ASSOCIATION BETWEEN PREDIAGNOSTIC WEIGHT CHANGE AND COLON CANCER RISK IN A PROSPECTIVE COHORT

by
Kexin Jin

A thesis submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Science

Baltimore, Maryland
May, 2015

ABSTRACT

Background and Objectives: Obesity is defined by World Health Organization (WHO) as a BMI value over 30 and is associated with an increased risk of colon cancer in many studies. Whether weight change during adulthood is related to risk of colon cancer is not clearly related to the risk of cancer. This study not only investigates the relationship between body size at different ages and colorectal cancer risks but also focuses on the effect of weight changes throughout the adult years as related to both gender and stage of life.

Design and analysis: A prospective cohort of 15,008 cancer-free people is followed up 1989 through 2007. Cox proportional hazard regression models adjusted for life style risk factors were used to calculate hazard ratios and 95% confidence intervals of incident colorectal/colon cancer. Age standardized incidence and age adjusted risk ratios are compared to address the association between different categorization of BMI and colorectal cancers. Stratification by stage of life and by gender is conducted to evaluate effect modification by these factors.

Results: People with higher BMI at baseline tend to have higher risk of colorectal cancer during almost 20 years of follow up The risk of colon cancer for people with moderate weight gain between age 21 and study baseline is 1.35(95% CI is 0.91 to 1.99) compared to people with constant or lower weight gains. If the weight change occurred between age 21 and age 65, the hazard ratio is 1.45 (95%CI is 0.93 to 2.25). Hazard ratio of weight gain between age 21 and study baseline for men and women is 1.23(95% CI is 0.63 to 2.41) and 1.16(95% CI is 0.65 to 2.07) respectively.

Conclusion: The data from this study suggest that high BMI and high weight gain might increase the risk of colon but not rectal cancer. The life stage during which weight change is evaluated may modify the effect of weight change on risk of colon cancer. There is no significant effect modification of gender on the effects of weight gain.

ACKNOWLEDGEMENT

I would like to express my sincerest thanks to my advisor, Professor Genevieve Matanoski, for her continuous encouragement, advice and expertise, which made this thesis project an enriching experience to me. I'm also grateful to Professor Hsin-Chieh Jessica Yeh, for her secure financial support and excellent mentoring, which made this project possible and meaningful. I would also like to extend my sincere gratitude to Drs Kala Visvanathan, Judith Hoffman-Bolton, Nae-Yuh Wang, Elizabeth A. Platz and Corinne E. Joshu, for their inspiration, guidance and intellectual contribution in this project.

I also want to take this opportunity to express my appreciation to the faculty of Johns Hopkins Bloomberg School of Public Health and my colleagues from Epidemiology program. In addition, I express my gratefulness to my parents who have been supported me unconditionally during all phases of this project.

Kexin Jin

Baltimore, USA

May 19, 2015

Advisor: Genevieve Matanoski

Readers: Genevieve Matanoski, Hsin-Chieh Jessica Yeh

TABLE OF CONTENTS

BACKGROUND

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in both men and women in the United States [1, 2]. The prevalence of obesity was reported to occur in more than one third (34.9%) of U.S adults in 2012. Body Mass Index (BMI) values over 30 kg/m2 are reported to occur in 39.5% of middle age (40 to 59 year-old) adults, 30.3% of younger (20 to 39year-old) adults and 35.4% of older adults (over 60 years old) have BMI (body mass index) values over 30 kg/m^2 [3]. This prevalence of obesity is reducing the duration of healthy life by up to 19 years and has shortened people's life expectancy by up to eight years in the United States[4]. Medical expenditure for obesity has rise from $78.5 to $147 million per year from 1998 to 2008 in the United States[5], including both inpatient and non-inpatient medical costs from diseases including cardiovascular disease, diabetes and cancers [6].

The association between obesity and cancers has been identified for a long time. Obesity has been found to contribute to approximately 20% of all cancer cases[7] and 14% and 20% of all cancer deaths in men and women, respectively[8]. Epidemiologic evidence shows associations between obesity and a variety of cancer types [9-17]. Endometrial cancer is one of the cancers consistently related to obesity. Higher BMI contributes to increased incidence and mortality of endometrial cancer in a positive dose response manner[7, 18]. The association between obesity and breast cancer is dependent on hormone receptor status, hormone replacement therapy (HRT) use and menopausal status[19]. The association between obesity and prostate cancer depends on the stage of the cancer. While obesity is shown to be protective to localized prostate cancer, it is positively associated with advanced prostate cancer [20-23]. This observation of varying effects by stage for localized versus advanced cases has been hypothesized to be due to low androgen level[24].

The biological mechanisms of the obesity-cancer relationship have been most frequently proposed to relate to insulin resistance. In vivo, in vitro and epidemiological studies have all provided evidence for this hypothesis. Insulin increases lipid synthesis of fatty acid esters to triglycerides in human body[25]. Obese individuals develop insulin resistance in order to produce less body fat and maintain balance[26].

Molecular biology indicates that the initial molecular signal for insulin involves activation of the insulin receptor tyrosine kinase, which results in phosphorylation of insulin receptor substrates (IRSs) on multiple tyrosine residues. These tyrosine residues act as docking sites of PI3K pathway. Obesity causes a signaling defect by increasing expression and activity of several protein tyrosine phosphatases (PTPs) which dephosphorylate and thus terminate signaling propagated through phosphorylation events[26]. In this way, insulin resistance is induced. Insulin resistance then causes beta-cell compensation. Increased insulin secretion finally increases synthesis of IGF-1which stimulates the proliferation of tumor cells lines [27]. Also, hyperglycemia provides a high glucose level, which supports the demands for tumor cell growth. Cytokines and adipokines may also play roles in the obesity-colon cancer relationship[24].

During the recent 30 years, multiple case-control studies [28-37] and prospective cohort studies[38-55] have consistently shown positive associations between BMI and colon cancer risks in men, but insignificant or no association in women. The association does not include rectal cancer with most studies showing no association between BMI and rectal cancer risks in both men and women[29-31, 36, 42, 52, 55, 56]. A systematic review and meta-analysis in 2007 reported that obesity (BMI>30 kg/m^2) is significantly associated with colorectal cancer when compared obese to normal body size (BMI<25 kg/m^2) and this positive association is more significant among men than among women, and more significant in colon cancer than in rectal cancer[57]. Another systematic review and meta-analysis in 2007 summarized from 31 prospective studies found a positive association between BMI/waist circumference/waist-hip ratio and colon cancer. These associations are significant among both men and women, though the association for women was weaker. That meta-analysis also found that BMI is positively associated with rectal cancer among men, but not in women [58].

The discrepancy between men and women in terms of BMI and colon cancer risk might be due different body composition, postmenopausal hormone replacement therapy use (HRT), and parity. Men are tend to have abdominal obesity while women are tend to have lower body or gluteofemoral obesity[59]. Hormone replacement therapy has been shown to reduce the risk of colon cancer among postmenopausal women[60, 61].

A human's weight changes during their lifespan but the dynamic influence of weight change on colorectal cancer is not fully understood. However, one way to look at it is to distinguish changes in the body size at middle life to body size at earlier adulthood and weight changes during that period[18]. Multiple studies have addressed this topic, but the association has not been clarified.

Early adulthood obesity has been shown to increase the risk of colorectal cancer [50, 62-64]. However, observations are not consistent. Two studies [50, 62] showed higher BMI at adolescent (age range 15-19) significantly increases colorectal cancer incidence. Another study [64] showed higher BMI at 20 years old is statistically significantly associated with risk of distal colon cancer but not other colon or rectal cancer subtypes. Three other [65-67] studies showed no association between BMI at age 18 or 20 and colon cancer risk. Han et al. [18] showed no association between BMI at age 25 and risk of incident colorectal cancer. Nimptsch et al. [63]showed in 2011 in Nurses' Health Study II pictogram body shape at age 20 is not significantly associated with risk of distal colorectal adenoma.

