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Association of Individual and Combined Metabolic Risk Factors with Cancer

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Keywords: Metabolic syndrome, metabolic risk factors, cancer, meta-analysis, breast cancer

Abstract

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Introduction: The prevalence of metabolic risk factors (MRFs), individually and in the aggregate, is growing rapidly. There is limited biologic and epidemiologic evidence indicating an association between MRFs and cancer. The goal of this dissertation was to examine the association between individual and combined MRFs with subsequent risk of overall and site-specific cancers of the breast, digestive system, and lung.
Methods: A systematic review with meta-analysis on the association between metabolic syndrome (a cluster of MRFs) and breast cancer was conducted. In addition, associations between MRFs and risk of overall and site-specific cancers were assessed by multivariable Cox proportional hazards regression models. Lastly, associations between MRFs and age at cancer onset were examined by multiple linear regression analyses, using the general linear model. Data were derived from the NHANES I Epidemiologic Follow-up Study, and comprised participants ages 25 to 74 years at baseline. The primary metabolic risk factors were obesity (measured by BMI), high blood pressure, high total serum cholesterol, and diabetes. Analyses were adjusted for age, race, education, family income, physical activity, smoking status, and family history of cancer, and stratified by age and gender. All analyses incorporated the complex sample design and sample weights to produce national estimates.
Results: Results from the meta-analysis show that metabolic syndrome was modestly associated with an increased risk for breast cancer in adult women. Findings from the study on the association between individual and combined MRFs and cancer risk suggest that diabetes independently, and presence of a combination of MRFs, may serve as markers for postmenopausal breast cancer risk. The association between diabetes and a combination of three or four MRFs and earlier age at onset was observed not only for postmenopausal breast cancer, but also for overall cancer in women 50 and older, digestive cancer in women, and lung cancer in males.
Conclusion: Future research needs to examine this association between MRFs and site-specific cancers using specific, objective metabolic markers. The positive association of MRFs with postmenopausal breast cancer points toward the need to develop public health strategies to manage these risk factors.

Keywords: Metabolic syndrome, metabolic risk factors, cancer, meta-analysis, breast cancer

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CHAPTER 1. INTRODUCTION

1.1 Introduction

Cancer, the "plague of our generation,"[1] will have been diagnosed in 1.7 million men and women in the US in 2013.[2] Accounting for one in four deaths, cancer is the second most common cause of death in the United States (US) after heart disease.[3] There are four important causes of cancer: (a) genetic factors, (b) lifestyle factors, (c) infections, and (d) environmental exposures.[4] Only 5-10% of all cancers can be attributed to genetic causes.[4] Lifestyle factors play a significant role in cancer development and progression. The World Cancer Research Fund estimates that 25-33% of new cancer cases in the US in 2013 are related to behavioral and lifestyle factors, such as overweight or obesity, physical inactivity, and poor nutrition.[5] Research studies estimate half of the cancer burden can be prevented or significantly reduced by modifying lifestyle factors.[6, 7]

Lifestyle factors can generate metabolic abnormalities that include overweight and obesity, and high blood pressure, cholesterol, and blood glucose. Epidemiologic evidence supports the association between each of these individual metabolic risk factors (MRFs) and cancer risk.[8-22] A few studies have also reported that cancer risk increases with the number of MRFs.[23-33]

Several complex biological mechanisms have been proposed to show metabolic risk factors promoting carcinogenesis. In brief, metabolic risk factors, functioning through various mechanisms, including increased inflammatory markers, such as tumor necrosis factor-alpha and interleuken-6, increased adipokines such as leptin, and decreased adiponectin, increased levels of free fatty acids and triglycerides, insulin resistance, increased insulin-like growth factor-1, and increased oxidative stress, can cause angiogenesis, cell migration, mitogenesis, and DNA damage.[34]

Despite the epidemiologic studies and limited experimental evidence supporting the biological role of MRFs in cancer development and progression, results from studies examining the association between individual and combined MRFs and overall cancer are inconsistent. Therefore, the goal of this dissertation was to assess the individual and combined effects of MRFs on subsequent risk of cancer. It comprises three inter-related studies on cancer risk from metabolic risk factors. The background and methods of each of the three papers from the dissertation are discussed briefly.

1.2 Study 1 Background: Metabolic Syndrome is associated with increased breast cancer risk: A systematic review with meta-analysis

In the first paper of this dissertation, a systematic review with meta-analysis was conducted to comprehensively synthesize existing literature on the association between metabolic syndrome and breast cancer incidence. The most common cancer in women worldwide is breast cancer, which accounted for 1.38 million new cases in 2008, comprising approximately a quarter (23%) of all new cancer cases.[35] Traditional risk factors for breast cancer are well known as age, family history of cancer, and reproductive and menstrual history, but lifestyle risk factors such as overweight, lack of physical activity, and consumption of alcohol are also crucial.[36] Several of these risk factors are associated with metabolic syndrome (MS).[37]

Metabolic syndrome (MS) is a cluster of pathophysiological disorders comprising central obesity, insulin resistance, high blood pressure, and dyslipidemia.[37] MS has been identified as a risk factor for several cancers, particularly breast, pancreatic, colorectal, and prostate cancers.[25, 26, 28, 30-32, 38-45] Individual components of MS are positively associated with the development of certain cancers, most notably breast cancer.[46-52] Yet, studies show mixed results in these

associations.[29, 33, 53] Although some of the components of MS may not be strongly associated with the development of breast cancer, they may all work together to elevate the risk.[34] This possibility suggests that MS may influence breast tumorigenesis by activating different molecular pathways through endocrine, metabolic, and immune cell changes.[54]

However, results from previous epidemiologic studies are inconsistent with respect to MS and breast cancer risk. Given the conflicting results from individual studies of MS and breast cancer risk in all adult women, this study used the aggregate data meta-analytic approach to examine the association between MS and BC risk in women. Studies were retrieved by searching four electronic reference databases [PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and PROQUEST - June 30, 2012], and cross-referencing from retrieved articles. Eligible for inclusion were longitudinal studies that reported associations between MS and breast cancer risk among females aged 18 years and older. Relative risks (RR) and associated 95% confidence intervals (95% CI) were calculated for each study, and then pooled using fixed and random-effects models. Publication bias was assessed both quantitatively (trim and fill)[55] and qualitatively (funnel plots). Heterogeneity was examined using Q and I^2 statistics.[56]

1.3 Study 2 Background: Association between individual and combined metabolic risk factors and subsequent risk of cancer

Comprehensive reviews provide evidence of association between individual MRFs, such as obesity, hypertension, diabetes, hypercholesterolemia, and overall and site-specific cancers. Epidemiologic reviews provide evidence of individuals with diabetes at a higher risk for most cancers.[9, 10, 12, 16, 18, 49] Studies also show an association between obesity and several cancers.[11, 13-

[15, 17, 47, 48, 57-59] However, results are less consistent for studies examining the association between blood pressure, cholesterol, and cancer.[19, 20, 60-66]

There is adequate evidence that the risk for heart disease and stroke increases with number of MRFs.[67, 68] A combination of three or more of the MRFs is generally termed as metabolic syndrome.[37] Metabolic syndrome is estimated to be prevalent in over a third of US adults.[69] A recent meta-analysis found that the combination of MRFs (metabolic syndrome) also elevated the risk for several cancers.[24]

Findings from observational as well as intervention studies have raised the hypothesis of an etiologic link between the clustering of MRFs and elevated risk of cancer.[70] Several complex biological mechanisms have been proposed to show that MRFs promote carcinogenesis. The prevalence of hyper-insulinemia and insulin resistance is higher in obese individuals. Hyper-insulinemia reduces the production of insulin-like growth factor (IGF) binding protein, resulting in increased bioavailability of IGF-1.[8] IGF-1 may promote tumor development by stimulating cell proliferation and inhibiting apoptosis. Increased circulating insulin can also reduce the levels of sex-hormone-binding-globulin, thereby increasing endogenous sex-steroid levels.[8] Breast, endometrial, and colorectal cancers may be affected by this mechanism.[71] Another carcinogenic mechanism involves cytokines. Increased adiposity raises cytokine production in obese women, which in turn can induce estradiol production.[34] Estradiol is a strong growth factor for breast and endometrial cancers. Leptin, another adipocyte-specific hormone, is directly related to adiposity and insulin resistance. It has direct stimulatory effects on cancer cells and may serve as an important link between obesity and carcinogenesis.[34]

However, studies are not consistent in predicting an elevated cancer risk from MRFs. With the background of increasing prevalence of metabolic syndrome, and epidemiologic

evidence and biologic possibility of the association between MRFs and cancer risk, this study examined the association of MRFs (obesity, high blood pressure, high total serum cholesterol, and diabetes), individually and in combination, and subsequent risk of overall and site-specific cancers of the breast, digestive system, and lung respectively.

Data were derived from the NHANES I Epidemiologic Follow-up Study, and comprised participants ages 25 to 74 years at baseline. Multivariable Cox proportional hazards regression models were fitted to assess the association between individual and combined MRFs and cancer incidence. Analyses were adjusted for age, race, education, family income, physical activity, smoking status, and family history of cancer, and stratified by age and gender. All analyses incorporated the complex sample design and sample weights in order to generate national estimates.

1.4 Study 3 Background: Association between metabolic risk factors and age at cancer onset

Several epidemiologic studies have shown that MRFs elevate the risk of overall and several site-specific cancers.[8-22, 23-33] However, very few studies have examined whether MRFs are associated with earlier age at cancer onset. There are a few studies showing overweight, obesity, and hypertension being associated with earlier age at cancer onset.[59, 66, 72]

Animal studies suggest that mechanisms which prevent metabolic abnormalities, by reducing serum IGF-1 or androgen concentrations, may delay the growth and progression of breast and prostate cancers.[73] An animal study found that mammary tumors developed earlier in diet-induced obese rats than in lean rats, supporting the role of hormones and adipokines (produced by adipose tissue) in cell proliferation and carcinogenesis.[74]

The aim of this study was to examine whether MRFs, either individually or in combination, were associated with age at onset of all-site cancer, and cancer of the breast, digestive system, and lung respectively. It is an important research question for several reasons. First, studies show that age at onset of certain cancers, such as breast, cervical, and prostate cancers, is temporally decreasing.[75] Second, earlier cancer onset shortens life expectancy, signifying major loss of potential years of life.[76-78] Third, compared with older patients, younger cancer patients are likely to have more aggressive cancers, less favorable prognosis, and poorer outcomes.[76-78] Fourth, earlier age at cancer onset in a family may increase cancer risk for the next generation.[79, 80]

Data were derived from the NHANES I Epidemiologic Follow-up Study, and comprised participants ages 25 to 74 years at baseline. The outcome variable was age at cancer onset, and the primary metabolic risk factors were obesity, high blood pressure, high total serum cholesterol, and diabetes. Analyses were adjusted for age, race, education, family income, physical activity, smoking status, and family history of cancer, and stratified by age and gender. Multiple linear regression analyses, using the general linear model, were conducted to assess the relationship between MRFs and age at cancer onset. All analyses incorporated the complex sample design and sample weights to produce national estimates.

Each of the three papers is presented in detail in the next three chapters (Chapters 2-4). The last chapter (Chapter 5) summarizes the findings from each of the papers and raises key discussions points before concluding this research study.

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CHAPTER 2. METABOLIC SYNDROME IS ASSOCIATED WITH INCREASED BREAST CANCER RISK: A SYSTEMATIC REVIEW WITH META-ANALYSIS

2.1 Abstract

Background

While positive and statistically significant associations between individual metabolic risk factors and breast cancer risk have been reported, controversy surrounds risk of breast cancer from metabolic syndrome (MS). We report the first systematic review and meta-analysis of the association between MS and breast cancer risk in all adult females.

Methods

Studies were retrieved by searching four electronic reference databases [PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and PROQUEST - June 30, 2012], and cross-referencing from retrieved articles. Eligible for inclusion were longitudinal studies that reported associations between MS and breast cancer risk among females aged 18 years and older. Relative risks (RR) and associated 95% confidence intervals (95% CI) were calculated for each study, and then pooled using random-effects models. Publication bias was assessed both quantitatively (trim and fill) and qualitatively (funnel plots). Heterogeneity was examined using Q and I^2 statistics.

Results

Representing nine independent cohorts and 97,277 adult females, eight studies met the inclusion criteria. A modest, positive association was observed between MS and breast cancer risk (RR: 1.47, 95% CI, 1.15-1.87; z = 3.13; p = 0.002; Q = 26.28, p =.001; I^2 = 69.55%). No publication bias was observed.

Conclusions

MS is associated with an increased risk for breast cancer in adult women.

2.2 Introduction

Breast cancer, the most common cancer in women worldwide, accounted for 1.38 million new cases in 2008, comprising approximately a quarter (23%) of all new cancer cases.[1] While traditional risk factors for breast cancer include age, family history of cancer, and reproductive and menstrual history, the National Cancer Institute also recognizes overweight, lack of physical activity, and consumption of alcohol as risk factors.[2] Several of these risk factors are associated with metabolic syndrome.[3]

Metabolic syndrome (MS) is a cluster of pathophysiological disorders comprising central obesity, insulin resistance, high blood pressure, and dyslipidemia. Reaven's definition of MS in 1988[4] was followed by definitions from the World Health Organization,[5] National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III),[6] American Heart Association/National Heart, Lung, and Blood Institute,[7] and the International Diabetes Federation.[8] The NCEP's ATP III guidelines are the most commonly used criteria in the U.S.[6] These criteria include the presence of three or more of the following[3]: abdominal obesity (waist circumference ≥ 35 inches in women), triglycerides ≥ 150 mg/dL, high density lipoprotein cholesterol (HDL-C) < 50 mg/dL, blood pressure (BP) ≥ 130/85 mmHg, and fasting glucose ≥ 110 mg/dL. MS is estimated to be prevalent in at least a quarter of the adults in the Americas, in Europe, and in India.[9]

MS has been identified as a risk factor for several cancers, particularly breast, pancreatic, colorectal, and prostate cancers.[10-15] Individual components of MS, for example, abdominal obesity, high blood glucose, high BP, high triglycerides, and low HDL, are positively associated with the development of certain cancers, most notably breast cancer.[16-27] While studies show a positive association of breast cancer with diabetes[19, 28-33] and obesity,[16, 34, 35] others show a

negative association with obesity in premenopausal women.[36-38] Mixed results also characterize hypertension[22, 23,39, 40] and dyslipidemia[22, 41, 42] as risk factors for breast cancer.

Although individual components of MS may not be strongly associated with the development of breast cancer, their combination may elevate the risk.[13, 14, 43-56] For example, MS may activate different molecular pathways through endocrine, metabolic, and immune cell changes, which in turn influence breast tumorigenesis.[47] Such pathways that enhance breast cancer cell proliferation and inhibit apoptosis, include: (1) increased levels of circulating estrogen, e.g., estradiol,[52, 54, 57] (2) higher levels of insulin,[58, 59] (3) decreased level of circulating adiponectin,[60] and (4) increased plasma leptin concentration.[60]

Results from previous epidemiologic studies are inconsistent with respect to MS and breast cancer risk. For example, only four[13, 14, 43, 51] of eight studies[13, 14, 43, 48, 51, 61-63] reported a statistically significant association between MS and risk of breast cancer. Therefore, one might conclude that the association between MS and breast cancer risk is unknown. However, such a conclusion would be based on the vote-counting approach, an approach that ignores the magnitude of the association.[64]

A recent systematic review and meta-analysis of MS and postmenopausal breast cancer found that MS was moderately associated with the risk of postmenopausal breast cancer.[10] However, to the best of our knowledge, no meta-analytic research has addressed the conflicting results from individual studies of MS and breast cancer risk in all adult women. Therefore, the purpose of this study was to use the aggregate data meta-analytic approach to examine the association between MS and breast cancer risk in women.

2.3 Methods

2.3.1 Study Eligibility

The *a priori* inclusion criteria for this study were as follows: (1) observational studies using cohort (both prospective and retrospective), case-control, or nested case-control study designs; (2) studies examining the association between MS (presence of a cluster of three or more metabolic abnormalities) and breast cancer incidence, as defined by the authors; (3) studies with adult females ≥ 18 years of age as participants; (4) English-language studies published as journal articles, doctoral dissertations, or masters' theses; (5) published and indexed studies up to June 30, 2012; and (6) studies reporting sufficient data (e.g., rate ratios, risk ratios, odds ratios, standardized incidence ratios, hazard ratios, or frequencies) for calculating a common effect size.

