0.091$)

Conclusions: Adherence to the WCRF/AICR cancer prevention recommendations developed to reduce incidence of common cancers could substantially reduce cancer mortality in older adults in the United States.

Introduction

In 2007 the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) issued eight recommendations related to body fatness, diet and physical activity aimed at reducing incidence of the most common cancers worldwide, based on a comprehensive literature review.[25] The aim of these recommendations was to analyze and interpret the available evidence related to cancer prevention and to combine them into one set of lifestyle guidelines aimed at reducing cancer risk.

Previous indexes have been developed based on overall dietary patterns with the goal of reducing chronic disease risk more generally. Although diet quality indexes such as the Healthy Eating Index (HEI), the Alternate Healthy Eating Index (AHEI), the Recommended Food Score (RFS) and the Diet Quality Index (DQI) have been associated with lower chronic disease generally and reduced cardiovascular disease risk and mortality in particular,[38-42] previous research has found no association between those diet scores and total cancer incidence[41-45] or total cancer mortality,[40,46] with some exceptions.[47-50] Indexes that include risk factors such as smoking, body fatness and physical activity in addition to diet have been found to predict both cancer incidence[51,52] and cancer mortality,[49,53-56] but little is known about meeting recommendations specific to cancer prevention and cancer outcomes, including cancer mortality. Adherence to the American Cancer Society cancer prevention guidelines, including recommendations related to obesity, dietary behaviors, alcohol intake and physical activity, was associated with a 30% reduction in cancer mortality among men and a 24% reduction among women.[57] A study of an earlier version of the WCRF/AICR recommendations (released by AICR in 1997[58]) found that cancer mortality was 43% higher in women who met the fewest recommendations compared to those with the highest adherence.[59] One recent study examined

the association between the more recent WCRF/AICR recommendations and total and site-specific cancer incidence and reported an 18% reduction in total cancer incidence among adults with the highest concordance with the recommendations compared with those with the lowest concordance in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[60] However, the association between adherence to the latest WCRF/AICR cancer prevention recommendations and cancer mortality has not been investigated.

The purpose of this study is to assess whether a cancer-specific index of behaviors related to body fatness, physical activity and diet based on the 2007 WCRF/AICR cancer prevention recommendations is associated with reduced cancer mortality in a United States cohort and whether the association is consistent by sex, age and smoking status.

Methods

Study Cohort

The VITamins And Lifestyle (VITAL) study is a prospective cohort study designed to investigate the associations between use of dietary supplements and cancer risk and has previously been described in detail.[61] Women and men were eligible to join the cohort if they were between the ages of 50 and 76 and lived in one of the 13 counties included in the Western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry at baseline.

Using names purchased from a commercial mailing list, baseline questionnaires were mailed to 364,418 men and women between October, 2000 and December, 2002 and were followed two weeks later by reminder postcards. A total of 79,300 questionnaires were returned, of which 77,719 passed quality control checks. Overall, 57,841 men and women were included in the current analysis after excluding the following: respondents with a history of cancer other than non-melanoma skin cancer (n = 11,259) or whose cancer history was missing (n=214);

those who were missing data on body mass index (BMI) at baseline and age 45 (n = 2,478) or missing physical activity data (n = 1,093); and those whose food frequency questionnaires (FFQs) had fewer than five items completed on a single page (n = 4,331) or whose estimated energy consumption from the FFQ was less than 600 calories per day for women or 800 calories for men (n = 2,304) or greater than 4,000 calories per day for women or 5,000 calories for men (n = 547) (numbers of exclusions reported are not mutually exclusive). Additionally, the first year of follow-up (including 61 cancer deaths and 545 other censoring events among those with no history of cancer at baseline), was excluded to avoid potential reverse causality where symptoms of undiagnosed disease may have affected body weight, physical activity or dietary behaviors.

This research was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Data Collection

Baseline questionnaires included detailed information on medical history, self-reported height and weight, physical activity over the previous 10 years, cancer screening behaviors, reproductive history, medication use, and a 126-item FFQ covering diet in the year before baseline.

The FFQ was adapted from the questionnaire developed for use in the Women's Health Initiative and other studies. The measurement properties of earlier versions of the FFQ have been published previously.[62] The FFQ included usual frequencies and portion sizes of 110 foods and food groups, 13 adjustment questions, and three summary questions regarding the frequency of use of fats in cooking and servings of fruits and vegetables. Numbers of servings were based on the sex-specific medium portion size of each food and beverage. The University of Minnesota's

Nutrition Coding Center database was used to convert food frequency information into nutrients.[63]

Operationalization of the WCRF/AICR Recommendations

The main exposures of this study were whether respondents met or did not meet each individual WCRF/AICR cancer prevention recommendation and the number of recommendations met. The WCRF/AICR recommendations include eight broad recommendations, with between one and four more-specific personal recommendations and several public health goals for each. An expert panel of four nutritional epidemiologists (Ruth Patterson, Alan Kristal, Shirley Beresford, and Emily White) with knowledge of the VITAL cohort data made recommendations on the operationalization of six of the eight recommendations. The key components of each recommendation were identified (noted in italics in Table 1) and specific cutoffs for meeting the key components were selected based on information provided in the recommendations or from external sources (e.g. the World Health Organization)[64] (Table 1). The recommendation to limit salt-preserved foods and moldy cereals and legumes was not operationalized because those exposures are not common in the United States food supply and because data were not available in VITAL. The recommendation to meet nutritional needs through diet alone was not operationalized because while it does not recommend dietary supplements, it also does not recommend against supplement use.

Body fatness. The recommendation to be as lean as possible within the normal range of body weight was operationalized as having a BMI of at least 18.5 but less than 25 kg/m^2 based on height and weight reported at baseline. This range was based on that set by the World Health Organization[64] as normal weight.[25]

For participants with missing weight at baseline but who reported BMI at age 45 (n = 922), BMI at baseline was imputed by calculating the average annual change in BMI (assuming a linear association between BMI and age) within 36 sex-, age-, and race/ethnicity-specific strata, multiplying that value by the difference between respondents' baseline age and 45 and adding the product to their BMI at age 45.

Physical activity. The recommendation to be physically active as a part of everyday life was operationalized as engaging in moderate or fast walking and/or moderate or strenuous activity for an average of at least 30 minutes per day, on at least 5 days per week, and in at least 7 of the past 10 years. Respondents who were missing data for this constructed variable but whose physical activity responses were complete enough to estimate their metabolic equivalent task (MET) hours per week of walking and/or moderate/strenuous physical activity (n= 3,604) were categorized as meeting this recommendation if they engaged in an average of at least 10 MET-hours of walking and/or moderate/strenuous physical activity per week (based on an estimate of 4.0 METs per hour x 0.5 hours per day x 5 days per week) over the previous 10 years.

Energy density. The recommendation to limit consumption of energy-dense foods and to avoid sugary drinks was operationalized as consuming a diet where the energy density of foods consumed was less than 125 kcal per 100 g based on responses to the FFQ, and also consuming less than one serving of regular (not diet) soda, fruit drinks and/or cranberry juice per week. Fruit juices which typically do not have added sugar (e.g. orange juice) were not counted as sugary drinks. The energy density cutoff was based on a public health goal included in the WCRF/AICR recommendation. Beverages were not included in the energy density calculation.

***Plant foods*.** The recommendation to eat mostly foods of plant origin, specifically the personal recommendations to eat at least 5 servings of a variety of non-starchy vegetables and fruits every day and to eat relatively unprocessed grains and/or legumes with every meal, was operationalized as consuming at least 5 servings of fruits and/or vegetables and also at least one serving of whole grains and/or legumes per day. Servings of fruits and non-starchy vegetables included 25 foods or food groups, adjusted by portion size and by summary questions on total numbers of fruits and vegetables eaten to reduce over-estimation by participants. It excluded fruit juices and potatoes. Because the VITAL FFQ only included 5 items relevant to whole grains (covering breads and breakfast cereals) and these failed to fully separate whole grains from other grains (e.g., brown rice from white rice), we used a cutoff of one serving per day rather than per meal to represent those who habitually eat whole grains and/or legumes. Legume servings included 3 items on bean dishes and one item on tofu and tempeh.

Red meat. The recommendation to limit intake of red meat and to avoid processed meat was operationalized as consuming fewer than 18 ounces of red or processed meat per week. Red and processed meat from mixed dishes in the FFQ were also included by assuming that red or processed meat accounted for one-quarter of their weight.

Alcohol. The recommendation to limit alcoholic drinks was operationalized as consuming no more than one alcoholic beverage per day on average for women and no more than two per day on average for men. A drink was classified as a 12-ounce bottle or can of beer; 4-ounce glass of wine; or one shot (1.5 ounces) of liquor or one mixed drink.

Case Ascertainment and Censoring

Deaths due to cancer were ascertained through December 31, 2010 by annual linkage with the Washington State death file. Linkage between VITAL and the death file is largely

automated and based on ranking agreement between items common to both sets of data, such as Social Security number, name, and date of birth. Matches with high concordance were linked automatically whereas visual inspection was used to adjudicate incomplete matches. After excluding the first year of follow-up, a total of 1,595 cancer deaths were identified in an average of 7.7 years of follow-up.

Participants who did not die of cancer in Washington State were right-censored at the date of the earliest of the following events: date they requested removal from the study (n = 15), date they moved out of Washington State (n = 2,896), date of death due to other causes (n = 2,498) or December 31, 2010 (n = 50,837). Moves out of Washington State were identified through linkage with the National Change of Address System.

Statistical Analyses

Each of the recommendations was coded as met (1) or not met (0), and the total number of recommendations met was summed across the six recommendations operationalized. Hazard ratios (HRs) and 95% confidence intervals (CIs) of death due to cancer associated with meeting (vs. not meeting) each recommendation individually and for the number of recommendations met compared with meeting no recommendations were estimated using Cox proportional hazards models. We used participant age as the time scale, with participants entering the analysis at their age one year after completing the baseline questionnaire and exiting at age at death due to cancer or age at censoring event, as described above. Proportional hazards assumptions were examined using scaled Schoenfeld residuals. No significant ($p<0.05$) deviations from proportionality were observed. *P*-values for trend were calculated using the Wald test associated with modeling the number of recommendations met as a continuous variable. All statistical tests were two-sided.

Multivariate analyses included adjustment for potential confounders selected *a priori*, including known risk factors associated with cancer incidence and mortality. These analyses included categorical variable adjustment for sex, education (high school graduate/GED or below, some college/technical school, college graduate, advanced degree), race/ethnicity (white, Hispanic, African-American, American Indian/Alaska Native, Asian/Pacific Islander, other/missing), marital status (married, living with partner, never married, separated/divorced, widowed), pack-years of smoking (continuous), receipt of mammogram in previous two years (women only), receipt of prostate-specific antigen (PSA) test in previous two years (men only), receipt of colonoscopy or sigmoidoscopy in previous 10 years, cancers diagnosed in first-degree relatives (0, 1, 2+), non-steroidal anti-inflammatory medication use (none, <4 days per week in <4 of previous 10 years, 4+ days per week in at least 4 of past 10 years), regular or low-dose aspirin use (none, <4 days per week in <4 of previous 10 years, 4+ days per week in at least 4 of past 10 years), and kilocalories of average daily energy intake. Several additional reproductive factors were included for women, including: age at menarche (≤11, 12, 13, 14, 15+), age at birth of first child (≤19, 20-24, 25-29, 30-34, 35+, no children), years of estrogen-only and of combined estrogen plus progestin hormone therapy use (each categorized as none or <1, 1-4, 5-9, 10+), and age at menopause (≤39, 40-44, 45-49, 50-54, 55+, peri-menopausal at baseline). Participants with missing data were treated as their own category for each potential confounder. All analyses were conducted using Stata 12.1 (StataCorp LP, College Station, TX).

Analyses of the association between number of recommendations met and cancer mortality were also stratified by sex and smoking status (ever/never) and effect modification was assessed by including interaction terms in models estimating the hazard ratios associated with meeting each additional recommendation.

Results

Of all the recommendations, the highest proportion of all respondents and of those who died of cancer during follow-up (85.5% and 83.5%, respectively) met the recommendation to limit alcohol consumption, followed by the recommendations to limit consumption of red and processed meat (55.1% and 49.3%), and to maintain normal body weight (33.2% and 30.5%) (Table 1.1). Fewer respondents met the recommendations to be physically active (18.9% and 15.7%), limit consumption of energy dense foods and sugary drinks (19% and 14.2%), and to consume mostly plant foods (11.4% and 8.2%).

Table 1.22 gives baseline characteristics of the overall study population and those who died of cancer during follow-up. The average age at baseline was 60.7 years for the entire study population and 65.5 for those who died of cancer. Both groups were predominantly white and a similar proportion reported having at least one family member previously diagnosed with cancer. Compared with the cohort as a whole, a smaller proportion of respondents who subsequently died of cancer were women, college graduates, or married. Respondents who died of cancer reported an average of 28 pack-years of smoking compared to 13.1 in the entire cohort and reported somewhat lower receipt of cancer screening.

The leading cause of cancer mortality in the cohort was lung cancer (30.6%) followed by hematologic cancers (9.7%), cancers of the pancreas (9.2%), colon or rectum (6.9%), breast (3.0%), and prostate (2.4%) (data not shown).

Table 1.3 gives hazard ratios (HRs) and 95% confidence intervals (CIs) for death from cancer associated with meeting (vs. not meeting) each of the individual WCRF/AICR recommendations. In analyses controlling for potential confounders, all HR estimates were less than one; the recommendations to consume mostly plant foods (HR: 0.75, 95% CI: 0.62, 0.91),

limit the energy density of the diet (HR: 0.78, 95% CI: 0.67, 0.91) and to be physically active (HR: 0.87, 95% CI: 0.75, 1.00) were each associated with reductions in cancer mortality. After also adjusting for whether respondents met each of the other recommendations, these associations attenuated somewhat but remained associated with 10-18% reductions in cancer mortality (HR for plant foods: 0.82, 95% CI: 0.67, 1.00; HR for energy density: 0.82, 95% CI: 0.70, 0.97; HR for physical activity: 0.90, 95% CI: 0.78, 1.03).

Table 1.4 gives hazard ratios and 95% confidence intervals associated with the number of WCRF/AICR recommendations met. After adjusting for potential confounders, each additional recommendation met was associated with a 9% reduction in cancer mortality (HR: 0.91; 95% CI: 0.87, 0.96) ($P_{trend} < 0.001$). Compared with meeting no recommendations, meeting one or two recommendations was associated with a 12-22% reduction in cancer mortality and meeting three or four recommendations was associated with a statistically significant 29-30% reduction in risk. Meeting five or six recommendations was associated with a 60% reduction in cancer mortality compared with meeting no recommendations (HR: 0.40, 95% CI: 0.25, 0.62). Results did not differ in sensitivity analyses that did not exclude the first year of follow-up.