Between 2008 and 2014, nine case-control or prospective studies on the association between weight/BMI change and colorectal cancer were published [18, 64-71]. However, these studies relied on different weight change measures and reached inconsistent conclusions. The study design, exposure measures and results are summarized in **Table 0**. The earliest of those studies is a case-control study composed of colon cancer cases from Kentucky Cancer Registry[65] and controls from random digital dialing within State of Kentucky. The weight change measure in this study is the difference in BMI between age 20 and study baseline. Results show a 10kg/m^2 increase in BMI is associated with 174% increased risk for women to develop colon cancer. (Odds ratio 2.74(95% CI= 1.27–5.92)). An increase in BMI among men was not shown to be associated with colon cancer risk among men.

Five of the studies [64, 66, 68, 70, 71] focused on absolute value of weight change in kilograms between young adult age and the study recruitment time or another time point. Among these five studies, the Health Professionals Follow-Up Study (HPFS)[71], the Melbourne Collaborative Cohort Study[66] and the

Norwegian Counties Study[70] showed significantly increased colon cancer risk for men with larger weight gain. Weight change measure in HPFS is the difference of weight values during each two-year follow-up cycle and the risk period of colon cancer onset was set to be the second or the third next two-year follow-up cycle in order to give a lag time of two to four years. The significant association between this weight change measure and colon cancer risk also suggests that short-term weight change before colon cancer may play a major role. In the second study, weight change measure is the difference of weight in kilogram between study recruitment and age 18. In Norwegian Counties Study, the statistical significance only exists in men with BMI values over 25 at the study baseline. Netherlands Cohort Study [64] and EPIC [70] study suggested no significant association between this weight change measure and colon cancer risk in men. There is no association of absolute weight change in most of the studies for women [64, 66, 70] except EPIC study, where women did show a significant association between absolute weight change and colon cancer risk.

In 2015, a systematic review and meta-analysis published in Journal of National Institute of Cancer [72] synthesized four of those studies using a linear dose-response. Each 5 kg of weight gain in men is associated with 9% increase of colon cancer risk (Relative Risk = 1.09 with 95% confidence interval of 1.04 to 1.13, $I^2 = 0.0\%$, $P_{heterogeneity} = 0.76$). The association is not significant in women.

Three of the nine studies[67-69] defined the weight change as annual change in weight by kilograms. Their results are different from each other. The association for men is significant in NIH-AARP study and PANACEA study, but is not significant in EPIC. The association for women is significant in EPIC but not significant in NIH-AARP and PANACEA.

Han et al.[18] described the association between percentage weight change and colorectal cancer in Atherosclerosis Risk in Communities (ARIC) study. Their study population consists of participants within a narrow age range between 45 and 64 and the results shows a 5% increased risk of colorectal cancer with every 5% increase in percent weight change between age 25 and study baseline (Hazard ratio is 1.05 (1.02–1.07), adjusted for BMI at age 25 and lifestyle confounders for colorectal cancer).

A set of risk factors of colorectal cancer (CRC) has been reported in many studies. These factors include family history of CRC, education level, anti-diabetic medication use, cigarette smoking, alcohol assumption, red meat consumption and physical inactivity[73]. These factors might confound the association between weight change and colon cancer risk and are often adjusted in the Cox proportional hazard regression model in previous studies.

CLUE II cohort study started at 1989 and is composed of male and female adult residents with a very wide age range between 18 and 94. This population could add information regarding the association between BMI at various ages ,, the roles of obesity at young adulthood and prediagnostic weight change from early adulthood to later years in the risk of colorectal cancer and to compare which of these weight measures is more influential. The population also enables us to study the association between prediagnostic weight change and colorectal cancer risk by subsite of colon cancer, by different genders and at different stages of life during which weight change is defined. Through this investigation, we could better understand the roles gender and anatomic location may play and perhaps identify the most important stage of life in terms of risk of colon cancer from weight change.

Therefore, the conclusions from this study could be useful in developing public health strategies for reducing the epidemic of obesity and its related risks of cancer by identifying at what age weight interventions are likely to have the greatest impact on the risk of the disease. This knowledge will help planners target population in which the greatest risk reduction might be achieved related to specific public health programs.

Table 0. A Summary of Epidemiologic Studies of Weight/BMI change and risk of colorectal cancers[4,5]

Year	Author/Study	Design/ Sample/ No. cases	Baseline BMI		Young Adult BMI		Weight Change	
			Age (Range)	Effect size(categBMI)	Age	Effect size	Measure for weight change	Effect size
2008 [65]	Nock / Kentucky Cancer Registry	Case-control/ 438 cases and 491 controls	~60 (40-)	Colon: Sig[4]	20s, 30s, 40s, 50s	Nonsig[4]	1. BMI, baseline-age 20 2. BMI, baseline-age 30 Categorical: 5, 10	Sig; ♂: Noassoc; ♀: Sig
2008 [71]	Thygesen/HPFS	Cohort/ 46,349 (100%male)/ 765 colon	~54 (40,75), mean BMI[1]	Sig	21	NA	1. Weight change during two years with 2-4 years lag time [2] 2. Weight change from age 21 to 2-4 years lag time [3]	Sig
2010 [66]	Bassett/ Melbourne Collaborative Cohort Study	Cohort/ 39,626/ 569 colon	~56 (40, 69)	Colon♂:Sig	18	Noassoc	Weight, baseline-age18, kg 1. Per 5-kg increment 2. Categorical: ±3, 10, 20	♂per 5kg: Sig ♀: Nonsig
2010 [70]	Laake/ Norwegian Counties Study	Cohort/ 76,179/ 798 colon (proximal/distal)	~40 (mostly 20, 49)	Colon ♂♀: Sig Distal♂♀: Sig Other: Nonsig	NA	NA	Weight, last measurement-baseline, kg, Categorical: ±2, 5, 10	♂BMI>25 at baseline: Sig trend; Other trend: Nonsig/Nonassoc
2011 [64]	Hughes/ Nether- lands Cohort Study	Case-cohort/ 120,852/ 2,316 colorectal	~61 (55, 69) BMI Quin-tiles	♂:sig; Proximal: Nonsig Distal: Sig Rectosigmoid: Sig Rectum: Nonsig ♀: Nonsig	20, Quin -tiles	♂: Nonsig; Distal: Sig ♀: Nonsig	Weight, baseline-age20, kg; Categorical: 0, 4, 8	Nonsig
2012 [67]	Renehan/ NIH-AARP	Cohort/ 273,679/ 4,076 colorectal	~62 (50, 71)	Colon-baseline/age 50: Sig Rectal: Noassoc	18	Colon: Nonsig	Rate of weight change, kg/year 1. Age 35-age 18; 2. baseline-age 18; 3. others	Colon♂: 1/2: Sig; 3.Nonsig ♀: Nonsig
2013 [69]	Aleksan-drova/ EPIC	Cohort/ 201,696 (63% female)/ 2,384 colorectal	50 (wide)	NA	20	NA	1. Weight, baseline-age20, kg, Categorical ±2,5,10,15,20 2. Rate of weight change, baseline-age 20, Categorical 0.1, 0.3, 0.5, 1	CRC: 1. Sig; ♂: Sig; ♀: Nonsig; 2. Sig; ♂: Sig; ♀: Sig Colon: 1. Sig; ♂: Nonsig; ♀: Sig; 2. Sig; ♂: Nonsig; ♀: Sig
2014 [68]	Steins Bisschop/ EPIC-PANACEA	Cohort/ 328,781 (75% female)/ 1,261colon	~52 (25, 70)	Colon♂: Sig Colon♀: Nonsig Rectal♂♀: Nonsig (decreasing risk)	NA	NA	Rate of weight change, kg/year, baseline-2nd assessment, Q2+Q3 as ref	Colon♂: Q4 Sig, Q5 unexpected trend; Colon♀: Nonsig Rectal♂♀: Nonsig protective
2014 [18]	Han/ ARIC	Cohort/ 13,901/ 147 colorectal	~54 (45, 64)	NA	25	CRC♂♀: Noassoc[4]	Weight change percent, baseline-age 25, Categorical±3%, 5%	Colorectal♂: linear Sig(5% kg)