Studies not meeting all inclusion criteria were excluded from this review. Excluded studies were those that: (1) were not published as full reports, such as conference abstracts and letters to editors; (2) only examined individual components of MS; (3) measured the MS variables at the time of cancer diagnosis; (4) used cancer mortality, rather than incidence, as the outcome; and (5) studies published in a language other than English.

2.3.2 Data Sources

A comprehensive and systematic search was conducted using four electronic databases: PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and PROQUEST (from their commencement to June 30, 2012). Since the term MS dates back to the late 1950s, with variations in use as early as the 1920s, the start dates of each of the databases were used as the commencement date for study search; Web of Science (1900), CINAHL (1952), PubMed (1966), and Proquest (1861). In addition, cross-referencing from retrieved studies was also performed. Major keywords used in the search for potentially eligible studies included "metabolic syndrome" ("insulin resistance syndrome," "syndrome x,") and "breast cancer" ("neoplasm and breast"). Using the most recent publication, trials published as duplicate reports

(parallel publications) were only included once. All electronic searches were conducted using the graphical user interface for each database. The last search was conducted on June 30, 2012.

2.3.3 Study Selection

At the first screening, one author screened all abstracts and selected articles for full-text examination. At the second level of the study selection process, two of the authors examined the full-text articles and then selected the included studies following mutual discussion and consensus.

2.3.4 Data Extraction

Two of the authors reviewed every study selected and independently extracted data from studies onto electronic coding forms. These forms could hold up to 52 items per study. Attempts were made to contact authors of three of the original studies for missing information,[13, 61, 63] but only one provided the requested information.[13] After initial coding, the two coders reviewed each item for agreement. Discrepancies were resolved by consensus. Using Cohen's kappa (*k*) statistic,[65] the overall inter-rater agreement rate prior to correcting discrepant items, was 0.96 for all included studies.

2.3.5 Risk of Bias Assessment

Risk of bias was assessed using a modified version of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[66] The items assessed included: (1) study design, (2) adjustments for confounders, (3) selection of participants and their eligibility criteria, (4) measurement of predictor variables, (5) breast cancer diagnosis, (6) study size, (7) handling of missing data, and (8) reasons for non-participation of individuals at each stage of the study. A description of the criteria for risk of bias assessment is shown in Table 1. Two of the

authors conducted all assessments, independent of each other. Disagreements were resolved through discussion. No study was excluded based on the results of the risk of bias assessment.

2.3.6 Statistical Analysis

Calculation of study-level effect sizes. Risk estimates were used to examine the association between MS and risk of breast cancer. These were derived from reported relative risks, odds ratios, hazard ratios, incident rate ratios, or standardized incidence ratios, together with their respective 95% CIs, from the original studies. Where necessary and possible, all metrics were converted to risk ratios (RRs). Adjusted risk estimates from multivariable models in the original studies were pooled for analysis. However, for two case-control studies that were included,[14, 51] adjusted odds ratios were used because data necessary to convert to RR were not available.

Effect size pooling. All RR results were pooled using a random-effects model, an approach that incorporates between-study heterogeneity into the model.[67] A *z-score* two-tailed alpha value ≤ 0.05 was considered as statistically significant. In addition, 95% confidence intervals (CIs) were calculated for each result from each study as well as for pooled estimates. Heterogeneity was calculated using the Q[68] and I^2 statistics.[69] An alpha level ≤ 0.10 for the Q statistic was considered as evidence of statistically significant heterogeneity. While somewhat arbitrary, I^2 values of 25%, 50%, and 75% were considered to represent low, moderate and high amounts of heterogeneity.[69] Publication bias was assessed using the Trim and Fill approach of Duval and Tweedie.[70] In addition, Rosenthal's Fail-Safe N test was used to compute the number of missing null studies that would be needed to nullify the overall pooled RR as being statistically significant.[71] Statistically significant standardized residuals ($p \leq 0.05$) were considered as outliers.

Sensitivity analyses. In order to examine the effects of each result from each study on the overall pooled results, influence analysis was conducted with each result from each study deleted from the model once. Cumulative meta-analysis, ranked by year, was also conducted in order to examine the accumulation of results over time. A separate pooled analysis limited to postmenopausal women was conducted because studies show that MS in postmenopausal women increases the risk of breast cancer.[13, 14, 43, 48, 51, 61] In addition, pooled analyses were conducted with the following caveats *post hoc*: (1) deletion of results from two case-control studies because odds ratios were used instead of RR,[14, 51] (2) deletion of results from studies that were not prospective cohort designs,[13, 14, 51] and (3) limiting the results to studies that controlled for four or more of the important confounders (as listed in Table 1).[14, 43, 48, 51] All analyses were performed using Comprehensive Meta-Analysis, Version 2.2.[72]

2.4 Results

2.4.1 Study Characteristics

Figure 1 presents a flow diagram of the selection of studies for the meta-analysis. Of the 291 studies screened, 47 (16.2%) were selected for full-text review: 25 from PubMed,[14, 43-55, 63, 73-82] 17 from the Web of Science,[13, 39, 62, 83-96] one from CINAHL,[97] and four from ProQuest.[61, 98-100] Of the 47 that underwent a full-text review, eight (17.0%) met the eligibility criteria.[13, 14, 43, 48, 51, 61-63] One article[14] presented results for two independent cohorts; therefore, each cohort was treated independently.

A general description of the included studies is shown in Table 2. Studies were published between 2008 and 2012 and from five different countries. The study designs included four prospective cohorts,[48, 61-63] one retrospective cohort,[13] one prospective nested case-control,[43] and two case-control.[14, 51] The baseline year for cohort inception ranged from 1983 to 2004, with

average follow-up ranging between 2.7 and 13.5 years. Sample sizes ranged from 792 to 49,172 (total 97,277) adult females, excluding one study that did not report this data.[63] The ages of the participants ranged from 21 to 86 years. Six studies conducted analyses on postmenopausal women.[13, 14, 43, 48, 51, 61] The results of each cohort or case-control study were initially reported as a hazard ratio,[13, 48, 62] incidence rate ratio,[43, 61] standardized incidence ratio,[63] or odds ratio.[14, 51] Methods for exposure assessment, cancer identification and the controlling of confounders varied across the eight included studies (Table 3). Seven of the eight studies identified the outcome (breast cancer) through histological reports, medical reports, or from a cancer registry,[13, 14, 43, 48, 51, 61, 63] while one used self-report.[62] Only three studies examined invasive breast cancer cases.[43, 48, 63] One study also reported on the in situ breast cancer cases but there were only seven such cases in that study.[43] Another study analyzed all breast cancer cases (in situ and invasive) as well as invasive cancers separately, and the results remained the same in both analyses.[48]

2.4.2 Risk of Bias Assessment

Risk of bias results are shown in Table 4. All the studies were considered to be at low risk for selection of participants and meeting eligibility criteria as well as providing adequately powered sample sizes. Out of eight studies, a majority were also considered low risk with respect to study design (six studies) and measurement of the outcome variable (seven studies). In terms of handling potential confounders, half the studies were low risk, three were high risk, and one was unclear. Missing confounding variables included education, smoking status, alcohol use, family history of cancer, contraceptive use, or hormonal history. Similarly, half the studies had objective measurements of predictor variables, while the remainder relied on self-report, and were consequently considered high risk. Four studies deleted the participants with missing variables in their analyses (high risk), while two did not report how they handled missing data.

Lastly, six studies were considered high risk because they did not report the reasons for non-participation of subjects at each stage of follow-up.

2.4.3 Statistical Analysis

Overall Results. Overall, a statistically significant increase of 47% in the risk for incident breast cancer was observed for adult females with MS (RR: 1.47, 95% CI, 1.15-1.87; z = 3.13; p < 0.002; Q = 26.28, p <0.001; I^2 = 69.55%) (Figure 2). With the exception of one study,[62] all other studies had RR in the direction of increased risk.[13, 14, 43, 48, 51, 61, 63] Funnel plot results for potential publication bias are shown in Figure 3. Using the Trim and Fill approach that resulted in two imputations, the risk decreased by 16% but remained significant (RR: 1.31, 95% CI, 1.01-1.70). The fail-safe N was 69, implying that 69 'null' studies would be needed to nullify the statistically significant association between MS and breast cancer risk in adult females. No statistically significant outliers were identified (p = 0.06-0.82).

Sensitivity analysis. With each study deleted from the model once, results remained positive and statistically significant (Figure 4). As can be seen, the pooled RR fell within a range of 20% (RR = 1.36-1.56) and none of the CIs for the point estimates was less than 1.0. Cumulative meta-analysis, ranked by year, revealed that results have been statistically significant since 2011 (Figure 5). Deleting the two case-control studies from the model, the RR for incident breast cancer for women with MS decreased by 18% but was still statistically significant with moderate heterogeneity (RR: 1.29, 95% CI, 1.003-1.67; z = 1.98; p = 0.05; Q = 14.13, p = .01; I^2 = 64.61%). When limited to studies with only prospective designs, the RR decreased by 30% but remained statistically significant with very low heterogeneity (RR: 1.17, 95% CI, 1.01-1.36; z = 2.04; p =0.04; Q = 4.30, p = 0.37; I^2 = 7.04%). When limited to postmenopausal women, breast cancer risk increased by 34% and was still statistically significant with high heterogeneity (RR:

1.81, 95% CI, 1.28-2.56; z = 3.37; p =0.001; Q = 23.36, p =0.001; I^2 = 74.32%). Lastly, when limiting the results to studies that controlled for four or more of the important confounders (as listed in Table 1),[14, 43, 48, 51] breast cancer risk increased by 17% and was statistically significant with moderate heterogeneity (RR: 1.64, 95% CI, 1.23-2.20; z = 3.34; p =0.001; Q = 8.55, p =0.07; I^2 = 53.21%).

2.5 Discussion

The purpose of this aggregate data meta-analysis was to examine the association between MS and the risk for breast cancer in adult females. Overall results suggest that a modest positive association exists between MS and risk of breast cancer. This finding is strengthened by the robustness of results from other analyses. These include: (1) examination for publication bias, (2) influence analysis with each study deleted from the model once, (3) deletion of the two case-control studies with odds ratios from the overall model, (4) limiting the analysis to prospective designs, (5) including only postmenopausal women in the analysis, and (6) limiting the results to studies that controlled for four or more of the important confounders. The results from cumulative meta-analysis, ranked by year, indicate an increasingly statistically significant association since 2011.

Assessment for risk of bias indicated that a majority of studies were at low risk regarding study design, cancer assessment, and sample size. However, a majority were at high risk or unclear risk in terms of handling of missing data and non-participation of subjects at each stage of follow-up. It is suggested that future studies provide complete information on the handling of missing data and on the non-participation of subjects at each stage of follow-up.

When limited to postmenopausal women, a stronger association between MS and breast cancer was observed. This association was stronger in case-control and retrospective cohort

study designs compared with prospective cohort study designs. These findings concur with the recent meta-analysis on MS and breast cancer risk in postmenopausal women.[10] Several studies have shown that MS in postmenopausal women increases the risk of breast cancer,[43, 46, 101] suggesting that the etiology of breast cancer may differ among pre and postmenopausal women.

There are several potential mechanisms linking MS with the increased risk of breast cancer. First, obese postmenopausal women produce higher levels of estrogens, which in turn increase the biologically available fraction of circulating estradiol by reducing plasma concentration of sex hormone binding globulin (SHBG).[102] Low plasma SHBG levels are associated with insulin resistance[103, 104] and other components of MS.[105, 106] Second, adipose tissue produces two adipokines (cytokine-like factors), leptin and adiponectin, that affect breast cancer biology.[107] Higher plasma leptin levels are associated with obesity,[54, 57, 108] insulin resistance,[109, 110] and MS.[111, 112] Leptin stimulates human breast cancer cell lines, whereas adiponectin acts protectively, inhibiting the growth of these cell lines.[57, 107, 113] Obesity is associated with reduced adiponectin levels.[114] Third, insulin has been shown to have a mitogenic effect upon breast cancer cells in vitro through several mechanisms.[57] It can act synergistically with estradiol and stimulate proliferation of the cell line.[115] Insulin can also lower SHBG production,[116] thereby increasing biologically available estradiol. Moreover, low serum HDL-C concentrations indicate higher circulating bioactive estrogen levels, which in turn may stimulate target breast tissue.[76]

The increasing prevalence of MS, and its association with breast cancer, among other co-morbidities, point toward the critical need to develop public health strategies to manage MS. Given the increasingly large global burden of metabolic risk factors, even a small association with breast cancer can have a substantial public health impact. Risk assessment tools can be

developed that incorporate MS as a risk factor for breast cancer. Healthcare providers will then be better equipped to identify high-risk women for primary and secondary prevention.

This study has several strengths. First, to the best of our knowledge, this is the first systematic review and meta-analysis to examine the association between MS and risk of breast cancer in *all* adult women. The analysis incorporates all women, and a sub-analysis of post-menopausal women. The overlapping meta-analysis on metabolic syndrome and breast cancer was confined to post-menopausal women only.[10] Second, a number of other analyses were performed that strengthened the robustness of findings. Third, the results of this study provide direction for future research on this topic.

This study also has several potential limitations. These include (1) the different methods used to assess exposure, identify cancer, control for confounders, and define MS, (2) limiting studies to those published in English, which may have led to inflated results,[117] (3) the relatively small number of studies that met the inclusion criteria, (4) the inability of some studies to provide raw data for calculating the RR, (5) the different study designs employed, and (6) the varied populations studied.

In order to inform and undergird a biological rationale for the observed positive association between MS and breast cancer risk in adult females, future studies should consist of analyses based on a standard definition of MS and employ objective and standard biomarkers for assessing each MS component. In addition, adjustments for all important potential confounders need to be made. It would be helpful if future studies examined the relationship between MS and breast cancer risk separately in perimenopausal and premenopausal women since breast cancer in women may be estrogen-independent. Along those lines, not all studies adjusted for hormone replacement therapy, a potential confounder. Future studies should report this information.

Furthermore, future research needs to examine in situ and invasive cancers separately in relation to metabolic syndrome. Finally, a focus on obese women with respect to MS and breast cancer seems appropriate.

In conclusion, the overall results of this meta-analysis suggest that there is a modest positive association between MS and risk of breast cancer in adult females.

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Tables and Figures

The working tables and figures can be found in Appendix A.

CHAPTER 3. ASSOCIATION BETWEEN INDIVIDUAL AND COMBINED METABOLIC RISK FACTORS AND CANCER RISK

3.1 Abstract

Introduction

Cancer is the second most common cause of death in the United States. A third of the cancer burden is estimated to be associated with metabolic risk factors (MRFs), such as obesity, high blood glucose, hypertension, and dyslipidemia. However, studies have shown inconsistent results for the association between these MRFs and cancer risk. The aim of this study was to examine whether MRFs, either individually or in combination, were associated with the subsequent risk of overall and selected site-specific cancers of the breast, digestive system, and lung.

Methods

Data were derived from the NHANES I Epidemiologic Follow-up Study, and comprised participants ages 25 to 74 years at baseline. Multivariable Cox proportional hazards regression models were fitted to assess the association between individual and combined MRFs (obesity, high blood pressure, high total serum cholesterol, and diabetes) and cancer incidence. Analyses were adjusted for age, race, education, family income, physical activity, smoking status, and family history of cancer, and stratified by age and gender. All analyses incorporated the complex sample design and sample weights in order to generate national estimates.

Results

Diabetes, high BP, and the presence of a combination of three or four MRFs were associated with higher breast cancer risk among postmenopausal women. Obesity in males less than 50 years of age elevated the risk of digestive cancer.

Conclusion

In this large, prospective cohort study, MRFs, either individually or aggregated, were not consistently associated with cancer risk in either men or women. The association of individual and combined MRFs was stronger with postmenopausal breast cancer risk.