Results were similar for men and women, with each additional recommendation met associated with an 8% reduction in cancer mortality among men (HR: 0.92, 95% CI: 0.86, 0.98) and an 11% reduction among women (HR: 0.89, 95% CI: 0.83, 0.96; $P_{interaction} = 0.265$) in covariate-adjusted analyses. The association between the number of recommendations met and cancer mortality was also similar in respondents younger than 65 years at baseline (HR associated with each additional recommendation met: 0.85, 95% CI: 0.79, 0.97) compared with those 65 and older (HR: 0.90, 95% CI: 0.83, 0.98; $P_{interaction} = 0.761$) (data not shown). Among never-smokers each additional recommendation met was associated with a 15% reduction in

cancer mortality (HR: 0.85, 95% CI: 0.78, 0.93) compared with a 6% reduction for current or former smokers (HR: 0.94, 95% CI: 0.88, 1.00; $P_{interaction} = 0.091$) (Supplementary Table 1.A). This could be driven by differences in the association between meeting the recommendation related to body fatness and cancer mortality by smoking status (HR for meeting the recommendation among ever-smokers: 1.11, 95% CI: 0.97, 1.27; HR for never-smokers: 0.71, 95% CI: 0.57, 0.88; $P_{interaction} = 0.001$) (Supplementary Table B).

Discussion

In this cohort of adults in the Puget Sound area in Washington State, each additional WCRF/AICR cancer prevention recommendation met was associated with a 9% reduction in cancer mortality (HR: 0.91; 95% CI: 0.87, 0.96). Additional analyses suggest that this association is consistent among men and women and those younger than and at least 65 at baseline, but that the association is somewhat stronger in never-smokers than in ever-smokers. Meeting five or six recommendations was associated with a 60% reduction in cancer mortality compared with meeting no recommendations (HR: 0.40, 95% CI: 0.25, 0.62), a stronger result than would be expected from the HR of 0.91 per recommendation in the linear model (which would yield expected HRs of 0.62 for meeting 5 recommendations and 0.57 for meeting 6 recommendations, compared with meeting none). It should be noted that this estimate is based on a small number of cancer deaths (31) among respondents meeting at least five recommendations. However, the individual recommendations associated with the greatest reductions in cancer mortality (the recommendations related to energy density and plant foods) are also the least-commonly met, and the particularly strong association among respondents meeting five or six recommendations could be due to respondents meeting the most recommendations also meeting the recommendations with the strongest independent effects.

This is the first study to examine the association between the most recent WCRF/AICR recommendations and cancer mortality, and our results are stronger than two previous studies that reported inverse associations between adherence to cancer prevention recommendations and cancer mortality. Women with the lowest adherence scores to a previous version of AICR cancer prevention recommendations were at a 43% greater risk of cancer mortality than women with the highest adherence in the Iowa Women's Health Study (HR: 1.43, 95% CI: 1.11, 1.85).[59] Similarly, a recent paper also reported that meeting the American Cancer Society cancer prevention guidelines related to BMI, physical activity, diet, and alcohol was inversely associated with cancer mortality (HR for high vs. low adherence: 0.70, 95% CI: 0.61, 0.80 among men; HR: 0.76, 95% CI: 0.65, 0.79 among women).[57]

Differences in our analyses compared to the previous studies could account for the stronger associations presented here. In the previous papers, participants were assigned partial points on the risk score for near-adherence to each recommendation where in our analyses participants were counted only as meeting or not meeting each recommendation. Our operationalization of the recommendations was similar to what was considered full adherence in the previous paper that examined the most recent recommendations, with some exceptions. In the previous study the recommendation related to energy density was counted separately from intake of sugary drinks; in addition to fruit and vegetable intake, a separate item for daily fiber intake (with ≥25 g/day counted as meeting the recommendation) was added, but whole grains and legumes were not directly included; and a measure of cumulative breastfeeding was included for women.[60] Additionally, where the previous papers grouped participants meeting no recommendations with those meeting one recommendation, our analyses treated participants meeting no recommendations as their own category. These analytic differences would act to

strengthen our observed association relative to previous results. However, when we reanalyzed our data using 0-1 recommendations met as the reference group, we found that each additional recommendation met remained associated with a 9% risk reduction of cancer mortality (HR: 0.91, 95% CI: 0.86, 0.96).

The WCRF/AICR recommendations were designed to focus on body fatness, diet and physical activity. Other previous studies of ad hoc health behavior risk scores (i.e. not based on specific sets of recommendations) and cancer mortality have also included smoking as one of the behaviors considered. Several studies have reported inverse associations between positive health behavior scores including measures of smoking, physical activity, alcohol consumption and dietary behaviors and cancer mortality in European cohorts, with reported hazard ratios of 0.31 (95% CI: 0.19, 0.50) for respondents with the highest compared to the lowest health behavior scores,[49] and HRs of 1.7 (95% CI: 1.1, 2.7),[53] 3.35 (95% CI: 1.67, 6.70)[54] and 3.74 (95% CI: 2.34, 5.98)[55] for respondents with the lowest (compared with highest) health behavior scores. The stronger association between most of these risk scores that include smoking and cancer mortality relative to our results is not surprising given that tobacco use is the single largest cause of cancer in Western countries[26] and smoking was the most significant predictor of cancer mortality in two of the previous studies.[49,54] Interestingly, although several previous studies reported no association between diet quality indexes and cancer outcomes, they found protective associations between those indexes and cardiovascular outcomes,[40-45] suggesting that dietary behaviors could me more closely related to cardiovascular outcomes than with cancer.

Our results suggest that the association between meeting the WCRF/AICR cancer prevention recommendations and cancer mortality could be stronger in never-smokers (HR per additional recommendation met: 0.85, 95% CI: 0.78, 0.93) than in ever-smokers (HR per

additional recommendation met: 0.94, 95% CI: 0.88, 1.00; $P_{interaction}$ = 0.091). This is consistent with two previous studies of cancer prevention recommendations and cancer mortality, each of which also reported stronger associations among never-smokers compared with current or former smokers, although the interactions were not statistically significant ($P_{interaction}$ = 0.1 for men and 0.3 for women)[57] or not reported.[59] This difference in association by smoking status could be plausible given previous findings that higher BMI is associated with lower incidence and mortality of lung cancer,[65] which accounts for more than 30% of the cancer deaths in our sample. However, these results should be interpreted with caution given the small number of cancer deaths among respondents meeting no and 5-6 recommendations, particularly among never smokers.

Strengths of this study include its large sample size, prospective design and the detailed information collected at baseline that allowed us to operationalize six of the WCRF/AICR cancer prevention recommendations and to control for several potential confounding factors. Linkage with the Washington State death file provided accurate and near-complete ascertainment of cancer deaths in this population. By excluding the first year of follow-up we reduced the possibility of reverse causality whereby respondents may have changed their behaviors due to symptoms of undiagnosed cancer.

Limitations of this study must also be acknowledged. Misclassification in our assessment of whether respondents met the individual binary recommendations would act to bias associations between each individual recommendation and cancer mortality toward the null. Similarly, misclassification of the total number of recommendations met would also bias our results toward the null assuming that the mean value of the measured exposure (number of recommendations met) increased monotonically with the true exposure.[66] Although our analyses

controlled for many potential confounding factors, residual confounding may exist due to missing or misspecified confounders. Additionally, because of its emphasis on recruiting supplement users, participants in the VITAL cohort may have had more positive health behaviors than the general population. However, selection bias is not likely to affect our results due to the prospective design of this study where future cancer outcomes are unknown at baseline. Respondents missing data on one or more recommendations were excluded from our analyses. This could bias our results to the extent that the association between meeting the WCRF/AICR cancer prevention recommendations and cancer mortality differed among respondents with incomplete questionnaires compared to participants with complete data, which is unlikely. By limiting our study to respondents with no history of cancer at baseline, deaths from cancers that are rapidly fatal may be overrepresented in our results compared with their actual proportion of cancer deaths in the population. Although lung cancer is the leading cause of cancer death among men and women nationally and accounts for more deaths than any other malignancy in our study, breast, prostate and colorectal cancer deaths are underrepresented here relative to their share of all cancer deaths.[67]

This study is the first to examine adherence to the 2007 WCRF/AICR cancer prevention recommendations related to body fatness, diet and physical activity and cancer mortality. Although these recommendations were developed to reduce cancer incidence worldwide, we found a 9% reduction in cancer *mortality* associated with each additional recommendation met. Our results suggest that, in addition to reducing cancer incidence, increased adherence to the WCRF/AICR cancer prevention recommendations could substantially reduce mortality from cancer.

Table 1.1: WCRF/AICR cancer prevention recommendations,[25] and their operationalization in this study

WCRF/AICR recommendation	Associated personal recommendations	Met/did not meet recommendation in this study if:	VITAL cohort (N=57,841)		Cancer deaths (N=1,595)	
			N	%	N	%
1. Body fatness *Be as lean as possible within the normal range of body weight*	• Ensure that weight through childhood and adolescent growth projects toward the lower end of the normal BMI range at age 21 • Maintain body weight within the normal range from age 21 • Avoid weight gain and increases in waist circumference throughout adulthood	**Met:** 18.5 kg/m^2 ≤ BMI < 25 kg/m^2	19,176	33.2	486	30.5
		Did not meet: BMI < 18.5 kg/m^2 or BMI ≥ 25 kg/m^2	38,665	66.9	1,109	69.5
2. Physical activity Be physically active as part of everyday life	• *Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day* • As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day • Limit sedentary habits such as watching television	**Met:** ≥ 30 minutes per day of moderate or fast walking and/or moderate or strenuous activity on at least 5 days per week in at least 7 of the past 10 years	10,910	18.9	250	15.7
		Did not meet: < 30 minutes per day or < 5 days per week or < 7 of the previous 10 years of moderate or fast walking and/or moderate or strenuous activity	46,931	81.1	1,345	84.3
3. Energy density Limit consumption of energy dense foods; avoid sugary drinks	• *Consume energy-dense foods sparingly* • *Avoid sugary drinks* • Consume 'fast foods' sparingly, if at all	**Met:** Energy density of diet < 125 kcal per 100 g and < 1 sugary drink per week	10,963	19.0	226	14.2
		Did not meet: Energy density of diet ≥ 125 kcal per 100 g or ≥ 1 sugary drink per week	46,878	81.1	1,369	85.8
4. Plant foods Eat mostly foods of plant origin	• *Eat at least five portions/servings (at least 400 g or 14 oz) of a variety of non-starchy vegetables and of fruits*	**Met:** ≥ 5 servings of fruits and vegetables and ≥ 1 serving of whole grains and/or legumes per day	6,605	11.4	130	8.2

	every day • *Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal* • Limit refined starchy foods • People who consume starchy roots or tubers as stables also to ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes)	**Did not meet:** < 5 servings of fruits and vegetables and/or < 1 serving of whole grains and/or legumes per day	51,236	88.6	1,465	91.9
5. Red meat Limit intake of red meat and avoid processed meat	• *People who eat red meat to consume less than 500 g (18 oz) a week, very little if any to be processed*	**Met:** < 18 oz red and/or processed meat per week	31,880	55.1	786	49.3
		Did not meet: ≥ 18 oz red and/or processed meat per week	25,961	44.9	809	50.7
6. Alcohol Limit alcoholic drinks	• *If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women*	**Met:** ≤ 1 drink per day for women; ≤ 2 drinks per day for men	49,475	85.5	1,331	83.5
		Did not meet: > 1 drink per day for women; > 2 drinks per day for men	8,366	14.5	264	16.6
7. Salt Limit consumption of salt; avoid moldy grains or legumes	• Avoid salt-preserved, salted, or salty foods; preserve foods without using salt • Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) a day • Do not eat moldy cereals (grains) or pulses (legumes)	**Not operationalized**	--	--	--	--
8. Supplements Aim to meet nutritional needs through diet alone	• Dietary supplements are not recommended for cancer prevention	**Not operationalized**	--	--	--	--

Italicized text indicates portions of the WCRF/AICR recommendations operationalized in this study. These represent the key components of the recommendations selected by an expert panel.

Table 1.2: Baseline characteristics of the study population and of cancer deaths

	VITAL cohort (N=57,841)		Cancer deaths (N=1,595)	
Characteristic	N	%	N	%
Sex				
Men	29,008	50.2	906	56.8
Women	28,833	49.9	689	43.2
Age (years)				
50-54	14,909	25.8	151	9.5
55-59	13,928	24.1	218	13.7
60-64	10,622	18.4	277	17.4
65-69	8,925	15.4	369	23.1
70 or older	9,457	16.4	580	36.4
Education				
High school graduate/GED or below	10,460	18.1	465	29.2
Some college/technical school	21,907	37.9	632	39.6
College graduate	14,808	25.6	338	21.2
Advanced degree	10,499	18.2	156	9.8
Missing	167	0.3	4	0.3
Race				
White	53,989	93.3	1,503	94.2
Hispanic	491	0.9	13	0.8
African American	615	1.1	13	0.8
American Indian/Alaska Native	838	1.5	26	1.6
Asian/Pacific Islander	1,353	2.3	26	1.6
Other/missing	555	1.0	14	0.9
Marital status				
Married	44,012	76.1	1,141	71.5
Living with partner	1,523	2.6	28	1.8
Never married	1,904	3.3	59	3.7
Separated/divorced	6,556	11.3	195	12.2
Widowed	3,581	6.2	168	10.5
Missing	265	0.4	4	0.3
Smoking status				
Never smoked	27,869	48.2	472	29.6
Former smoker (quit 10+ yrs. Before baseline)	4,663	8.1	293	18.4
Former smoker (quit <10 yrs. Before baseline)	3,731	6.5	191	12.0
Current smoker	21,247	36.7	618	38.8
Mammogram in 2 years prior to baseline (women only)				
No	2,491	8.6	96	13.9
Yes	26,249	91.0	592	85.9
Missing	93	0.2	1	0.1
PSA screening in 2 years prior to baseline				

(men only)				
No	8,088	27.9	286	31.6
Yes	20,601	71.0	609	67.2
Missing	319	1.1	11	1.2
Colonoscopy or sigmoidoscopy in 2 years prior to baseline				
No	25,580	44.2	721	45.2
Yes	31,860	55.1	855	53.6
Missing	401	0.7	19	1.2
Number of first-degree family members diagnosed with cancer				
None	30,940	53.5	847	53.1
One	18,223	31.5	470	29.5
Two or more	7,571	13.1	240	15.1

Table 1.3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer mortality associated with meeting (vs. not meeting) each WCRF/AICR recommendation

Recommendation	**Age- and sex-adjusted*** HR (95% CI)	**Covariate-adjusted†** HR (95% CI)	**Fully-adjusted‡** HR (95% CI)
Body fatness	0.84 (0.75, 0.93)	0.96 (0.86, 1.07)	0.97 (0.87, 1.09)
Physical activity	0.72 (0.63, 0.83)	0.87 (0.75, 1.00)	0.90 (0.78, 1.03)
Energy density	0.69 (0.60, 0.80)	0.78 (0.67, 0.91)	0.82 (0.70, 0.97)
Plant foods	0.67 (0.56, 0.80)	0.75 (0.62, 0.91)	0.82 (0.67, 1.00)
Red meat	0.79 (0.71, 0.88)	0.92 (0.82, 1.04)	0.97 (0.86, 1.09)
Alcohol	0.86 (0.76, 0.99)	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)

*Age is used as the timeline in the Cox proportional hazards model. Models include 57,841 respondents, of which 1,595 are cancer deaths.

† Adjusted for age (as the timeline in the Cox model), sex, education, race/ethnicity, marital status, mammography in previous 2 years, PSA screening in previous 2 years, colonoscopy or sigmoidoscopy in previous 10 years, family history of cancer, aspirin and non-aspirin NSAID use, age at menarche, age at first birth, age at menopause, hormone therapy use, hysterectomy, pack-years of smoking, and daily energy intake. Model includes 54,370 respondents, of which 1,479 are cancer deaths.

‡ Adjusted for the factors in the covariate-adjusted model, as well as for whether respondents met each of the other recommendations. Models include 54,370 respondents, of which 1,479 are cancer deaths.

