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Research Article

Metabolic Health Reduces Risk of Obesity-Related Cancer in Framingham Study Adults

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Abstract

Background: It is unknown whether the risk for obesity-related cancers differs between metabolically unhealthy and healthy overweight/obese adults.

Methods: Data on body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), and random blood glucose in Framingham Heart Study adults ($n = 3{,}763$) ages 55 to 69 years were used to estimate risks of obesity-related cancers ($n = 385$), including postmenopausal breast, female reproductive, colon, liver, gallbladder, pancreas, and kidney cancers, as well as esophageal adenocarcinomas. Multivariable-adjusted Cox proportional hazards models were used to estimate risk for obesity-related cancers associated with body fat and metabolic health (as defined by glucose levels) among subjects in three risk groups (vs. referent group with normal weight/normal glucose): normal weight/elevated glucose, overweight/normal glucose, and overweight/elevated glucose.

Results: Overweight adults [BMI $\geq$ 25 or WHtR $\geq$ 0.51 (men) and $\geq$0.57 (women)] with elevated glucose ($\geq$125 mg/dL) had a statistically significant 2-fold increased risk of developing obesity-related cancer, whereas overweight adults with normal glucose had a 50% increased risk. Normal-weight adults with elevated glucose had no excess cancer risk. The effects of BMI and WHtR were independent of one another. Finally, overweight women with elevated blood glucose had a 2.6-fold increased risk [95% confidence interval (CI), 1.4–4.9] of female reproductive (cervical, endometrial, uterine cancers) and postmenopausal breast cancers, whereas overweight women with normal glucose levels had only a 70% increased risk (95% CI, 1.1–2.5).

Conclusion: These results suggest that cancer risk may be lower among metabolically healthy overweight/obese older adults than among overweight/obese adults with metabolic dysfunction.

Impact: Metabolic dysfunction and obesity act synergistically to increase cancer risk. *Cancer Epidemiol Biomarkers Prev; 23(10); 2057–65. ©2014 AACR.*

Introduction

Rates of obesity and its attendant metabolic disturbances have been rising for decades (1). Growing numbers of studies suggest that obesity may be an important preventable cause of certain cancers (2, 3), such as colorectal, postmenopausal breast, those of the female reproductive, system, biliary tree (3, 4), and others (5). In an earlier report from the Framingham Study, we have shown both body mass index (BMI) and waist circumference (WC) to be independent predictors of incident colon cancer (6).

In a recently published report from Framingham, obesity-related cancers were found to be associated with prolonged exposure to impaired fasting glucose (7). Whether the excess risk of cancer found among obese individuals is a consequence of its association with metabolic dysfunction is not clear. An estimated 25% of obese adult Americans (8) are protected from metabolic dysfunction. These so-called "metabolically healthy overweight/obese" (MHO) persons have normal glucose tolerance, lipid levels, and blood pressure as well as less ectopic fat (9) than the more typical metabolically unhealthy overweight/obese (MUO) individuals. Whether they are protected from obesity-related cancers is unknown.

In inflamed adipose tissue, macrophages encircle stressed and apoptotic adipocytes in CD68-staining "crown-like structures" (CLS) (10). Fewer CLS in adipose tissues of MHO subjects has been associated with lower cardiovascular disease (CVD) risk (10, 11). The shared inflammatory basis for CVD, Type 2 diabetes mellitus (T2DM), and insulin-resistant obesity (12) has led to the hypothesis that the

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Table 1. Baseline subject characteristics according to category of BMI

Characteristic	BMI category (kg/m^2)			P
	<25 (n = 1,528)	25–<30 (n = 1,647)	≥30 (n = 588)	
Male, *N* (%)	557 (36.5)	870 (52.8)	222 (37.8)	0.0004
Education (>high school), *N* (%)	518 (33.9)	445 (27.0)	109 (18.5)	<0.0001
Age, mean (SD), y	56.1 (1.5)	56.0 (1.4)	56.2 (1.6)	0.0096
Height, mean (SD), cm	164.1 (8.6)	165.4 (9.3)	161.7 (9.0)	<0.0001
Weight, mean (SD), kg	61.6 (7.9)	74.5 (9.2)	87.3 (11.9)	<0.0001
BMI, mean (SD), kg/m^2	22.8 (1.6)	27.1 (1.4)	33.3 (3.5)	<0.0001
WC, mean (SD), cm	85.8 (6.2)	93.9 (6.6)	104.1 (9.2)	<0.0001
WHtR, mean (SD)	0.52 (0.04)	0.57 (0.05)	0.65 (0.07)	<0.0001
Blood glucose, mean (SD), mg/dL[a]	84.5 (21.7)	86.1 (23.5)	93.1 (37.2)	<0.0001
Alcohol intake, mean (SD), oz/week pure alcohol	3.7 (5.3)	3.9 (5.8)	3.2 (6.4)	0.0510
Cigarettes, mean (SD), per day	8.5 (11.5)	6.6 (11.0)	4.8 (10.1)	<0.0001
Physical activity, index (SD)	7.4 (7.9)	7.5 (8.1)	6.6 (7.4)	0.0444