3.2 Introduction

The "plague of our generation,"[1] cancer is the second most common cause of death in the United States. The American Cancer Society estimates 1.7 million new cancer cases in 2013.[2] Cancer incidence rates per 100,000 persons (age-adjusted to the 2000 US standard population) for 1995-2009 were 550.7 and 419.3 for males and females, respectively.[2]

Lifestyle factors, such as diet, obesity, physical activity, and smoking, play a significant role in carcinogenesis. Approximately half of the cancer burden can be prevented or significantly reduced by modifying lifestyle factors.[3, 4] Lifestyle factors can generate metabolic abnormalities that include overweight and obesity, and high blood pressure, cholesterol, and blood glucose.

Each of the aforementioned abnormalities has been separately implicated as a metabolic risk factor (MRF) for cancer.[5-25] Comprehensive reviews provide adequate evidence of an association between obesity and several cancers in both men and women.[14, 15, 17, 18, 26-28] Similarly, epidemiologic studies and reviews show that individuals with diabetes are at a higher risk for most cancers, although the association is unclear for prostate and lung cancers.[7, 12, 13, 16, 19, 29-32] Elevated blood pressure is also associated with several cancers, although the results are inconsistent across studies.[7, 10, 25] Results for the association between total serum cholesterol and cancer are similarly inconclusive.[33]

Research indicates that the risk for heart disease and stroke increases with number of MRFs.[34, 35] A few studies have also indicated a similar pattern of increased risk for certain types of cancer from combined MRFs.[6-10, 20-23, 36-38] A combination of three or more of the MRFs is generally termed as metabolic syndrome.[39] It is estimated to be prevalent in a third of US adults.[40] A meta-analysis on risk of various cancers found that metabolic syndrome elevated the risk for liver, colon, colorectal, pancreatic, thyroid, rectal, bladder, and prostate cancers in men,

and endometrial, pancreatic, breast, rectal, liver, colorectal, colon, and ovarian cancers in women.[6]

Each individual MRF can promote cancer through an independent biological mechanism. In turn, these mechanisms can complement each other, and act additively to promote cancer development. MRFs, functioning through various mechanisms, including increased inflammatory markers, such as tumor necrosis factor-alpha and interleuken-6, increased adipokines such as leptin, and decreased adiponectin, increased levels of free fatty acids and triglycerides, insulin resistance, increased insulin-like growth factor-1, and increased oxidative stress, can cause angiogenesis, cell migration, mitogenesis, and DNA damage.[41-43]

The prevalence of MRFs is high, and continues to rise.[44] At the same time, there is epidemiologic evidence of the association of MRFs with several cancers. Moreover, there are few animal studies supporting the biological role of MRFs in cancer development and progression. However, results from studies examining the association between individual and combined MRFs and overall cancer are inconsistent. Therefore, this study examined the association of MRFs (obesity, high blood pressure, high total serum cholesterol, and diabetes), individually and in combination, and subsequent risk of overall and site-specific cancers of the breast, digestive system, and lung.

3.3 Methods

3.3.1 Data Source and Study Population: Data were derived from the NHANES I Epidemiologic Follow-up Study (NHEFS). The NHEFS is a national, multi-stage, stratified probability sample of the non-institutionalized, civilian population in the U.S.[45] It includes participants from the NHANES I (National Health and Nutrition Examination Survey I) cohort aged 25-74 years who completed a medical examination at baseline (1971-75). Participants were

followed-up in 1982-84, 1986, 1987, and 1992. Only 5% of the original NHEFS sample was lost through attrition.[46]

Baseline data were acquired by merging five NHANES I datasets on anthropometry, biochemistry, medical history, medical needs, and medical examination. Since the NHEFS follow-up was conducted for participants aged ≥ 25 years and ≤ 74 years at the time of NHANES I interview, only this group was retained for the analysis. Cancer status was determined by merging data from each of the 1982-84, 1986, 1987, and 1992 surveys, in addition to the NHEFS vital statistics data.

The status variable, incident cancer cases, was defined using the International Classification of Diseases-9th revision (ICD-9), codes 140-208, excluding ICD-173 (skin cancer), and were followed up through interview and death certificate data. All cancer cases since the baseline period were obtained from the first, second and third diagnoses of cancer, along with their location (cancer-site). Skin cancer cases were not included among total cancer cases, since their etiology is different and does not involve MRFs. For subjects with multiple cancers, only the first occurring non-skin cancer was included. Year of death was used for cancer incidence if a death certificate was the only source of cancer information.

Study participants were considered to be at risk for cancer from their date of first examination until date of diagnosis of cancer, or death, or termination of follow-up, whichever occurred first. Event times were censored for participants who had not developed cancer by the end of follow-up or died from non-cancer causes.

A total of 14,407 persons from the NHANES dataset were followed up until 1993. Of these, 684 had a cancer diagnosis at baseline (determined from the question: Has a doctor ever told you that you have malignant tumor or growth?) or who died in the same year of examination

and were excluded from analysis. In order to reduce the possibility of reverse causation, another 146 who developed cancer in the first two years of the study were excluded from analysis. Participants with missing values on cancer status (n = 2,310), and on the covariates in the multivariable model (n=573) were also excluded from the analysis. The final sample was 10,694 persons who were cancer-free at the beginning of their study period.

Information on the following predictor variables was obtained from the baseline examination: obesity, assessed as body mass index in kg/m^2; resting systolic (SBP) and diastolic (DBP) blood pressure, measured as continuous variables in mmHg; total serum cholesterol, measured as continuous variable in mg/dL; and self-reported diabetes, coded as a dichotomous variable. Resting SBP and DBP were measured by a physician using a sphygmomanometer at the beginning of the physical examination while the subject was in a sitting position, as consistent with American Heart Association guidelines.[47] All of these readings were retrieved from NHANES I medical exam questionnaire. Total serum cholesterol was assessed using a semi-automated instrument in the Centers for Disease Control and Prevention's lipid standardization laboratory. Information on diabetes was gathered from NHANES I medical history questionnaire (Has a doctor ever told you had diabetes?) or from NHANES I healthcare needs questionnaire (Did a doctor tell you had diabetes? or, do you take any diabetes medicine or insulin?).

Analyses were adjusted for the following potentially confounding variables: age, race, education, family income, physical activity, smoking status, and family history of cancer. The baseline medical history questionnaire provided information on age, race, education, family income, and physical activity. At baseline, information on smoking status was very limited, and information on family history of cancer was not collected. Therefore, smoking information was

combined from the baseline and 1982 surveys, and information on family history of cancer was derived from the latter survey.[48-51]

3.3.2 Statistical analysis

Multivariable Cox proportional hazards regression models, with time since measurement as the time variable, and incident cancer cases as study events, were fitted to obtain hazard ratios of cancer incidence from MRFs. The model accounted for differential entry and exit times among the NHEFS participants. A time-interaction test was conducted with individual and combined MRFs in the full model with overall cancer to check whether the assumption of proportionality of hazard ratios over time was met.

Metabolic risk factors were classified as: (1) obesity: BMI$\geq$ 30 kg/m^2; (2) high blood pressure: systolic BP $\geq$ 140 mm/Hg and/or diastolic BP $\geq$ 90 mm/Hg); (3) high cholesterol: total serum cholesterol $\geq$ 240 mg/dL; and (4) diabetes: presence or absence of diabetes. The effect of individual MRF was assessed relative to the absence of that risk factor.

Analyses were adjusted for the following potential confounding variables: age, sex, race (white versus other), education (high school or less vs. above high school), family income (<$5,000, $5,000 to <$15,000, and >=$15,000, based on the poverty line for 1971-75, which was set at or below $5,000 as the annual income for a household of four members), physical activity (moderately active or very active vs. quite inactive), smoking (smoked 100 cigarettes in one's lifetime), and family history of cancer (dichotomous). In the NHANES I dataset, race was classified as white, black, or other at baseline. However, for this study, the latter two categories were combined and classified as nonwhite due to small numbers.[48]

Age was included in all models as an independent, continuous variable. In addition, analyses were further stratified by age categorized as <50 and $\geq$ 50 years as at baseline. The

rationale for this dichotomization was based on previous research that showed that adults 50 years and older bear the greatest cancer burden, with the largest proportion of cancer being diagnosed in this age group.[52] Another consideration was the biological changes, especially in women, which occur around age 50. In addition to age, analyses were also stratified by gender.

Besides examining the association between individual MRFs and cancer risk, a second analysis assessed the combined effect of MRFs on the risk of overall cancer. An additive summary of MRF scores was created by combining the individual MRFs. A score of three was assigned to participants with three or more MRFs. The summary score ranged from 0 (no MRF, the referent category) to 3 (three or four risk factors). Analyses were adjusted for the following potential confounders; age, race, education, family income, physical activity, smoking, and family history of cancer, and stratified by gender and dichotomized age.

Site-specific cancer (breast, digestive, and lung) were examined separately in evaluating an association between individual MRFs as well as the combined MRF score, and cancer risk. Cancers of the digestive system included those of the alimentary canal below the neck (i.e., esophagus, stomach, small and large intestines) and key digestive organs (i.e., pancreas, liver, and gallbladder).

In order to test the robustness of results, three different sensitivity analyses were conducted. Analysis one included all years of cancer incidence data after the baseline exam; analysis two excluded persons with missing data for diabetes; and analysis three was conducted with continuous variables for BMI, BP, and cholesterol.

All data were analyzed using the complex samples module in IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY: IBM Corp). These analyses incorporated the complex sample design and sample weights in order to produce national estimates.[53]

3.4 Results

Time-interaction test with individual and combined MRFs in the full model with overall cancer showed that the assumption of proportional hazards was not violated in the Cox proportional hazards regression analyses. Table 1 presents the baseline characteristics of the study population, incorporating the sampling weights and design specifications. Mean age at baseline was 48.8 years. Among 10,694 persons followed-up between 1971 and 1993, 59% were female, and most were white. Over a quarter of the sample had an annual family income below poverty level, and about three quarters had an education less than college. Most participants reported being moderately or very active in their non-recreational activity, and over half had smoked at least 100 cigarettes during their lifetime. A third of the participants reported having a family history of cancer. About 16.6% were obese, a little less than half had high BP, a third had high cholesterol, and half of the sample had one or more MRFs.

Tables 2 and 3 present the association between individual MRFs and cancer risk among males and females, respectively, after adjusting for potential confounding factors, and stratifying by age. Individual MRFs were not significantly associated with cancer risk in males in the multivariable Cox proportional hazards regression analyses, after controlling for age, race, education, family income, physical activity, smoking, and family history (Table 2). A decreased risk of overall cancer was observed among obese women 50 years of age and older (Table 3). High total cholesterol elevated the risk of overall cancer in older women. No association was observed in either gender between combined MRFs and overall cancer risk (Tables 4 and 5).

Tables 6 and 7 present the association of individual and combined MRFs respectively with breast cancer risk in all women and postmenopausal women. High BP, diabetes, and presence of a combination of three or four MRFs were associated with elevated breast cancer

risk in postmenopausal women. Obesity in males elevated the risk of digestive cancer (Table 8). Presence of a single MRF in women was associated with reduced risk of digestive cancer (Table 9). There was no association of MRFs with lung cancer in either gender (Tables 10 and 11).

Results were consistent with the main analysis in all sensitivity analyses. However, two associations in the main analysis (high cholesterol with increased overall cancer risk, and obesity with reduced overall cancer risk in older women) were not observed in other sensitivity analyses.

3.5 Discussion

In this large, prospective cohort study, MRFs, either individually or in the aggregate, were not consistently associated with cancer risk in either gender. Overall, diabetes, high BP, and the presence of a combination of three or four MRFs were associated with higher breast cancer risk among postmenopausal women. Obesity in males less than 50 elevated the risk of digestive cancer.

Study results show an association between diabetes and increased risk of breast cancer in postmenopausal women. A meta-analysis on diabetes and breast cancer showed that among postmenopausal women, diabetes was associated with a 16% increased risk of breast cancer.[16] Similarly, another recent meta-analysis showed a significant positive association of high blood pressure and high glucose/diabetes with postmenopausal breast cancer.[8] Diabetes is frequently associated with insulin resistance, increased circulating concentrations of insulin, and insulin-like growth factors. Studies have shown insulin has mitogenic effects on breast tissue.[54] In addition, insulin inhibits the production of sex hormone-binding globulin, resulting in an increase in bioavailable estradiol. Increased estradiol levels have been associated with the risk of developing breast cancer.[16, 55]

The finding that postmenopausal women with high BP were at an increased risk of breast cancer is also supported by the recent meta-analysis on breast cancer risk in postmenopausal women.[8] Cancer and hypertension are both characterized by the proliferation of smooth muscle cells.[56] Another hypothesis indicates abnormalities of carcinogen binding to DNA in lymphocytes of hypertensive women.[57]

The results showed a decreased risk of overall cancer from obesity, and an elevated risk from high total cholesterol in women 50 years of age or older. However, in the sensitivity analyses, these two results were not supported. Epidemiologic evidence suggests obesity is associated with increased risk of site-specific cancers in women, such as cancers of postmenopausal breast, esophagus, pancreas, endometrium, ovary, thyroid, and kidney.[5, 15, 58-60] The question regarding the association between total cholesterol and cancer risk remains unresolved in literature.[61]

When combined MRFs were examined, postmenopausal women with three or four MRFs were observed to be at a higher risk of breast cancer. A recent meta-analysis showed that the combined effect of MRFs on increased risk for postmenopausal breast cancer was greater than that of individual MRFs.[8] A combination of MRFs may activate different molecular pathways through metabolic, endocrine, and immune cell changes, which can result in breast tumorigenesis.[62]

Among men, the only significant association observed was between obesity and elevated risk of digestive cancer. Other studies have also observed a similar association between overweight/ obesity and digestive cancers, such as pancreatic[63, 64] and colorectal cancers[30] in men. There is also an elevated risk of adenocarcinoma of the esophagus and gastric cardia with increasing BMI.[65] In obese persons, there is an increase in free fatty acids, cytokines, and

hormones, resulting in increased insulin levels and insulin-like growth factor. High levels of insulin or insulin-like growth factors can promote digestive cancers by promoting cellular proliferation and inhibiting apoptosis.[63]

Several complex biological mechanisms have been proposed to show that MRFs promote carcinogenesis. The prevalence of hyper-insulinemia and insulin resistance is higher in obese individuals. Hyper-insulinemia reduces the production of insulin-like growth factor (IGF) protein, resulting in increased bioavailability of IGF-1.[30] IGF-1 may promote tumor development by stimulating cell proliferation and inhibiting apoptosis. Increased circulating insulin can reduce the levels of sex-hormone-binding-globulin, thereby increasing endogenous sex-steroid levels.[30] Breast, endometrial, and colorectal cancers may be affected by this mechanism.[66] Another carcinogenic mechanism involves cytokines. Increased adiposity raises cytokine production in obese women, which in turn can induce estradiol production.[41] Estradiol is a strong growth factor for breast and endometrial cancers. Leptin, another adipocyte-specific hormone, is directly related to adiposity and insulin resistance. It has direct stimulatory effects on cancer cells and may serve as an important link between obesity and carcinogenesis.[41]

Study results show the association of MRFs with overall and site-specific cancers varies by gender. These differences in the association between MRFs and cancer can arise for several reasons. Animal studies suggest that production of a protein, interleukin-6, which promotes inflammation, is linked to a higher incidence of liver cancer in men than in women.[67]

The current study has several potential limitations. For example, blood glucose levels were not measured directly, but rather, a self-reported diagnosis of diabetes indexed high levels. In addition, while total serum cholesterol levels were measured directly, there were no separate measures for triglycerides, or low and high-density lipoprotein cholesterol levels (LDL and

HDL). This may be important, since previous research has shown that high HDL may be inversely associated with site-specific and overall cancer.[68] However, a systematic review with meta-analysis showed no association between triglyceride or HDL levels and such site-specific cancers as colorectal cancer.[9] Although models were adjusted for race, stratified analysis could not be performed due to small sample size for races other than white. For this reason, nonwhite were combined into one category, although studies have observed racial differences in MRFs.[69] Analyses on lung and digestive cancer could not be stratified by age because of small number of cancer cases.