Table 1.4. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer mortality associated with number of WCRF/AICR recommendations met at baseline

Recommendations met	**VITAL cohort** (N = 57,841) N (%)	**Cancer deaths** (N = 1,595) N (%)	**Age- and sex-adjusted*** HR (95% CI)	**Covariate-adjusted†** HR (95% CI)
None	2,330 (4.0)	96 (6.0)	1.00	1.00
1	15,110 (26.1)	455 (28.5)	0.74 (0.59, 0.92)	0.78 (0.62, 0.99)
2	18,777 (32.5)	579 (36.3)	0.71 (0.57, 0.89)	0.88 (0.70, 1.10)
3	13,019 (22.5)	301 (18.9)	0.53 (0.42, 0.66)	0.70 (0.55, 0.90)
4	6,168 (10.7)	133 (8.3)	0.48 (0.37, 0.63)	0.71 (0.53, 0.94)
5-6	2,437 (4.2)	31 (1.9)	0.27 (0.18, 0.41)	0.40 (0.25, 0.62)
Per recommendation‡			0.83 (0.79, 0.87)	0.91 (0.87, 0.96)
P_{trend}‡			<0.001	<0.001

* Age is used as the timeline in the Cox proportional hazards model. Model includes 57,841 respondents, of which 1,595 are cancer deaths.

† Adjusted for age (as the timeline in the Cox model), sex, education, race/ethnicity, marital status, mammography in previous 2 years, PSA screening in previous 2 years, colonoscopy or sigmoidoscopy in previous 10 years, family history of cancer, aspirin and non-aspirin NSAID use, age at menarche, age at first birth, age at menopause, hormone therapy use, hysterectomy, pack-years of smoking and daily energy intake. Model includes 54,370 respondents, of which 1,479 are cancer deaths.

‡ Per recommendation HRs, 95% CIs and *P*-values were calculated using a two-sided test for linear trend modeling categories (0-6) as a continuous variable.

Supplementary Table 1.A. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer mortality associated with number of WCRF/AICR recommendations met at baseline, stratified by smoking status

Recommendations met	**Cohort** N (%)	**Cancer deaths** N (%)	**Age- and sex-adjusted*** HR (95% CI)	**Covariate-adjusted†** HR (95% CI)
Ever-smokers				
None	1,713 (5.8)	82 (7.4)	1.00	1.00
1	8,902 (29.9)	332 (30.0)	0.76 (0.60, 0.97)	0.75 (0.58, 0.96)
2	9,594 (32.2)	407 (36.7)	0.82 (0.64, 1.04)	0.90 (0.70, 1.16)
3	6,055 (20.3)	192 (17.3)	0.59 (0.46, 0.77)	0.72 (0.55, 0.95)
4	2,556 (8.6)	82 (7.4)	0.59 (0.43, 0.80)	0.76 (0.55, 1.06)
5-6	979 (3.3)	13 (1.2)	0.23 (0.13, 0.42)	0.38 (0.21, 0.69)
Per recommendation§			0.88 (0.84, 0.93)	0.94 (0.88, 1.00)
P_{trend}§			<0.001	0.034
Never-smokers				
None	610 (2.2)	12 (2.5)	1.00	1.00
1	6,160 (22.1)	119 (25.2)	0.99 (0.55, 1.79)	0.98 (0.53, 1.83)
2	9,133 (32.8)	168 (35.6)	0.83 (0.46, 1.50)	0.89 (0.48, 1.65)
3	6,926 (24.9)	105 (22.3)	0.66 (0.36, 1.20)	0.70 (0.37, 1.32)
4	3,589 (12.9)	50 (10.6)	0.59 (0.31, 1.12)	0.67 (0.34, 1.31)
5-6	1,451 (5.2)	18 (3.8)	0.50 (0.24, 1.05)	0.44 (0.19, 0.99)
Per recommendation§			0.88 (0.82, 0.95)	0.85 (0.78, 0.93)
P_{trend}§			0.001	<0.001
$P_{interaction}$			<0.001	0.091

* Age is used as the timeline in the Cox proportional hazards model. Model includes 29,799 smokers, of which 1,108 died of cancer and 27,869 never-smokers, of which and 472 died of cancer.

† Adjusted for age (as the timeline in the Cox model), education, race/ethnicity, marital status, mammography in previous 2 years, colonoscopy or sigmoidoscopy in previous 10 years, family history of cancer, aspirin and non-aspirin NSAID use, age at menarche, age at first birth, age at menopause, hormone therapy use, hysterectomy, pack-years of smoking (ever-smokers models only) and daily energy intake. Model includes 28,045 ever-smokers, 1,042 of which died of cancer and 26,325 never-smokers, 437 of which died of cancer.

§ HRs, 95% CIs and - values were calculated using a two-sided test for linear trend modeling categories (0-6) as a continuous variable.

Supplementary Table B. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer mortality associated with meeting (vs. not meeting) each WCRF/AICR recommendation, stratified by smoking status

Recommendation	Age- and sex-adjusted* HR (95% CI)	Covariate-adjusted† HR (95% CI)	Fully-adjusted‡ HR (95% CI)
Ever-smokers			
Body fatness	0.98 (0.86, 1.11)	1.09 (0.95, 1.25)	1.11 (0.97, 1.27)§
Physical activity	0.71 (0.60, 0.84)	0.86 (0.72, 1.02)	0.87 (0.74, 1.04)
Energy density	0.68 (0.57, 0.82)	0.80 (0.67, 0.97)	0.86 (0.71, 1.05)
Plant foods	0.59 (0.47, 0.76)	0.69 (0.54, 0.89)	0.74 (0.57, 0.96)
Red meat	0.79 (0.70, 0.90)	0.92 (0.80, 1.07)	0.95 (0.82, 1.10)
Alcohol	0.99 (0.85, 1.15)	0.99 (0.84, 1.15)	1.00 (0.86, 1.17)
Never-smokers			
Body fatness	0.68 (0.56, 0.83)	0.70 (0.57, 0.86)	0.71 (0.57, 0.88)§
Physical activity	0.80 (0.63, 1.02)	0.87 (0.68, 1.11)	0.94 (0.73, 1.20)
Energy density	0.72 (0.57, 0.92)	0.73 (0.56, 0.95)	0.75 (0.57, 0.99)
Plant foods	0.85 (0.64, 1.12)	0.85 (0.62, 1.15)	0.98 (0.71, 1.34)
Red meat	0.89 (0.73, 1.08)	0.92 (0.73, 1.15)	1.00 (0.80, 1.25)
Alcohol	0.89 (0.67, 1.20)	0.79 (0.58, 1.06)	0.77 (0.57, 1.04)

* Age is used as the timeline in the Cox proportional hazards model. The ever-smokers model includes 29,799 participants, 1,108 of which are cancer deaths and the never-smokers model includes 27,869 participants, of which 472 are cancer deaths.

† Adjusted for age (as the timeline in the Cox model), sex, education, race/ethnicity, marital status, mammography in previous 2 years, PSA screening in previous 2 years, colonoscopy or sigmoidoscopy in previous 10 years, family history of cancer, aspirin and non-aspirin NSAID use, age at menarche, age at first birth, age at menopause, hormone therapy use, hysterectomy, pack-years of smoking (ever-smokers only), and daily energy intake.

‡ Adjusted for the factors in the covariate-adjusted model, as well as for whether respondents met each of the other recommendations. The covariate-adjusted and fully-adjusted models include 28,045 ever-smokers, of which 1,042 are cancer deaths and 26,325 never-smokers, of which 437 are cancer deaths.

§ $P_{interaction}$ of ever vs. never smoking with meeting the recommendation related to body fatness = 0.001. Interactions between meeting other recommendations and smoking status were not statistically significant (all $P > 0.05$).

CHAPTER 2: Composition and context in the association between area-level socioeconomic status and cancer incidence and mortality

Abstract

Background: Area-level socioeconomic status (SES) has been associated with health outcomes and mortality; however, the association between area-level SES and cancer incidence and mortality is not well understood, and the extent to which observed associations are due to compositional versus contextual effects is unclear. The purpose of this paper is to estimate the association between area-level SES and total and site-specific cancer incidence and total cancer mortality and to assess whether any observed associations are explained by compositional factors including individual educational attainment and household income.

Methods: Participants included 60,756 men and women ages 50-76 years who were recruited into the VITamins And Lifestyle (VITAL) Study cohort between 2000-2002. We identified the census block groups of participants and constructed an area-level SES index using data from the 2000 U.S. Census. Cox proportional hazards models were used to estimate the association between quintile of area-level SES and first cancer diagnoses (n = 6,099) and cancer deaths (n = 2,487) tracked through the Western Washington Surveillance, Epidemiology and End Results (SEER) database and the Washington State death file, respectively, through December 31, 2010.

Results: After controlling for age, sex, race/ethnicity, and marital status, living in areas in the lowest quintile of area-level SES index was associated with increased risk of lung cancer (HR: 2.21, 95% CI: 1.69, 2.90) and colorectal cancer among men (HR: 1.75, 95% CI: 1.14, 2.70) and total cancer mortality (HR: 1.68, 95% CI: 1.47, 1.93) compared with areas in the highest quintile of area-level SES index. Further controlling for compositional factors including individual education and household income weakened but did not eliminate these associations (HR for lung cancer: 1.43, 95% CI: 1.07, 1.91; HR for colorectal cancer among men: 1.53, 95% CI: 0.99, 2.38; HR for total cancer mortality: 1.28, 95% CI: 1.11, 1.48).

Conclusions: Living in low-SES areas is associated with increased lung cancer incidence, increased colorectal cancer incidence among men, and higher total cancer mortality. These associations are largely, but not completely, explained by compositional factors, suggesting that area-level contextual factors could also play a role in the observed associations.

Introduction

Area-level socioeconomic status (SES) is increasingly acknowledged as a predictor of health outcomes.[8] Previous research has reported associations between the income, education, housing and employment characteristics of area residents and several health outcomes[2-5] and total and cause-specific mortality.[6-9] Area-level socioeconomic factors have also been associated with several cancer outcomes including cause-specific cancer risk and mortality.[10,12,14-17,68,69] Lower area-level SES has been associated with increased risk of colorectal,[14,68,70] lung,[70] and cervical cancer,[16,18] as well as with lung[71] and colorectal cancer mortality[71] and later stage of diagnosis of several cancers.[22,72-76] Higher area-level SES has been associated with increased risk of breast[15,18,77] and prostate cancer.[10,18,78]

Associations between area-level SES and health outcomes are likely due to some combination of compositional factors, such that people living in lower-SES areas are themselves of lower SES and would be at increased risk of disease and mortality regardless of where they lived, and contextual factors, or features of the areas themselves (e.g. environmental exposures or resources) that influence disease risk independent of individual characteristics.[22,79] Additionally, area-level SES could influence cancer incidence and cancer mortality by influencing individual health behaviors related to cancer. Health behaviors of individuals living in particular areas could also be due to compositional factors, such as level of education of area residents, or to contextual factors if features of the areas influenced health behaviors (e.g. through the food environment, opportunities for physical activity, health care infrastructure, prevailing social norms, etc.) such that an individual would behave differently in one area than in another.

Few previous studies of area-level socioeconomic factors and cancer incidence or mortality included information on individual socioeconomic factors,[14,15,68,69] or compared results with and without control for individual SES to attempt to determine whether observed associations are due to compositional factors such as individual SES.[15,68] We are unaware of previous work that has estimated the association between area-level SES and total cancer incidence and cancer mortality while also incorporating measures of individual socioeconomic status.

The purpose of this paper is to first estimate the association between area-level SES and cancer incidence (total and site-specific) and cancer mortality (total and stratified by history of cancer at baseline). We also assess whether observed associations remain after control for compositional factors including individual educational attainment and household income. While the first approach estimates the total area-level SES disparities in cancer outcomes, the second evaluates the degree of disparity that remains after control for compositional factors. Remaining area-level SES effects may represent contextual effects of areas on cancer outcomes.

Methods

Study Cohort

The VITamins And Lifestyle (VITAL) study is a prospective cohort study designed to investigate the associations of use of dietary supplements and other behaviors with cancer risk and mortality. It has previously been described in detail.[61] Women and men were eligible to join the cohort if they were between the ages of 50 and 76 and lived in one of the 13 counties included in the Western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry at baseline (2000-2002).

Using names purchased from a commercial mailing list, sex-specific baseline questionnaires including information on demographic factors, supplement use, health behaviors, medical history, diet and physical activity were mailed to 364,418 men and women between October, 2000 and December, 2002 and were followed two weeks later by reminder postcards. A total of 79,300 questionnaires were returned, of which 77,719 passed quality control checks. Overall, 60,756 men and women were included in the current analysis after excluding the following: respondents whose baseline addresses were post office boxes (n = 1,137) or could not be geocoded (n = 381); and respondents missing data on education (n = 1,333) or household income (n = 15,443). Models of area-level SES and total and site-specific cancer incidence further excluded respondents with a history of cancer other than nonmelanoma skin cancer (n = 11,259) or whose history of cancer was unknown (n = 214) (numbers of exclusions reported are not mutually exclusive).

This research was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Area-level Socioeconomic Status

Respondents' baseline addresses were geocoded using GPS Visualizer and Yahoo! Maps. A 1% sample of addresses was geocoded again using Google Maps and more than 95% of the addresses in the validation sample were geocoded to within 400 meters of one another using the two methods. Addresses were used to identify respondents' census block groups using TIGER/Line shapefiles for the 2000 Census in ArcMap 10 (Esri, Redlands, CA). In a previous review of geocoding accuracy, 96% of a sample of geocodable addresses were placed in the correct block groups.[80] Census block groups typically contain between 600 and 3,000 residents,

with an optimal population of 1,500. They do not cross county, state or census tract boundaries and most were delineated with input from local participants.[81]

Area-level socioeconomic status was measured using a method previously developed by Diez-Roux et al.[82] Information from the 2000 U. S. Census was used to create an index based on the income, education and employment characteristics of respondents' block groups. This index includes the log of median value of owner-occupied housing units; log of median household income; percent of households receiving net rental, interest or dividend income; percent of adults ages 25 and older who completed high school; percent of adults ages 25 and older who completed college; and percent of employed persons ages 16 and older in professional and managerial occupations. The standardized z-score was calculated for each variable based on the 3,346 block groups in the 13 counties included in the Western Washington SEER registry and then summed to create an index such that higher index scores corresponded with lower area-level SES. The index value for the block group in which the participant resided was assigned to that individual. An index using the same census variables has been used previously to examine associations between area-level SES and several cardiovascular[2,4,6,9] and other outcomes[3,5,21] including a previous study of the association between area-level SES and colon and rectal cancer.[14] In our population, index values ranged from -16.1 to 17.3 with a median value of -1.1 and mean of -1.3.

Case Ascertainment and Censoring

In cancer incidence analyses, participants with no history of cancer at baseline were followed for their first incident, invasive cancer via annual linkage with the Western Washington SEER cancer registry. Linkage between VITAL and SEER is largely automated and based on ranking agreement between items common to both sets of data, such as Social Security number,

name, and date of birth. Matches with high concordance are linked automatically whereas visual inspection is used to adjudicate incomplete matches. A total of 6,099 incident cancers were identified in an average of 8.1 years of follow-up.