[a]Nonfasting.

mechanisms that confer cardiometabolic protection to MHO persons might also provide protection against obesity-related cancers. We used data for adults ages 55 to 69 years in the original Framingham Study to estimate the risk of obesity-related cancers among overweight/obese (vs. normal weight subjects), according to their metabolic health.

Materials and Methods

Framingham Study

The prospective Framingham Heart Study was designed to evaluate determinants of CVD risk among residents of Framingham, Massachusetts; 5,209 adult men and women were enrolled beginning in 1948 and have been examined biennially ever since. Data collected include demographic information, anthropometric measurements, blood pressure, lifestyle factors, health and family history, and laboratory measures.

Height and weight were measured at each visit with a standard balance beam scale. To reduce error associated with height measurement and loss of height with age, we used the mean of all available adult height measurements through age 60 years in combination with exam-specific weights to determine BMI at each visit. WC was measured following a standardized protocol at examinations 4, 5, and 19 to 21. We used BMI as a standard measure of obesity and WC and waist-to-height ratio (WHtR) as anthropometric measures of central adiposity (13) because hip circumference was not available in Framingham. Glucose was measured in nonfasting blood specimens drawn at each biennial exam. We used a cutoff value of ≥125 mg/dL to reflect some degree of metabolic dysfunction. Although there is no perfect means for identifying glucose intolerance using a casual blood sample, it is has been shown that nonfasting glucose of 125 mg/dL has a sensitivity of about 70% to detect T2DM (14). Because we used a mean of two random glucose measures, taken 2 years apart, it is likely that this value has an even higher sensitivity for detecting metabolic dysfunction. Further, analyses from Framingham demonstrated that nonfasting samples could be used to identify cases of T2DM with sensitivity equal to that of fasting samples (15).

Data for the following potential confounders were included: age (years), sex, education (>high school vs. high school or less), height (centimeters, cm) and mean number of cigarettes per day, ounces of alcohol consumed per week, and a mean physical activity index (with the latter three variables averaged during the exposure period). The physical activity index was created by multiplying self-reported hours of moderate and vigorous physical activity by an appropriate weight derived from oxygen consumption required for that level of activity and taking a sum of the two products (for moderate and vigorous activity) (16).

Cancer ascertainment

Detailed assessment of cancer outcomes in Framingham began about 1970 with complete medical record review of all enrolled subjects (17). All diagnoses and outcomes were confirmed from laboratory and pathology reports, and clinical notes. Cancer outcomes have been verified for all subjects in the original cohort through 2006. We included the following cancers as potentially obesity-related (18, 19): postmenopausal breast cancer, female reproductive (i.e., cervical, endometrial, and uterine), colon, liver, gallbladder, pancreas, kidney, and esophageal adenocarcinoma. Cancer topography and histology for each case were coded using the International Classification of Diseases for Oncology (ICD-O) (20).

Statistical analysis

Men and postmenopausal women (ages 55–69 years) were selected for the current analyses beginning at the first exam visit at which they were in the age range and

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Table 2. Effect of BMI and waist size on risk of obesity-related cancers in men and women

