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Research Article

Metabolic Dysregulation of the Insulin–Glucose Axis and Risk of Obesity-Related Cancers in the Framingham Heart Study-Offspring Cohort (1971–2008)

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Abstract

Background: Obesity-related dysregulation of the insulin–glucose axis is hypothesized in carcinogenesis. We studied impaired fasting glucose (IFG) and other markers of insulin–glucose metabolism in the Framingham Heart Study-Offspring Cohort, which uniquely tracks these markers and cancer >37 years.

Methods: Participants were recruited between 1971 and 1975 and followed until 2008 ($n = 4{,}615$; mean age 66.8 years in 2008). Serum glucose, insulin, and hemoglobin A1c were determined from fasting blood in quart-annual exams. Lifestyle and demographic information was self-reported. HRs and 95% confidence intervals (CI) of cancer risk were computed using time-dependent survival analysis (SASv9.3), while accounting for temporal changes for relevant variables.

Results: We identified 787 obesity-related cancers, including 136 colorectal, 217 breast, and 219 prostate cancers. Absence versus presence of IFG 10 to 20 years and 20+ years before the event or last follow-up was associated with 44% (95% CI, 1.15–1.79) and 57% (95% CI, 1.17–2.11) increased risk of obesity-related cancers, respectively. When time-dependent variables were used, after adjusting for age, sex, smoking, alcohol, and body mass index, IFG was associated with a 27% increased risk of obesity-related cancer (HR = 1.27; CI, 1.1–1.5). Associations were stronger in smokers (HR = 1.41; CI, 1.13–1.76). Increased risk was noted among persons with higher insulin (HR = 1.47; CI, 1.15–1.88) and hemoglobin A1c (HR = 1.54; CI, 1.13–2.10) for the highest (≥5.73%) versus lowest (≤5.25%) category. A >2-fold increase in colorectal cancer risk was observed for all blood biomarkers of insulin–glucose metabolism, particularly with earlier IFG exposure. Nonsignificant increased risk of breast and prostate cancer was observed for blood biomarkers.

Conclusions: Earlier IFG exposure (>10 years before) increased obesity-related cancer risk, particularly for colorectal cancer.

Impact: Our study explicitly recognizes the importance of prolonged IFG exposure in identifying links between glucose dysregulation and obesity-related cancers. *Cancer Epidemiol Biomarkers Prev; 22(10); 1825–36. ©2013 AACR.*

Introduction

The prevalence of obesity has reached epidemic proportions in the United States with nearly 35% of the adults meeting the clinical criteria (1). Obesity has been associated with several chronic diseases including cancer (2). A landmark study by Calle and colleagues (3) brought attention to the amplitude of the obesity-cancer link. Subsequently, the World Cancer Research Fund/American Institute for Cancer Research Expert Panel Report judged excess adiposity to be a well-established risk factor for several cancers (4). One manifestation of excess adiposity is dysregulation of glucose and insulin metabolism, which is implicated in influencing cancer pathways by providing a biochemical environment that supports cell growth and proliferation (5, 6).

Despite an understanding of the possible mechanistic underpinnings of how perturbations in the insulin–glucose axis may influence cancer etiology, epidemiologic studies examining insulin and glucose metabolism in relation to cancer risk have been divergent and inconclusive (7). Among prospective cohort studies, elevated blood glucose is associated with a 20% to 31% increased overall cancer risk (8–10). However, these associations are equivocal depending on the cancer site and the biomarker used. For example, in prospective studies examining breast cancer risk, some noted an increased risk associated

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with elevated glucose (10), insulin (11, 12), or diabetes status (8), whereas some associations were null (8, 11, 12) or protective (10). Associations with colorectal (13, 14) and prostate cancer risk (15) are similarly ambiguous, depending on the exposure. The American Diabetes Association/American Cancer Society Consensus Report sounds alert to the incomplete understanding of metabolic dysregulation of insulin–glucose metabolism in relation to cancer and delineates the importance of examining these associations in large prospective studies (16).

Furthermore, the Consensus Report recognizes that timing and duration of exposure to metabolic disturbances in glucose may be critical in predicting cancer risk (16, 17). Evidence has showed that timing of exposure to perturbations in glucose metabolism is differentially associated with cancer risk (18, 19). However, few previous studies examine timing and accumulation of exposure encompassing early and late adulthood in relation to cancer, and this issue warrants further study (17).