[1]Mean of all available information on current weight up to the beginning of each 2- year follow-up cycle, which we call the cumulative mean weight. This time-varying variable combined with height reported in 1986 was utilized to calculate cumulative mean BMI (kg/m^2); [2]weight change between 1986-1988 on risk of colon cancer 1990–92, weight change 1988–1990 on risk 1992–94, etc. [3]weight change between age 21 and 1988 on risk of colon cancer 1990–92, weight change 21 years-1990 on risk 1992–94, etc. Weight change was calculated per 10 years to take account of different time periods from age 21 to age during follow-up. [4]Sig stands for statistically significant effect measures comparing any categories; Nonsig stands for none of the association comparing any categories is statistically significant, but there might be some trend; Noassoc means no significant or pattern detected; [5]♂ stands for male, ♀ stands for female; [6]Criteria for BMI categorization is according to WHO guideline, unless specified otherwise[74]

METHODS

STUDY POPULATION

CLUE II is a community-based population in Washington County, Maryland established for etiology research on cancer and cardiovascular diseases. During May and October of 1989, multiple mobile office trailers, covering all sections of the communities in Washington County, were stationed to take questionnaire surveys of demographic information, disease history and cancer-related life style characteristics. Both baseline questionnaires and blood samples were collected from 32,894 participants, which represents about 30% of the total Washington County adult population according to data from 1990 Census. Among those participants, 7,818 were excluded for non-residency in Washington County; 5,470 were excluded for ages less than 30 at baseline; 1,360 were excluded for prior history of cancer self-reported in the questionnaires in 1989 and verified by Washington County Cancer Registry in 1990(people with non-melanoma skin cancer and carcinoma in situ were not excluded) at baseline; and 3,238 were excluded for non-response to the 1989 baseline Food Frequency Questionnaires. This eligibility screening left a study population of 15,008 people at baseline.

Written informed consents were obtained from all CLUE II participants when the data collection questionnaire were filled out and the blood samples were taken. The CLUE II study was approved by the institutional review board (IRB) of Johns Hopkins School of Public Health (JHSPH). This masters' thesis research is approved by IRB of JHSPH and the George W. Comstock Center for Public Health Research & Prevention.

ASSESSMENT OF EXPOSURES AND OUTCOMES

Self reported weight (unit: kilogram) and height (unit: centimeter) in the 1989 baseline questionnaires were used to calculate individual BMI at baseline as weight/height^2 (unit: kg/m^2). BMI at age 21 were self-reported in the 1989 baseline data collection questionnaire. Weight change is defined as difference of body weight in kilograms between baseline at 1989 and age 21. Other cancer risk factors (cigarette smoking

status and years of education), population demographics (age, gender, residence status) and medication history (anti-diabetic medication use and hormone replacement therapy use in women) were also collected from the baseline data collection questionnaires. Red meat consumption includes intake of hamburger, beef, beef stew, pork, hot dog, ham/lunch meat, bacon, and sausage. The information is based on 13,276 participants with responses from 1989 food frequency questionnaires. The family history of colorectal cancer among first-degree relatives is recorded from the first active follow up questionnaire conducted in 1996. Physical activity level is ascertained from the second active follow-up survey in 1998. All the follow-ups were self-administered through postal mail to the participants. Response rates in 1996 and 1998 were 69.89% and 64.28% respectively. Many of theses variables have not been included in the final analyses.

Diagnosis of primary CRC is defined as first primary occurrence of colon (International Statistical Classification of Diseases and Related Health Problems-8th /9th revision codes 153.0-153.9, or ICD-10th revision codes C18.0-C18.9) or rectal cancer (International Statistical Classification of Diseases and Related Health Problems-8th /9th revision codes 154.0 and 154.1, or ICD-10th revision, codes C19 and C20), or second primary occurrence of them if the first primary cancer was non-melanoma skin cancer or carcinoma in situ. The last CRC case in this study was obtained from the Washington County Cancer Registry on June 30th, 2007.

Vital status and date of death were ascertained from linkage to National Death Index and Maryland death certificates. The last death in this study was detected on Sep 26th, 2008

ANALYSIS

STATA (version13.0, Stata Corporation, College Station, TX) is used in this study. Alpha is set to be 0.05 as statistically significant. Descriptive characteristics are based on Chi-Square or Fisher exact test for categorical variables and ANOVA for continuous variables with normal distribution. BMI categorization is based on: 1) the International Classification weight grouping for adult Caucasians: underweight: <18.5; normal weight: >=18.5 and <25; overweight: >=25 and <30; obesity: >=30 [74]; 2) quartiles. Age standardized incidence rate is based on age distribution of the whole study population as the standard population. Weight change categorization is based on tertiles.

Cox proportional hazard regression model is used to calculate hazard ratio (HR) and the corresponding 95% confidence interval (95%CI) for evaluation of colorectal cancer risks. Multivariate models are adjusted for confounders in the BMI-colon cancer causal pathway. These potential confounders include age, CRC family history in the first-degree relatives, cigarette smoking status, diabetic medication use, red meat consumption and physical activity level. They were identified according to literature[73]. Among these potential confounders, those included in the multivariate adjusted models are according to the criteria: 1) significantly associated with the exposure; 2) are risk factors for the outcome (a priori from the literature); 3) not the mediator between the exposure and the outcome; 4) with missing rate<15%. Rectal cancer incidence is regarded as the competing risk event in the estimation for colon cancer risks and vice versa. Calendar year is used as the time metric in the primary analysis and age is used as the time metric in the sensitivity analysis. Baseline in 1989 is the entry of each individual and exit is the date of death, date of diagnosis of incidence of primary colorectal cancer or date of administrative censoring on June 30th 2007, whichever happened first.

RESULTS

Descriptive characteristics at baseline are summarized in Table 1. Based on WHO criteria, more than half (56.63%) of the adult residents of Washington County in this study population are overweight or obese. The average age of this study population at the study baseline at 1989 is 52.81. The proportions of obesity by gender indicated that 11.7% women and 25.06% of men were overweight or obese at age 21 and the proportions at baseline were 49.12% for women and 67.01% for men. Men are more likely to be overweight or obese than women at both early adulthood and middle age. The average BMI increased from 22.08 at age 21 to 26.27 at baseline with 88% of the study population showing increased BMI between age 21 and date of study baseline.

The proportion of current smokers is 16.06% for women and 16.98% for men while the proportions for ever smokers are 39.11% and 60.47% for men and women respectively. These data indicate that men are

more likely to have smoked and also are more likely to have stopped before baseline. As shown from Table1, men with lower BMI and women with higher BMI are more likely to be smokers. This relationship between cigarette smoking and BMI are statistically significant in both genders.

People with higher BMI are more likely to report use of anti-diabetic medication, to consume higher amounts of red meat and to have lower level of physical activity than persons with lower BMIs. These patterns are all significant and they exist in both men and women. People with normal BMI values have the highest proportion of college graduates and the lowest proportion of persons with no higher education. Obese and underweight women are less likely to take hormone replacement therapy compared to normal weight women. Family history of cancer is not associated with BMI at baseline for men and women.

Among the total 15,008 eligible participants, 42.19% are men. The number of people with incident colorectal cancer onset during a 19.2 years of follow up (median follow up time is 17.96 years) was 247. The incidence rate for colorectal cancer was 0.10 per 100 person-year in this population. The total person-time at risk is 243661.5.

The upper left panel of Table 2 shows a suggestion of a positive dose-response relationship between BMI at baseline and risk of colorectal cancer. In the crude model, overweight and obese people show 1.12 and 1.13 times of hazard of incident primary colorectal cancer, comparing to normal weighted people, with 95% confidence intervals of (0.84, 1.47) and (0.79, 1.59). Although none of the effect estimates is statistically significant, the positive dose response relationship becomes stronger after adjusting for age at baseline and the set of confounders identified a priori. In this multivariate adjusted model, obese people have a 31% higher risk of developing colorectal cancer during the follow-up. The last column of the upper left panel of Table 2 shows the stratum-specific age standardized incidence rates of colorectal cancer. These incidence rates are weighted according to the age distribution of the whole population thus are age standardized and could be compared across the BMI strata. People with normal BMI have the lowest incidence rate.