This study has several strengths. For example, data were derived using a strong longitudinal cohort study design with high follow-up rates. Specifically, 96% of the study population was successfully traced at some point through the 1992 follow-up.[46] It is a large, nationally representative sample of the US population. All analyses utilized complex sample survey design for results representative of the population. In addition, self-report bias tended to be minimized because MRFs, such as total serum cholesterol, as well as blood pressure and anthropometry (BMI), were based on body measurements and laboratory data.

In conclusion, MRFs, either individually or in the aggregate, were not consistently associated with cancer risk in either gender in this large, prospective cohort study. The association of individual and combined MRFs was stronger with postmenopausal breast cancer risk.

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Tables

The working tables can be found in Appendix B.

CHAPTER 4. ASSOCIATION BETWEEN METABOLIC RISK FACTORS AND AGE AT CANCER ONSET

4.1 Abstract

Introduction

Cancer is the second most common cause of death in the United States. There is evidence that components of metabolic syndrome, a cluster of pathophysiological disorders comprising obesity, insulin resistance, hypertension, and dyslipidemia, elevate cancer risk. However, there is scant literature on the association between the components of metabolic syndrome and age at cancer onset. The aim of this study is to examine whether metabolic risk factors (MRFs), either individually or in combination, are associated with age at onset of all-site cancer, and cancer of the breast, digestive system, and lung, respectively.

Methods

Data were derived from the NHANES I Epidemiologic Follow-up Study, and comprised participants ages 25 to 74 years at baseline. The outcome variable was age at cancer onset, and the primary metabolic risk factors were obesity, high blood pressure, high total serum cholesterol, and diabetes. Analyses were adjusted for age, race, education, family income, physical activity, smoking status, and family history of cancer, and stratified by age and gender. Multiple linear regression analyses, using the general linear model, were conducted to assess the relationship between MRFs and age at cancer onset. All analyses incorporated the complex sample design and sample weights to produce national estimates.

Results

Study results showed an increased risk of diabetes associated with earlier age at (a) cancer onset in younger and older males, (b) cancer onset in older females, (c) postmenopausal breast cancer onset, and (d) lung cancer onset in both genders. Presence of a combination of three or four MRFs was associated with earlier age at onset of: (a) overall cancer in women 50

years and older, (b) postmenopausal breast cancer, (c) digestive cancer in females, and (d) lung cancer in males.

Conclusion

Overall, diabetes and a combination of three or four MRFs were found to be associated with earlier age at onset of overall and site-specific cancers. The association with combined MRFs was stronger in women. Future research needs to determine the underlying mechanisms that may predispose people with metabolic abnormalities to cancer.

4.2 Introduction

Accounting for one in four deaths, cancer is the second most common cause of death in the United States (U.S.) after heart disease.[1] The National Cancer Institute estimates 1.7 million new cancer cases in 2013.[2] Annualized cancer incidence rates for 2006-2010 were 535.9 and 411.2 per 100,000 males and females, respectively.[2] The World Cancer Research Fund estimates that 25-33% of new cancer cases in the U.S. in 2013 are related to behavioral and lifestyle factors such as overweight or obesity, physical inactivity, and poor nutrition.[3]

Metabolic syndrome is a cluster of pathophysiological disorders comprising central obesity, insulin resistance, hypertension, and dyslipidemia. Based on the application of various definitions of metabolic syndrome, an estimated one-third of US adults are afflicted by it.[4] There is substantial evidence that this cluster of metabolic risk factors accelerates onset of cardiovascular diseases.[5, 6] In addition, studies conducted over the past decade indicate that the combined metabolic risk factors (MRFs) are positively and significantly associated with overall cancer[7] and site-specific cancers, including breast cancer,[7-20] digestive cancer,[21] liver cancer,[14, 22] prostate cancer,[23-26] colorectal cancer,[27-32] and endometrial cancer.[33] A recent meta-analysis of prospective cohort studies concluded that metabolic syndrome is associated with an elevated overall cancer risk among adults.[34] This study found a significant association between metabolic syndrome and increased risk of liver, colorectal, and bladder cancers in men, and endometrial, pancreatic, postmenopausal breast, and colorectal cancers in women.[34]

Few epidemiologic studies have reported associations between MRFs and age at cancer onset. A large cohort study found that obesity in adulthood was linked to increased cancer mortality risk.[35] Overweight and obesity during early adulthood were also associated with earlier age at onset in obesity-related cancers, such as pancreatic cancer.[36] In this large case-control

study, obesity from the ages of 20 to 29 years was associated with earlier age of cancer onset by seven years.[36] A nested case-control study suggested hypertensive adults were at risk of developing cancer ten years earlier than normotensives.[37]

A paucity of literature exists on the association between individual and combined MRFs and age at cancer onset. Animal studies suggest that mechanisms, which prevent metabolic abnormalities, by reducing serum insulin-like growth factor-1 or androgen concentrations, may delay the growth and progression of breast and prostate cancers.[38] Another animal study found that mammary tumors developed earlier in diet-induced obese rats than in lean rats, thus supporting the role of hormones and adipokines (produced by adipose tissue) in cell proliferation and carcinogenesis.[39]

Given the associations between MRFs and several cancers, as suggested by epidemiologic human studies, as well as animal studies, an important research question is whether MRFs are associated with earlier age at cancer onset. This question is important for at least four reasons. First, age at onset of certain cancers is temporally decreasing. A population-based study, using data for England and Wales covering the period 1971-1999, found earlier age at onset of breast, cervical, and prostate cancer.[40] Second, earlier cancer onset signifies shorter life expectancy, and therefore, major loss of potential years of life.[41] Third, younger cancer patients are likely to have more aggressive cancers, less favorable prognosis, and poorer outcomes than older patients.[41-43] Fourth, earlier age at cancer onset in a family may increase the lifetime risk of developing cancer in the next generation.[44, 45] Therefore, it is important to understand the association between metabolic syndrome and age at cancer onset so that appropriate guidelines can be developed for cancer screening, prevention, and treatment.

This study assessed the influence of MRFs (obesity, high blood pressure, high total serum cholesterol, and diabetes), and their combination, on age at onset of all-site cancer, and cancer of the breast, digestive system, and lung.

4.3 Methods

4.3.1 Data Source and Study Population: Data were derived from a cohort study, the NHANES I Epidemiologic Follow-up Study (NHEFS).[46] The NHEFS is a national multi-stage, stratified probability sample of the non-institutionalized, civilian population in the US. It includes participants from the NHANES I cohort, who were ages 25 to 74 years, and completed a medical examination at baseline (1971-75).[46] Participants were followed-up in 1982-84, 1986, 1987, and 1992. Only 5% of the original NHEFS sample was lost through attrition.[47]

Baseline data were acquired by merging five NHANES I data files on anthropometry, biochemistry, medical history, medical needs, and medical examination. Since the NHEFS follow-up was conducted for participants aged ≥ 25 years and ≤ 74 years at time of NHANES I interview, only this group was retained for the analysis. Cancer status was determined by merging data from each of the 1982-84, 1986, 1987, and 1992 surveys, in addition to the NHEFS vital statistics data.

The outcome variable was age at cancer onset. Cancer cases were defined using the International Classification of Diseases-9th revision (ICD-9), codes 140-208, excluding ICD-173 (skin cancer), and were followed up through interview and death certificate data. All the cancer cases occurring after the baseline period and reported in 1982-84, 1986, 1987, and 1992 interviews, were obtained from the first, second and third diagnoses of cancer along with their location (cancer-site). Skin cancer cases were not included among total cancer cases since the mechanism of skin cancer development is different and does not involve metabolic risk factors.

For subjects with multiple cancers, only the first occurring non-skin cancer was included. All cancer cases were aligned with year of diagnosis. The final outcome variable, age at cancer onset, was computed by subtracting birth year from year of cancer diagnosis, and was computed for overall cancer and for cancer of the breast, digestive system, and lung, respectively.

A total of 14,407 persons from the NHANES I dataset were followed up in 1982-84. Of these, 684 had a cancer diagnosis at baseline (determined from the question "Has a doctor ever told you that you have malignant tumor or growth?") or who died within the year of baseline interview and were excluded from the analysis. In order to reduce the possibility of reverse causation, another 146 who developed cancer in the first two years of the study were excluded from analysis. Among those who were followed, 1,837 persons (13.5%) were diagnosed with cancer during the study period. Participants with missing data (n = 101) on covariates, which were included in the multivariable model, were also excluded from the analysis. The final sample was 1,736.

Information on the following predictor variables was obtained from the baseline examination: obesity, assessed as body mass index in kg/m^2, resting systolic (SBP) and diastolic (DBP) blood pressure, measured as continuous variables in mmHg, total serum cholesterol, measured as continuous variable in mg/dL, and self-reported diabetes, coded as a dichotomous variable. Consistent with American Heart Association guidelines, resting SBP and DBP were measured by a physician using a sphygmomanometer at the beginning of the physical examination while the subject was in a sitting position.[48] All of these readings were retrieved from the NHANES I medical exam questionnaire. Total serum cholesterol was assessed using a semi-automated instrument in the Centers for Disease Control and Prevention's lipid standardization laboratory. Information on diabetes was gathered from the NHANES I medical

history questionnaire (Has a doctor ever told you had diabetes?) or from the NHANES I healthcare needs questionnaire (Did a doctor tell you had diabetes? or, do you take any diabetes medicine or insulin?).

Analyses were adjusted for the following potentially confounding variables: age, race, education, family income, physical activity, smoking status, and family history of cancer. The baseline medical history questionnaire provided information on age, race, education, family income, and physical activity. At baseline, information on smoking status was very limited, and information on family history of cancer was not collected. Therefore, information on smoking status was combined from the baseline and 1982 surveys, and information on family history of cancer was derived from the latter survey.[49-52]

4.3.2 Statistical Analysis

Multiple linear regression analyses, using the general linear model, were used to assess the relationship between MRFs and age at cancer diagnosis.[36, 53] The severity of multicollinearity for each variable was assessed by calculation of the variance inflation factor. All data were analyzed using the complex samples module in IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY: IBM Corp). All analyses incorporated the complex sample design and sample weights in order to produce national estimates.

The outcome variable, age at cancer onset, was computed by subtracting birth year from year of cancer diagnosis, and analyzed as a continuous variable. Metabolic risk factors were classified as: (1) obesity: BMI$\geq$ 30 kg/m^2; (2) high blood pressure: systolic BP $\geq$ 140 mm/Hg and/or diastolic BP $\geq$ 90 mm/Hg); (3) high cholesterol: total serum cholesterol $\geq$ 240 mg/dL; and (4) diabetes: presence or absence of diabetes. Multiple linear regression models were used to examine the association between MRFs (obesity, high BP, high cholesterol, and diabetes) and

age at cancer diagnosis.[36, 53] The effect of individual MRF was assessed relative to the absence of that risk factor.

Analyses were adjusted for the following potentially confounding variables: age, race (whites versus others), education (high school or less vs. above high school), family income (<$5,000, $5,000 to $14,999, and ≥$15,000, based on the poverty line for 1971-75 that was set at or below $5,000 as the annual income for a household of four members), physical activity (moderately active or very active vs. quite inactive), smoking (smoked 100 cigarettes in one's lifetime), and family history of cancer (dichotomous). In the NHANES I dataset, race was classified as white, black, or other at baseline. However, for this study, the latter two categories were combined and classified as nonwhite due to small number.[50]

Age was included in all models as an independent, continuous variable. In addition, analyses were further stratified by age categorized as < 50 and ≥ 50 years as at baseline. The rationale for this dichotomization was based on previous research that has shown that adults 50 years or older bear the greatest burden of cancer, with the largest proportions of cancers being diagnosed in this age group.[54] Moreover, there are biological changes, especially in women, around age 50. Posthoc, all analyses were also stratified by gender after determining that the association between individual MRFs and age at cancer onset differed by gender.[55, 56]

Besides examining the association between individual MRFS and age at cancer onset, analyses were performed to assess the combined effect of MRFs on age at cancer onset. An additive summary of MRF scores was created by combining the individual MRFs. A score of three was assigned to participants with three or four MRFs. The summary score ranged from 0 (no MRF, the referent category) to 3 (three or four risk factors). Analyses were adjusted for the

following potential confounders: age, race, education, family income, physical activity, smoking, and family history of cancer, and stratified by gender and age (< 50 and ≥ 50 years of age).

Site-specific cancers (breast, digestive, and lung cancers) were examined separately in evaluating an association between individual MRFs as well as the combined MRF score, and age at cancer onset. Cancers of the digestive system included those of the alimentary canal below the neck (e.g., esophagus, stomach, small and large intestines) and key digestive organs (i.e., pancreas, liver, and gallbladder).

4.4 Results

Table 1 presents the baseline characteristics of the study population. Among the 1,736 persons diagnosed with cancer between 1973 and 1992, approximately half were women and most were white. Almost a third of the sample had an annual family income below the poverty level, while more than three fourths had a high school education or less. About 17% were obese, over half had hypertension, and more than a third had high total cholesterol. Very few participants had three or four MRFs.

Table 2 presents the association between individual MRFs and age at cancer onset among males, after adjusting for potential confounders, and stratifying by age and gender. Among males less than 50 years of age at baseline, obesity was associated with later age at cancer onset. Mean age at cancer onset for obese men who were younger than age 50 was (mean $\pm$ SE) 55.8 $\pm$ 1.52 years compared to 53.1 $\pm$ 1.32 years for those who were not obese. Diabetes was associated with earlier age at cancer onset in younger males. Mean age at cancer onset for men with diabetes, who were younger than age 50, was 52.2 $\pm$ 2.16 years compared to 56.6 $\pm$ 1.18 years for those who did not have diabetes. Among males 50 years and older, diabetes was again associated with

earlier age at cancer onset. Mean age at cancer onset for older men with diabetes was 68.1 ± 1.42 years compared to 70.9 ± 0.57 years for those who did not have diabetes.

Among women 50 years and older, diabetes was associated with earlier age at cancer onset (Table 3). Mean age at cancer onset for older women with diabetes was 70.4 ± 1.06 years compared to 72.4 ± 0.81 years for those who did not have diabetes.

Tables 4 and 5 present the association between the aggregate MRF score (ranging from 1 MRF to three or four MRFs, compared with the referent category of no MRF) and age at cancer onset among males and females, respectively, after adjusting for potential confounders, and stratifying by age. No significant association was observed among males Table 4). Among women younger than 50 years of age, presence of three or four MRFs was associated with later age at cancer onset (Table 5). Mean age at cancer onset for these women was 51.8 ± 0.97 years compared to 52.7 ± 0.98 years for those who had no MRF. This association reversed in older women. Presence of three or four MRFs in women 50 and older was associated with earlier age at cancer onset. Mean age at cancer onset for older women with combined MRFs was 70.2 ± 0.89 years compared to 72.9 ± 1.03 years for those who had no MRF.

Table 6 presents the associations between individual MRFs and age at breast cancer onset in all women, and in postmenopausal women. Diabetes was associated with earlier age at postmenopausal breast cancer onset. Mean age at onset was 66.0 ± 1.46 years compared to 68.7 ± 0.74 years for those who did not have diabetes. Presence of combined three or four MRFs was associated with earlier age at onset among all women and postmenopausal women (Table 7). Mean age at cancer onset for all women with combined MRFs was 59.1 ± 1.22 years compared to 62.4 ± 1.08 years for those who had no MRF. Among postmenopausal women with combined

MRFs, mean age at cancer onset was 67.0 ± 1.07 years compared to 70.9 ± 1.52 years for those who had no MRF.

Table 8 presents the associations between individual MRFs and age at digestive cancer onset among males and females. No association was observed in any strata. Examining the combined MRFs, presence of one, three or four MRFs was associated with earlier age at digestive cancer onset among females (Table 9). Mean age at onset among females with three or four MRFs was 68.5 ± 1.25 years compared to 72.9 ± 1.19 years for those who did not have any MRF.

Table 10 presents the association between individual MRFs and age at lung cancer onset among males and females. Overall, diabetes was associated with earlier age at onset among both males and females. Mean age at lung cancer onset for males with diabetes was 58.7 ± 1.77 years compared to 66.1 ± 0.90 years for those who did not have diabetes. Similarly, mean age at lung cancer onset for females with diabetes was 62.9 ± 1.78 years compared to 67.5 ± 1.05 years for those who did not have diabetes. When examining the combined MRFs, presence of three or four MRFs in males was also associated with earlier age at lung cancer onset (Table 11). Mean age at onset among males with three or four MRFs was 62.5 ± 1.57 years compared to 66.2 ± 1.25 years for those who did not have any MRF.