BMI (kg/m^2)	Lean (<25)	Overweight (25–<30)	Obese (≥30)
All subjects			
Number	1,528	1,647	588
Cancer cases/person-years[a]	130/26,699	185/28,463	70/9,140
IR/10,000 person-years	48.7	65.0	76.6
HR (95% CI)			
Unadjusted	1.0 (reference)	1.3 (1.1–1.7)	1.7 (1.2–2.2)
Adjusted[b]	1.0 (reference)	1.5 (1.2–1.9)	1.7 (1.3–2.3)
Males			
Cancer cases/person-years[a]	22/8,748	67/13,961	16/3,060
IR/10,000 person-years	25.1	48.0	52.3
HR (95% CI)			
Unadjusted	1.0 (reference)	1.9 (1.2–3.1)	2.3 (1.2–4.4)
Adjusted[b]	1.0 (reference)	1.9 (1.2–3.1)	2.3 (1.2–4.4)
Females			
Cancer cases/person-years[a]	108/17,951	118/14,502	54/6,081
IR/10,000 person-years	60.2	81.4	88.8
HR (95% CI)			
Unadjusted	1.0 (reference)	1.4 (1.0–1.8)	1.5 (1.1–2.1)
Adjusted[b]	1.0 (reference)	1.4 (1.1–1.8)	1.6 (1.2–2.3)
WAIST (cm)	**<84 (m), <81 (f)**	**84–<94 (m), 81–<91 (f)**	**≥94 (m), ≥91 (f)**
All subjects			
Number	517	1,567	1,679
Cancer cases/person-years[a]	31/8,166	135/27,520	219/28,616
IR/10,000 person-years	38.0	49.1	76.5
HR (95% CI)			
Unadjusted	1.0 (reference)	1.2 (0.84–1.8)	1.9 (1.3–2.8)
Adjusted[b]	1.0 (reference)	1.2 (0.79–1.7)	1.8 (1.2–2.6)
Males			
Cancer cases/person-years[a]	6/4,352	41/11,786	58/9,630
IR/10,000 person-years	13.8	34.8	60.2
HR (95% CI)			
Unadjusted	1.0 (reference)	2.4 (1.0–5.7)	4.4 (1.9–10.1)
Adjusted[b]	1.0 (reference)	2.2 (0.93–5.2)	3.9 (1.7–9.1)
Females			
Cancer cases/person-years[a]	25/3,815	94/15,733	161/18,986
IR/10,000 person-years	65.5	59.7	84.8
HR (95% CI)			
Unadjusted	1.0 (reference)	0.88 (0.57–1.4)	1.3 (0.82–1.9)
Adjusted[b]	1.0 (reference)	0.89 (0.57–1.4)	1.3 (0.86–2.0)

Abbreviation: IR, incidence rate.

[a]Follow-up time begins 4 years after end of exposure period.

[b]Adjusted for age, sex (in all-subjects models), height, education, alcohol, cigarettes/day, and physical activity.

had available data for BMI and WC, all potential confounders of interest, and were free of cancer (except nonmelanoma skin cancers). A total of 1,649 men and 2,114 women met the criteria and were included.

Separate Cox proportional hazard models were used to estimate the adjusted effects of BMI, WC, and WHtR on risk of obesity-related cancer. After excluding 35 subjects with BMI <18.5 kg/m^2 to eliminate the possibility of subclinical disease, subjects were classified into three BMI exposure categories (<25, 25–<30, and ≥30 kg/m^2) using the mean BMI value from two consecutive exams. For WC and WHtR categories, sensitivity analyses were used to determine the most appropriate cutoff values for defining excess body fat. For men, the resulting WC exposure categories were <84, 84–<94, and ≥94 cm. For women, the WC exposure categories were <81, 81–<91, and

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Table 3. Effect of WHtR on risk of obesity-related cancers in men and women

WHtR	<0.51 (m), <0.57 (f)	≥0.51 (m), ≥0.57 (f)
All subjects		
Number	1,492	2,271
Cancer cases/person-years[a]	124/25,523	261/38,779
IR/10,000 person-years	48.6	67.3
HR (95% CI)		
Unadjusted	1.0 (reference)	1.4 (1.1–1.7)
Adjusted[b]	1.0 (reference)	1.6 (1.3–2.0)
Males		
Cancer cases/person-years[a]	20/8,017	85/17,751
IR/10,000 person-years	24.9	47.9
HR (95% CI)		
Unadjusted	1.0 (reference)	1.9 (1.2–3.1)
Adjusted[b]	1.0 (reference)	2.0 (1.2–3.3)
Females		
Cancer cases/person-years[a]	104/17,506	176/21,027
IR/10,000 person-years	59.4	83.7
HR (95% CI)		
Unadjusted	1.0 (reference)	1.4 (1.1–1.8)
Adjusted[b]	1.0 (reference)	1.5 (1.2–2.0)

Abbreviation: IR, incidence rate.