The upper right panel shows the BMI measurements at age 21 and indicates a negative dose-response impact on colorectal cancer risk. This lower risk in overweight and obese could be due to its relationship with weight change between age 21 and baseline. The last column of this panel shows people with higher BMI at age 21 tend to gain less weight and this association is statistically significant.

The two lower panels of Table 2 shows the associations based on BMI quartiles. The left panel shows the association between BMI quartiles and colorectal cancer risks. The reference group is people with BMI between 23.0 and 25.5 and the third quartile is based on BMI values between 25.5 and 28.6. There is no significant or clear pattern for this association and. The lower right panel of Table 2 shows the relationship between BMI at 21 and colon cancer risk, as well as the distribution of weight change across the strata of early adult BMI. The second quartile and third quartile of young adults have BMI values ranges 19.8-21.5 and 21.5-23.7. These two strata shows similar hazard ratios. Higher BMI at age 21 decreases colon cancer risk, which is the same as the upper right panel. BMI at age 21 also shows a non-significant reverse relationship with weight change, just as that based on WHO guideline for body size classification for general Caucasian adults.

Table 3 shows people in the second and the third tertiles of weight gain have higher risks of developing colorectal cancer compared to those in the first tertile of weight gain. Though not statistically significant, this effect is more obvious after adjusting for BMI at age 21 and more obvious for colon cancer than the combined group of colon and rectal cancers. In fact the effect is not shown in rectal cancer. After adjusting for BMI at age 21 and other confounders, people with the weight gain of 11.70 kg (standard deviation=2.57kg) are 26% more likely to develop colorectal cancer and 35% more likely to develop colon cancer, comparing to people in the first tertile of weight gain. People with an average weight gain of 25.61kg (standard deviation = 8.47 kg) are 18% more likely to develop colorectal cancer and 24% more likely to develop colon cancer. For rectal cancer, a negative dose-response effect is shown, as larger weight gain results in higher risks of rectal cancer onset. Numbers of rectal cancer cases in the three weight gain tertiles are 12, 14 and 13.

Table 4 stratifies the population into two groups by people's age at baseline. The two subgroups of participants enter the study at average ages of 41 and 65. Therefore, the life stage of weight gain we calculated in this study is different for these two subgroups of people. The results from Table 4 shows that if a person is at his younger life stage (age range between 30 and 52), either losing weight or gaining too much weight could increase his risk of developing colon cancer. The hazard ratio is 1.57 (95% confidence interval is 0.66 to 3.72) for people who lose weight during the earlier life stage and 1.11(95% confidence interval is 0.48 to2.56) for people who gain a larger amount of weight during the earlier life stage, comparing to those who gain a smaller amount of weight during the earlier life stage. In the other subgroup of people, who weight gain period is from age 21 to 65 (range: 53-94), the hazard ratio for the third tertile of weight gain is 1.31(95% confidence interval is 0.81 to 2.11) , which is less than that for the second tertile:1.27(95% confidence interval is 0.80 to 1.99).

Table 5 shows the gender difference in association between weight gain and risk of colon cancer. For men, a larger weight gain is associated with higher risk of colon cancer, after adjusting for BMI at age 21 and all other confounders. Differently, women with the second highest tertile of weight gain are of the highest risk of incident colon caner (adjusted hazard ratio is 1.51, 95% confidence interval is (0.87, 2.61)), higher than women with highest tertile of weight gain (adjusted hazard ratio is 1.16, 95% confidence interval is (0.65, 2.07)).

In the sensitivity analysis, age was used as the time metric to test whether survival models are robust to this population. In this sensitivity analysis, age 0 is regarded as origin of time at risk; age at 1989 study recruitment is regarded as individual entry into the study. Everyone in this model is late entry. Hazard ratios gained from this model are comparing people with the same age at baseline. The results (not shown in this thesis) are consistent with that of the primary analysis.

Table 1. Descriptive characteristics of study population by gender and BMI at baseline[1]

	Man (N=6,332)					Women (N=8676)				
	Underweight (n=20)	Normal (n=2,074)	Overweight (n=3,154)	Obese (n=1,084)	P value	Underweight (n=174)	Normal (n=4,241)	Overweight (n=2,632)	Obese (n=1,629)	P value
n%	0.32	32.75	49.81	17.12		2.01	48.88	30.34	18.78	
Age: mean(SD)	51.15(16.72)	53.0(14.44)	53.11(13.09)	51.12(12.38)	0.0003	56.40(16.37)	51.69(14.18)	55.01(13.27)	52.13(12.66)	<0.0001
Smoking status					<0.001					<0.001
Never/%	45.00	41.13	38.87	38.87		55.17	60.24	60.94	63.11	
Former/%	20.00	39.73	45.66	44.23		14.94	21.53	24.92	24.86	
Current/%	35.00	19.14	15.47	16.90		29.89	18.23	14.13	12.03	
Diabetic medication					<0.001					<0.001
Yes/%	0.00	2.27	3.36	5.26		1.15	1.18	3.42	7.37	
No/%	100.00	97.73	96.64	94.74		98.85	98.82	96.58	92.63	
Education					<0.001					<0.001
No higher edu/%	30.00	16.92	21.49	20.61		22.41	16.04	25.02	29.12	
Some higher/%	55.00	69.33	67.69	68.15		70.11	75.34	69.73	66.89	
College graduate or above/%	15.00	13.74	10.82	11.24		7.47	8.62	5.25	3.99	
Cancer Family history					0.666					0.059
No	14.29	35.52	35.29	34.43		36.73	28.23	25.99	26.64	
Yes	85.71	64.48	64.71	65.57		63.27	71.77	74.01	73.36	
Red meat[2]	14.57(25.49)	6.72(5.94)	7.29(5.97)	5.87(6.50)	<0.0001	4.90(4.11)	4.85(3.51)	5.28(3.90)	6.16(5.00)	<0.0001
Physical Activity[3]					0.003					<0.001
Low/%	20	31.46	35.68	40.61		31.25	29.60	33.75	40.80	
Medium/%	40	37.25	37.30	35.49		28.12	38.13	36.43	37.59	
High/%	40	31.30	27.01	23.89		40.62	32.27	29.82	21.61	
Hormone replacement therapy use for females										<0.001
Never %	NA	NA	NA	NA	NA	86.75	83.58	83.27	87.61	
Former %	NA	NA	NA	NA	NA	6.63	3.78	4.39	3.72	
Ever %	NA	NA	NA	NA	NA	6.63	12.64	12.34	8.66	

[1]All factors except physical activity are at baseline; [2]Based on 13276 participants with response from 1989 food frequency questionnaire, unit=serving per week; [3]Based on 9202 participants with response from 1998 exercise questionnaire

Table 2. Association between BMI measures, weight change and colorectal cancer risk[1]

BMI at baseline						BMI at age 21			
BMI categories	No. CRC cases	Crude HR (95% CI)	MV HR [2] (95% CI)	Age standardized incidence rate/100,000 person-time (95% CI)	BMI categories	No. CRC cases	Crude HR (95% CI)	MV HR [3] (95% CI)	Weight change (SD) unit: pound
Underweight BMI <18.5	3	1.09 (0.34, 3.43)	0.42 (0.06, 3.00)	116.71 (0, 265.89)	Underweight BMI <18.5	30	1.14 (0.78, 1.68)	1.03 (0.65,1.63)	37.68 (37.68)
Normal 18.5≤BMI<25	98	1.00 (ref)	1.00 (ref)	98.16 (78.90,117.64)	Normal 18.5≤BMI<25	184	1.00 (ref)	1.00 (ref)	26.86 (23.12)
Overweight 25≤BMI<30	99	1.12 (0.84, 1.47)	1.02 (0.74, 1.41)	99.40 (79.78, 119.03)	Overweight 25≤BMI<30	29	0.82 (0.56, 1.22)	0.85 (0.55, 1.30)	19.54 (28.26)
Obese BMI≥30	47	1.13 (0.79,1.59)	1.31 (0.89, 1.93)	114.22 (81.13, 147.30)	Obese BMI≥30	4	0.44 (0.16, 1.18)	0.42 (0.13, 1.30)	3.71 (41.89)
P-value		>0.05	>0.05		P_{trend}		>0.05	>0.05	<0.001