4.5 Discussion

The aim of this study was to examine whether MRFs and their combination were associated with age at cancer onset. Since there are several definitions of metabolic syndrome, and thus several possible combinations, the independent effect of each single component was also examined.

Study results show an increased risk of diabetes associated with earlier age at cancer onset in younger and older males, and in older females. Diabetes was also associated with early age at onset of postmenopausal breast cancer, and lung cancer in both genders. Epidemiologic reviews and meta-analytic studies suggest that people with diabetes were at a higher risk for overall cancer and cancers of several sites, such as liver, pancreas, endometrium, colon, rectum, breast, and bladder.[57, 58] Although several observational studies do not show an association between diabetes and lung cancer, the Metabolic Syndrome and Cancer project that comprises six large prospective cohorts found that a one millimole per liter increase in glucose levels in men was associated with increased risk for incidence and mortality from cancer of lung, trachea, and bronchus.[59] Another cohort study found an increased risk for lung cancer mortality in diabetic women.[60]

Study results also show that obesity was associated with later age at cancer onset in males less than 50 years of age. While epidemiologic evidence suggests obesity is associated with an increased risk of cancer in men,[61] studies on the association between obesity and age at cancer onset are scant.

Presence of a combination of three or four MRFs was associated with later age at cancer onset among females less than 50 years of age. This association was reversed in older women. Presence of three or four MRFs was associated with earlier age at onset of: (a) overall cancer in women 50 and older, (b) postmenopausal breast cancer, (c) digestive cancer in females, and (d) lung cancer in males. A meta-analysis found that metabolic syndrome was positively associated with postmenopausal breast, endometrial, pancreatic, and colorectal cancers in women.[34] A large cohort study showed that metabolic syndrome was associated with increased liver and breast cancer risk in women.[14] Another cohort study concluded with a significant increase in breast

cancer risk among older women with two or three MRFs, suggesting that the combined MRFs may elevate breast cancer risk beyond a single MRF, such as obesity.[62] However, studies on the association between combined MRFs and age at cancer onset are lacking.

Studies have suggested potential biological mechanisms that link MRFs with various cancers. In brief, through various mechanisms, including obesity, increased inflammatory markers such as tumor necrosis factor -α and interleuken-6, increased adipokines such as leptin and decreased adiponectin, increased levels of free fatty acids and triglycerides, insulin resistance, increased insulin-like growth factor-1, and increased oxidative stress, MRFs have been shown to cause angiogenesis, cell migration, mitogenesis, and DNA damage.[63] There is, therefore, an emerging hypothesis that a combination of MRFs may be an important etiologic factor for the onset of cancer.[64]

Gender differences in the association between MRFs and cancer can arise for several reasons. Components of metabolic syndrome operate differently by gender.[55, 56] Metabolic hormones that control cell growth can elevate cancer risk in women, whereas obesity-related hyperinsulinemia can increase the risk in men.[65] Longitudinal studies show that the association between metabolic syndrome and elevated cancer risk is stronger in women.[14] Animal studies have shown that obesity-related adipokines enhance cell proliferation and elevate breast cancer risk.[66]

The current study has several potential limitations. For example, blood glucose levels were not measured directly but rather, a self-reported diagnosis of diabetes was used as an indicator of high levels. In addition, while total serum cholesterol levels were measured directly and not self-reported, there were no separate measures for triglycerides, or low and high-density lipoprotein cholesterol levels (LDL and HDL). This may be important since previous research

has shown that high HDL may be inversely associated with site-specific and overall cancer,[67] although others reported no association between triglyceride or HDL levels and such site-specific cancers as colorectal cancer.[32]

Prior research has reported differences in age at cancer onset among different racial/ethnic populations for overall and site-specific cancers.[68, 69] However, while models were adjusted for race, a stratified analysis could not be performed due to the small sample size for races other than white. For this reason, nonwhite were combined into one category, although studies show racial differences related to MRFs.[70]

This study has several strengths. For example, data for this study were derived from a longitudinal cohort study design with high follow-up rates. Specifically, 96% of the study population was successfully traced at some point through the 1992 follow-up.[47] It is a large nationally representative sample of the US population. In addition, self-report bias tended to be minimized because MRFs, such as total serum cholesterol, as well as blood pressure and anthropometry (BMI), were based on body measurements and laboratory data. All analyses utilized complex sample survey design for results representative of the population.

In conclusion, diabetes and a combination of three or four MRFs were found to be associated with earlier age at onset of overall and site-specific cancers. The association with combined MRFs was stronger in women. Future research needs to determine the underlying mechanisms that predispose people with metabolic abnormalities to cancer. To this end, it is essential to examine the relationship among site-specific cancers, stratified by gender and race, with detailed information on LDL and HDL cholesterol levels, abdominal and visceral adiposity, blood glucose levels, time period of each abnormality, and medications and their period of use.

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Tables

The working tables can be found in Appendix C.

CHAPTER 5. DISCUSSION

5.1 Discussion

The three dissertation studies were conducted with the overall goal of examining the association between individual and combined metabolic risk factors (MRFs) and subsequent risk of overall and site-specific cancers of the breast, digestive system, and lung. This chapter discusses the findings from the three studies, lists their strengths and limitations, and concludes with a suggested future course of action.

5.2 Study 1 Discussion: Metabolic Syndrome is associated with increased breast cancer risk: A systematic review with meta-analysis

The purpose of this aggregate data meta-analysis was to examine the association between metabolic syndrome and the risk for breast cancer in adult females. Of the 291 studies screened, 47 underwent a full-text review, of which eight studies with nine independent cohorts met the eligibility criteria. The overall results of this aggregate data meta-analysis show a modest positive association between metabolic syndrome and breast cancer risk in adult females, with a 47% elevated risk for incident breast cancer for adult females with metabolic syndrome.

This finding is strengthened by the robustness of results from other analyses. These include: (1) examination for publication bias, (2) influence analysis with each study deleted from the model once, (3) deletion of the two case-control studies with odds ratios from the overall model, (4) limiting the analysis to prospective designs, (5) restricting the study to only postmenopausal women in the analysis, and (6) limiting the results to studies that controlled for four or more of the important confounders.

Risk of bias was low for a majority of studies with respect to study design, cancer assessment, and sample size; but it was high or unclear for a majority of them concerning the handling of missing data and non-participation of subjects at each stage of follow-up. This risk

was higher in case-control and retrospective cohort study designs compared with prospective cohort study designs. The association between metabolic syndrome and breast cancer risk was stronger when limited to postmenopausal women. These findings are supported by the recent meta-analysis on metabolic syndrome and breast cancer risk in postmenopausal women.[1]

The current meta-analysis identified some of the methodological challenges when pooling results from various studies examining the association between metabolic syndrome and breast cancer risk. These include (1) the different methods used to assess exposure, identify cancer, control for confounders, and define metabolic syndrome, (2) limiting studies to those published in English, which may have led to inflated results, (3) the relatively small number of studies that met the inclusion criteria, (4) the inability of a few studies to provide raw data for calculating the risk estimates, (5) the different study designs employed, and (6) the varied populations studied.

This study has several strengths. First, to the best of my knowledge, this is the first systematic review and meta-analysis to examine the association between metabolic syndrome and breast cancer risk in all adult women, with a sub-analysis of post-menopausal women. Second, all included studies were longitudinal, reported the results of multivariable analyses, and in eight of the nine cohorts, breast cancer was objectively determined. Third, with robust results, tested after conducting several analyses, the findings provide direction for future.

In conclusion, the overall results of this meta-analysis suggest that there is a modest positive association between MS and risk of breast cancer in adult females.

5.3 Study 2 Discussion: Association between individual and combined metabolic risk factors and cancer risk

The aim of this study was to examine whether MRFs, either individually or in combination, were associated with the risk of overall and selected site-specific cancers of the breast, digestive system, and lung. The overall results from this large, prospective cohort study showed that diabetes, high BP, and the presence of a combination of three or four MRFs were associated with higher breast cancer risk among postmenopausal women. Obesity in males less than 50 elevated the risk of digestive cancer.

Epidemiologic evidence points toward increased risk of breast cancer in postmenopausal diabetic women.[1, 2] Diabetes is frequently associated with insulin resistance, increased circulating concentrations of insulin, and insulin-like growth factors. Studies have shown insulin has mitogenic effects on breast tissue.[3] In addition, insulin inhibits the production of sex hormone-binding globulin, resulting in an increase in bioavailable estradiol.[4] Increased estradiol levels have been associated with the risk of developing breast cancer.[5]

The finding that postmenopausal women with high BP were at an increased risk of breast cancer is also supported by the recent meta-analysis on breast cancer risk in postmenopausal women.[1] Cancer and hypertension are both characterized by the proliferation of smooth muscle cells.[6] Another hypothesis indicates abnormalities of carcinogen binding to DNA in lymphocytes of hypertensive women.[7]

Study results showing an association between a combination of three or four MRFs and a higher risk of postmenopausal breast cancer, are supported by findings from a recent meta-analysis, suggesting that the increased risk for postmenopausal breast cancer was greater from the combined effect of MRFs than from individual MRFs.[1] A combination of MRFs may activate different molecular pathways through metabolic, endocrine, and immune cell changes, which can result in breast tumorigenesis.[8]

Among men, the only significant association observed was that of obesity with elevated risk of digestive cancer. Other studies have also observed a similar association between overweight/ obesity and digestive cancers, such as pancreatic[9, 10] and colorectal[11] cancers in men.

Current study has certain potential limitations. For example, blood glucose levels were self-reported. There were no separate measures for triglycerides, or low and high-density lipoprotein cholesterol levels (LDL and HDL). A stratified analysis could not be performed due to small sample size for races other than white, and nonwhite had to be combined into one category. Analyses on digestive and lung cancer could not be stratified by age because of small number of cancer cases.

This study has several strengths. For example, data were derived using a strong longitudinal cohort study design with high follow-up rates. In addition, self-report bias tended to be minimized by measuring serum total cholesterol as well as blood pressure and anthropometry (body mass index).

5.4 Study 3 Discussion: Association between metabolic risk factors and age at cancer onset

The aim of this study was to examine whether MRFs, either individually or in combination, were associated with age at onset of all-site cancer, and cancer of the breast, digestive system, and lung, respectively.

Study results showed an increased risk of diabetes associated with earlier age at cancer onset in younger and older males, and in older females. Diabetes was also associated with earlier age at onset of postmenopausal breast cancer, and lung cancer in both genders. Presence of a combination of three or four MRFs was associated with earlier age at onset of: (a) overall cancer

in women 50 years and older, (b) postmenopausal breast cancer, (c) digestive cancer in females, and (d) lung cancer in males.

Epidemiologic studies show an association between individual and combined MRFs and elevated cancer risk. However, there are very few studies on the association of these risk factors with age at cancer onset. Epidemiologic reviews and meta-analytic studies show people with diabetes were at a higher risk for overall cancer and cancers of several sites, such as liver, pancreas, endometrium, colon, rectum, breast, and bladder.[5, 12] The Metabolic Syndrome and Cancer project that comprises six large prospective cohorts found an association between increasing levels of glucose and increased risk for incidence and mortality from cancer of lung, trachea, and bronchus in men.[13] Another cohort study found an increased risk for lung cancer mortality in diabetic women.[14]

Study results show earlier age at cancer onset among older women with a combination of three or four MRFs. This finding is supported in the literature. A meta-analysis found that metabolic syndrome was positively associated with postmenopausal breast, endometrial, pancreatic, and colorectal cancers in women.[15] A large cohort study showed that metabolic syndrome was associated with increased liver and breast cancer risk in women.[16] Another cohort study concluded with a significant increase in breast cancer risk among older women with two or three MRFs, suggesting that the combined MRFs may elevate breast cancer risk beyond a single MRF, such as obesity.[17] However, studies on the association between combined MRFs and age at cancer onset are lacking.

Studies have suggested potential biological mechanisms that link MRFs with various cancers. In brief, through various mechanisms, including obesity, increased inflammatory markers such as tumor necrosis factor -α and interleuken-6, increased adipokines such as leptin,

decreased adiponectin, increased levels of free fatty acids and triglycerides, insulin resistance, increased insulin-like growth factor-1, and increased oxidative stress, MRFs have been shown to cause angiogenesis, cell migration, mitogenesis, and DNA damage.[18] There is, therefore, an emerging hypothesis that a combination of MRFs may be an important etiologic factor for the onset of cancer.[19]

This study shares similar strengths and limitations as those from the previous study. Some of the potential limitations include self-reported diabetes diagnosis, no separate measures for triglycerides, or low and high-density lipoprotein cholesterol levels, and small sample size for races other than white. The study has strengths that include a longitudinal cohort study design with high follow-up rates, and MRFs, such as total serum cholesterol as well as blood pressure and anthropometry (body mass index) based on body measurements and laboratory data. More importantly, there is very little research conducted on this subject.

5.5 Conclusion

The prevalence of MRFs, individually and in the aggregate, is growing rapidly.[20] There is limited biologic and epidemiologic evidence indicating an association between MRFs and cancer. The goal of this dissertation was to examine the association between individual and combined MRFs with subsequent risk of overall and site-specific cancers of the breast, digestive system, and lung. Results from the meta-analysis show that the combined MRFs (metabolic syndrome) are modestly associated with an increased risk for breast cancer in all adult women. Results from the association between individual and combined MRFs showed that diabetes, high BP, and the presence of a combination of three or four MRFs were associated with higher breast cancer risk among postmenopausal women. Diabetes was also associated with earlier age at (a) cancer onset in younger and older males, (b) cancer onset in older females, (c) postmenopausal

breast cancer onset, and (d) lung cancer onset in both genders. Lastly, presence of a combination of three or four MRFs was associated with earlier age at onset of: (a) overall cancer in women 50 and older, (b) postmenopausal breast cancer, (c) digestive cancer in females, and (d) lung cancer in males.

In conclusion, study results suggest that diabetes and metabolic syndrome (or a combination of MRFs) may serve as markers for postmenopausal breast cancer risk, but not for overall or any other site-specific cancer risk. The association between diabetes and a combination of three or four MRFs and earlier age at onset was observed not only for postmenopausal breast cancer, but also for overall cancer in women 50 and older, digestive cancer in women, and lung cancer in males.

Future research needs to determine the underlying mechanisms that may predispose people with metabolic abnormalities to cancer. To this end, it is essential to examine the relationship among site-specific cancers, stratified by age, gender and race, with detailed information on triglycerides, low and high-density lipoprotein cholesterol levels, abdominal and visceral adiposity, blood glucose levels, duration of each abnormality, and medications and their period of use.

The positive association of a combination of MRFs with breast cancer in the meta-analysis points toward the need to develop public health strategies to manage these risk factors. Diabetes may also serve as a marker for postmenopausal breast cancer risk. Given the increasingly large global burden of metabolic risk factors, even a small association with breast cancer can have a substantial public health impact. Risk assessment tools can be developed that incorporate MRFs as a risk factor for breast cancer. Healthcare providers will then be better equipped to identify high-risk women for primary and secondary prevention.

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APPENDIX A

Appendix A: Table 1. Criteria for Risk of Bias Assessment.

Criteria	Low Risk	High Risk	Unclear Risk
Study design	Prospective or retrospective cohort, nested case-control	Case-control	Information not reported
Adjustment of confounders	Adjusted for 4 or more of the following: age, education/income, family history of cancer, hormone therapy use/oral contraceptive use/reproductive history, smoking status, and alcohol consumption	Adjusted for 3 or less of the following: age, education/income, family history of cancer, hormone therapy use/oral contraceptive use/reproductive history, smoking status, and alcohol consumption	Information not reported
Selection of participants and their eligibility criteria	Studies clearly stating their eligibility criteria and the sources and methods of selection of participants	Studies not clearly stating their eligibility criteria and the sources and methods of selection of participants	Information not reported
Measurement of predictor variables	Identified through objective measures	Self-reported or pharmaceutical prescriptions	Information not reported
Breast cancer diagnosis	Histologically confirmed or identified through cancer registry/ medical records	Self-reported	Information not reported
Study size	Large enough for adequate power	Not large enough for adequate power	Information not reported
Handling of missing data	Missing data analysis specified	Missing data deleted from analysis	Information not reported
Reasons for non-participation of individuals at each stage of the study	Reasons clearly reported for each stage of study	Reasons not reported for each stage of study	Information not reported

Appendix A: Table 2. Characteristics of Studies.