[a]Follow-up time begins 4 years after end of exposure period.

[b]Adjusted for age, sex (in all-subjects models), height, education level, alcohol, cigarettes/day, and physical activity.

≥91 cm. The WHtR exposure categories were <0.51 and ≥0.51 for men and <0.57 and ≥0.57 for women. Follow-up began 4 years after the exposure measure to eliminate the possibility of including subjects with preclinical cancers whose disease might affect levels of body fat. Follow-up ended with the first of four censoring events: incidence of a primary obesity-related cancer, loss to follow-up when alive and cancer-free, end of study, or death. Incidence of obesity-associated cancer for each category was calculated as number of cases occurring during follow-up time divided by total person-years in a given category. Multivariate analyses estimating effects of BMI or WC on risk of obesity-related cancer were conducted with and without WC or BMI adjustment, respectively.

Cox proportional hazard models were also used to estimate the combined effects of BMI or WHtR and categories of random blood glucose on risk of obesity-associated cancers. Subjects considered to have abnormal glucose control were those with diabetes (nonfasting glucose ≥200 mg/dL or being treated for diabetes) and those with a nonfasting blood glucose ≥125 mg/dL. Subjects were cross-classified into one of four categories based on BMI (<25 vs. ≥25 kg/m^2) and glucose level (abnormal or not). Subjects were similarly cross-classified using WHtR categories and random glucose levels.

Lastly, to explore the possibility that development of obesity or glucose dysregulation during the follow-up period (among those without such conditions at baseline) might affect the risk of obesity-related cancers, we carried out separate analyses using time-dependent exposure variables. Up to 18 biennial BMI/glucose measures (median = 7) were included in these models, from the beginning of the follow-up period up to 4 years before the end of follow-up (or development of cancer). The time-dependent analyses were restricted to models with BMI exposure because WC was not measured repeatedly. All proportional hazard models were checked for violations of the proportional hazards assumptions and none were found.

Results

The descriptive characteristics of the subjects are shown in Table 1 according to category of BMI. The proportion of subjects with more than a high school education declined across BMI category. As expected, WC and WHtR increased with BMI as did mean blood glucose level. Obese individuals (BMI ≥30 kg/m^2) smoked fewer cigarettes per day.

Of the 3,763 men and women ages 55 to 69 years at the time of BMI and glucose measurements, 385 developed an obesity-associated cancer (Table 2). Overall, lean subjects (BMI < 25) had a cancer incidence rate of 4.87 per 1,000 person-years of follow-up compared with 6.50 and 7.66 cancer cases per 1,000 person-years among overweight and obese, respectively. After adjusting for age, sex, height, education level, alcohol intake, cigarette smoking, and physical activity, overweight men and women had about a 50% increased risk of obesity-associated cancer, and obese men and women a 73% increased risk. Analyses stratifying by sex showed that the effects of obesity were stronger in men than in women. For men in particular, a higher WC (≥94 cm) was associated with almost a 4-fold increased risk of developing an obesity-associated cancer than those in the lowest WC category (<84 cm).

To account for central adiposity, we also used WHtR (Table 3) as an exposure variable. These results were consistent with results that used a standard BMI measure as the primary exposure variable. For both Tables 2 and 3, we carried out a separate analysis restricting the sample to nonsmokers. Although the results for men were very slightly weaker (approximately 10% reduction in the HRs in the highest category of body fat), those for women were slightly stronger (about 10%), with correspondingly wider confidence limits for both due to the smaller sample sizes.

Table 4 explores the combined effects of overweight (dichotomized BMI ≥25 vs. <25 kg/m^2) and nonfasting blood glucose (dichotomized as ≥125 vs. <125 mg/dL). There was no excess cancer risk amongt the relatively few normal-weight subjects with a high nonfasting glucose. By contrast, subjects who were overweight had a higher cancer risk whether or not they had elevated blood glucose. However, subjects who were overweight and had

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Table 4. Combined effects of BMI and glucose levels on risk of obesity-related cancers