BMI at baseline						BMI at age 21			
BMI Quartiles	No. CRC cases	Crude HR (95% CI)	MV HR [2] (95% CI)	Age standardized incidence rate/100,000 person-time (95% CI)	BMI Quartiles	No. CRC cases	Crude HR (95% CI)	MV HR [3] (95% CI)	Weight change (SD) unit: pound
Q1 (<23.0)	48	0.70 (0.48, >1.00)	0.80 (0.52, 1.21)	87.99 (63.01, 112.98)	Q1 (<19.8)	69	1.11 (0.79, 1.56)	1.09 (0.73, 1.62)	33.00 (23.83)
Q2 (23.0-25.5)	70	1.00 (ref)	1.00 (ref)	111.49 (85.31, 137.66)	Q2 (19.8-21.5)	63	1.00 (ref)	1.00 (ref)	27.66 (22.58)
Q3 (25.5-28.6)	66	0.92 (0.66, 1.29)	0.92 (0.62, 1.34)	100.28 (74.56, 126.00)	Q3 (21.5-23.7)	61	1.00 (0.71, 1.43)	1.08 (0.73, 1.60)	25.14 (23.13)
Q4 (>28.6)	63	0.88 (0.62, 1.23)	1.07 (0.73, 1.56)	104.25 (78.35, 130.15)	Q4 (>23.7)	53	0.88 (0.61, 1.27)	0.96 (0.64, 1.45)	18.65 (30.39)
P-value		>0.05	>0.05		P_{trend}		>0.05	>0.05	<0.001

[1]Time metric is calendar time in the Cox regression model for hazard ratios
[2]Mutivariate models adjusted for age at baseline, education, cigarette smoking status and red meat consumption
[3]Multivariate models adjusted for education, cigarette smoking status and red meat consumption

Table3. Association between weight gain and colon/rectal cancer

weight change (Tertile)	Mean(SD) of weight gain, unit: kg	CRC			Colon			Rectal		
		No. CRC/person-time at risk	HR: weight change (95% CI)[1]	HR: weight change adjusted for BMI at 21[1]	No. colon cancer	HR: weight change (95% CI)[1]	HR: weight change adjusted for BMI at 21[1]	No. rectal cancer	HR: weight change (95% CI)[1]	HR: weight change adjusted for BMI at 21[1]
T1	1.18(6.00)	75/91106.36	1.00(ref)	1.00(ref)	63	1.00(ref)	1.00(ref)	12	1.00(ref)	1.00(ref)
T2	11.70(2.57)	94/81230.05	1.23(0.87, 1.74)	1.26(0.89, 1.79)	80	1.33(0.91, 1.94)	1.35(0.91, 1.99)	14	0.87(0.38, 1.99)	0.93(0.41, 2.13)
T3	25.61(8.47)	77/70852.52	1.14(0.79, 1.63)	1.18(0.81, 1.72)	64	1.22(0.82, 1.82)	1.24(0.82, 1.88)	13	0.85(0.36, 1.99)	0.94(0.40, 2.18)

[1]Mutivariate models adjusted for age at baseline, education, cigarette smoking status and red meat consumption; HR: hazard ratio

Table4. Association between weight gain and risk of colon cancer by life stage of weight change

Weight gain tertiles	Younger life stage weight change --Age 21 to 41 (range: 30-52)					Middle life stage weight change --Age 21 to 65 (range: 53-94)				
	Mean(SD) of weight gain, unit: kg	Age at baseline (SD)	No. colon cancer	Hazard Ratios		Mean(SD) of weight gain, unit: kg	Age at baseline (SD)	No. colon cancer	Hazard Ratios	
				Weight Change (95% CI)[1]	Weight Change Adjusted for BMI at age 21[1]				Weight Change (95% CI)[2]	Weight Change Adjusted for BMI at age 21[2]
T1	0.19 (6.19)	39.39 (6.11)	12	1.54 (0.66,3.60)	1.57 (0.66, 3.72)	1.08 (5.85)	64.81 (8.37)	53	1.00 (ref)	1.00 (ref)
T2	9.89 (2.49)	40.74 (6.15)	12	1.00 (ref)	1.00 (ref)	12.00 (2.60)	63.97 (7.71)	65	1.42 (0.92, 2.18)	1.45 (0.93, 2.25)
T3	24.15 (9.11)	42.39 (5.85)	13	1.11 (0.48, 2.56)	1.11 (0.48, 2.56)	25.53 (8.04)	63.48 (7.31)	53	1.27 (0.80, 1.99)	1.31 (0.81, 2.11)
P-value	<0.001	<0.032		>0.05	>0.05	<0.001	<0.001		>0.05	>0.05

[1]Mutivariate models adjusted for education, cigarette smoking status and red meat consumption

Table5. Association between weight gain and colon cancer by gender

Men				
weight gain Tertiles	Mean(SD) of weight gain Unit: kg	No. colon cancer	Weight Change (95% CI)[1]	Weight Change Adjusted for BMI at 21 (95% CI)[1]
T1	1.26 (6.55)	27	1.00(ref)	1.00(ref)
T2	11.80(2.52)	26	1.08(0.61, 1.92)	1.03(0.57, 1.87)
T3	25.23(8.14)	33	1.33(0.75, 2.36)	1.23(0.63, 2.41)
Women				
weight gain Tertiles	Mean(SD) of weight gain Unit: kg	No. colon cancer	Weight Change (95% CI)[2]	Weight Change Adjusted for BMI at 21 (95% CI) [2]
T1	1.17(5.56)	31	1.00(ref)	1.00(ref)
T2	11.63(2.61)	59	1.45(0.85, 2.48)	1.51(0.87, 2.61)
T3	25.87(8.69)	31	1.11(0.62, 1.98)	1.16(0.65, 2.07)

[1]Mutivariate models adjusted for education, cigarette smoking status and red meat consumption; [2]adjusted for education, cigarette smoking status, red meat consumption and hormone replacement therapy use

CONCLUSION

BMI at baseline suggests a possible association with risk of colorectal cancer. BMI at age 21 suggests a negative association with risk of colorectal cancer. People in the intermediate level of weight gain seem to have the highest increase in the risk of colon cancer. This pattern is not shown in rectal cancer. Weight gain at different ages in one's life may influence people's future colon cancer risk differently and the association may have to do with the characteristics of body weight and fat at different ages.

DISCUSSION

In this study, higher BMI at age 21 is not significantly and shows a negative relationship with future colon cancer risk, which is consistent with previous findings[18, 65-67]. . This negative pattern could be due to the close association between BMI at age 21 and weight change from age 21to baseline for this study. In this population, people with higher BMI at age 21 are less likely to gain much weight perhaps because weight tends to plateau at higher weights. Larger weight gain from age 21 to study baseline leads to a higher risk of colorectal cancer incidence. The effect size becomes larger when adjusting for weight at age 21 in addition to all other confounding risk factors. This means BMI at age 21 influenced the effect of weight change moving the risk toward the null.

The body size classification used in most studies is based on WHO guidelines for adults[74], and is used in this study for both BMI at baseline and BMI at age 21. However, the body size categorization for the adult population and for people at young adulthood who are aged 21 may not be entirely similar. Therefore, we conducted the analysis of associations based on quartiles of BMI values. The result based on BMI quartiles at age 21 shows that the second and the third stratum are very close in terms of the risk of future colon cancer. Persons within the lowest BMI stratum show a slightly increased risk and those within the highest stratum shows slightly decreased risk. These findings suggest that young people at age 21 who fall within the middle 75% of the BMI distribution have no difference risk in colon cancer onset in later life. However, if the young person has a BMI in the lowest or the highest quartiles of the population, he or she will have increased or decreased risk of colon cancer, respectively. This observation could be due to differences in the magnitude of weight gain as they age with thinner young adults more likely to gain weight later in life and higher possibility for heavier young adults to control weight gain later in life.

Table 3 shows the differences in the risk of weight gain by cancer site, with colon cancer risk increasing with weight gain and rectal cancer suggesting a pattern of decreasing risk with increasing weight gain This is consistent with results from multiple studies[67, 68].