Author	Year	Country	Study Design	Sample Size	Baseline Year	Follow-up Years	Age	Breast Cancer Cases	Menopausal Status	Statistic
Agnoli et al.[43]	2010	Italy	Prospective nested case-control	792	1987-92	2003	35-69	163	Post	Rate ratios
Bosco[61]	2011	USA	Prospective cohort	49,172	1995	2007	21-69	1228	Mixed, post	Incidence rate ratios
Inoue et al.[62]	2009	Japan	Prospective cohort	18,176	1990-94	2004	40-69	120	Mixed, post	Hazard ratios
Kabat et al.[48]	2009	USA	Prospective cohort	4,888	1993-98	2005	50-79	165	Post	Hazard ratios
Osaki et al.[13]	2012	Japan	Retrospective cohort	15,386	1992-2000	2007	20+	77	Mixed, post	Hazard ratios
Ronco et al.[51]	2012	Uruguay	Case-control	912	2004	2009	<70	367	Post	Odds ratios
Rosato et al. - Cohort I[14]	2011	Italy	Case-control	3,858	1983	1994	33-86	1,988	Post	Odds ratios
Rosato et al.- Cohort II[14]	2011	Italy and Switzerland	Case-control	4,093	1991	2007	33-79	1,881	Post	Odds ratios
Russo et al.[63]	2008	Italy	Prospective cohort	Not reported	1999	2005	≥40	99	Mixed	Standardized incidence ratios

Note: Citations for the included studies are in the reference section of Chapter 2, pages 28-36.

Appendix A: Table 2 (continued).

Author	Exposure Assessment	Cancer Identification	Confounders
Agnoli et al.[43]	Questionnaire, anthropometric measures, fasting blood draw	Cancer registry	age, age at menarche, age at first birth, years from menopause, number of full-term pregnancies, oral contraceptives, hormone therapy, education, cancer in first degree relatives, breastfeeding, smoking, alcohol consumption
Bosco[61]	Questionnaire	Medical records or cancer registry data	age, education, BMI at 18, vigorous activity
Inoue et al.[62]	Questionnaire, anthropometric measures, fasting and non-fasting blood draw	Self-report	age, study area, smoking status, ethanol intake, physical activity, total cholesterol
Kabat et al.[48]	Questionnaire, anthropometric measures, fasting blood draw	Self-report confirmed by medical records and tumor registry abstracts	age, education, ethnicity, BMI, oral contraceptive use, postmenopausal hormone therapy, age at menarche, age at first birth, age at menopause, alcohol, family history of breast cancer, history of breast biopsy, physical activity, energy intake, smoking status
Osaki et al.[13]	Questionnaire, anthropometric measures, fasting blood draw	Cancer registry	age, smoking, heavy drinking
Ronco et al.[51]	Questionnaire, anthropometric measures after cancer	Histologically confirmed breast cancer	age, residence, age at menarche, parity, age at first live birth, months of breastfeeding, use of oral contraceptives, BMI, menopausal status, family history of BC, and intake of beef, tomatoes and oranges
Rosato et al.[14]	Questionnaire, waist circumference measure	Histologically confirmed breast cancer	age, study center, study period, education, alcohol consumption, age at menarche, parity and age at first birth, age at menopause, hormone replacement therapy use, family history of breast cancer
Russo et al.[63]	Pharmaceutical prescriptions for MS	Cancer registry	Not reported

Note: Citations for the included studies are in the reference section of Chapter 2, pages 28-36.

Appendix A: Table 3. Definitions and Criteria for Metabolic Syndrome in the Included Studies.

Agnoli et al.[43]	2 definitions (≥ 3 of the following components): 1. Highest or lowest (HDL-C) tertiles in controls: WC > 86 cm; Triglycerides > 126 mg/dL; HDL-C ≤= 55 mg/dL; Fasting Glucose > 88 mg/dL (or previously diagnosed T2DM); Mean BP ≥ 106.5 mmHg (or treatment for previously diagnosed HTN). 2. NCEP: WC > 88 cm; Triglycerides ≥150 mg/dL; HDL-C < 50 mg/dL; SBP ≥130 mmHg or Diastolic BP ≥ 85 mmHg; Fasting Glucose ≥ 110 mg/dL.
Bosco[61]	≥ 3 of the following components: WC ≥ 88 cm; T2DM self-reported diagnosis at ≥ 30 years at baseline; HTN self-reported diagnosis plus diuretics or hypertensive medication use at baseline; Cholesterol self-reported diagnosis of high cholesterol and cholesterol-lowering medication at baseline.
Inoue et al.[62]	2 definitions: 1. Grundy (NHLBI 2005): Any 3 or more: BMI ≥ 25 kg/m^2; HTN ≥130/85 mmHg or medication use; Glucose ≥ 100 mg/dL fasting or 140 mg/dL non-fasting or on treatment; low HDL-C < 50 mg/dL; Triglycerides ≥150 mg/dL,; 2. IDF: overweight and at least 2 other components.
Kabat et al.[48]	ATP III modified to exclude those with Glucose ≥ 126 mg/dL or those taking diabetic medication
Osaki et al.[13]	6 definitions: Japan 2005, Modified NCEP 2001, Modified NCEP 2004, Modified IDF 2006, Modified WHO 1999, NCEP 2001 with BP 140/90
Ronco et al.[51]	2 definitions: 1. Diabetes+Overweight+HTN 2. Diabetes+Overweight+Dyslipidemia
Rosato et al.[14]	Combined presence of diabetes, drug-treated HTN, drug-treated hyperlipidemia (as a proxy indicator of elevated Triglycerides and reduced HDL-C), WC ≥ 88 cm or BMI ≥30 kg/m^2 when WC was missing
Russo et al.[63]	Pharmacological definition - who chronically received antihypertensive, glucose-lowering, and lipid modifying drugs

Notes: BMI = Body Mass Index; BP = Blood Pressure; HDL-C = High Density Lipoprotein Cholesterol; HTN = Hypertension; WC = Waist circumference; IDF = International Diabetes Federation; NCEP ATP III = National Cholesterol Education Program's Adult Treatment Panel III; NHLBI = National Heart, Lung, and Blood Institute; WHO = World Health Organization.

Note: Citations for the included studies are in the reference section of Chapter 2, pages 28-36.

Appendix A: Table 4. Study-Level Results for Risk of Bias Assessment.

Methods	Agnoli et al.[43]	Bosco[61]	Inoue et al.[62]	Kabat et al.[48]	Osaki et al.[13]	Ronco et al.[51]	Rosato et al.[14]	Russo et al.[63]
Study design	Low	Low	Low	Low	Low	High	High	Low
Variables (confounders)	Low	High	High	Low	High	Low	Low	Unclear
Participants (eligibility, selection)	Low	Low	Low	Low	Low	Low	Low	Low
Data sources/ predictor measurement	Low	High	Low	Low	Low	High	High	High
Data sources/ outcome measurement	Low	Low	High	Low	Low	Low	Low	Low
Study size (adequate power)	Low	Low	Low	Low	Low	Low	Low	Low
Missing data analysis	High	High	High	Low	High	Low	Unclear	Unclear
Results								
Participants (non-participation)	High	High	High	High	Low	Low	High	High

Note: Citations for the included studies are in the reference section of Chapter 2, pages 28-36.

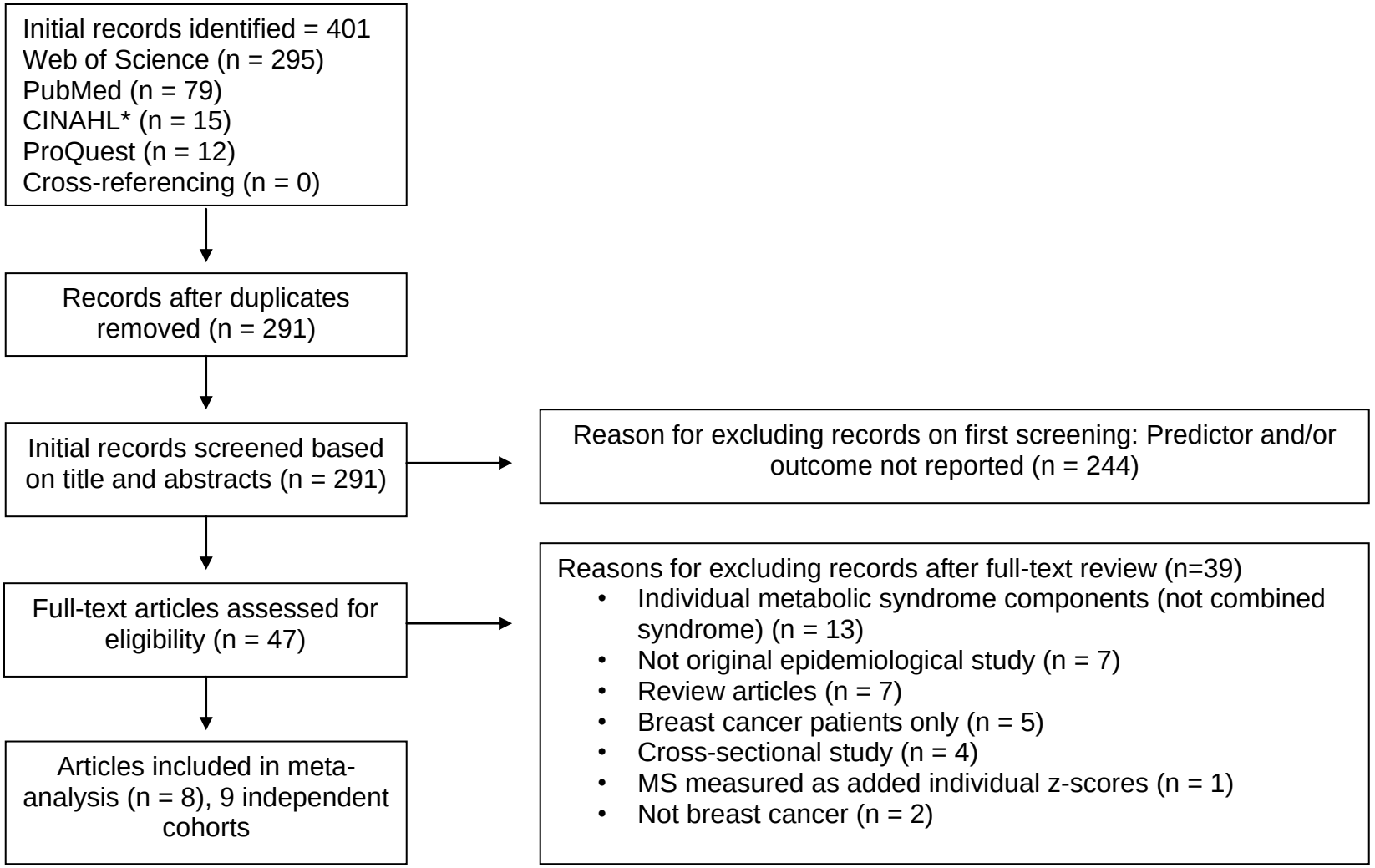

Figure 1. Flow diagram describing the selection of studies.
*CINAHL: Cumulated Index to Nursing and Allied Health Literature.

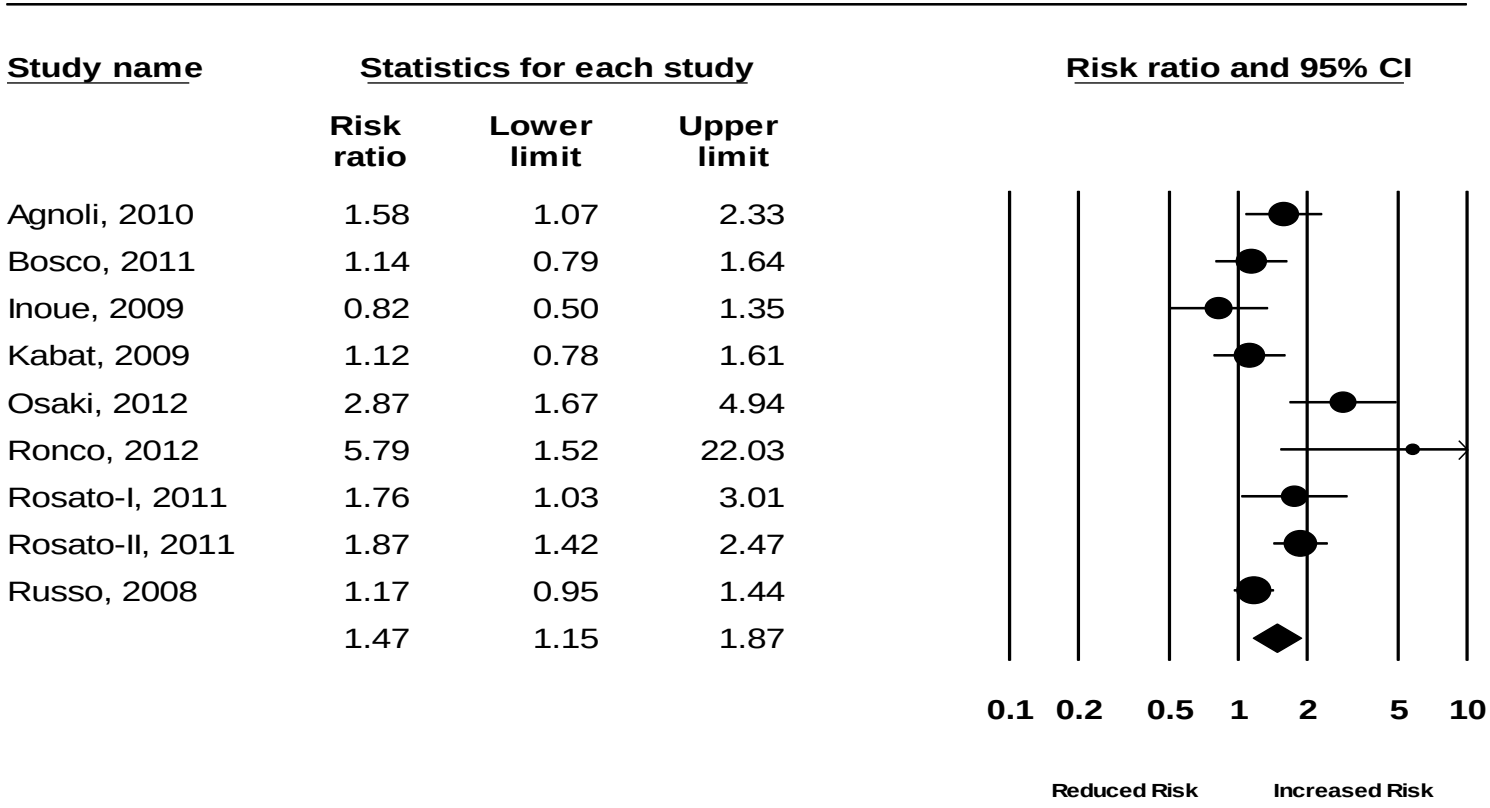

Figure 2. Forest plot for metabolic syndrome and breast cancer risk (random-effects model).
The black circles represent the weighted risk ratio (RR) for each result from each study while the horizontal lines represent the lower and upper 95% confidence intervals (CI) for the RR. The black diamond represents the overall pooled RR while the left and right sides of the diamond represent the lower and upper 95% CI for the pooled RR. For studies that included more than one definition of metabolic syndrome, the following were used: Agnoli et al. (tertile definition), Bosco (time-independent definition), Osaki et al. (modified NCEP 2001 definition), Ronco et al. (diabetes, overweight and hypertension definition).