Participants who were not diagnosed with cancer were right-censored at the date of the earliest of the following events: date they requested removal from the study (n = 8), date they moved out of the 13-county area covered by the SEER registry (n = 3,898), date of death (n = 2,214) or December 31, 2010 (n = 39,967). Moves out of area were identified through linkage with the US National Change of Address System. For analyses of site-specific cancer risk, participants diagnosed with cancers other than the one of interest were censored at the age of cancer diagnosis.

Cancer deaths were ascertained through annual linkage with the Washington State death file using procedures similar to those described above. In cancer mortality analyses, participants who did not die of cancer were right-censored at the date of the earliest of the following events: date they requested removal from the study (n = 9), date they moved out of Washington State (n = 3,536), date of death due to other causes (n = 3,116) or December 31, 2010 (n = 51,608). A total of 2,487 cancer deaths were observed in an average of 8.5 years of follow-up.

Statistical Analyses

Area-level SES was divided into quintiles based on the distribution of the index values associated participants included in our analyses. Using these categories, Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer incidence and cancer mortality associated with living in areas in each of the lowest four quintiles of area-level SES compared with living in the reference highest-SES quintiles. Participant age was used as the time scale, with participants entering the analysis at their age at

baseline and exiting at age at outcome (cancer diagnosis for cancer incidence analyses, death due to cancer for cancer mortality analyses) or age at censoring event, as described above. Proportional hazards assumptions were examined using scaled Schoenfeld residuals. No significant ($p<0.05$) deviations from proportionality were observed. All statistical tests were two-sided.

Multivariate analyses included categorical variable adjustment for sex, race/ethnicity (white, Hispanic, African-American, American Indian/Alaska Native, Asian/Pacific Islander, other/missing) and marital status (married, living with partner, never married, separated/divorced, widowed) (Model 1). Models further controlling for individual SES included adjustment for education (high school graduate/GED or below, some college/technical school, college graduate, advanced degree) and household income (<$20,000, $20,000-39,999, $40,000-59,999, $60,000-79,999 and $80,000 or more), as ascertained via the baseline questionnaire (Model 2). *P*-values for trend are from the Wald test associated with area-level SES index modeled as a continuous variable.

Statistical analyses were conducted using Stata 12.1 (StataCorp LP, College Station, TX). All models of area-level SES and cancer incidence and mortality utilize the cluster option to obtain standard errors that account for correlation among residents of the same block groups. This option was selected over shared frailty models that model the correlation between observations in the same block groups because the correlation itself was not of interest.

Results

Table 2.1 gives information on the mean, standard deviation and range of area-level SES index values, as well as baseline demographic characteristics of the study population by quintiles of area-level SES. Compared with participants who resided in the highest-SES areas, those who

resided in the lowest-SES areas tended to be older and a lower proportion were male, white, married, college-educated and reported household incomes of at least $40,000 at baseline.

In models adjusted for age, sex, race/ethnicity and marital status, compared with living in the highest-SES areas, living in the lowest SES block groups was marginally associated with a small increase in total cancer incidence (HR: 1.08, 95% CI: 0.99, 1.17; $P_{trend} = 0.067$) and was associated with substantially increased risk of lung (HR: 2.21, 95% CI: 1.69, 2.90; $P_{trend} < 0.001$) and colorectal cancer (HR: 1.52, 95% CI: 1.11, 2.09; $P_{trend} = 0.003$) (Table 2.2, Model 1). Prostate cancer risk decreased with decreasing quintiles of area-level SES ($P_{trend} = 0.015$) and risk in the lowest-SES areas was modestly lower than in the highest-SES areas (HR: 0.88, 95% CI: 0.76, 1.02). Results were similar for men and for women, except for colorectal cancer where living in lower-SES areas was associated with increased colorectal cancer incidence in men (HR for quintile 1 vs. quintile 5: 1.75, 95% CI: 1.14, 2.10; $P_{trend} = 0.003$) but the evidence was weaker for women (HR for quintile 1 vs. quintile 5: 1.31, 95% CI: 0.83, 2.06; $P_{trend} = 0.265$). Area-level SES was not associated with risk of breast cancer or of other cancers combined.

In models further adjusting individual education and income, the association between area-level SES and total cancer incidence was attenuated (HR for quintile 1 vs. quintile 5: 1.06, 95% CI: 0.97, 1.16; $P_{trend} = 0.215$) and eliminated for area-level SES and prostate cancer (HR for quintile 1 vs. quintile 5: 1.01, 95% CI: 0.86, 1.18; $P_{trend} = 0.662$) (Table 2.2, Model 2). The association between area-level SES and lung cancer incidence attenuated substantially, but living in the lowest-SES areas remained associated with a 43% increase in lung cancer incidence compared with living in the highest-SES areas (HR: 1.43, 95% CI: 1.07, 1.91). The association between area-level SES and colorectal cancer also weakened after adjustment for individual education and income: it remained moderately associated overall (HR for quintile 1 vs. quintile

5: 1.35, 95% CI: 0.97, 1.88; $P_{trend} = 0.067$) and for men (HR for quintile 1 vs. quintile 5: 1.53, 95% CI: 0.99, 2.38; $P_{trend} = 0.062$) but not for women (HR for quintile 1 vs. quintile 5: 1.18, 95% CI: 0.72, 1.93; $P_{trend} = 0.659$).

Table 2.3 gives results for cancer mortality overall and stratified by whether respondents were diagnosed with cancer at baseline. In models adjusted for age, sex, race/ethnicity and marital status, living in low-SES areas was associated with greater cancer mortality than living in higher-SES areas (HR for quintile 1 vs. quintile 5: 1.68, 95% CI: 1.47, 1.93; $P_{trend} < 0.001$) (Table 2.3, Model 1). The association between area-level SES and cancer mortality was somewhat weaker in respondents who were diagnosed with cancer before baseline (HR for quintile 1 vs. quintile 5: 1.54, 95% CI: 1.26, 1.87; $P_{trend} < 0.001$) than among those diagnosed after baseline (HR for quintile 1 vs. quintile 5: 1.81, 95% CI: 1.52, 2.16; $P_{trend} < 0.001$). Controlling for individual education and income substantially weakened these results; however, living in lower-SES areas remained associated with greater cancer mortality, particularly among all respondents (HR for quintile 1 vs. quintile 5: 1.28, 95% CI 1.11, 1.48; $P_{trend} < 0.001$) and among participants diagnosed after baseline (HR for quintile 1 vs. quintile 5: 1.40, 95% CI: 1.16, 1.69; $P_{trend} < 0.001$). These associations were similar among men and women.

Discussion

The purpose of this study was to estimate the association between area-level SES and total and site-specific cancer incidence and total cancer mortality, and to assess whether observed associations are explained by compositional effects including individual education and income. In analyses which controlled for demographic factors but excluded individual education and income, living in the lowest-SES areas was associated with a 121% increase in lung cancer risk, a 75% increase in colorectal cancer risk among men, and a 68% increase in cancer mortality

compared with living in the highest-SES areas (all $P_{trend} \leq 0.003$). These associations weakened but were not eliminated after also controlling for individual education and income: a 43% increase for lung cancer, a 53% increase for colorectal cancer among men, and a 28% increase for cancer mortality remained (all $P_{trend} < 0.05$). These results suggest that there are moderate-to-large area-level SES associations with these specific cancer outcomes, and that although compositional factors explain 29-64% of the observed associations, area-level SES effects remain even after controlling for individual education and income. The remaining associations could be due at least partly to contextual effects of the areas themselves.

Although measures of area-level socioeconomic status should summarize information about socioeconomic conditions in a given area in a meaningful way and use socioeconomic data that can be compared between different locations and at different times,[69] there are no established standards for measuring area-level SES, making it difficult to directly compare results from different studies. However, although previous studies have largely used different measures of area-level SES, many have also presented results using quintiles of those measures, allowing for comparisons of relative socioeconomic status and cancer outcomes.[15]

Where our results suggest a small increase in total cancer incidence in low-SES areas compared with high-SES areas, the only previous study of a composite area-level SES index (including percentage of residents below the U.S. federal poverty line, percentage of residents in working class occupations and percentage of owner-occupied homes worth at least $300,000) and total cancer incidence reported incidence rate ratios (IRRs) suggesting lower incidence in the most-deprived quintile compared with the least-deprived in Massachusetts (IRR: 0.92, 95% CI: 0.87, 0.96) and no association in Rhode Island (IRR: 0.99, 95% CI: 0.85, 1.14).[69] These analyses were based on characteristics of census block groups, similar to our study, but did not account

for individual socioeconomic factors. However in the same study, the authors did account for individual educational attainment as reported on death certificates in an analysis of area-level SES and cancer mortality, and they reported IRRs of 1.25 (95% CI: 0.98, 1.58) and 1.09 (95% CI: 0.98, 1.20) in the most-deprived areas relative to the least-deprived areas in Massachusetts and Rhode Island, respectively.[69] These results are comparable to the 28% increase in cancer mortality we observed in the lowest-SES block groups relative to the highest-SES block groups after accounting for individual education and income. However, in a sensitivity analysis removing individual income from the model, cancer mortality was 40% higher in VITAL participants in the lowest (vs. highest) quintile of area-level SES (HR: 1.40, 95% CI: 1.22, 1.61).

A study based in Oakland, CA reported a rate ratio of cancer mortality of 1.97 (95% CI: 1.29, 3.00) associated with living in a federally-designated poverty area (defined as contiguous census tracts in major metropolitan areas in the lowest quartile based on weighting of proportions of low-income families, presence of substandard housing, children living in single-parent households, unskilled men in the labor force and low educational attainment in adults) compared with living in a non-poverty area among adults ages 25-54 after controlling for age, race and sex.[83] Unlike our results, these results were unchanged after adjusting for income, education, and several health behaviors and no association was observed between living in a poverty area and cancer mortality among adults ages 55-74.[83]

Relatively few studies have reported associations between area-level SES and site-specific cancer incidence controlling for individual socioeconomic factors,[14,15,68,69] and even fewer present results with and without individual SES.[15,68] A case-control study conducted in Wisconsin reported an odds ratio (OR) of breast cancer of 1.23 for women in the highest quintile of community-level SES (including median family income, percent of adults in poverty, percent

unemployment, and percent of adults ages 25 and older who completed college measured at the census tract level) relative to those in the lowest quintile, an association that weakened to an OR of 1.16 (95% CI: 1.02, 1.32) after also accounting for educational attainment.[15] In contrast, we observed no association between area-level SES and breast cancer incidence regardless of whether individual SES was included.

A large cohort study reported an incidence rate ratio for colorectal cancer of 1.16 (95% CI: 1.05, 1.28) associated with living in census tracts in the lowest quintile of area-level SES (as measured by a deprivation index created using principal components analysis and including percent of persons with less than a high school education, percent unemployed, percent non-Hispanic blacks, and percent in managerial occupations; and percentage of households below the federal poverty level, on public assistance, with no car, headed by a female with dependent children, and with incomes of less than $30,000 per year) compared with living in the highest-SES areas after controlling for individual education.[68] This is somewhat weaker than our results controlling for individual education and income, and also weaker than results of an additional analysis controlling for demographics and education (but not income) that found an HR of colorectal cancer incidence associated with living in areas in the lowest vs. highest quintile of area-level SES of 1.39 (95% CI: 1.01, 1.91; data not shown).

Analyses in the Nurses' Health Study found lower incidence of rectal cancer in women living in areas in the highest quintile of area-level SES index (including the same block group measures used in our study and also based on the methods used by Diez-Roux[2]) relative to the women living in areas in the lowest quintile of area-level SES index when accounting for educational attainment (relative risk (RR): 0.64, 95% CI: 0.44, 0.93), but a non-significant association between area-level SES and colon cancer (RR: 0.91, 95% CI: 0.74, 1.10).[14] We found

no clear trends of area-level SES with risk of colon and rectal cancer combined when our analyses were restricted to women and did not have sufficient numbers of cases to look at colon and rectal cancer separately among women.

Important limitations of this study should be noted. VITAL recruited participants from one region of the United States and a large majority of participants were white, which could limit its generalizability to other populations. Although baseline addresses were successfully geocoded for almost all VITAL respondents, a small proportion (<5%) of those geocodes did not match when geocoded again using a different mapping tool. This could lead to misclassification of quintile of area-level SES for participants whose addresses were geocoded into the wrong block group; however, because geocoding of baseline address is unlikely to affect future cancer incidence or mortality, this misclassification would be nondifferential with regard to the outcome considered and would attenuate our observed associations assuming that the mean value of the measured exposure (quintile of area-level SES) increased monotonically with the true exposure.[66] Another limitation is the potential for measurement error in individual education and household income. When a strong confounder is measured with error its effects are not fully removed, and in this case, residual confounding by individual education and income would lead to insufficient control for potential compositional factors and the remaining observed associations between area-level SES and cancer incidence and mortality (Model 2) could be biased away from the null.

Strengths of this study include its prospective design and large sample size, allowing for examination of several site-specific cancers as well as total cancer incidence and cancer mortality. Information collected from the detailed baseline questionnaires allowed us to control for demographic factors and to include two measures of individual-level SES (individual

education and income). Linkage with SEER and the Washington State death file allowed for accurate and near-complete ascertainment of new cancer diagnoses and cancer deaths.

In summary, although area-level SES is increasingly examined as a potential risk factor for disease, little is known about the associations between area-level SES and cancer incidence and mortality and the extent to which any such observed association could be due to compositional factors such as individual education and income. To our knowledge this is the first study to systematically examine associations between area-level SES and total and cause-specific cancer incidence and total cancer mortality with and without control for individual SES. Our results suggest that although area-level SES is only weakly associated with total cancer incidence, living in lower-SES areas is associated with increased risk of lung cancer and colorectal cancer (among men) as well as with total cancer mortality. Our results for these outcomes are consistent with a review by Picket and Pearl[79] for a range of outcomes in that area-level effects on health outcomes remained after controlling for compositional factors, and the resulting contextual effects were weaker than the compositional effects.

In order to better understand how area-level factors could influence cancer outcomes, future research should examine whether behaviors such as smoking, diet, physical activity and screening explain the observed associations between area-level SES and cancer outcomes and attempt to identify features of low-SES areas that could affect cancer outcomes directly or by influencing health behaviors.