This study prospectively investigates associations between perturbations in the insulin–glucose axis and obesity-related cancers in the Framingham Heart Study (FHS) over a period of approximately 37 years. The FHS data are innovatively used herein to capture time-varying exposures of glucose dysregulation in relation to risk of obesity-related cancers. Importantly, this study also examines timing of exposure during adulthood in relation to cancer risk, to provide a better understanding of potentially "critical periods of sensitivity" that may guide future strategies for cancer control.

Materials and Methods

Study population

The Framingham Offspring Cohort. The FHS is an ongoing study based in Framingham, Massachusetts, consisting of data from 3 familial generations (20). Clinic exams were conducted, on average, every 4 years from 1971 to 2008 (21, 22). The analytical dataset includes participants from the second generation referred to as the Offspring Cohort, who were 20+ years, without cancer diagnosis or type 1 diabetes at time of entry into the study. Data on women who were pregnant at the time of a particular exam were excluded for that exam only because of a nonrepresentative body mass index (BMI) and potential alterations in blood insulin and glucose levels related to the pregnancy.

Participation rate. From the total population of the offspring population (n = 5,013), 2,191 adults (44%) completed all exams, 3,019 (60%) had at least 7 exams, 3,379 (67%) had at least 6 exams, and 3,707 (74%) had at least 5 exams completed. There were 2,012 fewer participants in exam 8 compared to baseline. Over the study follow-up period, 1,160 (23.7%) individuals died and others were lost to follow-up, explaining the participant rates for exam 1 to 8. As is inherent to studies with long follow-up periods, participants of this cohort intermittently missed exams. For example, individuals who missed exam 3 returned in exam 4. To maximize power, we included available data for all individuals in the analyses. This approach is consistent with previous FHS analyses (23, 24).

Data Collection

Exposure measurements and definitions. The main exposures of interest were biomarkers of insulin and glucose metabolism and waist circumference, a measure associated with metabolic dysregulation of the insulin–glucose axis (25, 26). Another primary exposure of interest was timing of exposure to abnormal fasting glucose concentrations. Blood was drawn at clinic exams and was used to measure biomarkers. Fasting blood glucose was measured at every exam, hemoglobin A1c (HbA1c), an indicator of long-term glycemic control and fasting insulin concentrations were measured at select exams. Waist circumference was measured by trained personnel in 5 of 8 exams.

Impaired fasting glucose (IFG) was defined per the Adult Treatment Panel III (ATP) and World Health Organization (fasting glucose > 110 mg/dL; refs. 27, 28). Homeostatic model assessment-insulin resistance (HOMA-IR) that dually measures pancreatic β-cell function and insulin resistance was computed from blood glucose and insulin concentrations (29) from data available at exams 5 and 7. Waist circumference was divided into sex-specific categories representing "normal," "increased risk," and "substantially increased risk" of metabolic complications (<31.5, 31.5–34.6, and >34.6 inches for women; <37, 37–40.2, and >40.2 inches for men; ref. 26, 30) and then combined for the analyses.

Other covariates

Height, weight, and blood pressure were measured by trained personnel at each visit. Physical activity was self-reported, and participants were queried about the number of hours per day they spent engaging in sedentary activity, slight activity, moderate activity, and heavy activity. The physical activity index (PAI) was calculated from the participant responses as has been previously published for the FHS cohorts (31). Information on education, occupation, ethnicity, alcohol, smoking, multivitamin use, medication, and medical history was collected during in-person interviews. Self-reported diet was assessed since 1989 during exams 5 to 8, using the validated Harvard food frequency questionnaire (32).

Outcome

The primary outcome is obesity-related cancers and includes cancers of the gastrointestinal tract, reticuloendothelial system (blood, bone, and spleen), female reproductive tracts, genitourinary organs, and the thyroid gland (3, 4, 33, 34). Although melanoma has been associated with obesity in the literature (35), we excluded all forms of skin cancers in this analyses. The FHS cancer files include confirmed primary cancers from

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pathologic reports with date of diagnosis (36). A small proportion of the cancer cases (<5%) were confirmed by clinical reports without pathology reports or from death certificates (36). Self-reported or suspected cases without pathologic reports were not considered to have cancer. Histologic grading and differentiation of the cancer was reported per the World Health Organization-International Classification of Diseases coding (37). The database continues to be updated from pathologic reports. Seven hundred and eighty-seven confirmed primary cases of obesity-related cancers were identified, including 136 colorectal cancers, 219 prostate cancer, and 217 breast cancer cases.