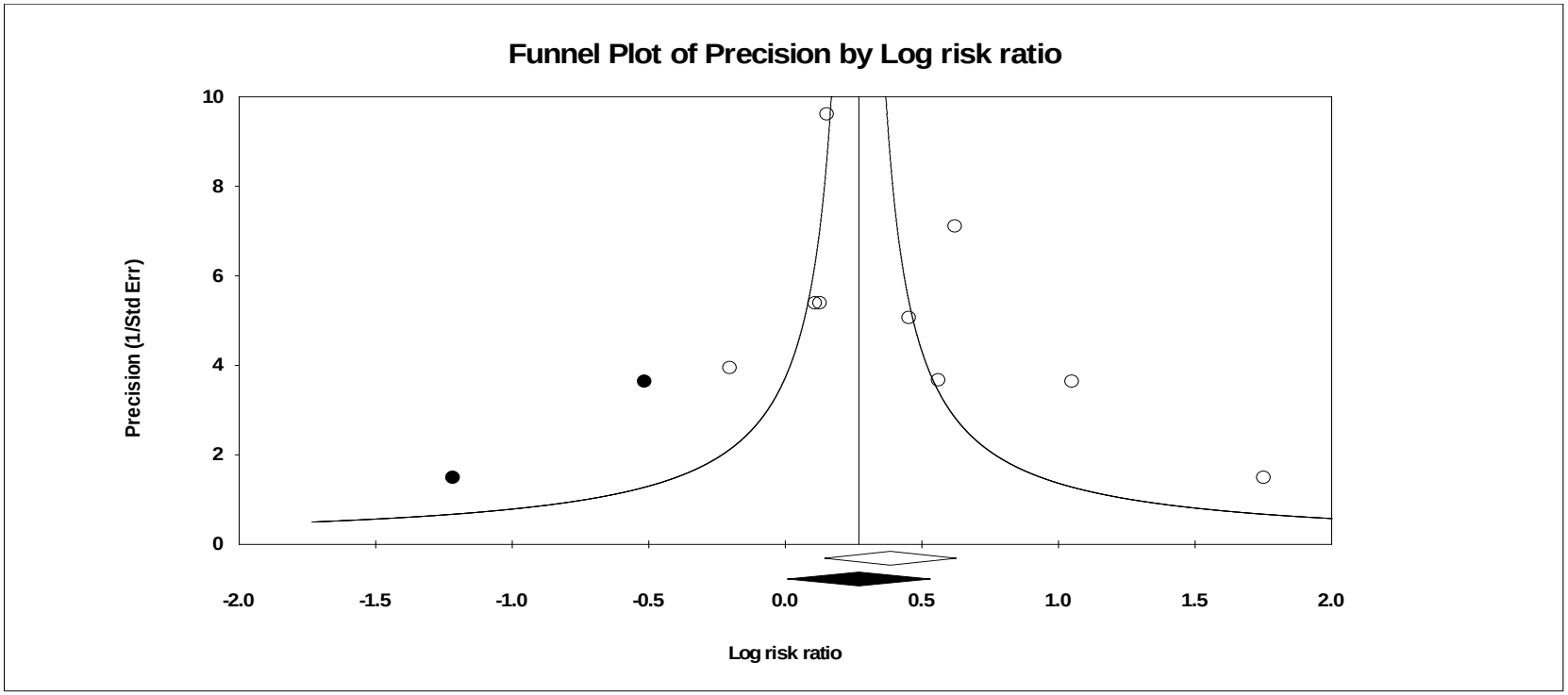

Figure 3. Funnel plot and Trim and Fill procedure for assessing publication bias.
The white circles represent the log risk ratios (LRR) for each result from each study while the black circles represent the imputed LRR (n = 2). The white diamond represents the pooled LRR while the black diamond represents the pooled LRR, including the two imputed values. The left and right sides of each diamond represent the lower and upper 95% confidence intervals. For those studies that included more than one definition of metabolic syndrome, the following were used: Agnoli et al. (tertile definition), Bosco (time independent definition), Osaki et al. (modified NCEP 2001 definition), and Ronco et al. (diabetes, overweight and hypertension definition).

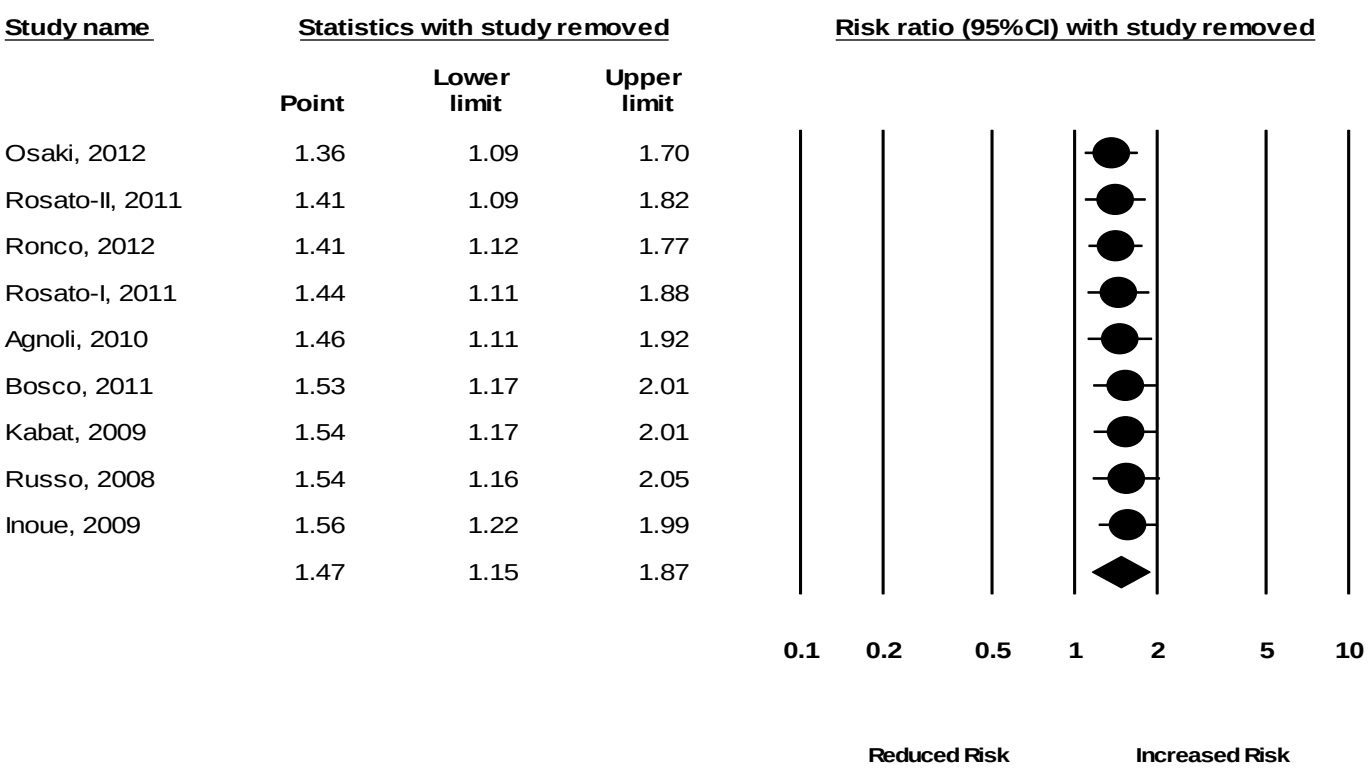

Figure 4. Influence analysis with each result from each study deleted from the random-effects model once.
The black circles represent the risk ratio (RR) for each result from each study while the horizontal lines represent the lower and upper 95% confidence interval (CI) for the RR. The black diamond represents the overall pooled result while the left and right sides of the diamond represent the lower and upper 95% CI for the pooled RR. For studies that included more than one definition of metabolic syndrome, the following were used: Agnoli et al. (tertile definition), Bosco (time-independent definition), Osaki et al. (modified NCEP 2001 definition), and Ronco et al. (diabetes, overweight and hypertension definition).

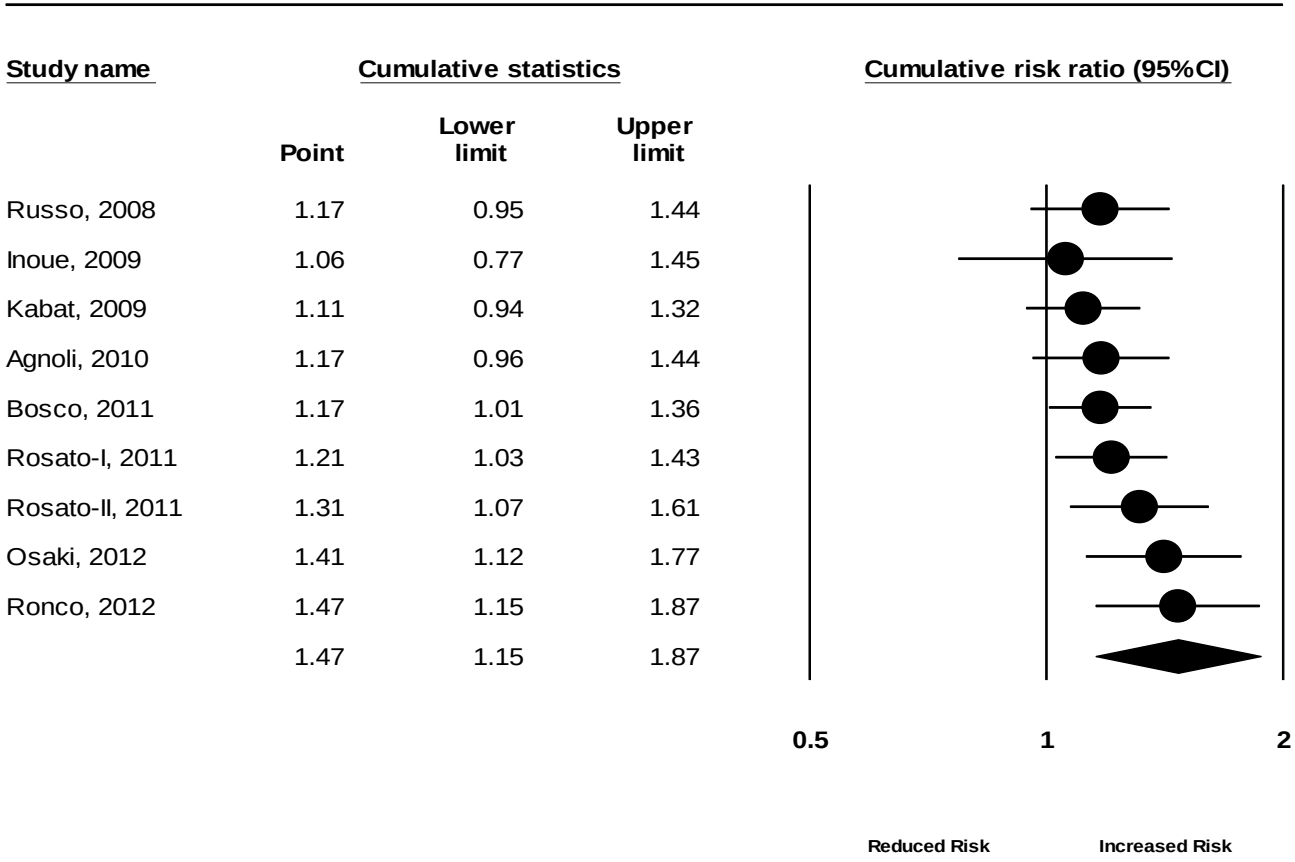

Figure 5. Cumulative meta-analysis, ranked by year and based on a random-effects model.
The black circles represent the cumulative risk ratios (RR) for each result from each study while the horizontal lines represent the lower and upper 95% confidence intervals for the RR. The black diamond represents the overall pooled RR while the left and right sides of the diamond represent the lower and upper 95% confidence intervals for the pooled RR. For those studies that included more than one definition of metabolic syndrome, the following were used: Agnoli et al. (tertile definition), Bosco (time independent definition), Osaki et al. (modified NCEP 2001 definition), and Ronco et al. (diabetes, overweight and hypertension definition).

APPENDIX B

Appendix B: Association between metabolic risk factors and cancer risk

Table 1: Characteristics of the Study Population, National Health and Nutrition Examination Survey I (NHANES I) Epidemiologic Follow-up Study, 1971-1992
(Unweighted sample size = 10,694)

Characteristics of the study population	Total	%	Mean (SE)
Age at baseline (years)			48.78 (0.15)
Women	6339	59.3	
Men	4355	40.7	
Race/ethnicity			
White	9125	85.3	
Non-white	1569	14.7	
Family income			
Below $5,000	2794	26.1	
$5,001 - $15,000	5558	52.0	
Above $15,000	2342	21.9	
Education			
High school or less	8159	76.3	
Above high school	2535	23.7	
Physical activity			
Moderately or very active	9652	90.3	
Quite inactive	1042	9.7	
Smoked 100 cigarettes in lifetime			
Yes	5786	54.1	
No	4477	41.9	
Missing	431	4.0	
Family history of cancer			
Yes	3763	35.2	
No	6006	56.2	
Missing	925	8.6	
BMI, kg/m^2			25.68 (0.05)
BMI categories			
Underweight	333	3.1	
Healthy weight	5020	46.9	
Overweight	3562	33.3	
Obese	1779	16.6	
Blood pressure			
High BP	4851	45.4	
No high BP	5843	54.6	
Diastolic (mmHg)			83.54 (0.13)
Systolic (mmHg)			134.03 (0.23)

Continued...

Serum cholesterol (mg/dL)			220.82 (0.47)
High (>=240 mg/dL)	3383	31.6	
Not high cholesterol	7311	68.4	
Diabetes			
Yes	518	4.8	
No	7969	74.5	
Missing	2207	20.6	
Metabolic Risk Factor (MRF)			
MRF 0	3031	28.3	
MRF 1	2925	27.4	
MRF 2	1924	18.0	
MRF 3 or 4	607	5.7	
Missing	2322	21.7	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; MRF, Metabolic Risk Factor; SE, Standard Error.

Appendix B

Table 2: Association between Individual Metabolic Risk Factors and Cancer Risk among Males

	Age <50 Years (n = 1972, Cancer cases = 140)			Age ≥ 50 Years (n = 2383, Cancer cases = 691)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
BMI≥30	18	244	1.00 (0.57, 1.76)	89	323	1.08 (0.81, 1.46)
BMI<30	122	1728	Referent	602	2060	Referent
High BP	56	741	0.89 (0.63, 1.25)	398	1498	0.84 (0.68, 1.05)
< High BP	84	1231	Referent	293	885	Referent
Cholesterol≥240	44	484	1.21 (0.85, 1.72)	232	855	1.00 (0.81, 1.23)
Cholesterol<240	96	1488	Referent	459	1528	Referent
Diabetes	4	37	1.02 (0.32, 3.29)	34	175	1.05 (0.60, 1.84)
No Diabetes	102	1350	Referent	524	1794	Referent
Missing	34	585		133	414	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 3: Association between Individual Metabolic Risk Factors and Cancer Risk among Females

	Age <50 Years (n = 3722, Cancer cases = 364)			Age ≥ 50 Years (n = 2617, Cancer cases = 572)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
BMI≥30	70	575	1.18 (0.80, 1.74)	129	637	**0.74 (0.54, 0.99)**
BMI<30	294	3147	Referent	443	1980	Referent
High BP	96	843	1.02 (0.71, 1.46)	375	1769	0.97 (0.78, 1.21)
< High BP	268	2879	Referent	197	848	Referent
Cholesterol≥240	83	617	1.20 (0.89, 1.61)	322	1427	**1.27 (1.01, 1.58)**
Cholesterol<240	281	3105	Referent	250	1190	Referent
Diabetes	10	72	0.91 (0.38, 2.17)	39	234	1.12 (0.70, 1.78)
No Diabetes	293	2898	Referent	441	1927	Referent
Missing	61	752		92	456	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 4: Association between Combined Metabolic Risk Factors Score and Cancer Risk among Males

	Age <50 Years (n = 1987, Cancer cases = 141)			Age ≥ 50 Years (n =2396, Cancer cases = 692)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
MRF 3 or 4	5	53	1.09 (0.40, 2.98)	23	120	0.63 (0.35, 1.12)
MRF 2	21	205	1.11 (0.68, 1.80)	148	591	0.81 (0.59, 1.12)
MRF 1	37	501	0.92 (0.55, 1.55)	250	850	0.93 (0.67, 1.28)
MRF 0	43	628	Referent	137	408	Referent
Missing	35	600		134	427	

Abbreviations: CI, Confidence Interval; MRF, Metabolic Risk Factor.