Table 2.1: Mean, standard deviation (SD) and range of area-level SES index values and baseline demographic factors of VITAL cohort participants by quintiles of area-level socioeconomic status (SES)

		Area-level SES index			Demographic factors				
Quintiles of area-level SES index	**N**	**Mean**	**SD**	**Range**	**Age** Mean (SD)	**White** %	**Married** %	**College degree** %	**Annual household income ≥$40,000** %
Quintile 1 (High SES)	12,145	-8.4	2.21	-16.1, <-5.6	60.3 (7.2)	94.1	78.4	67.9	86.9
Quintile 2	12,249	-3.8	0.98	-5.6, <-2.3	60.6 (7.3)	94.2	75.7	51.4	78.2
Quintile 3	12,018	-1.1	0.73	-2.3, <0.28	61.0 (7.4)	94.1	76.1	41.8	72.3
Quintile 4	12,181	1.6	0.79	0.28, <3.0	61.2 (7.4)	92.7	73.0	31.4	63.4
Quintile 5 (Low SES)	12,164	5.3	1.88	3.0, 17.31	61.6 (7.5)	90.6	66.4	23.3	52.6

Table 2: Hazard ratios (HRs) and 95% confidence intervals (CIs) of total and site-specific cancer incidence associated with quintiles of area-level socioeconomic status (SES)

Area-level SES	VITAL cohort N	Incident cancers N	Age- and sex-adjusted HR (95% CI)	Model 1[a] Demographics only HR (95% CI)	Model 2[b] Demographics and individual SES HR (95% CI)
Total cancer incidence					
All respondents	52,186	6,099			
Quintile 5 (Highest SES)	10,410	1,160	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	10,407	1,154	1.00 (0.92, 1.09)	1.00 (0.92, 1.08)	1.00 (0.91, 1.08)
Quintile 3	10,480	1,242	1.04 (0.96, 1.13)	1.04 (0.96, 1.13)	1.04 (0.95, 1.13)
Quintile 2	10,402	1,250	1.06 (0.98, 1.15)	1.06 (0.97, 1.15)	1.05 (0.96, 1.14)
Quintile 1 (Lowest SES)	10,487	1,293	1.08 (1.00, 1.18)	1.08 (0.99, 1.17)	1.06 (0.97, 1.16)
P_{trend}[c]			0.042	0.067	0.215
Women	25,260	2,421			
Quintile 5 (Highest SES)	4,863	432	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	4,955	443	0.99 (0.86, 1.13)	0.98 (0.86, 1.13)	0.97 (0.85, 1.11)
Quintile 3	4,953	486	1.07 (0.94, 1.22)	1.06 (0.93, 1.21)	1.04 (0.91, 1.19)
Quintile 2	5,146	510	1.06 (0.93, 1.21)	1.06 (0.93, 1.20)	1.03 (0.90, 1.18)
Quintile 1 (Lowest SES)	5,343	550	1.09 (0.96, 1.24)	1.08 (0.95, 1.23)	1.04 (0.90, 1.19)
P_{trend}[c]			0.140	0.196	0.601
Men	26,926	3,678			
Quintile 5 (Highest SES)	5,547	728	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,452	711	1.01 (0.91, 1.12)	1.01 (0.91, 1.12)	1.01 (0.91, 1.12)
Quintile 3	5,527	756	1.03 (0.93, 1.14)	1.03 (0.93, 1.14)	1.03 (0.93, 1.15)
Quintile 2	5,256	740	1.06 (0.96, 1.18)	1.06 (0.95, 1.17)	1.06 (0.95, 1.18)
Quintile 1 (Lowest SES)	5,144	743	1.09 (0.98, 1.20)	1.08 (0.97, 1.20)	1.07 (0.96, 1.20)
P_{trend}[c]			0.112	0.151	0.256
Prostate cancer incidence					
Men	26,926	1,712			
Quintile 5 (Highest SES)	5,547	394	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,452	333	0.88 (0.76, 1.01)	0.88 (0.76, 1.01)	0.92 (0.80, 1.06)
Quintile 3	5,527	349	0.88 (0.77, 1.02)	0.88 (0.77, 1.02)	0.95 (0.82, 1.10)
Quintile 2	5,256	318	0.85 (0.73, 0.98)	0.85 (0.73, 0.98)	0.94 (0.81, 1.10)
Quintile 1 (Lowest SES)	5,144	318	0.87 (0.75, 1.01)	0.88 (0.76, 1.02)	1.01 (0.86, 1.18)
P_{trend}[c]			0.012	0.015	0.662
Breast cancer incidence					
Women	25,260	856			
Quintile 5 (Highest SES)	4,863	159	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	4,955	147	0.90 (0.72, 1.13)	0.90 (0.72, 1.14)	0.91 (0.72, 1.14)
Quintile 3	4,953	182	1.11 (0.89, 1.38)	1.11 (0.89, 1.38)	1.12 (0.90, 1.40)
Quintile 2	5,146	189	1.10 (0.89, 1.36)	1.10 (0.89, 1.36)	1.11 (0.90, 1.39)
Quintile 1 (Lowest SES)	5,343	179	1.00 (0.80, 1.24)	1.00 (0.80, 1.25)	1.02 (0.81, 1.29)
P_{trend}[c]			0.666	0.635	0.525
Lung cancer incidence					
All respondents	52,186	676			
Quintile 5 (Highest SES)	10,410	74	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	10,407	123	1.64 (1.22, 2.19)	1.62 (1.21, 2.17)	1.37 (1.02, 1.85)
Quintile 3	10,480	130	1.65 (1.24, 2.19)	1.64 (1.22, 2.19)	1.26 (0.93, 1.71)
Quintile 2	10,402	160	2.04 (1.55, 2.70)	2.00 (1.51, 2.65)	1.41 (1.05, 1.89)
Quintile 1 (Lowest SES)	10,487	189	2.34 (1.79, 3.07)	2.21 (1.69, 2.90)	1.43 (1.07, 1.91)

P_{trend}[c]			<0.001	<0.001	0.041
Women	25,260	292			
Quintile 5 (Highest SES)	4,863	32	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	4,955	49	1.44 (0.92, 2.25)	1.43 (0.91, 2.22)	1.28 (0.82, 2.00)
Quintile 3	4,953	50	1.43 (0.92, 2.21)	1.41 (0.91, 2.19)	1.17 (0.74, 1.84)
Quintile 2	5,146	75	2.01 (1.33, 3.03)	1.94 (1.29, 2.93)	1.51 (0.97, 2.35)
Quintile 1 (Lowest SES)	5,343	86	2.15 (1.43, 3.22)	2.02 (1.34, 3.02)	1.46 (0.94, 2.26)
P_{trend}[c]			<0.001	<0.001	0.078
Men	26,926	384			
Quintile 5 (Highest SES)	5,547	42	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,452	74	1.79 (1.25, 2.58)	1.77 (1.23, 2.55)	1.46 (1.01, 2.12)
Quintile 3	5,527	80	1.83 (1.26, 2.67)	1.81 (1.24, 2.66)	1.34 (0.90, 1.98)
Quintile 2	5,256	85	2.07 (1.44, 2.96)	2.03 (1.42, 2.92)	1.34 (0.91, 1.97)
Quintile 1 (Lowest SES)	5,144	103	2.51 (1.77, 3.57)	2.37 (1.66, 3.37)	1.43 (0.97, 2.09)
P_{trend}[c]			<0.001	<0.001	0.229
Colorectal cancer incidence					
All respondents	52,186	461			
Quintile 5 (Highest SES)	10,410	64	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	10,407	86	1.33 (0.96, 1.84)	1.33 (0.96, 1.84)	1.29 (0.93, 1.78)
Quintile 3	10,480	94	1.40 (1.02, 1.92)	1.39 (1.01, 1.91)	1.32 (0.96, 1.81)
Quintile 2	10,402	106	1.58 (1.15, 2.16)	1.55 (1.13, 2.12)	1.43 (1.03, 1.98)
Quintile 1 (Lowest SES)	10,487	111	1.61 (1.18, 2.20)	1.52 (1.11, 2.09)	1.35 (0.97, 1.88)
P_{trend}[c]			0.001	0.003	0.062
Women	25,260	217			
Quintile 5 (Highest SES)	4,863	30	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	4,955	41	1.29 (0.80, 2.08)	1.28 (0.79, 2.07)	1.27 (0.78, 2.07)
Quintile 3	4,953	43	1.31 (0.82, 2.10)	1.30 (0.81, 2.08)	1.24 (0.77, 2.01)
Quintile 2	5,146	51	1.46 (0.93, 2.30)	1.42 (0.90, 2.23)	1.34 (0.82, 2.17)
Quintile 1 (Lowest SES)	5,343	52	1.40 (0.89, 2.20)	1.31 (0.83, 2.06)	1.18 (0.72, 1.93)
P_{trend}[c]			0.143	0.265	0.659
Men	26,926	244			
Quintile 5 (Highest SES)	5,547	34	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,452	45	1.36 (0.87, 2.13)	1.37 (0.88, 2.16)	1.32 (0.84, 2.06)
Quintile 3	5,527	51	1.48 (0.96, 2.28)	1.48 (0.95, 2.28)	1.38 (0.90, 2.13)
Quintile 2	5,256	55	1.68 (1.10, 2.57)	1.65 (1.08, 2.53)	1.49 (0.96, 2.31)
Quintile 1 (Lowest SES)	5,144	59	1.83 (1.19, 2.81)	1.75 (1.14, 2.70)	1.53 (0.99, 2.38)
P_{trend}[c]			0.001	0.003	0.031
Other cancers					
All respondents	52,186	2,389			
Quintile 5 (Highest SES)	10,410	469	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	10,407	465	0.99 (0.88, 1.12)	0.99 (0.87, 1.12)	0.99 (0.87, 1.12)
Quintile 3	10,480	486	1.00 (0.89, 1.13)	1.00 (0.89, 1.13)	1.00 (0.88, 1.13)
Quintile 2	10,402	476	0.99 (0.87, 1.12)	0.99 (0.88, 1.13)	0.98 (0.86, 1.12)
Quintile 1 (Lowest SES)	10,487	493	1.01 (0.89, 1.15)	1.01 (0.89, 1.15)	1.00 (0.87, 1.15)
P_{trend}[c]			0.833	0.762	0.986
Women	25,260	1,056			
Quintile 5 (Highest SES)	4,863	211	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	4,955	206	0.94 (0.78, 1.13)	0.94 (0.78, 1.13)	0.93 (0.77, 1.13)
Quintile 3	4,953	211	0.95 (0.79, 1.14)	0.94 (0.78, 1.14)	0.94 (0.77, 1.14)
Quintile 2	5,146	195	0.83 (0.69, 1.01)	0.84 (0.69, 1.01)	0.83 (0.68, 1.02)
Quintile 1 (Lowest SES)	5,343	233	0.95 (0.79, 1.14)	0.95 (0.79, 1.15)	0.95 (0.77, 1.16)

P_{trend}[c]			0.331	0.352	0.377
Men	26,926	1,333			
Quintile 5 (Highest SES)	5,547	258	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,452	259	1.03 (0.87, 1.22)	1.03 (0.87, 1.22)	1.03 (0.87, 1.23)
Quintile 3	5,527	275	1.05 (0.89, 1.24)	1.05 (0.90, 1.24)	1.05 (0.89, 1.24)
Quintile 2	5,256	281	1.14 (0.96, 1.35)	1.14 (0.96, 1.35)	1.12 (0.94, 1.34)
Quintile 1 (Lowest SES)	5,144	260	1.07 (0.90, 1.27)	1.07 (0.90, 1.27)	1.04 (0.86, 1.26)
P_{trend}[c]			0.210	0.208	0.424

[a]Model 1: Adjusted for age, sex, race/ethnicity, marital status

[b]Model 2: Adjusted for all factors in Model 1, plus education and annual household income at baseline

[c] *P*-value associated with continuous area-level SES index

Table 2.3: Hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer mortality associated with quintiles of area-level socioeconomic status (SES)

Area-level SES	VITAL cohort N	Cancer deaths N	Age- and sex-adjusted HR (95% CI)	Model 1[a] Demographics only HR (95% CI)	Model 2[b] Demographics and individual SES HR (95% CI)
All respondents					
Women and men	60,756	2,487			
Quintile 5 (Highest SES)	12,145	354	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	12,249	421	1.18 (1.02, 1.37)	1.17 (1.01, 1.36)	1.06 (0.91, 1.23)
Quintile 3	12,018	507	1.40 (1.22, 1.60)	1.38 (1.20, 1.58)	1.18 (1.02, 1.36)
Quintile 2	12,180	553	1.51 (1.32, 1.73)	1.48 (1.30, 1.70)	1.20 (1.04, 1.38)
Quintile 1 (Lowest SES)	12,164	652	1.75 (1.53, 2.00)	1.68 (1.47, 1.93)	1.28 (1.11, 1.48)
P_{trend}[c]			<0.001	<0.001	<0.001
Women	30,095	1,062			
Quintile 5 (Highest SES)	5,810	139	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,974	179	1.22 (0.97, 1.53)	1.20 (0.95, 1.50)	1.10 (0.88, 1.40)
Quintile 3	5,787	204	1.41 (1.13, 1.75)	1.38 (1.11, 1.73)	1.22 (0.97, 1.54)
Quintile 2	6,158	245	1.54 (1.25, 1.91)	1.51 (1.22, 1.86)	1.27 (1.02, 1.59)
Quintile 1 (Lowest SES)	6,366	295	1.75 (1.43, 2.15)	1.67 (1.36, 2.06)	1.33 (1.06, 1.67)
P_{trend}[c]			<0.001	<0.001	0.006
Men	30,661	1,425			
Quintile 5 (Highest SES)	6,335	215	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	6,275	242	1.16 (0.96, 1.41)	1.15 (0.95, 1.40)	1.03 (0.85, 1.25)
Quintile 3	6,231	303	1.39 (1.16, 1.66)	1.38 (1.15, 1.65)	1.15 (0.96, 1.39)
Quintile 2	6,022	308	1.49 (1.25, 1.77)	1.49 (1.23, 1.75)	1.15 (0.95, 1.38)
Quintile 1 (Lowest SES)	5,798	357	1.75 (1.48, 2.08)	1.75 (1.43, 2.02)	1.24 (1.03, 1.50)
P_{trend}[c]			<0.001	<0.001	0.002
Participants diagnosed with cancer before baseline					
Women and men	8,557	979			
Quintile 5 (Highest SES)	1,657	152	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	1.612	162	1.15 (0.92, 1.44)	1.13 (0.91, 1.42)	1.01 (0.80, 1.27)
Quintile 3	1,670	197	1.30 (1.06, 1.60)	1.28 (1.04, 1.58)	1.10 (0.88, 1.37)
Quintile 2	1,775	216	1.38 (1.13, 1.69)	1.35 (1.10, 1.66)	1.09 (0.88, 1.35)
Quintile 1 (Lowest SES)	1,843	252	1.58 (1.30, 1.93)	1.54 (1.26, 1.87)	1.17 (0.94, 1.45)
P_{trend}[c]			<0.001	<0.001	0.137
Women	4,829	441			
Quintile 5 (Highest SES)	905	61	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	902	72	1.20 (0.85, 1.70)	1.18 (0.84, 1.68)	1.10 (0.77, 1.57)
Quintile 3	910	96	1.60 (1.15, 2.21)	1.57 (1.13, 2,18)	1.42 (1.01, 1.99)
Quintile 2	1,005	99	1.50 (1.09, 2.08)	1.45 (1.05, 2.01)	1.27 (0.90, 1.80)
Quintile 1 (Lowest SES)	1,107	113	1.54 (1.12, 2.11)	1.45 (1.06, 1.99)	1.19 (0.84, 1.67)
P_{trend}[c]			0.002	0.009	0.312
Men	3,728	538			
Quintile 5 (Highest SES)	752	91	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	710	90	1.11 (0.82, 1.50)	1.10 (0.81, 1.48)	0.93 (0.69, 1.27)
Quintile 3	760	101	1.10 (0.83, 1.44)	1.09 (0.83, 1.44)	0.89 (0.66, 1.19)
Quintile 2	770	117	1.30 (0.99, 1.70)	1.27 (0.97, 1.67)	0.96 (0.72, 1.28)
Quintile 1 (Lowest SES)	736	139	1.64 (1.26, 2.15)	1.65 (1.26, 2.17)	1.17 (0.87, 1.57)
P_{trend}[c]			<0.001	<0.001	0.304
Participants not diagnosed with cancer before baseline					