This study shows people with highest weight gain during middle life stage will have increased risk of colon cancer comparing to the reference group and this finding may not occur for weight gain at younger ages. If this is correct the data suggest that a person may not increase their risk of colon cancer with moderate weight gain during ages 21 to 41 but may increase their risk at older from weight gain at older ages. Life stage may modify effects of weight change. This trend might suggest that moderate weight gain before 41 years is not harmful unless this weight gain continued through the next 20 years of life. Older people (aged 53 and above at study baseline) with the highest tertile of weight gain shows less high colon cancer risk than those with the middle tertile of weight gain. This could be influenced by the fact that the average age of persons in the highest weight gain stratum is younger than ages of the middle stratum and age is an influential risk factor in colon cancer development[73].

The risk of colon cancer for men and women shows no significant difference. In both genders, increasing weight is associated with a higher risk of colon cancer. However the pattern is less clear in women than in men. An explanation for this observation could be that additional factors in women play a role in colon cancer development that are not adjusted for in this study. It is also possible that further research may identify differences in the role of accrual of fat in women than in men, because there are biological differences between men and women, which are important predictors of colon cancer risk.

One of the limitations of this study is its lack of statistical significance. Patterns are detected but none of them are statistically significant. This population of 15,008 participants with 247 colorectal cancer cases does not have enough power to detect statistically significant associations. A solution to this problem is to combine other populations together for analysis or update the cancer outcome surveillance to 2014.

Another limitation of this study is the response rate. The missing rates of cigarette smoking status, diabetic medication use, hormone replacement therapy (HRT) use and education are less than 4%. However, the variable for red meat consumption is missing in 15% and for physical activity for 38.7% of the population. This makes it difficult to adjust for these variables because of loss of population. In the multivariate adjusted models, current and former smokers and people with diabetic medication, HRT, higher red meat consumption and lower level of education are associated with higher risk. The associations are not significant. Physical activity is not included in the model because of the missing rate.

The third limitation is the variety in the age period of weight change. In the sensitivity analysis, age at baseline is shown to have dramatic impact on the risk estimates. The primary analysis based on a time metric of age is able to compare the risk among people with the same age at baseline. In the primary analysis stratified to two subgroups by age at baseline, differences in the effects are noted. In order to get better effect estimates, a larger sample size compose of people with smaller range of age is needed.

The current study has been unable to demonstrate statistically significant results for many of the observed patterns of change. However, the observations suggest that future research should focus more on the effect

of weight change during different periods of life. Longitudinal repeated measurements and the potential of adding biological measurements should be proposed. Methods to handle missing data must be included in any such study. In summary, it remains to be seen at what age weight interventions are likely to have the greatest impact, which is a significant issue in selecting appropriate populations for specific public health strategies. Equally important will be the addition of use and development of biological measures that may better identify the actual pathways that increase the risk of cancer and other diseases in relation to obesity.

REFERENCE

1. Siegel, R., C. Desantis, and A. Jemal, *Colorectal cancer statistics, 2014.* CA Cancer J Clin, 2014. **64**(2): p. 104-17.
2. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA Cancer J Clin, 2015. **65**(1): p. 5-29.
3. Ogden, C.L., et al., *Prevalence of childhood and adult obesity in the United States, 2011-2012.* Jama, 2014. **311**(8): p. 806-14.
4. Grover, S.A., et al., *Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study.* Lancet Diabetes Endocrinol, 2015. **3**(2): p. 114-22.
5. Finkelstein, E.A., et al., *Annual medical spending attributable to obesity: payer-and service-specific estimates.* Health Aff (Millwood), 2009. **28**(5): p. w822-31.
6. NHLBI_Obesity_Education_Initiative, *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, in *The Evidence Report*. 1998: NIH.
7. Wolin, K.Y., K. Carson, and G.A. Colditz, *Obesity and cancer.* Oncologist, 2010. **15**(6): p. 556-65.
8. Calle, E.E., et al., *Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults.* N Engl J Med, 2003. **348**(17): p. 1625-38.
9. Renehan, A.G., et al., *Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.* Lancet, 2008. **371**(9612): p. 569-78.
10. Reeves, G.K., et al., *Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study.* BMJ, 2007. **335**(7630): p. 1134.
11. Jain, R., et al., *Clinical studies examining the impact of obesity on breast cancer risk and prognosis.* J Mammary Gland Biol Neoplasia, 2013. **18**(3-4): p. 257-66.
12. Karagozian, R., Z. Derdak, and G. Baffy, *Obesity-associated mechanisms of hepatocarcinogenesis.* Metabolism, 2014. **63**(5): p. 607-17.
13. Bracci, P.M., *Obesity and pancreatic cancer: overview of epidemiologic evidence and biologic mechanisms.* Mol Carcinog, 2012. **51**(1): p. 53-63.
14. Allott, E.H., E.M. Masko, and S.J. Freedland, *Obesity and prostate cancer: weighing the evidence.* Eur Urol, 2013. **63**(5): p. 800-9.
15. Research, W.C.R.F.A.I.f.C., *Food, nutrition, physical activity, and the prevention of cancer: a global perspective.* . 2007, AICR: Washington, DC.
16. Cancer, I.A.f.R.o., *IARC handbooks of cancer prevention*, in *Weight control and physical activity*. 2002: Lyon.
17. *Body weight and cancer risk*, in *Excess body weight: A major health issue in America* 2013, American Cancer Society.
18. Han, X., et al., *Body mass index at early adulthood, subsequent weight change and cancer incidence and mortality.* Int J Cancer, 2014. **135**(12): p. 2900-9.
19. Munsell, M.F., et al., *Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status.* Epidemiol Rev, 2014. **36**(1): p. 114-36.