[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 5: Association between Combined Metabolic Risk Factors Score and Cancer Risk among Females

	Age <50 Years (n = 3773, Cancer cases = 371)			Age ≥ 50 Years (n = 2653, Cancer cases = 580)		
Variable	Sample size	Cancer cases	Hazard ratio[a] (95% CI)	Sample size	Cancer cases	Hazard ratio[a] (95% CI)
MRF 3 or 4	13	70	1.30 (0.65, 2.60)	75	364	1.14 (0.69, 1.90)
MRF 2	50	351	1.41 (0.90, 2.20)	175	777	0.99 (0.68, 1.44)
MRF 1	81	816	1.04 (0.75, 1.43)	165	758	0.92 (0.64, 1.32)
MRF 0	159	1733	Referent	65	262	Referent
Missing	68	803		100	492	

Abbreviations: CI, Confidence Interval; MRF, Metabolic Risk Factor.

[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 6: Association between Individual Metabolic Risk Factors and Breast Cancer Risk among Females

	All women (n = 6339, Cancer cases = 236)			Postmenopausal women (n =2954, Cancer cases =124)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
BMI≥30	50	1212	0.81 (0.51, 1.31)	33	700	0.80 (0.43, 1.50)
BMI<30	186	5127	Referent	91	2254	Referent
High BP	107	2612	1.19 (0.81, 1.73)	83	1847	**1.70 (1.001, 2.88)**
< High BP	129	3727	Referent	41	1107	Referent
Cholesterol≥240	89	2044	1.13 (0.78, 1.63)	66	1487	1.16 (0.75, 1.79)
Cholesterol<240	147	4295	Referent	58	1467	Referent
Diabetes	14	306	1.63 (0.81, 3.29)	13	245	**2.32 (1.09, 4.95)**
No Diabetes	177	4825	Referent	83	2171	Referent
Missing	45	1208		28	538	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 7: Association between Combined Metabolic Risk Factors Score and Breast Cancer Risk among Females

	All women (n = 6426, Cancer cases = 239)			Postmenopausal women (n = 2998, Cancer cases = 126)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
MRF 3 or 4	21	434	1.44 (0.68, 3.04)	**19**	**365**	**3.26 (1.23, 8.65)**
MRF 2	46	1128	1.09 (0.62, 1.92)	34	819	2.16 (0.89, 5.22)
MRF 1	56	1574	0.93 (0.57, 1.52)	30	837	1.53 (0.64, 3.62)
MRF 0	68	1995	Referent	13	395	Referent
Missing	48	1295		30	582	

Abbreviations: CI, Confidence Interval; MRF, Metabolic Risk Factor.

[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 8: Association between Individual Metabolic Risk Factors and Digestive Cancer Risk by Gender

	Males (n = 4355, Cancer cases = 196)			Females (n = 6339, Cancer cases = 207)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
BMI≥30	36	567	**1.92 (1.15, 3.21)**	52	1212	0.86 (0.58, 1.29)
BMI<30	160	3788	Referent	155	5127	Referent
High BP	116	2239	1.02 (0.65, 1.59)	132	2612	1.36 (0.93, 1.99)
< High BP	80	2116	Referent	75	3727	Referent
Cholesterol≥240	57	1339	0.90 (0.58, 1.38)	107	2044	1.32 (0.93, 1.87)
Cholesterol<240	139	3016	Referent	100	4295	Referent
Diabetes	9	212	1.47 (0.54, 4.01)	13	306	0.89 (0.36, 2.17)
No Diabetes	148	3144	Referent	168	4825	Referent
Missing	39	999		26	1208	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 9: Association between Combined Metabolic Risk Factors and Digestive Cancer Risk by Gender

Males (n = 4383, Cancer cases = 196)				Females (n = 6426, Cancer cases = 211)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
MRF 3 or 4	7	173	1.32 (0.42, 4.16)	28	434	1.05 (0.54, 2.05)
MRF 2	43	796	1.32 (0.66, 2.65)	67	1128	0.98 (0.58, 1.65)
MRF 1	69	1351	1.35 (0.71, 2.56)	44	1574	**0.49 (0.26, 0.91)**
MRF 0	38	1036	Referent	42	1995	Referent
Missing	39	1027		30	1295	

Abbreviations: CI, Confidence Interval; MRF, Metabolic Risk Factor.

[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 10: Association between Individual Metabolic Risk Factors and Lung Cancer Risk by Gender

	Males (n = 4355, Cancer cases = 174)			Females (n = 6339, Cancer cases = 81)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
BMI≥30	20	567	0.97 (0.48, 1.95)	15	1212	0.85 (0.38, 1.91)
BMI<30	154	3788	Referent	66	5127	Referent
High BP	86	2239	0.86 (0.60, 1.24)	39	2612	0.62 (0.33, 1.14)
< High BP	88	2116	Referent	42	3727	Referent
Cholesterol≥240	56	1339	1.22 (0.85, 1.75)	38	2044	1.51 (0.80, 2.84)
Cholesterol<240	118	3016	Referent	43	4295	Referent
Diabetes	9	212	1.14 (0.45, 2.87)	6	306	1.70 (0.52, 5.56)
No Diabetes	131	3144	Referent	58	4825	Referent
Missing	34	999		17	1208	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

Appendix B

Table 11: Association between Combined Metabolic Risk Factors and Lung Cancer Risk by Gender

	Males (n = 4383, Cancer cases = 175)			Females (n = 6426, Cancer cases = 83)		
Variable	Cancer cases	Sample size	Hazard ratio[a] (95% CI)	Cancer cases	Sample size	Hazard ratio[a] (95% CI)
MRF 3 or 4	5	173	1.05 (0.25, 4.46)	6	434	0.66 (0.14, 3.09)
MRF 2	30	796	0.93 (0.51, 1.68)	20	1128	0.76 (0.31, 1.84)
MRF 1	65	1351	1.22 (0.66, 2.26)	20	1574	0.63 (0.26, 1.57)
MRF 0	40	1036	Referent	18	1995	Referent
Missing	35	1027		19	1295	

Abbreviations: CI, Confidence Interval; MRF, Metabolic Risk Factor.

[a] Hazard ratios were adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

APPENDIX C

Appendix C: Association between metabolic risk factors and age at cancer onset

Table 1. Characteristics of the Study Population, National Health and Nutrition Examination Survey I (NHANES I) Epidemiologic Follow-up Study, 1971-1992
(Unweighted sample size = 1,736)

Characteristics of the study population	Frequency	%	Mean (SE)
Age at baseline (years)			56.4 (0.31)
Age at cancer (years)			67.9 (0.31)
Women	914	52.6	
Men	822	47.4	
Race/ethnicity			
White	1502	86.5	
Non-white	234	13.5	
Family income			
Below $5,000	543	31.3	
$5,001 - $15,000	864	49.8	
Above $15,000	329	19.0	
Education			
High school or less	1400	80.6	
Above high school	336	19.4	
Physical activity			
Moderately or very active	1559	89.8	
Quite inactive	177	10.2	
Smoked 100 cigarettes in lifetime			
Yes	984	56.7	
No	673	38.8	
Missing	79	4.6	
Family history of cancer			
Yes	707	40.7	
No	845	48.7	
Missing	184	10.6	
BMI, kg/m^2			26.0 (0.12)
BMI categories			
Underweight	31	1.8	
Healthy weight	765	44.1	
Overweight	641	36.9	
Obese	299	17.2	
Blood pressure (mmHg)			
Diastolic			84.3 (0.31)
Systolic			137.7 (0.57)
High BP	902	52.0	
No high BP	834	48.0	

Continued...

Serum cholesterol (mg/dL)			228.7 (1.23)
High (>=240 mg/dL)	668	38.5	
Low (< 240 mg/dL)	1068	61.5	
Diabetes			
Yes	84	4.8	
No	1334	76.8	
Missing	318	18.3	
Metabolic Risk Factor (MRF)			
MRF 0	400	23.0	
MRF 1	522	30.1	
MRF 2	383	22.1	
MRF 3 or 4	113	6.5	
Missing	335	19.3	

Abbreviations: BMI, Body mass index; SE, Standard error.

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Table 2: Association between Individual Metabolic Risk Factors and Age at Cancer Onset among Males

	Age <50 Years (n= 140)		Age ≥ 50 Years (n = 682)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
BMI≥30 kg/m^2	18	**2.71 (0.96, 4.47)**	87	0.27 (-0.99, 1.53)
BMI<30 kg/m^2	122	Referent	595	Referent
High BP	56	1.47 (-0.25, 3.20)	391	0.04 (-0.96, 1.05)
< High BP	84	Referent	291	Referent
Cholesterol≥240 mg/dL	44	-1.47 (-3.45, 0.51)	230	0.45 (-0.39, 1.30)
Cholesterol<240 mg/dL	96	Referent	452	Referent
Diabetes	4	**-4.36 (-7.77, -0.96)**	33	**-2.78 (-5.34, -0.22)**
No Diabetes	102	Referent	517	Referent
Missing	34		132	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 3: Association between Individual Metabolic Risk Factors and Age at Cancer Onset among Females

	Age <50 Years (n = 362)		Age ≥ 50 Years (n = 552)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
BMI≥30 kg/m^2	69	-0.80 (-2.39, 0.79)	125	-0.89 (-2.29, 0.51)
BMI<30 kg/m^2	293	Referent	427	Referent
High BP	96	1.25 (-0.10, 2.61)	359	-0.05 (-1.13, 1.02)
< High BP	266	Referent	193	Referent
Cholesterol≥240 mg/dL	83	0.32 (-0.77, 1.41)	311	-0.20 (-1.12, 0.72)
Cholesterol<240 mg/dL	279	Referent	241	Referent
Diabetes	9	-0.20 (-3.47, 3.08)	38	**-1.97 (-3.72, -0.21)**
No Diabetes	292	Referent	423	Referent
Missing	61		91	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 4: Association between Combined Metabolic Risk Factors and Age at Cancer Onset among Males

	Age <50 Years (n = 141)		Age ≥ 50 Years (n = 683)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
MRF 3 or 4	5	2.65 (-0.79, 6.10)	22	0.73 (-2.36, 3.82)
MRF 2	21	0.90 (-2.50, 4.30)	146	0.13 (-1.35, 1.61)
MRF 1	37	-0.18 (-2.30, 1.95)	247	-0.40 (-1.71, 0.92)
MRF 0	43	Referent	135	Referent
Missing	35		133	

Abbreviations: CI, Confidence Interval, MRF, Metabolic Risk Factor.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 5: Association between Combined Metabolic Risk Factors and Age at Cancer Onset among Females

	Age <50 Years (n = 369)		Age ≥ 50 Years (n = 560)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
MRF 3 or 4	13	**2.78 (0.41, 5.14)**	73	**-2.64 (-4.60, -0.68)**
MRF 2	50	0.48 (-1.08, 2.05)	166	0.29 (-1.62, 2.20)
MRF 1	79	-0.77 (-2.38, 0.85)	159	-0.25 (-2.05, 1.55)
MRF 0	159	Referent	63	Referent
Missing	68		99	

Abbreviations: CI, Confidence Interval, MRF, Metabolic Risk Factor.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 6: Association between Individual Metabolic Risk Factors and Age at Breast Cancer Onset among Females

	All women (n = 223)		Postmenopausal women (n = 112)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
BMI≥30 kg/m^2	48	-1.78 (-3.78, 0.23)	31	-0.37 (-2.64, 1.90)
BMI<30 kg/m^2	181	Referent	81	Referent
High BP	101	1.02 (-0.96, 3.00)	75	0.10 (-2.30, 2.50)
< High BP	128	Referent	37	Referent
Cholesterol≥240 mg/dL	88	-0.60 (-2.53, 1.33)	60	-0.93 (-3.30, 1.43)
Cholesterol<240 mg/dL	141	Referent	52	Referent
Diabetes	14	-2.78 (-5.82, 0.25)	13	**-2.61 (-4.89, -0.33)**
No Diabetes	169	Referent	72	Referent
Missing	46		27	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 7: Association between Combined Metabolic Risk Factors and Age at Breast Cancer Onset among Females

	All women (n = 226)		Postmenopausal women (n = 114)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
MRF 3 or 4	21	**-3.31 (-6.12, -0.50)**	**19**	**-3.84 (-6.71, -0.96)**
MRF 2	44	-0.98 (-4.08, 2.13)	29	-2.55 (-6.31, 1.20)
MRF 1	51	-2.13 (-4.27, 0.01)	26	-2.46 (-5.41, 0.48)
MRF 0	67	Referent	11	Referent
Missing	50		29	

Abbreviations: CI, Confidence Interval, MRF, Metabolic Risk Factor.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 8: Association between Individual Metabolic Risk Factors and Age at Digestive Cancer Onset by Gender

	Males (n = 194)		Females (n = 203)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
BMI≥30 kg/m^2	34	0.17 (-2.01, 2.36)	51	-1.66 (-3.45, 0.13)
BMI<30 kg/m^2	160	Referent	152	Referent
High BP	114	0.79 (-1.08, 2.66)	128	-1.03 (-2.80, 0.75)
< High BP	80	Referent	75	Referent
Cholesterol≥240 mg/dL	57	0.34 (-1.53, 2.22)	104	0.17 (-1.75, 2.08)
Cholesterol<240 mg/dL	137	Referent	99	Referent
Diabetes	9	-0.21 (-3.04, 2.62)	13	-2.21 (-4.88, 0.46)
No Diabetes	147	Referent	164	Referent
Missing	38		26	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 9: Association between Combined Metabolic Risk Factors and Age at Digestive Cancer Onset by Gender

	Males (n = 194)		Females (n = 207)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
MRF 3 or 4	7	0.98 (-2.26, 4.22)	27	**-4.42 (-6.63, -2.22)**
MRF 2	42	1.04 (-1.73, 3.82)	65	-1.35 (-3.64, 0.95)
MRF 1	69	-0.67 (-2.83, 1.50)	43	**-3.09 (-5.41, -0.77)**
MRF 0	38	Referent	42	Referent
Missing	38		30	

Abbreviations: CI, Confidence Interval, MRF, Metabolic Risk Factor.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 10: Association between Individual Metabolic Risk Factors and Age at Lung Cancer Onset by Gender

	Males (n = 174)		Females (n = 80)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
BMI≥30 kg/m^2	20	-0.44 (-2.78, 1.91)	15	1.34 (-0.73, 3.40)
BMI<30 kg/m^2	154	Referent	65	Referent
High BP	86	0.66 (-1.02, 2.34)	38	1.07 (-0.90, 3.04)
< High BP	88	Referent	42	Referent
Cholesterol≥240 mg/dL	56	0.29 (-1.60, 2.17)	37	0.46 (-1.71, 2.62)
Cholesterol<240 mg/dL	118	Referent	43	Referent
Diabetes	9	**-7.40 (-10.37, -4.43)**	6	**-4.59 (-8.18, -1.01)**
No Diabetes	131	Referent	57	Referent
Missing	34		17	

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CI, Confidence Interval.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).

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Table 11: Association between Combined Metabolic Risk Factors and Age at Lung Cancer Onset by Gender

	Males (n = 175)		Females (n = 82)	
Variable	Cancer cases	Mean difference[a] (95% CI)	Cancer cases	Mean difference[a] (95% CI)
MRF 3 or 4	5	**-3.76 (-6.63, -0.88)**	6	-2.92 (-8.93, 3.10)
MRF 2	30	0.44 (-2.44, 3.32)	19	-0.05 (-3.53, 3.44)
MRF 1	65	-1.36 (-3.53, 0.82)	20	-0.87 (-4.00, 2.25)
MRF 0	40	Referent	18	Referent
Missing	35		19	

Abbreviations: CI, Confidence Interval, MRF, Metabolic Risk Factor.
[a]Adjusted for age (years, continuous), race (White, others), education (high school or less, college), family income (<$5,000, $5,000 to <$15,000, and >=$15,000), smoking status (smoked 100 cigarettes in one's lifetime, yes, no or missing data), family history of cancer (yes, no or missing data), and physical activity (moderately or very active, quite inactive).