Women and men	52,199	1,508			
Quintile 5 (Highest SES)	10,488	202	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	10,637	259	1.25 (1.03, 1.52)	1.24 (1.02, 1.50)	1.13 (0.93, 1.38)
Quintile 3	10,348	310	1.48 (1.24, 1.77)	1.47 (1.23, 1.76)	1.28 (1.06, 1.53)
Quintile 2	10,405	337	1.60 (1.34, 1.91)	1.58 (1.32, 1.89)	1.29 (1.07, 1.56)
Quintile 1 (Lowest SES)	10,321	400	1.87 (1.57, 2.23)	1.81 (1.52, 2.16)	1.40 (1.16, 1.69)
P_{trend}[c]			<0.001	<0.001	<0.001
Women	25,266	621			
Quintile 5 (Highest SES)	4,905	78	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,072	107	1.27 (0.93, 1.73)	1.25 (0.92, 1.71)	1.16 (0.85, 1.59)
Quintile 3	4,877	108	1.30 (0.97, 1.75)	1.28 (0.95, 1.73)	1.13 (0.83, 1.54)
Quintile 2	5,153	146	1.60 (1.20, 2.13)	1.58 (1.19, 2.09)	1.33 (0.98, 1.81)
Quintile 1 (Lowest SES)	5,259	182	1.90 (1.43, 2.51)	1.83 (1.38, 2.42)	1.47 (1.09, 1.99)
P_{trend}[c]			<0.001	<0.001	0.009
Men	26,933	887			
Quintile 5 (Highest SES)	5,583	124	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	5,565	152	1.24 (0.98, 1.57)	1.24 (0.98, 1.57)	1.12 (0.88, 1.43)
Quintile 3	5,471	202	1.60 (1.28, 2.00)	1.59 (1.27, 1.99)	1.36 (1.08, 1.72)
Quintile 2	5,252	191	1.60 (1.28, 2.01)	1.58 (1.26, 1.98)	1.26 (0.99, 1.61)
Quintile 1 (Lowest SES)	5,062	218	1.85 (1.49, 2.30)	1.78 (1.43, 2.21)	1.34 (1.05, 1.69)
P_{trend}[c]			<0.001	<0.001	0.001

[a]Model 1: Adjusted for age, race/ethnicity, marital status and for sex in models including both men and women

[b]Model 2: Adjusted for all factors in Model 1, plus education and annual household income

[c] P-value associated with continuous area-level SES index

CHAPTER 3: Contribution of health behaviors to the association between area-level socioeconomic status and cancer mortality

Abstract

Background: Area-level socioeconomic status (SES) is increasingly recognized as an important predictor of health outcomes; however, its association with cancer mortality is not established and mediators of the association between area-level factors and health outcomes are not well understood. The purpose of this study is to quantify the association between area-level SES and cancer mortality and to identify whether and to what extent behaviors mediate the association.

Methods: Participants included 54,736 men and women ages 50-76 who were recruited into the VITamins And Lifestyle (VITAL) Study cohort and who had no history of cancer at baseline between 2000-2002. We identified the census block groups of participants and constructed an SES index using data from the 2000 U.S. Census. Cox proportional hazards models were used to estimate the association between quintile of area-level SES and cancer deaths (n = 1,488) tracked through the Washington State death file over 7.7 years of follow-up. We tested whether eight modifiable risk factors (e.g. body mass index, physical activity, diet, alcohol, smoking, screening) mediated the association between area-level SES and cancer mortality.

Results: Cancer mortality was 77% higher in participants living in areas in the lowest quintile of area-level SES compared to participants living in areas in the highest quintile of area-level SES (hazard ratio (HR): 1.77, 95% confidence interval (CI): 1.50, 2.11). Adding individual-level modifiable risk factors into the models reduced the association by 45% (95% CI: -72%, -15%). In models controlling for individual education and income, area-level SES remained associated with cancer mortality (HR for highest vs. lowest quintile of area-level SES: 1.37, 95% CI: 1.14, 1.65) and adding modifiable risk factors reduced the association by 37% (95% CI: -93%, 22%). Smoking, screening and physical activity explained the largest proportion of the association.

Conclusions: Low area-level SES is associated with increased cancer mortality. This association persists after accounting for individual education and income and is partially explained by behavior, particularly smoking, physical activity and screening.

Introduction

Area-level socioeconomic status (SES) is recognized as an important predictor of health outcomes.[8] Measures of area-level SES, including incomes, home values, employment characteristics and educational attainment of area residents have been associated with a range of health outcomes[2,4,7-9,37] including cancer risk[14-16] and cancer mortality.[29,84]

Although research into area-level effects on health is becoming more common, less is known about which features of areas affect health and how.[22,23,85] The association between area-level SES and health outcomes could be due to compositional effects such that poorer people live in poorer areas and that individual SES is associated with risk factors for disease regardless of location. On the other hand, area-level SES could influence health through contextual effects such as environmental exposures, resources and social characteristics of areas which operate independently of individual characteristics. In reality, associations between area-level SES and health outcomes are likely explained by both compositional and contextual factors, but conceptual frameworks explaining how areas affect health are still being developed.[22]

At least part of the association between area-level SES and health outcomes could be due to differences in health behaviors. Area-level socioeconomic factors have been associated with several chronic disease risk factors, including diet, body weight, smoking, alcohol consumption, sedentary behaviors and screening.[19,21,32-37,85] These risk factors have been found to at least partially explain associations between individual socioeconomic factors and health outcomes[86,87] and total[88-94] and cause-specific mortality,[88,93-96] but much less is known about the extent to which modifiable risk factors might explain associations between area-level SES and health outcomes. Results of previous studies suggest that diet, physical activity, smoking and body mass index (BMI) each explained 9-15% of the association between area-level SES and

colorectal cancer incidence[97] and that the association between area-level SES and rectal cancer risk is partially mediated by BMI and multivitamin use.[14] However, prior studies have not attempted to identify behaviors that could explain the association between area-level SES and cancer mortality.

The purpose of this paper was to estimate the association between area-level socioeconomic status and cancer mortality, and to identify whether and to what extent modifiable risk factors explain (mediate) the observed association. Eight modifiable factors were selected as potential mediators. Six (BMI, physical activity, dietary energy density, fruit and vegetable consumption, red and processed meat intake, and alcohol consumption) were identified from the cancer prevention recommendations of the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR).[25] Two additional behaviors were also considered based on their associations with cancer incidence and mortality (pack-years of smoking[26] and cancer screening behaviors including colonoscopy or sigmoidoscopy, mammography in women and prostate-specific antigen (PSA) testing in men[29,31,84]).

Two analysis approaches were taken. The aim of the first approach was to identify modifiable behaviors that help explain the overall association between area-level SES and cancer mortality in a model that did not control for individual socioeconomic status. Behaviors identified as potential mediators in these analyses could help inform future interventions to reduce the disparity between low- and high-SES areas in cancer deaths, whether those behaviors were influenced by the people living in low SES areas (compositional effects) or by characteristics of the areas themselves (contextual effects). The second approach controlled for individual-level education and income when assessing the association between area-level SES and cancer mortality and identifying behaviors that could mediate this association. The aim of

this approach was to identify behaviors that could mediate the association between area-level SES and cancer mortality, independent of the compositional effects of individual SES.

Methods

Study Cohort

The VITamins And Lifestyle (VITAL) study is a prospective cohort study designed to investigate the associations of use of dietary supplements and other behaviors with cancer risk and mortality. It has previously been described in detail.[61] Women and men were eligible to join the cohort if they were between the ages of 50 and 76 and lived in one of the 13 counties included in the Western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry at baseline.

Using names purchased from a commercial mailing list, baseline questionnaires were mailed to 364,418 men and women between October, 2000 and December, 2002 and were followed two weeks later by reminder postcards. A total of 79,300 questionnaires were returned, of which 77,719 passed quality control checks. Overall, 54,736 men and women were included in the current analysis after excluding the following: respondents with a history of cancer other than nonmelanoma skin cancer (n = 11,259) or whose history of cancer was unknown (n = 214) and respondents whose baseline addresses were post office boxes (n = 1,137) or whose baseline addresses could not be geocoded (n = 381). Respondents missing data for one or more potential mediators were also excluded, including 3,861 missing height or weight, 1,093 missing metabolic equivalent task units (METs) of physical activity, 7,182 with incomplete diet data or whose reported energy intake was too high or too low, 934 missing pack-years of smoking, and 1,686 missing data on screening behaviors (numbers of exclusions reported are not mutually exclusive). Participants missing either individual educational attainment or annual household

income remained in the analysis, but 977 respondents were excluded for missing both items. Additionally, the first year of follow-up (including 43 cancer deaths and 531 persons with other censoring events among those with no history of cancer at baseline), was excluded to avoid potential reverse causality.

Area-level Socioeconomic Status

Respondents' baseline addresses were geocoded using GPS Visualizer and Yahoo! Maps. A 1% sample of addresses was geocoded again using Google Maps and more than 95% of the addresses in the validation sample were geocoded within 400 meters of one another using the two methods. Addresses were used to identify respondents' census block groups using TIGER/Line shapefiles for the 2000 Census in ArcMap 10 (Esri, Redlands, CA). In a previous review of geocoding accuracy, 96% of a sample of geocodable addresses were placed in the correct block groups.[80] Census block groups typically contain between 600 and 3,000 residents, with an optimal population of 1,500. They do not cross county, state or census tract boundaries and most were delineated with input from local participants.[81]

Area-level socioeconomic status was measured using a method previously developed by Diez-Roux et al.[82] Information from the 2000 Census was used to create an index based on the income, education and employment characteristics of respondents' block groups. This index includes the log of median value of owner-occupied housing units; log of median household income; percent of households receiving net rental, interest or dividend income; percent of adults ages 25 and older who completed high school; percent of adults ages 25 and older who completed college; and percent of employed persons ages 16 and older in professional and managerial occupations. The standardized z-score was calculated for each variable based on the 3,346 block groups in the 13 counties included in the Western Washington SEER registry and

then summed to create an index such that higher values corresponded with lower area-level SES. An index using these variables has been used previously to examine associations between area-level socioeconomic status and several cardiovascular[2,4,6,9] and other outcomes[3,5,21] as well as in a previous study attempting to identify behaviors that explained the association between area-level SES and colon and rectal cancer risk.[14] Index values of participants included in these analyses ranged from -16.1 to 16.7 with a median value of -1.2 and a mean of -1.5.

Data collection

Sex-specific baseline questionnaires included information on smoking, self-reported height and weight, physical activity, cancer screening behaviors, medical history, and diet. Physical activity was assessed by a one-page questionnaire covering participation in 14 types of activities over the past 10 years, including years and days per week, plus intensity for walking. Diet was assessed by a 126-item food frequency questionnaire (FFQ) covering diet in the year before baseline. The FFQ was adapted from the questionnaire developed for use in the Women's Health Initiative and other studies and the measurement properties of earlier versions of the FFQ have been published previously.[62] The University of Minnesota's Nutrition Coding Center database was used to convert food frequency information into nutrients, and numbers of servings were based on the sex-specific medium portion size of each food and beverage.[63]

This research was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Health Behaviors

Data on participants' health behaviors were taken from the VITAL baseline questionnaires. BMI (kg/m^2) was calculated using respondents' self-reported height and weight at baseline. Physical activity was assessed using a continuous measure of average MET-hours per week over the 10 years prior to baseline from moderate or fast walking and moderate or

strenuous physical activity. Energy density was calculated by dividing the energy (kcal) of foods consumed by the estimated weight (grams) of those foods. Beverages were excluded from the energy density calculations. Daily servings of fruits and vegetables included 25 foods and food groups, adjusted by portion size and by summary questions on total numbers of fruits and vegetables eaten to reduce over-estimation by participants and excluded fruit juices and potatoes. Ounces of red and processed meat consumed per week were estimated by multiplying the adjusted weekly frequencies of consumption of red or processed meat (including from mixed dishes) by sex-specific grams of meat per serving. Alcohol consumption was measured in drinks per day where a drink was classified as a 12-ounce bottle or can of beer; 4-ounce glass of red, white or rosé wine; or one shot (1.5 ounces) of liquor or one mixed drink. Pack-years of smoking was the product of respondents' reports of the average number of cigarettes smoked per day and total years smoked. For screening behaviors, women were asked whether they received a mammogram and men were asked whether they received a PSA test within the two years before baseline. Both women and men were asked whether they received a sigmoidoscopy or colonoscopy in the ten years before baseline.

Case Ascertainment and Censoring

Deaths due to cancer were ascertained through December 31, 2010 by annual linkage with the Washington State death file. Linkage between VITAL and the death file is largely automated and based on ranking agreement between items common to both sets of data, such as Social Security number, name, and date of birth. Matches with high concordance were linked automatically whereas visual inspection was used to adjudicate incomplete matches. After excluding the first year of follow-up, a total of 1,488 cancer deaths were identified in an average of 7.7 years of follow-up.

Participants who did not die of cancer in Washington State were right-censored at the date of the earliest of the following events: date they requested removal from the study (n = 14), date they moved out of Washington State (n = 2,757), date of death due to other causes (n = 2,295), or December 31, 2010 (n = 48,182). Moves out of Washington State were identified through linkage with the National Change of Address System.

Statistical Analyses

Hazard ratios (HRs) and 95% confidence intervals (CIs) of death due to cancer associated area-level SES were estimated using Cox proportional hazards models with area-level SES categorized into quintiles. The test for trend by area-level SES and the mediation effects (described below) were based on the continuous area-level SES index. In all models of the association between quintiles of area-level SES and cancer mortality, cancer mortality increased monotonically with decreasing area-level SES (Supplementary Table A). We used participant age as the time scale, with participants entering the analysis at their age one year after completing the baseline questionnaire and exiting at age at death due to cancer or age at censoring event, as described above. Proportional hazards assumptions were examined using scaled Schoenfeld residuals. No significant ($p<0.05$) deviations from proportionality were observed when examining the area-level SES index. All statistical tests were two-sided.

Multivariate analyses included categorical variable adjustment for potential confounders selected *a priori*, including sex, race/ethnicity (white, Hispanic, African-American, American Indian/Alaska Native, Asian/Pacific Islander, other/missing), marital status (married, living with partner, never married, separated/divorced, widowed), and cancers diagnosed in first-degree relatives (0, 1, 2+) (Model 1). Models further controlling for individual SES included adjustment for education (high school graduate/GED or below, some college/technical school, college

graduate, advanced degree) and household income (<$20,000, $20,000-39,999, $40,000-59,999, $60,000-79,999 and $80,000 or more) (Model 2). Participants with missing data were treated as their own category for each potential confounder, including participants missing data on individual education or household income.

Mediation was assessed by first modeling the direct effect of area-level SES on cancer mortality in a model controlling for Model 1 covariates (age, sex, race/ethnicity, marital status and family history of cancer) and then modeling the indirect effects of area-level SES in models adding each of the potential mediators one at a time. The proportion mediated was calculated by dividing the difference between the direct and indirect effects by the direct effect ($\beta_{\text{Model 1 + health behavior}} - \beta_{\text{Model 1}}$) / ($\beta_{\text{Model 1}}$) in models treating area-level SES as a continuous variable. This approach to mediation analysis is equivalent to the product of coefficients method commonly used in the social sciences when both the mediator and outcome are continuous in linear regression.[98] The two methods are also approximately equivalent in Cox models with a rare outcome.[99] The proportion mediated is presented here because it is more easily interpretable than the product of coefficients approach.

Additional analyses were conducted in order to identify the subset behaviors that mediated the largest proportion of the association between area-level SES and cancer mortality via non-overlapping pathways. Each potential mediator was added sequentially to the direct effects model, beginning with the behavior that mediated the largest proportion of the association between area-level SES and cancer mortality and then adding the behavior that mediated the next largest proportion and so on until the addition of a subsequent behavior resulted in less than a three percentage point increase in the total proportion mediated by the behaviors in the model. Finally all health behaviors (regardless of evidence of mediation) were included in one model.