BMI/blood glucose[a]	<25/Nl glucose	<25/Abnl glucose	≥25/Nl glucose	≥25/Abnl glucose
All subjects				
N	1,356	172	1,911	324
Cancer cases/person-years	121/24,122	10/2,576	221/33,193	34/4,410
IR/10,000 person-years	50.2	38.8	66.6	77.1
HR (95% CI)				
Unadjusted	1.0 (reference)	0.74 (0.38–1.5)	1.3 (1.1–1.7)	1.7 (1.2–2.5)
Adjusted model 1[b]	1.0 (reference)	0.77 (0.39–1.5)	1.5 (1.2–1.8)	2.1 (1.4–3.0)
Adjusted model 2[c]	1.0 (reference)	0.77 (0.39–1.5)	1.5 (1.1–2.0)	2.1 (1.4–3.3)
Adjusted model 3[d]	1.0 (reference)	0.78 (0.40–1.5)	1.4 (1.1–1.8)	2.0 (1.3–3.0)
Adjusted model 4[e]	1.0 (reference)	0.80 (0.40–1.6)	1.6 (1.2–2.1)	2.2 (1.4–3.4)
Male subjects				
IR/10,000 person-years	25.9	19.3	48.8	48.4
HR (95% CI)				
Unadjusted	1.0 (reference)	0.81 (0.19–3.5)	1.9 (1.2–3.1)	2.1 (1.0–4.4)
Adjusted model 1[b]	1.0 (reference)	0.82 (0.19–3.5)	1.9 (1.2–3.1)	2.2 (1.1–4.5)
Adjusted model 2[c]	1.0 (reference)	0.83 (0.19–3.5)	1.9 (0.95–3.8)	2.0 (0.85–4.8)
Adjusted model 3[d]	1.0 (reference)	0.86 (0.20–3.7)	1.4 (0.81–2.5)	1.6 (0.71–3.5)
Adjusted model 4[e]	1.0 (reference)	0.90 (0.21–3.8)	1.6 (0.90–2.9)	1.9 (0.83–4.1)
Female subjects				
IR/10,000 person-years	61.5	45.4	80.4	113.8
HR (95% CI)				
Unadjusted	1.0 (reference)	0.78 (0.36–1.7)	1.3 (1.0–1.7)	2.0 (1.3–3.2)
Adjusted model 1[b]	1.0 (reference)	0.75 (0.35–1.6)	1.4 (1.1–1.8)	2.2 (1.4–3.5)
Adjusted model 2[c]	1.0 (reference)	0.75 (0.35–1.6)	1.4 (1.0–2.0)	2.3 (1.3–3.9)
Adjusted model 3[d]	1.0 (reference)	0.75 (0.35–1.6)	1.4 (1.0–1.9)	2.2 (1.3–3.7)
Adjusted model 4[e]	1.0 (reference)	0.76 (0.35–1.6)	1.5 (1.1–2.1)	2.5 (1.5–4.2)

Abbreviations: Abnl, abnormal; IR, incidence rate; Nl, normal.

[a]Nl versus Abnl glucose: <125 (not on insulin or oral hypoglycemics) versus ≥125 mg/dL or treated.

[b]Model 1: Adjusted for age, sex (in all-subjects models), height, education level, alcohol, cigarettes/day, and physical activity.

[c]Model 2: Model 1 variables plus adjustment for BMI (kg/m^2) within categories.

[d]Model 3: Model 1 variables plus WC.

[e]Model 4: Model 1 variables plus WC and occurrence of elevated glucose and obesity (BMI > 28) during follow-up (up to 4 years before cancer occurrence) modeled as time-varying covariates.

elevated glucose (MUO subjects) were twice as likely to develop cancer [HR, 2.1; 95% confidence interval (CI), 1.4–3.0] as were normal weight subjects with normal glucose levels, whereas overweight individuals with normal glucose levels (MHO) had only a 47% increased risk of cancer. To determine whether difference in BMI within categories might confound these results, model 2 includes BMI as a continuous covariate. There was no meaningful change in the effect estimates, so this variable was dropped from future models. Models 3 and 4 address the important question of whether controlling for WC explains the effects of a high BMI. Model 4 additionally includes BMI and glucose levels during the follow-up period as time-dependent covariates. The addition of WC to the model attenuated cancer risks among overweight men (both with and without abnormal glucose levels) but not women. The addition of the time-dependent BMI and glucose variables strengthened the results, even when controlling for waist size. In this final model (model 4), the development of overweight (BMI > 28 kg/m^2) during the follow-up period led to a 30% increased risk of cancer (HR, 1.3; 95% CI, 1.0–1.7) and the development of an elevated glucose led to a 26% increased cancer risk (95% CI, 1.0–1.6; data not shown).