Statistical analyses

Descriptive characteristics were generated to examine the predictors and outcome of interest over the study duration of approximately 37 years. Cox-proportional hazards model with time-dependent covariates were used to evaluate the impact of each exposure with obesity-related cancer risk using all available data. HRs (95% CI) adjusted for age only and adjusted for other covariates were computed for obesity-related cancers. Tertiles were derived for serum insulin and HBA1c by dividing the ordered distribution of the population values into approximately thirds. We also computed HR (95% CI) for obesity-related and site-specific cancers for IFG exposure 5 to 10, 10 to 20, and 20+ years before the event or last follow-up, compared to persons without IFG. *P*-values for linear trends were computed. Lack of long-term data for the other biomarkers limited our ability to conduct similar analyses.

Persons were considered censored if they died, were lost to follow-up, or at the last exam in which they participated if the event had not yet occurred. If the person missed an exam and participated in the subsequent exam, they were included in the analyses and considered at risk for cancer. To generate adjusted models, each potential confounding variable was first included singly in the model to determine whether it influenced the HR. Variables that influenced HRs >10% were retained in the final model. Potential covariates that were tested include age, smoking, BMI, cardiovascular risk factors, physical activity, hormone use, aspirin use, race, education, energy intake, total dietary fat, total polyunsaturated, saturated and monounsaturated fats, and antioxidant vitamins including vitamins C, A, and E, folate, and β-carotene. Alcohol and smoking, known to be associated with cancer risk from previous literature, were included in the final model. All analyses were done using SASv9.3 (SAS Institute Inc.).

Planned subgroup and exploratory analyses. Exploratory analyses were conducted to examine the relationships of IFG to cancer risk stratified by smoking and sex. Interactions were considered significant if the *P*-value ≤ 0.1. Evidence for cancer and physical activity, a lifestyle attribute that may favorably influence the insulin–glucose axis, is insufficient per the World Cancer Research Fund/American Institute for Cancer Research Expert Panel Report (4). Therefore, we conducted analyses of blood glucose stratified by physical activity to understand how physical activity potentially influences these associations. We report herein the results of these exploratory analyses with the caveat of limited power.

Results

Characteristics of the study population

Table 1 presents the population characteristics evaluated at baseline and at each of the 7 subsequent exams, representing a study period of approximately 37 years. The FHS population is 99% Caucasian. The mean age at baseline was 37.5 years versus 66.8 years at the last exam (exam 8). Approximately half the population was female. An overall increase in the rate of IFG was observed over the follow-up period (15% to almost 25%; $P < 0.0001$). The average BMI of the participants also increased over time (25.6–28.3 kg/m^2; $P < 0.0001$), as did waist circumference for both men (38.5–41.4 inches; $P < 0.0001$) and women (32.4–38.9 inches; $P < 0.0001$). Measures of healthy lifestyles were also assessed. There was no evidence of variation in energy intake over the dietary follow-up period. PAI scores (31) ranged from 34.6 to 37.7 units representing a moderate physical activity level for the population. Notably, the proportion of past smokers increased over time (20.2–51.3%; $P < 0.0001$).

Period of IFG exposure and risk of obesity-related cancers

We computed HR for obesity-related cancers and for each cancer site by IFG exposure periods, among individuals with versus without IFG (Table 2). We observed that individuals who had IFG 10 to 20 years before the event had a 44% (95% CI, 1.15–1.79) increased risk after adjustment for age and other covariates. Persons with IFG detected 20+ years before the event had a 57% (95% CI, 1.17–2.11) increased risk of obesity-related cancers when adjusted for age and other covariates. Although the HRs were >1, these relationships were not significant among persons with IFG exposure 5 to 10 years prior. For colorectal cancer, the risk significantly increased across the exposure period categories ($P_{trend} = 0.0196$), with a risk estimate exceeding 3 among individuals who were exposed to IFG >20 years before the event. Differently, there were no significant associations observed for either prostate or breast cancer, although the majority of the HRs were greater than 1.