20. Giovannucci, E., et al., *Body mass index and risk of prostate cancer in U.S. health professionals.* J Natl Cancer Inst, 2003. **95**(16): p. 1240-4.
21. Freedland, S.J., E. Giovannucci, and E.A. Platz, *Are findings from studies of obesity and prostate cancer really in conflict?* Cancer Causes Control, 2006. **17**(1): p. 5-9.
22. Hsing, A.W., L.C. Sakoda, and S. Chua, Jr., *Obesity, metabolic syndrome, and prostate cancer.* Am J Clin Nutr, 2007. **86**(3): p. s843-57.
23. MacInnis, R.J. and D.R. English, *Body size and composition and prostate cancer risk: systematic review and meta-regression analysis.* Cancer Causes Control, 2006. **17**(8): p. 989-1003.
24. Gallagher, E.J. and D. LeRoith, *Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer.* Diabetes Care, 2013. **36 Suppl 2**: p. S233-9.
25. Dimitriadis, G., et al., *Insulin effects in muscle and adipose tissue.* Diabetes Res Clin Pract, 2011. **93 Suppl 1**: p. S52-9.
26. Kahn, B.B. and J.S. Flier, *Obesity and insulin resistance.* J Clin Invest, 2000. **106**(4): p. 473-81.
27. Giovannucci, E., *Nutrition, insulin, insulin-like growth factors and cancer.* Horm Metab Res, 2003. **35**(11-12): p. 694-704.
28. Graham, S., et al., *Dietary epidemiology of cancer of the colon in western New York.* Am J Epidemiol, 1988. **128**(3): p. 490-503.
29. Kune, G.A., S. Kune, and L.F. Watson, *Body weight and physical activity as predictors of colorectal cancer risk.* Nutr Cancer, 1990. **13**(1-2): p. 9-17.
30. Dietz, A.T., et al., *The association of body size and large bowel cancer risk in Wisconsin (United States) women.* Cancer Causes Control, 1995. **6**(1): p. 30-6.
31. Le Marchand, L., et al., *Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer.* Cancer Res, 1997. **57**(21): p. 4787-94.
32. Caan, B.J., et al., *Body size and the risk of colon cancer in a large case-control study.* Int J Obes Relat Metab Disord, 1998. **22**(2): p. 178-84.
33. Russo, A., et al., *Body size and colorectal-cancer risk.* Int J Cancer, 1998. **78**(2): p. 161-5.
34. Slattery, M.L., et al., *Energy balance and colon cancer--beyond physical activity.* Cancer Res, 1997. **57**(1): p. 75-80.
35. West, D.W., et al., *Dietary intake and colon cancer: sex- and anatomic site-specific associations.* Am J Epidemiol, 1989. **130**(5): p. 883-94.
36. Le Marchand, L., L.R. Wilkens, and M.P. Mi, *Obesity in youth and middle age and risk of colorectal cancer in men.* Cancer Causes Control, 1992. **3**(4): p. 349-54.
37. Slattery, M.L., et al., *Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States).* Cancer Causes Control, 2003. **14**(1): p. 75-84.
38. Ford, E.S., *Body mass index and colon cancer in a national sample of adult US men and women.* Am J Epidemiol, 1999. **150**(4): p. 390-8.
39. Murphy, T.K., et al., *Body mass index and colon cancer mortality in a large prospective study.* Am J Epidemiol, 2000. **152**(9): p. 847-54.
40. Lee, I.M. and R.S. Paffenbarger, Jr., *Quetelet's index and risk of colon cancer in college alumni.* J Natl Cancer Inst, 1992. **84**(17): p. 1326-31.
41. Bostick, R.M., et al., *Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States).* Cancer Causes Control, 1994. **5**(1): p. 38-52.
42. Chyou, P.H., A.M. Nomura, and G.N. Stemmermann, *A prospective study of colon and rectal cancer among Hawaii Japanese men.* Ann Epidemiol, 1996. **6**(4): p. 276-82.
43. Giovannucci, E., et al., *Physical activity, obesity, and risk for colon cancer and adenoma in men.* Ann Intern Med, 1995. **122**(5): p. 327-34.
44. Martinez, M.E., et al., *Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group.* J Natl Cancer Inst, 1997. **89**(13): p. 948-55.
45. Lin, J., et al., *Body mass index and risk of colorectal cancer in women (United States).* Cancer Causes Control, 2004. **15**(6): p. 581-9.
46. MacInnis, R.J., et al., *Body size and composition and colon cancer risk in men.* Cancer Epidemiol Biomarkers Prev, 2004. **13**(4): p. 553-9.
47. Moore, L.L., et al., *BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults.* Int J Obes Relat Metab Disord, 2004. **28**(4): p. 559-67.
48. Terry, P., et al., *Body weight and colorectal cancer risk in a cohort of Swedish women: relation varies by age and cancer site.* Br J Cancer, 2001. **85**(3): p. 346-9.
49. Garfinkel, L., *Overweight and cancer.* Ann Intern Med, 1985. **103**(6 (Pt 2)): p. 1034-6.
50. Must, A., et al., *Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935.* N Engl J Med, 1992. **327**(19): p. 1350-5.
51. Nomura, A., L.K. Heilbrun, and G.N. Stemmermann, *Body mass index as a predictor of cancer in men.* J Natl Cancer Inst, 1985. **74**(2): p. 319-23.

52. Phillips, R.L. and D.A. Snowdon, *Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists.* J Natl Cancer Inst, 1985. **74**(2): p. 307-17.
53. Thun, M.J., et al., *Risk factors for fatal colon cancer in a large prospective study.* J Natl Cancer Inst, 1992. **84**(19): p. 1491-500.
54. Wu, A.H., et al., *Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study.* Br J Cancer, 1987. **55**(6): p. 687-94.
55. Chute, C.G., et al., *A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women.* Cancer Causes Control, 1991. **2**(2): p. 117-24.
56. Gerhardsson de Verdier, M., et al., *Diet, body mass and colorectal cancer: a case-referent study in Stockholm.* Int J Cancer, 1990. **46**(5): p. 832-8.
57. Moghaddam, A.A., M. Woodward, and R. Huxley, *Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(12): p. 2533-47.
58. Ning, Y., L. Wang, and E.L. Giovannucci, *A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies.* Obes Rev, 2010. **11**(1): p. 19-30.
59. Pischon, T., et al., *Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC).* J Natl Cancer Inst, 2006. **98**(13): p. 920-31.
60. Nelson, H.D., et al., *Postmenopausal hormone replacement therapy: scientific review.* Jama, 2002. **288**(7): p. 872-81.
61. Rossouw, J.E., et al., *Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.* Jama, 2002. **288**(3): p. 321-33.
62. Bjorge, T., et al., *Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents.* Am J Epidemiol, 2008. **168**(1): p. 30-7.
63. Nimptsch, K., et al., *Body fatness during childhood and adolescence, adult height, and risk of colorectal adenoma in women.* Cancer Prev Res (Phila), 2011. **4**(10): p. 1710-8.
64. Hughes, L.A., et al., *Body size and colorectal cancer risk after 16.3 years of follow-up: an analysis from the Netherlands Cohort Study.* Am J Epidemiol, 2011. **174**(10): p. 1127-39.
65. Nock, N.L., et al., *Associations between obesity and changes in adult BMI over time and colon cancer risk.* Obesity (Silver Spring), 2008. **16**(5): p. 1099-104.
66. Bassett, J.K., et al., *Body size, weight change, and risk of colon cancer.* Cancer Epidemiol Biomarkers Prev, 2010. **19**(11): p. 2978-86.
67. Renehan, A.G., et al., *Body mass index at different adult ages, weight change, and colorectal cancer risk in the National Institutes of Health-AARP Cohort.* Am J Epidemiol, 2012. **176**(12): p. 1130-40.
68. Steins Bisschop, C.N., et al., *Weight change later in life and colon and rectal cancer risk in participants in the EPIC-PANACEA study.* Am J Clin Nutr, 2014. **99**(1): p. 139-47.
69. Aleksandrova, K., et al., *Adult weight change and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition.* Eur J Cancer, 2013. **49**(16): p. 3526-36.
70. Laake, I., et al., *A prospective study of body mass index, weight change, and risk of cancer in the proximal and distal colon.* Cancer Epidemiol Biomarkers Prev, 2010. **19**(6): p. 1511-22.
71. Thygesen, L.C., et al., *Prospective weight change and colon cancer risk in male US health professionals.* Int J Cancer, 2008. **123**(5): p. 1160-5.
72. Keum, N., et al., *Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies.* J Natl Cancer Inst, 2015. **107**(3).
73. *What are the risk factors for colorectal cancer?* Dec 13, 2014 [cited 2015 Jan 28]; Available from: http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-risk-factors.
74. WHO, *Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee*, in *WHO Technical Report Series* 1995, World Health Organization: Geneva.

Kexin Jin

Address: 929 North Wolfe Street, Baltimore MD 21205, USA
Email: kjin5@jhu.edu
Phone: +1-410-736-1735

PROFILE

- Master of Science candidate in Epidemiology
- Excellent analytical and statistical skills with proficient mastery of STATA, SAS and R.
- Trained as a physician in China, fluent in Chinese

EDUCATION

Master of Science (ScM) **expected May 2015**

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
Major/Track: Epidemiology / Cancer Epidemiology
Thesis: Association between prediagnostic weight change and colon cancer risk in a prospective cohort (Dr. Genevieve Matanoski)
Accumulative GPA: 3.9/4.0
Relevant Coursework: Epidemiologic Methods (4 terms), Methods in Biostatistics (4 terms), Statistical Methods in Public Health (4 terms), Principle of Genetic Epidemiology (4 terms), Advanced Methods for Design and Analysis of Cohort Studies, Etiology Prevention and Control of Cancer, Epidemiology of Infectious Disease, Molecular Epidemiology and Biomarkers in Public Health, Introduction to SAS package, STATA programming, Statistical Computing, Introduction to Clinical Trials, Introduction to Systematic Reviews and Meta-Analysis

Certificates **expected May 2015**

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
Pharmacoepidemiology and Drug Safety
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
Environmental and Occupational Health

Bachelor of Medicine **July 2013**

Nanjing Medical University, P.R. China
Major: Preventive Medicine/Public Health
Accumulative GPA: 3.92/4.00
Relevant Coursework:

College level of Maths, Physics, Chemistry and social sciences;
Basic Medical Sciences:
Systematic Anatomy, Histology and Embryology, Physiology, Pathoanatomy, Pathophysiology, Microbiology and Immunology, Sanitary Microbiology, Human Parasitology;
Clinical Medicine:
Diagnostics, Internal Medicine, Basis of Surgery, Surgery, Obstetrics and Gynecology, Pediatrics, Infectious Diseases, Otorhinolaryngology, Neurology and Psychiatry, Ophthalmology, Stomatology, Dermatology and Venereology, Nuclear Medicine, Medical Imageology;
Public Health:
Medical Statistics, Fundamentals of Epidemiology, Data Management and Analysis of Medical Research, Toxicology, Environmental Health Sciences, Occupational Health and Occupational Medicine, Nutrition and Food Hygiene, Child and Adolescent Health

PUBLICATIONS

• Ji X., Wu B., **Jin K,** et al. 2014. MUC5B Promoter Polymorphisms and Risk of Coal Workers' Pneumoconiosis in a Chinese Population. Mol Biol Rep, 2014:41(7): p. 4171-6.