Table 5 shows the combined effects of WHtR and nonfasting glucose adjusting for age, sex, height, education level, alcohol intake, cigarette smoking, and physical activity. A higher WHtR combined with elevated glucose (MUO category) was associated with a 2-fold increased risk of cancer, whereas the MHO had only a 50% increased risk, adjusting for BMI. These results suggest that there is a positive interaction between increased waist size and nonfasting glucose in terms of obesity-associated cancer risk; 55% of obesity-related cancers in this analysis were attributable to the interaction of WHtR and elevated glucose.

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Table 5. Combined effects of WHtR and blood glucose level on risk of obesity-related cancers

WHtR/blood glucose[a]	Low WHtR[b]/ Nl glucose	Low WHtR[b]/ Abnl glucose	High WHtR[b]/ Nl glucose	High WHtR[b]/ Abnl glucose
All subjects				
N	1,312	180	1,955	316
Person-years	112/22,767	12/2,755	230/34,548	31/4,231
IR/10,000 person-years	49.2	43.5	66.6	73.3
HR (95% CI)				
Unadjusted	1.0 (reference)	0.94 (0.52–1.7)	1.3 (1.1–1.7)	1.6 (1.1–2.4)
Adjusted model 1[c]	1.0 (reference)	0.97 (0.53–1.8)	1.5 (1.2–2.0)	2.1 (1.4–3.2)
Adjusted model 2[d]	1.0 (reference)	0.97 (0.53–1.8)	1.5 (1.1–2.0)	2.0 (1.3–3.2)
Males				
Cancers/person-years	18/6,974	2/1,043	73/15,281	12/2,470
IR/10,000 person-years	25.8	19.2	47.8	48.6
HR (95% CI)				
Unadjusted	1.0 (reference)	0.79 (0.18–3.4)	1.8 (1.1–3.0)	2.1 (1.0–4.4)
Adjusted model 1[c]	1.0 (reference)	0.76 (0.18–3.3)	1.9 (1.1–3.2)	2.3 (1.1–4.8)
Adjusted model 2[d]	1.0 (reference)	0.76 (0.18–3.3)	1.7 (0.92–3.0)	1.9 (0.85–4.4)
Females				
Cancers/person-years	94/15,793	10/1,713	157/19,267	19/1,760
IR/10,000 person-years	59.5	58.4	81.5	107.9
HR (95% CI)				
Unadjusted	1.0 (reference)	1.0 (0.53–2.0)	1.3 (1.0–1.7)	1.9 (1.2–3.2)
Adjusted model 1[c]	1.0 (reference)	1.0 (0.52–1.9)	1.5 (1.1–1.9)	2.3 (1.4–3.8)
Adjusted model 2[d]	1.0 (reference)	1.0 (0.52–1.9)	1.5 (1.1–2.0)	2.2 (1.3–3.9)

Abbreviations: Abnl, abnormal; IR, incidence rate; Nl, normal.

[a]Nl versus Abnl glucose: <125 (not on insulin or oral hypoglycemics) versus ≥125 mg/dL or treated.

[b]Low versus high WHtR: <0.51 versus ≥0.51 for men; <0.57 versus ≥0.57 for women.

[c]Model 1: adjusted for age, sex (in all-subjects models), height, education level, alcohol intake, cigarettes/day, and physical activity.

[d]Model 2: model 1 plus BMI.

To explore whether the results described above are restricted to those with selected cancer sites, we looked at the rates of individual cancers in Supplementary Table S1. That table shows that although numbers are very small for many individual cancers, there is a tendency for most cancer types (i.e., colon, liver, gallbladder, breast, uterus, cervix, endometrium) to be found amongt the overweight/obese subjects. The association between obesity and esophageal and kidney cancers is less clear in these data. In Table 6, we explore the risk of three of the selected types of obesity-associated cancers: colon, female reproductive cancers (excluding ovarian) and female reproductive cancers plus postmenopausal breast cancer. In each category, the risks were highest for MUO subjects (overweight plus elevated random glucose). MHO (overweight with normal glucose) subjects had an intermediate risk. Finally, there was no evidence that metabolic dysfunction in the absence of overweight/obesity led to any increased risk of these cancers.