Associations of multiple measures of the insulin–glucose axis and obesity-related cancer risk

We evaluated the associations of 4 different measures of insulin–glucose metabolism and waist circumference in relation to obesity-related cancers combined (Table 3). The risk of developing obesity-related cancers was 27% higher after adjusting for age, sex, alcohol, smoking, and

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Table 1. Characteristics of the Framingham Heart Study Offspring Cohort (1971–2008)[a]

	Exam 1	Exam 2	Exam 3	Exam 4	Exam 5	Exam 6	Exam 7	Exam 8	*P*-value
	N = 4,615	*N* = 3,720	*N* = 3,751	*N* = 3,893	*N* = 3,686	*N* = 3,412	*N* = 3,473	*N* = 2,987	for trend[b]
Age (years)	37.5 (9.4)	44.3 (10.0)	48.3 (10.1)	51.5 (10.1)	54.8 (9.9)	58.6 (9.7)	61.3 (9.6)	66.8 (9.2)	<0.0001
IFG (fasting glucose >110 mg/dl)[c,d] (%)	15.16	11.22	7.50	8.58	13.48	18.60	20.12	24.97	<0.0001
BMI (kg/m^2)	25.6 (4.4)	25.9 (3.8)	26.2 (4.7)	26.9 (4.9)	27.4 (5.0)	27.9 (5.2)	28.2 (5.3)	28.3 (5.4)	<0.0001
Waist circumference[e] (inches)									
Men	–	–	–	38.5 (4.2)	39.0 (4.3)	39.9 (4.3)	40.7 (4.5)	41.4 (4.7)	<0.0001
Women	–	–	–	32.4 (5.4)	34.4 (5.8)	37.1 (5.9)	38.1 (6.1)	38.9 (6.2)	<0.0001
Energy intake (kcal)	–	–	–	–	1867.7 (623.9)	1852.1 (615.6)	1826.2 (594.7)	1875.9 (635.6)	0.8197
PAI[f]	–	34.6 (5.6)	–	36.8 (7.0)	34.7 (6.1)	–	37.7 (6.5)	35.2 (5.4)	<0.0001
Smoking (never) (%)	34.2	–	37.2	36.6	37.2	37.9	38.1	39.6	<0.0001
Smoking (current) (%)	45.6	–	29.1	24.9	19.7	15.3	13.7	9.1	
Smoking (past) (%)	20.2	–	33.6	38.6	43.1	46.8	48.2	51.3	

[a]The characteristics are presented as either weighted frequencies for categorical variables or means ± SD for continuous variables.

[b]*P*-value for trend is based on Cochran-Armitage trend test for categorical variables, and test of linear trend for continuous variables.

[c]Impaired fasting glucose (IFG) is defined as >110 mg/dL by the Adult Treatment Panel III (27, 28).

[d]The reduced prevalence of IFG in exams 3 and 4 was related to a large percentage of missing data at those exams.

[e]A waist circumference >35 inches in women or 40 inches in men is considered abdominally obese (26).

[f]Physical activity status was categorized as above or below the mean activity level based on the PAI calculation. The PAI is calculated by multiplying the time spent in sleep, sedentary, moderate, and vigorous activity per week by a standardized factor for metabolic cost (31).

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Table 2. Periods[a] of IFG exposure and risk of obesity-related cancers combined and by cancer site