• **Jin K**, et al. 2012. The MIF -173G/C Polymorphism and Risk of Coal Workers' Pneumoconiosis in a Chinese Population. Int J Interferon Cytokine Mediator Res, 2012:4, p. 37-42（full article can be downloaded from http://dx.doi.org/10.2147/IJICMR.S30329)
• Ji X, Hou Z, Wang T, **Jin K**, et al. 2012. Polymorphisms in Inflammasome Genes and Risk of Coal Workers' Pneumoconiosis in a Chinese Population. PLoS One, 2012:7(10).

RESEARCH SKILLS

Data Analysis
• Proficient with: STATA, SAS, R and MS Excel;
• Familiar with: Haploview, PLINK, MERLIN, Visual Foxpro and Visual Basic
Lab Skills
• Biochemistry/Molecular Biological/Immunology experiments including TaqMan Real Time PCR, indirect ELISA, Western Blot and SDS-PAGE; in vivo Physiological/Pharmacological/Toxicological experiments; instrumental analysis including HPLC, GC, LC, AAS and MFS; bacteria culture, isolation and identification experiments
Protocol Development, Manuscript Preparation, Draft reports etc.

RESEARCH/TEACHING EXPERIENCE

Research Assistant
Dpt of Epidemiology, Johns Hopkins Bloomberg School of Public Health 06/2014 to present
US Cochrane Center
• Doing article screening, data abstraction, risk of bias evaluation for systematic review and meta-analyses of clinical trials

Teaching Assistant
02/2014 to 06/2014
Dpt of Epidemiology, Johns Hopkins Bloomberg School of Public Health
• Lab instructor for *Fundamentals of Epidemiology* Course; Held lab sessions, TA office hours, and did homework grading

Research Assistant
07/2011~06/2013
Dpt of Occupational Medicine and Environmental Health, Nanjing Medical University SPH
• Investigated the possible relationship between single nucleotide polymorphisms (SNPs, including MIF, MUC5B etc.) and their susceptibility to coal workers' pneumoconiosis (CWP) in a Chinese population

Lead Researcher
06/2010~06/2011
National Experiment Teaching and Demonstration Center of Preventive Medicine, Nanjing Medical University SPH
• Studied the dietary apigenin exposure level of Nanjing residents and investigated apigenin's DNA damage protection and Designed and carried out an dietary investigation among more than 1000 citizens; determined the apigenin level in vegetables and fruits and estimated its exposure level in Nanjing Residents' daily meals

RESEARCH PROJECTS

- SNP susceptibility to coal workers' pneumoconiosis (CWP) in a Chinese population 2012
  - Methods: Applied unconditional logistical regression to address MIF-173 CC genotype and its association with CWP; population: CWP case-control population from Xuzhou, China
  - Results: MIF-173 CC genotype was associated with a significantly decreased risk of CWP compared with the GG/GC genotype, particularly among smokers (adjusted odds ratio=0.44(0.22-0.85)); The MUC5B rs2672794 CC genotype was associated with a significantly increased risk of CWP (Odds ratio of CC genotype: 1.55 (1.08–2.21) , Odds ratio of C allele: 1.22 (1.04–1.43))
  - Advisors: Chunhui Ni
  - Pulications:
    • Ji X., Wu B., **Jin K,** et al. 2014. MUC5B promoter polymorphisms and risk of coal workers' pneumoconiosis in a Chinese population. Mol Biol Rep, 2014:41(7): p. 4171-6.

- **Jin K**, et al. 2012. The MIF -173G/C Polymorphism and Risk of Coal Workers' Pneumoconiosis in a Chinese Population. Int J Interferon Cytokine Mediator Res, 2012:4, p. 37-42（article at http://dx.doi.org/10.2147/IJICMR.S30329)

- Socioeconomic factors on all-cause mortality among seroconverted men who had sex with men: the Multicenter AIDS Cohort Study
  2014
  - Methods: Applied generalized gamma distribution models to address the impact of SES (income and education) on death of HIV-positive homosexual men
  - Results: higher income level has consistent protective effect on relative time to all-cause mortality among homosexual men initiated with HAART both with and without inverse probability weighting on other socioeconomic factors (Relative Hazard = 0.47(0.34,0.56) and 0.44(0.32, 0.62))
  - Advisors: Alvaro Muñoz, Christopher Cox

- Smoking and Progression to AIDS Among MSM In The Pre-HAART Era: Addressing Confounding Bias
  2014
  - Methods: Applied propensity score method to address bias in the association between smoking and progression to AIDS among homosexual men in the pre-HAART era in MACS
  - Results: found no statistically significant effect for smoking with propensity score matched with six subclasses or with double robust estimate (Relative hazard=1.01909(0.9046, 1.1480) and 1.0092(0.8961, 1.1366))
  - Advisors: Alison Abraham

- Medical Interventions for Primary Open Angle Glaucoma Network Meta-Analysis 2014
  - Advisors: Tianjing Li, Kay Dickersin
  - Responsibilities:
    - Manuscript preparation
    - Title/abstract/full text screening for meta-analyses for clinical trials on eye diseases;
    - Data abstraction, recording and discrepancies adjudication using Systematic Review Data Repository (SRDR) data system

- Intrastromal corneal ring segments for treating keratoconus
  2014
  - Advisors: Tianjing Li, Kay Dickersin, Kristina Lindsley
  - Responsibilities:
    - Manuscript preparation
    - Title/abstract/full text screening for meta-analyses for clinical trials on eye diseases;
    - Data abstraction, recording and discrepancies adjudication using Systematic Review Data Repository (SRDR) data system

PUBLIC HEALTH EXPERIENCE

Data abstractor 05/2014 to 08/2014
International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health
- Data Abstraction

Public Health Administrator
07/2012~08/2012
Nanjing Health Supervision State at Qinhuai District
- Assisted in issuing of health administrative licenses

Physician Assistant/Surgeon Assistant
02/2011~01/2012
Yixing People's Hospital
- Assisted in surgeries, performed physical examinations, wrote and maintained medical records, interacted with and comforted patients, developed key medical skills

Public Health Administrator
07/2010~07/2010
Jiangsu Provincial Center for Disease Control

- Collected data about the situation of iodine deficiency diseases (IDD) in Jiangsu Province
- Assisted in voluntary counseling and testing program for homosexual men

VOLUNTEER ACTIVITIES

Volunteer

12/2011~08/2013

The Second Youth Olympic Games/The Second Asian Youth Games

- Participated overall preparations for games: oral interpretation for visitors and maintenance of YOG website

Vice President

11/2008~03/2010

Wind Orchestra of Nanjing Medical University

- Coordinated rehearsals and logistics for orchestra and performed at several universities

Peer educator

11/2008~01/2009

The Red Ribbon Peer Association

- Hosted AIDS Peer Education among college students

AWARD AND HONORS

- BSPH Masters Tuition Scholarship for Academic Year 2014-2015
- Excellent Student Scholarship for Academic Year 2008-2009, 2009-2010 and 2010-2011
- Best Student Leader Award for the Year of 2008, 2009 and 2010
- Innovation Scholarship for Academic Year 2009-2010
- Shanghai Interpretation Accreditation (SIA)(gained in Nov 2010)
- Third Prize in National English Contest for College Students (gained in May 2010)