These models were then repeated with additional adjustment for education and household income (Model 2). Ninety-five percent confidence intervals around the proportion of the association between area-level SES and cancer mortality were calculated by using a bias-corrected bootstrap procedure with 2000 replications and including re-sampling.[100]

Statistical analyses were conducted using Stata 12.1 (StataCorp LP, College Station, TX). All models of area-level SES and cancer mortality utilize the cluster option in Stata to obtain standard errors that account for correlation among residents of the same block groups. This option was selected over shared frailty models that model the correlation between observations in the same block groups because the correlation itself was not of interest.

Results

Table 3.1 presents baseline characteristics of the study population as well as the health behaviors considered as potential mediators of the association between area-level SES and cancer mortality. Compared to participants who lived in higher-SES areas, residents of lower-SES areas were older, and a lower proportion was male, white, college-educated and had annual household incomes of at least $40,000. A socioeconomic gradient is evident for all of the health behaviors considered, such that living in lower-SES areas was associated with higher BMI and several adverse health behaviors including higher dietary energy density, consumption of red and processed meat, and pack-years of smoking and lower moderate or strenuous physical activity, fruit and vegetable consumption, and receipt of mammograms, PSA tests and colonoscopy or sigmoidoscopy. Living in lower-SES areas was associated with one positive health behavior; decreased alcohol intake.

Table 3.2 gives beta coefficients and 95% confidence intervals of the association between continuous area-level SES index and each of the individual health behaviors considered as

potential mediators controlling for demographic factors (age, sex, race/ethnicity, marital status and family history of cancer) (Model 1a) and additionally controlling for demographic factors and each of the other health behaviors (Model 1b), demographic factors and individual SES (Model 2a), and demographic factors, health behaviors and individual SES simultaneously (Model 2b). In Model 1a, decreasing area-level SES was associated with increases in BMI and negative health behaviors including dietary energy density, red and processed meat intake and pack-years of smoking. Decreases in area-level SES were also associated with lower levels of positive health behaviors including physical activity, fruit and vegetable consumption, and cancer screening. Lower area-level SES was also associated with lower alcohol intake. These associations were attenuated by 32-87% after also controlling for the other potential mediators and individual SES (Models 1a and 2b), but area-level SES remained associated with each of these modifiable risk factors except for mammography and PSA screening.

Table 3.3 presents associations between the modifiable risk factors considered and cancer mortality. Increasing BMI, energy density, alcohol consumption and smoking were all positively associated with cancer mortality, while physical activity, fruit and vegetable consumption, mammography, PSA screening and sigmoidoscopy or colonoscopy were inversely associated. The hazard ratios changed very little across models with different sets of covariates.

A socioeconomic gradient was evident in cancer mortality (Table 3.4). Compared with residents of areas in the highest quintile of SES, residents of areas in quintiles 1-4 had between a 35% and 77% increased risk of cancer mortality after adjusting for age, sex, race/ethnicity, marital status and family history of cancer (HR for quintile 5 vs. quintile 1: 1.77, 95% CI: 1.50, 2.11; $P_{trend} < 0.001$). The increased risk associated with living in lower-SES areas attenuated after adding individual educational attainment and annual household income to the adjusted

models; however, 23-37% increases in cancer mortality remained for each of the lower four quintiles of area-level SES compared with the highest-SES areas (HR for quintile 5 vs. quintile 1: 1.37, 95% CI: 1.14, 1.65; $P_{trend} < 0.001$).

Results of models examining the mediating role of cancer-related health behaviors in the association between area-level SES and cancer mortality are presented in Table 3.5. In comparison to the model without any health behaviors included, the percent decrease in beta for the effect of area-level SES can be interpreted as the proportion mediated by each health behavior.[101] When individual health behaviors were added to this model, pack-years of smoking attenuated this association most substantially, reducing the hazard ratio associated with living in the lowest-SES areas from 1.77 to 1.50 (95% CI: 1.26, 1.79) and reducing the beta coefficient associated with continuous area-level SES index by 29% (95% CI: -57%, -1%). Physical activity attenuated the association between area-level SES and cancer mortality by 10%, screening by 9%, fruit and vegetable consumption by 6%, and BMI and intake of red and processed meats by 5% each; however, none of the bootstrapped 95% confidence intervals for the percent change excluded zero.

In forward selection models when physical activity was added to the model including only pack-years of smoking, 35% of the association between area-level SES and cancer mortality was explained (up from 29% when including pack-years only) (Table 3.5). Further adding screening explained 41%. Adding additional behaviors increased the proportion explained by less than 3 percentage points. After controlling for smoking, screening and physical activity, living in the lowest-SES areas was associated with a 41% increase in cancer mortality relative to the highest-SES areas (HR: 1.41, 95% CI: 1.18, 1.69).When all health behaviors considered were included in one model, the association between continuous area-level SES index and cancer

mortality was reduced by 45% (95% CI: -72%, -15%) and the hazard ratio associated with living in the lowest- (vs. highest-) SES areas was 1.38 (95% CI: 1.16, 1.64).

To understand which behaviors mediate the association between area-level SES and cancer mortality independent of the compositional effects of individual-level SES, we analyzed a model (Model 2) adding individual educational attainment and annual household income to the other covariates in Model 1. In these models smoking explained 23% of the remaining association between area-level SES and cancer mortality after accounting for individual SES, while screening, physical activity, red and processed meat intake and BMI each explained 5-8%. In sequential addition models, pack-years of smoking and screening explained 31% of the association (up from 23% explained by smoking alone). Further adding physical activity explained 34%. After controlling for smoking, screening and physical activity, the HR associated with living in the lowest-SES areas relative to the highest-SES areas was 1.23 (1.02, 1.48). No other additional behavior led to at least a 3 percentage point increase in the proportion explained.

The inclusion of all potential mediators in the same model with individual education and income resulted in a hazard ratio reduction to 1.22 (95% CI: 1.02, 1.48) for residents of the lowest-SES areas compared to the highest-SES areas and a 37% reduction in the association between continuous area-level SES and cancer mortality.

Discussion

The purpose of this study was to quantify the association between area-level SES and cancer mortality and to identify modifiable risk factors that contribute to the association. In analyses not controlling for individual education and income, a socioeconomic gradient exists such that living in the lowest-SES areas is associated with a 77% increase in cancer mortality

compared with the highest-SES areas. When individual SES was accounted for, the excess risk for lower-SES areas was reduced to 37%.

Previous studies have reported associations between area-level SES and total and cause-specific mortality.[7,71,102-104] Ecologic evidence suggests an association between county-level SES and cancer mortality,[71,104] but a previous study examining area-level SES and cancer mortality found no association in women and an association in men in age-adjusted models that was no longer evident after controlling for educational attainment and other demographic factors and health behaviors.[103] In contrast, we have demonstrated an association between area-level SES and cancer mortality above and beyond individual socioeconomic and other risk factors.

Several possibilities have been proposed to explain the association between area-level SES and health outcomes, including both compositional effects including demographic and socioeconomic characteristics of those who live in an area and contextual effects such as the physical environment, social factors, and neighborhood resources and services.[105] Both compositional and contextual factors would influence health behaviors of the individuals who live in an area; however, little previous research has attempted to identify the specific health behaviors that could explain the relationship between area-level SES and cancer outcomes.[14,97] A recent report suggests that diet, BMI, physical activity and smoking account for approximately 36% of the observed association between area-level SES and colorectal cancer risk,[97] and a previous study found that BMI and multivitamin use partially explained the association between area-level SES and rectal cancer risk among women.[14] To our knowledge, we are the first to conduct a similar study regarding cancer mortality.

Models with and without adjustment for individual education and income identified smoking, physical activity and screening as the behaviors that explained the largest proportion of

the association between area-level SES and cancer mortality. Pack-years of smoking explained the majority of the area-level SES gradient in cancer mortality in both approaches. Screening and physical activity explained 7-10% of the association; while BMI explained 5% and the three dietary behaviors considered (energy density, fruit and vegetable intake, and consumption of red and processed meats) each accounted for 2-6% of the association. Our results suggest that differences in alcohol use do not explain the relationship between living in lower-SES areas and higher cancer mortality—the association between area-level SES and cancer mortality actually increased when controlling for alcohol consumption.

Individual SES and health behaviors both account for some, but not all, of the association between area-level SES and cancer mortality. The attenuation of the association between area-level SES and cancer mortality when individual income and education are added to the models suggests that some of the effect is compositional; however, even after accounting for age, race, gender, individual SES, and eight modifiable risk factors, cancer mortality remains higher in residents of low-SES areas. This remaining association could be due at least in part to mediation by factors not included in the models, such as access to health care or contextual features of the areas such as environmental exposures that could influence cancer mortality directly and not through the behaviors considered here. This remaining association could also be due to measurement error in individual education or household income. To the extent these variables were measured with error their effects would not be fully removed, and residual confounding by individual education and income would lead to insufficient control for those compositional factors and the remaining observed associations between area-level SES and cancer incidence and mortality (Model 2) would be biased away from the null. Measurement error in the modifiable risk factors as measured at baseline is unlikely to be associated with future health

outcomes and would lead to non-differential misclassification of those potential mediators with respect to cancer mortality and an underestimation of the proportion of the association they explain assuming that the measured mean values of those behaviors increased monotonically with the true values.[66] Another limitation of this study is that the sample was drawn from one region of the United States and included predominantly white respondents, which may limit its generalizability to other populations.

This study also features several important strengths including its large sample size and prospective design. The detailed information collected at baseline allowed us to successfully geocode almost all respondents; to examine several individual-level modifiable risk factors as potential mediators of the association between area-level SES and cancer mortality; to adjust for individual income and education; and to control for several potential confounding factors. Linkage with the Washington State death file provided accurate and near-complete ascertainment of cancer mortality outcomes in this population. Excluding the first year of follow-up reduced the possibility that our results could be due to reverse causality such that pre-diagnosis cancer symptoms could lead to changes in some of the behaviors considered here; however, our results did not differ in sensitivity analyses that did not exclude the first year of follow-up. Additionally, in our analyses we controlled for two measures of individual SES (annual household income and individual educational attainment), reducing the potential for residual confounding that exists when including only one measure of individual SES.[106] A previous review of multilevel studies of area-level socioeconomic context and health outcomes found that studies including more than one measure of individual-level SES reported smaller measures of association than studies including only one measure of individual SES.[79]

Substantial socioeconomic disparities exist such that living in lower-SES areas is associated with higher cancer mortality. Our results suggest that several behaviors, particularly smoking, physical activity, and cancer screening could be effective targets of interventions aimed at reducing these disparities, and that area-level SES remains associated with cancer mortality even after accounting for several modifiable risk factors as well as individual education and income.

Table 3.1: Baseline demographic factors and health behaviors by area-level socioeconomic status (SES)

	Area-level SES[a]				
	Quintile 1 (High SES) (N = 10,971)	**Quintile 2** (N = 10,921)	**Quintile 3** (N = 10,950)	**Quintile 4** (N = 10,919)	**Quintile 5 (Low SES)** (N = 10,975)
Demographic factors					
Age, mean (SD)	60.6 (7.1)	60.9 (7.3)	61.3 (7.2)	61.4 (7.3)	61.7 (7.4)
Male, %	51.8	51.0	51.0	49.7	48.0
White, %	94.1	94.4	94.8	93.6	91.9
College degree, %	68.4	52.5	43.0	32.7	24.7
Annual household income of at least $40,000, %	88.5	80.9	75.7	67.0	57.3
Health behaviors					
Body mass index (kg/m^2), mean (SD)	26.2 (4.5)	27.1 (4.9)	27.5 (5.1)	28.0 (5.3)	28.4 (5.6)
Moderate/strenuous activity (MET-hours/week), mean (SD)	11.4 (14.4)	9.5 (13.5)	8.4 (12.9)	7.4 (11.9)	6.6 (11.4)
Energy density (kcal/g), mean (SD)	1.69 (0.44)	1.73 (0.48)	1.76 (0.48)	1.78 (0.53)	1.81 (0.54)
Fruits and vegetables (servings/day), mean (SD)[a]	4.2 (2.5)	3.9 (2.4)	3.7 (2.4)	3.6 (2.4)	3.4 (2.4)
Red and processed meat (ounces/week), mean (SD)	17.9 (14.7)	19.3 (15.9)	20.4 (16.3)	21.1 (16.8)	21.4 (17.5)
Alcohol (drinks/week), mean (SD)	6.1 (8.7)	5.1 (8.5)	4.7 (8.4)	4.3 (8.4)	3.8 (8.5)
Smoking (pack-years), mean (SD)	9.1 (16.9)	12.1 (19.8)	13.3 (20.7)	14.4 (21.6)	16.5 (23.6)
Mammogram in previous 2 years (women only), %	93.6	92.0	91.5	90.6	89.4
Prostate-specific antigen test in previous 2 years (men only), %	75.5	73.2	70.1	69.1	71.9
Colonoscopy or sigmoidoscopy in previous 10 years, %	61.2	57.4	54.7	52.9	55.5

[a]Fruit and vegetable servings exclude potatoes and fruit juice

Table 2: Beta coefficients and 95% confidence intervals (CIs) of health behaviors associated with decreasing area-level SES index

	Model 1a[a] Demographics only	**Model 1b**[b] Demographics and other health behaviors	**Model 2a**[c] Demographics and individual SES	**Model 2b**[d] Demographics, individual SES and other health behaviors
Health behaviors	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Body mass index (per kg/m^2)	0.161 (0.1525, 0.171)	0.110 (0.100, 0.119)	0.122 (0.111, 0.132)	0.092 (0.082, 0.101)
Moderate/strenuous activity (per 5 MET-hours/week)	-0.354 (-0.378, -0.329)	-0.162 (-0.186, -0.139)	-0.181 (-0.207, -0.156)	-0.075 (-0.099, -0.050)
Energy density (per kcal/g)	0.0089 (0.0081, 0.0098)	0.0027 (0.0020, 0.0034)	0.0035 (0.0026, 0.0044)	0.0012 (0.0004, 0.0019)
Fruits and vegetables (per serving/day)[c]	-0.056 (-0.061, -0.052)	-0.021 (-0.025, -0.018)	-0.025 (-0.030, -0.020)	-0.011 (-0.015, -0.007)
Red and processed meat (per 5 ounces/week)	0.311 (0.285, 0.338)	0.158 (0.131, 0.184)	0.223 (0.194, 0.251)	0.135 (0.107, 0.163)
Alcohol (per drink/day)	-0.022 (-0.025, -0.020)	-0.022 (-0.024, -0.020)	-0.016 (-0.019, -0.014)	-0.015 (-0.017, -0.013)
Smoking (per 10 pack-years)	0.486 (0.450, 0.522)	0.379 (0.343, 0.415)	0.200 (0.161, 0.239)	0.163 (0.124, 0.202)
Mammogram in previous 2 years (vs. none; women only, N=27,213)	-0.039 (-0.048, -0.030)	-0.022 (-0.032, -0.013	-0.018 (-0.028, -0.008)	-0.008 (-0.018, 0.002)
Prostate-specific antigen test in previous 2 years (vs. none; men only, N=27,523)	-0.029 (-0.035, -0.023)	-0.013 (-0.019, -0.007)	-0.014 (-0.020, -0.007)	-0.006 (-0.012, 0.0008)
Colonoscopy or sigmoidoscopy in previous 10 years (vs. none)	-0.037 (-0.041, -0.033)	-0.029 (-0.033, -0.025)	-0.023 (-0.028, -0.019)	-0.021 (-0.025, -0.016)

All models utilize the cluster option to account for correlation between respondents living in the same block groups and include 54,376 respondents unless otherwise noted. Area-level SES is treated as a continuous variable.