Discussion

This is the first long-term population-based study to examine the combined effects of obesity and metabolic dysfunction on cancer risk. This study found that overweight and obese 55- to 69-year-old adults had higher risks for several cancers, particularly female reproductive cancers (including postmenopausal breast cancer) and colon cancer. This confirms earlier results from the large prospective Cancer Prevention Study II reporting 52% and 62% higher cancer mortality rates among obese men and women (3). In addition, cancer risks were even higher in the subset of overweight subjects with elevated blood glucose levels (i.e., MUO subjects), whereas MHO subjects had a risk for obesity-related cancer that was intermediate to that of MUO and healthy lean adults. These findings share similarities with studies showing MHO women to have a CVD risk that is intermediate to that of MUO and healthy lean women (21).

The roles of molecular, cellular, and inflammatory pathways as predictors of cancer risk (22) are not well understood. Several lines of evidence implicate metabolic dysfunction and inflammation in the pathogenesis of cancer (5). Insulin-resistant obesity is a chronic, inflammatory disorder with both local (23) and systemic manifestations (24). Visceral or "central" adipose tissue, often estimated using WC, waist-to-hip ratio, or WHtR

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Table 6. Combined effects of BMI and blood glucose on risk of selected obesity-related cancers

BMI/blood glucose[a]	<25/Nl glucose	<25/Abnl glucose	≥25/Nl glucose	≥25/Abnl glucose
Colon cancers				
N	1,356	172	1,911	324
Cancers/person-years	36/24,569	3/2,614	94/34,016	14/4,555
IR/10,000 person-years	14.7	11.5	27.6	30.7
HR (95% CI)				
Unadjusted	1.0 (reference)	0.83 (0.26–2.7)	1.9 (1.3–2.8)	2.3 (1.3–4.3)
Adjusted model 1[b]	1.0 (reference)	0.83 (0.25–2.7)	1.8 (1.2–2.7)	2.2 (1.2–4.1)
Adjusted model 2[c]	1.0 (reference)	0.84 (0.26–2.7)	1.6 (1.0–2.5)	1.8 (0.93–3.6)
Female reproductive cancers[d]				
N	876	94	1,006	137
Cancers/person-years	59/16,588	5/1,546	94/18,959	13/1,960
IR/10,000 person-years	35.6	32.3	49.6	66.3
HR (95% CI)				
Unadjusted	1.0 (reference)	0.95 (0.38–2.4)	1.4 (1.0–1.9)	2.0 (1.1–3.7)
Adjusted model 1[b]	1.0 (reference)	0.92 (0.37–2.3)	1.5 (1.1–2.1)	2.2 (1.2–4.1)
Adjusted model 2[c]	1.0 (reference)	0.91 (0.36–2.3)	1.7 (1.1–2.5)	2.6 (1.4–4.9)
Female reproductive cancers, excluding breast cancer				
N	876	94	1,006	137
Cancers/person-years	9/16,896	1/1,583	19/19,558	3/2,040
IR/10,000 person-years	5.3	6.3	9.7	14.7
HR (95% CI)				
Unadjusted	1.0 (reference)	1.2 (0.15–9.5)	1.8 (0.83–4.1)	2.8 (0.74–10.2)
Adjusted model 1[b]	1.0 (reference)	1.3 (0.17–10.5)	2.1 (0.91–4.7)	3.4 (0.90–13.1)
Adjusted model 2[c]	1.0 (reference)	1.3 (0.17–10.7)	1.9 (0.76–4.9)	3.2 (0.75–13.3)

Abbreviations: Abnl, abnormal; IR, incidence rate; Nl, normal.

[a]Nl versus Abnl glucose: <125 (not on insulin or oral hypoglycemics) versus ≥125 mg/dL or treated.

[b]Model 1: Adjusted for age, sex (for colon cancer model), height, education level, alcohol, cigarettes/day, and physical activity.

[c]Model 2: Model 1 plus WC.

[d]Female reproductive cancers include postmenopausal breast, cervical, endometrial, and uterine cancers.

in epidemiologic studies, is the adipose tissue depot most strongly associated with insulin resistance, systemic inflammation (25), and cardiometabolic sequelae (26). Lower body obesity typified by "pear-shaped" distributions of body fat has been linked with metabolic protection (27).