[a]Model 1a: Adjusted for age, sex, race/ethnicity, marital status, family history of cancer.

[b]Model 1b: Adjusted for Model 1a covariates and each of the other health behaviors considered.

[c]Model 2a: Adjusted for Model 1a covariates, individual education and annual household income.

[d]Model 2b: Adjusted for Model 1a covariates, individual education and annual household income and each of the other health behaviors considered.

[e]Fruit and vegetable servings exclude potatoes and fruit juice

Table 3.3: Hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer mortality associated with health behaviors

Health behaviors	**Model 1a**[a] Demographics only HR (95% CI)	**Model 1b**[b] Demographics and area-level SES HR (95% CI)	**Model 2a**[c] Demographics and individual SES HR (95% CI)	**Model 2b**[d] Demographics, area-level and individual SES HR (95% CI)
Body mass index (per 5 kg/m^2)	1.10 (1.05, 1.16)	1.08 (1.02, 1.14)	1.06 (1.01, 1.12)	1.06 (1.00, 1.11)
Moderate/strenuous activity (per 5 MET-hours/week)	0.92 (0.89, 0.94)	0.93 (0.90, 0.95)	0.94 (0.91, 0.96)	0.94 (0.91, 0.97)
Energy density (per kcal/g)	1.25 (1.16, 1.34)	1.22 (1.15, 1.31)	1.18 (1.09, 1.28)	1.17 (1.09, 1.26)
Fruits and vegetables (per serving/day)[c]	0.95 (0.92, 0.97)	0.95 (0.93, 0.98)	0.97 (0.95, 0.99)	0.97 (0.95, 1.00)
Red and processed meat (per 5 ounces/week)	1.04 (1.03, 1.06)	1.04 (1.02, 1.05)	1.03 (1.02, 1.05)	1.03 (1.02, 1.05)
Alcohol (per drink/day)	1.02 (0.98, 1.07)	1.04 (1.00, 1.08)	1.04 (1.00, 1.08)	1.04 (1.00, 1.09)
Smoking (per 10 pack-years)	1.21 (1.19, 1.23)	1.20 (1.18, 1.22)	1.19 (1.17, 1.21)	1.19 (1.17, 1.21)
Mammogram in previous 2 years (vs. none; women only)[f]	0.58 (0.46, 0.72)	0.59 (0.47, 0.74)	0.61 (0.49, 0.77)	0.62 (0.49, 0.77)
Prostate-specific antigen test in previous 2 years (vs. none; men only)[g]	0.61 (0.53, 0.71)	0.63 (0.54, 0.74)	0.65 (0.56, 0.76)	0.66 (0.56, 0.76)
Colonoscopy or sigmoidoscopy in previous 10 years (vs. none)	0.73 (0.66, 0.81)	0.75 (0.68, 0.84)	0.77 (0.70, 0.86)	0.78 (0.70, 0.87)

All models include 54,736 respondents, of which 1,488 are cancer deaths, unless otherwise noted.

[a]Model 1a: Adjusted for age, sex, race/ethnicity, marital status, family history of cancer.

[b]Model 1b: Adjusted for Model 1a covariates and area-level SES index and includes the cluster option to account for correlation between respondents in the same block group.

[c]Model 2a: Adjusted for Model 1a covariates, individual education and annual household income.

[d]Model 2b: Adjusted for Model 1a covariates, area-level SES index, individual education and annual household income and includes the cluster option to account for correlation between respondents in the same block group.

[e]Fruit and vegetable servings exclude potatoes and fruit juice

[f]Model includes 27,213 women, of which 647 are cancer deaths

[g]Model includes 27,523 men, of which 841 are cancer deaths

Table 3.4: Hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer mortality associated with quintiles of area-level socioeconomic status (SES)

Area-level SES	**Cohort** (N = 54,736)	**Cancer deaths** (N = 1,488)	**Age- and sex-adjusted** HR (95% CI)	**Model 1**[a] Demographics only HR (95% CI)	**Model 2**[b] Demographics and individual SES HR (95% CI)
Quintile 5 (Highest SES)	10,971	198	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quintile 4	10,921	271	1.36 (1.13, 1.64)	1.35 (1.12, 1.62)	1.23 (1.02, 1.48)
Quintile 3	10,950	299	1.46 (1.23, 1.74)	1.45 (1.21, 1.73)	1.26 (1.05, 1.51)
Quintile 2	10,919	336	1.64 (1.38, 1.95)	1.62 (1.36, 1.93)	1.32 (1.10, 1.59)
Quintile 1 (Lowest SES)	10,975	384	1.83 (1.55, 2.17)	1.77 (1.50, 2.11)	1.37 (1.14, 1.65)
P-value for trend associated with quintiles of area-level SES index			<0.001	<0.001	0.002
P-value for trend associated with continuous area-level SES index			<0.001	<0.001	<0.001

All models include the cluster option to account for correlation between respondents in the same block group.
[a]Model 1: Adjusted for age, sex, race/ethnicity, marital status, family history of cancer.
[b]Model 2: Adjusted for all factors in Model 1, plus education and annual household income

Table 5: Role of health behaviors in explaining the association between area-level socioeconomic status (SES) and cancer mortality

	Model 1[a] Demographics only		**Model 2**[b] Demographics and individual SES	
	Q1 vs. Q5 HR (95% CI)[c]	**Percent change in *β*** **(**95% CI)[d]	**Q1 vs. Q5** HR (95% CI)[c]	**Percent change in *β*** (95% CI)[e]
Model 1 or 2, covariates only	1.77 (1.50, 2.11)	--	1.37 (1.14, 1.65)	--
Plus body mass index	1.72 (1.45, 2.05)	-5 (-33, 21)	1.35 (1.12, 1.62)	-5 (-51, 62)
Plus physical activity	1.68 (1.41, 1.99)	-10 (-37, 18)	1.34 (1.12, 1.62)	-7 (-52, 62)
Plus energy density	1.73 (1.46, 2.06)	-4 (-33, 22)	1.36 (1.13, 1.64)	-2 (-50, 64)
Plus fruits and vegetables[f]	1.72 (1.44, 2.04)	-6 (-36, 19)	1.36 (1.13, 1.63)	-3 (-54, 62)
Plus red and processed meat	1.73 (1.45, 2.05)	-5 (-35, 19)	1.34 (1.12, 1.62)	-6 (-60, 54)
Plus alcohol	1.79 (1.51, 2.13)	2 (-25, 30)	1.38 (1.15, 1.66)	3 (-41, 72)
Plus pack-years of smoking	1.50 (1.26, 1.79)	-29 (-57, -1)	1.27 (1.06, 1.53)	-23 (-77, 38)
Plus screening[g]	1.70 (1.43, 2.01)	-9 (-36, 18)	1.34 (1.12, 1.62)	-8 (-62, 49)
Behaviors based on forward selection model (smoking, screening and physical activity)	1.41 (1.18, 1.69)	-41 (-68, -11)	1.23 (1.02, 1.48)	-34 (-91, 26)
All behaviors[h]	1.38 (1.16, 1.64)	-45 (-72, -15)	1.22 (1.02, 1.48)	-37 (-93, 22)

All models include 54,736 respondents, of which 1,488 are cancer deaths and include the cluster option to account for correlation between respondents in the same block group.

[a]Model 1: Adjusted for age, sex, race/ethnicity, marital status, family history of cancer

[b]Model 2: Adjusted for all factors in Model 1, plus education and annual household income

[c]Hazard ratio (HR) and 95% confidence interval (CI) associated with the lowest vs. highest quintile of area-level SES

[d]Percent change = 100 x ($\beta_{\text{Model 1+ health behavior}} - \beta_{\text{Model 1}}$) / ($\beta_{\text{Model 1}}$); 95% CI based on bias-corrected bootstrap estimation with 2,000 repetitions

[e]Percent change = 100 x ($\beta_{\text{Model 2+ health behavior}} - \beta_{\text{Model 2}}$) / ($\beta_{\text{Model 2}}$); 95% CI based on bias-corrected bootstrap estimation with 2,000 repetitions

[f]Fruit and vegetable servings exclude potatoes and fruit juice

[g]Screening model includes mammogram in the previous two years (women), prostate-specific antigen screening in the previous two years (men) and colonoscopy or sigmoidoscopy in the previous 10 years.

[i]All behaviors models include all of the modifiable risk factors listed in the table in addition to Model 1 or Model 2 covariates.

Supplementary Table 3.A. Hazard ratios (HRs) and 95% confidence intervals (CIs) associated with each quintile of area-level SES with and without controlling for individual SES and health behaviors

	Model 1[a] Demographics only HR (95% CI)[c]	**Model 2**[b] Demographics and individual SES HR (95% CI)[c]
Demographics only		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.35 (1.12, 1.62)	1.23 (1.02, 1.48)
Quintile 3	1.45 (1.21, 1.73)	1.26 (1.05, 1.51)
Quintile 2	1.62 (1.36, 1.93)	1.32 (1.10, 1.59)
Quintile 1	1.77 (1.50, 2.11)	1.37 (1.14, 1.65)
Plus body mass index		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.33 (1.11, 1.61)	1.22 (1.02, 1.48)
Quintile 3	1.42 (1.19, 1.70)	1.24 (1.04, 1.49)
Quintile 2	1.58 (1.33, 1.89)	1.31 (1.08, 1.57)
Quintile 1	1.72 (1.45, 2.05)	1.35 (1.12, 1.62)
Plus physical activity		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.32 (1.10, 1.59)	1.22 (1.01, 1.47)
Quintile 3	1.40 (1.17, 1.66)	1.24 (1.03, 1.48)
Quintile 2	1.54 (1.29, 1.84)	1.30 (1.08, 1.56)
Quintile 1	1.68 (1.41, 1.99)	1.34 (1.12, 1.62)
Plus energy density		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.34 (1.11, 1.61)	1.23 (1.02, 1.48)
Quintile 3	1.43 (1.20, 1.70)	1.25 (1.04, 1.50)
Quintile 2	1.59 (1.34, 1.89)	1.31 (1.09, 1.58)
Quintile 1	1.73 (1.46, 2.06)	1.36 (1.13, 1.64)
Plus fruits and vegetables[c]		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.33 (1.11, 1.60)	1.23 (1.02, 1.48)
Quintile 3	1.42 (1.19, 1.69)	1.25 (1.04, 1.50)
Quintile 2	1.58 (1.33, 1.88)	1.31 (1.09, 1.58)
Quintile 1	1.72 (1.44, 2.04)	1.36 (1.13, 1.63)
Plus red and processed meat		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.34 (1.11, 1.61)	1.22 (1.02, 1.48)
Quintile 3	1.42 (1.19, 1.70)	1.24 (1.04, 1.49)
Quintile 2	1.59 (1.33, 1.89)	1.30 (1.08, 1.57)
Quintile 1	1.73 (1.45, 2.05)	1.34 (1.12, 1.62)
Plus alcohol		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.35 (1.13, 1.63)	1.24 (1.02, 1.49)

Quintile 3	1.46 (1.22, 1.74)	1.26 (1.05, 1.51)
Quintile 2	1.64 (1.38, 1.95)	1.33 (1.11, 1.60)
Quintile 1	1.79 (1.51, 2.13)	1.38 (1.15, 1.66)
Plus smoking		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.21 (1.01, 1.46)	1.18 (0.98, 1.43)
Quintile 3	1.24 (1.04, 1.49)	1.21 (1.00, 1.45)
Quintile 2	1.33 (1.12, 1.59)	1.26 (1.04, 1.52)
Quintile 1	1.50 (1.26, 1.79)	1.27 (1.06, 1.53)
Plus screening[d]		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.33 (1.10, 1.60)	1.22 (1.02, 1.47)
Quintile 3	1.41 (1.18, 1.68)	1.24 (1.04, 1.49)
Quintile 2	1.56 (1.31, 1.86)	1.30 (1.08, 1.56)
Quintile 1	1.70 (1.43, 2.01)	1.34 (1.12, 1.62)
All behaviors[e]		
Quintile 5	1.00 (ref)	1.00 (ref)
Quintile 4	1.21 (1.01, 1.46)	1.17 (0.97, 1.41)
Quintile 3	1.24 (1.04, 1.49)	1.17 (0.98, 1.41)
Quintile 2	1.33 (1.12, 1.59)	1.22 (1.01, 1.47)
Quintile 1	1.38 (1.16, 1.64)	1.22 (1.02, 1.48)

All models include 54,736 respondents, of which 1,488 are cancer deaths and include the cluster option to account for correlation between respondents in the same block group. Quintile 5 represents the highest-SES block groups; Quintile 1 represents the lowest-SES block groups

[a]Model 1: Adjusted for age, sex, race/ethnicity, marital status, family history of cancer

[b]Model 2: Adjusted for all factors in Model 1, plus education and annual household income

[c]Fruit and vegetable servings exclude potatoes and fruit juice

[d]Screening model includes mammogram in the previous two years (women), prostate-specific antigen screening in the previous two years (men) and colonoscopy or sigmoidoscopy in the previous 10 years.

[e]All behaviors models include all of the modifiable risk factors listed in the table in addition to Model 1 or Model 2 covariates.

CONCLUSION

In this project we sought to test whether and to what extent adherence to the WCRF/AICR cancer prevention recommendations was associated with reduced cancer mortality; to estimate the associations between area-level SES and total and site-specific cancer incidence and total cancer mortality; and to determine whether and to what extent individual-level modifiable risk factors explain the observed association between area-level SES and cancer mortality, with and without also accounting for individual-level SES.

Our results suggest that each additional WCRF/AICR cancer prevention recommendation met was associated with a 9% reduction in cancer mortality. This association was consistent among men and women and participants older and younger than 65 at baseline, but was somewhat stronger in non-smokers than in smokers. Meeting at least five recommendations was associated with a 60% reduction in cancer mortality compared with meeting none.

In models controlling for age, sex, race/ethnicity and marital status, area-level SES was inversely associated with colorectal cancer incidence among men, lung cancer incidence, and total cancer mortality. These associations weakened but remained after also controlling for individual SES.

Among participants with no history of cancer at baseline, cancer mortality was 77% higher in participants living in the lowest-SES areas compared with the highest-SES areas when not accounting for individual SES. Individual modifiable risk factors explained nearly half of that increased risk, but living in the lowest-SES areas remained associated with increased cancer mortality. When also accounting for the compositional effect of individual SES, cancer mortality was 37% higher among participants living in the lowest-SES areas compared with the highest-SES areas. Again, individual-level modifiable risk factors accounted for part of the association, but living in the lowest-SES areas remained associated with a 22% increase in cancer mortality

compared with living in the highest-SES areas, suggesting that contextual factors associated with low area-level SES could affect cancer mortality above and beyond individual SES and behaviors.

Substantial socioeconomic disparities exist such that living in lower-SES areas is associated with higher cancer mortality. Our results suggest that several behaviors, particularly smoking, physical activity, and cancer screening could be effective targets of interventions aimed at reducing these disparities, and that area-level SES remains associated with cancer mortality even after accounting for several modifiable risk factors as well as individual education and income.

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