Obese, insulin-resistant adults exhibit abnormal serum levels of adipokines, characterized by reduced adiponectin and elevated leptin (28), which have also been associated with higher risk for obesity-associated cancers (29, 30). Better insulin sensitivity in MHO individuals may also contribute to lower levels of fasting insulin and IGF1, which have also been linked with cancer (31). However, results from the Women's Health Initiative linked colon cancer risk with elevated glucose, but not insulin or insulin resistance (32). The state of insulin-resistant obesity is thought to promote signal transduction cross-talk between adipokines and elevated fasting glucose, insulin, IGF1, and leptin. Whether this interplay influences risk for obesity-associated cancers is unknown. It is likely that the metabolic risk profile for each obesity-related cancer will exhibit both common and unique features, but studying these separate cancers will require larger cohorts to provide sufficient power.

The HRs for obesity and cancer risk in this study (data not shown) closely reflect previously published values for colon, postmenopausal breast and female reproductive cancers (4). We found an approximately 2-fold increased risk of all obesity-related cancers among MUO subjects but more than a 3-fold increased risk of female reproductive cancers. After controlling for WC in models estimating the independent effects of BMI, we found that cancer risk among MUO men (but not women) was attenuated. In contrast, the direct effects of WC on cancer remained after controlling for BMI suggesting that WC may be a stronger predictor of cancer risk than BMI in men, a finding also evident in earlier results from this same cohort (6). Given the close connection between central adiposity and metabolic health, studies with more precise measures of total body fat and fat distribution are needed to evaluate these risks.

This study has a number of important strengths, starting with essentially complete lifetime follow-up for cancer occurrence beginning in the middle adult years. All cancer

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outcomes were validated through a careful review of medical records using standardized procedures (17). In addition, BMI was measured repeatedly at each biennial examination visit and detailed data on potential confounders of interest were also available.

There are a number of limitations of this study as well. We used simple anthropometric measures of body fat (BMI, WC, WHtR) and a simple measure of metabolic dysfunction (random blood glucose). In this historical cohort, no measures of hip circumference were available, nor were measures of fasting glucose (until very late in the study). The composite measure of WHtR that we used has been shown in other studies to be predictive of metabolic dysfunction (33). Although more sophisticated and precise measures of body fat/composition and metabolic health would be useful, the error introduced by the use of these simple measures is most likely nondifferential, thereby resulting in effect estimates that are biased toward the null. Thus, the estimates in this study are likely underestimates of the true effects in these obesity/metabolic phenotypes. Another important limitation of the study is the limited power associated with small numbers of subjects in some categories (e.g., those with normal weight and abnormal glucose levels) as well as the small numbers of subjects with some of the individual cancer types.

The Framingham Study began in 1948 and the subjects were leaner and more metabolically healthy than in more recent generations. Thus, we were not able to evaluate effects of higher levels of obesity/morbid obesity. There were also insufficient numbers of some obesity-related cancers (e.g., liver, pancreas, gallbladder) to allow for the estimation of effects on these individual cancer types. Furthermore, Framingham Study subjects were exclusively Caucasian so these results may not be representative of risks in a multiethnic population.

We did not have sufficient power in this study to separate subjects with T2DM from those with earlier stages of glucose dysregulation and it is possible that the immunometabolic mechanisms that affect cancer risk may differ in these two types of individuals (12). Finally, although obesity is associated with increased estrogen levels and breast cancer risk in postmenopausal women, we are unable to comment on the role of estrogen in cancer risk among the obese female subjects because such data were not available in this data set.

Conclusion

This is the first large prospective cohort study to show that metabolic health modifies risks of obesity-related cancers among overweight and obese individuals. Similar findings have been shown previously for CVD outcomes. In this study, we found that overweight/obese individuals with a healthier metabolism have lower risks of obesity-related cancers. Given rising rates of insulin-resistant obesity worldwide, rates of obesity-related cancers are likely to rise as well. Treatment strategies targeting metabolic health among overweight individuals may lead to reductions in risks for cancer as well as cardiometabolic disorders.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L.L. Moore, G.V. Denis
Development of methodology: L.L. Moore, B.E. Kreger
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.L. Moore, B.E. Kreger
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.L. Moore, S. Chadid, M.R. Singer, B.E. Kreger
Writing, review, and/or revision of the manuscript: L.L. Moore, S. Chadid, B.E. Kreger, G.V. Denis
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.L. Moore, S. Chadid, M.R. Singer
Study supervision: L.L. Moore

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