Period of fasting glucose (>110 mg/dL)	Number of cases/*N*[b]	Age-adjusted HR (95% CI)	Adjusted HR (95% CI)[c,d]
Obesity-related cancers[e]			
5–10 y	630/3,312	1.11 (0.90–1.36)	1.13 (0.91–1.41)
10–20 y	739/4,082	1.35 (1.10–1.66)	1.44 (1.15–1.79)
20+ y	539/3,076	1.64 (1.23–2.17)	1.57 (1.17–2.11)
P_{trend}		0.0346	0.1477
Colon cancer			
5–10 y	103/3,865	1.80 (1.15–2.80)	1.76 (1.09–2.84)
10–20 y	127/4,737	2.50 (1.65–3.78)	2.55 (1.60–4.05)
20+ y	83/3,589	3.47 (1.92–6.26)	3.26 (1.73–6.14)
P_{trend}		0.0593	0.0196
Breast cancer			
5–10 y	172/1,858	1.25 (0.80–1.94)	1.22 (0.75–1.96)
10–20 y	209/2,278	1.39 (0.89–2.19)	1.50 (0.92–2.44)
20+ y	141/1,797	0.87 (0.35–2.14)	0.999 (0.41–2.46)
P_{trend}		0.5009	0.7099
Prostate cancer			
5–10 y	188/1,734	0.88 (0.61–1.26)	0.93 (0.64–1.36)
10–20 y	215/2,154	1.15 (0.81–1.64)	1.29 (0.89–1.86)
20+ y	170/1,525	1.26 (0.78–2.04)	1.39 (0.86–2.26)
P_{trend}		0.1518	0.2008

[a]Number of years before censoring time (end of follow-up or event); 0 to 5 years before the event was not computed due to overlapping exposure assessment and disease latency period that may result in reverse causality.
[b]*N* represents the number of people with relevant data during each time interval (5–10, 10–20, and 20 + y), before the event or last follow-up.
[c]Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and >30).
[d]Smoking status (never, past, and current smoker) were based on self-reported data from most recent exam.
[e]Obesity-related cancers were defined as cancers of the gastrointestinal tract, reticulo-endothelial systems, female reproductive tracts, genitourinary organs, and the thyroid gland (3, 4, 33, 34).

BMI among persons with IFG (HR = 1.27; 95% CI, 1.06–1.53), compared to individuals without IFG. Additional adjustment for physical activity did not change these associations. Furthermore, a value of >2.6 for HOMA-IR that is considered abnormal (38) was associated with a 45% increase in risk in the adjusted model (HR = 1.45; 95% CI, 1.18–1.78). There associations persisted for HbA1c, with 54% (95% CI, 1.13–2.1) increase in risk of developing obesity-related cancers in the adjusted model, among persons within the highest (5.73%) versus the lowest (5.25%) category of HbA1c concentrations. Associations were also in the same direction with a 47% (95% CI, 1.15–1.88) increased risk of cancer, after adjusting for age and other covariates, among persons within the highest (≥9.94 pmol/L) versus lowest (<4.94 pmol/L) category of blood insulin concentrations. However, there were no associations detected for the highest versus lowest category of waist circumference after age adjustment only or after adjusting for other covariates.

Next, we tested for interactions for the relationships between markers of glucose and insulin metabolism and obesity-related cancers, *a priori* considered significant at $P = 0.1$. Smoking was a significant effect modifier ($P = 0.09$) for the relationships of IFG and obesity-related cancers but not for other measures of the insulin–glucose axis. Analyses were stratified by smoking status ("never" and "ever" smokers). We observed increased risk among past or current smokers with higher glucose concentrations (HR = 1.41; 95% CI, 1.13–1.76; Table 4). For exploratory purposes only, we also evaluated the associations between the biomarkers of glucose metabolism by sex and level of physical activity. We noted evidence of females having qualitatively stronger associations for all biomarkers of glucose metabolism with the exception of waist circumference, albeit not always significant. Associations did not differ by physical activity level (data not shown).

Associations of multiple measures of the insulin–glucose axis and site-specific cancer risk

We reexamined all associations by the 3 most commonly detected nonskin obesity-related cancer sites

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Table 3. Exposure to markers of insulin–glucose metabolism and risk of obesity-related cancers

	Number of cases/*N*	Age-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Fasting glucose[b]	787/4,233		
<110 mg/dL		1.0	1.0
>110 mg/dL		1.27 (1.07–1.50)	1.27 (1.06–1.53)
P-value[c]		0.0070	0.0093
HOMA-IR[d]	476/2,927		
<2.6		1.0	1.0
>2.6		1.31 (1.08–1.58)	1.45 (1.18–1.78)
P-value[c]		0.0059	0.0004
Hemoglobin A1c (%)[e]	263/2,488		
<5.25		1.0	1.0
5.25–5.72		1.13 (0.83–1.52)	1.205 (0.89–1.64)
≥5.73		1.40 (1.04–1.89)	1.54 (1.13–2.10)
P-value[c]		0.0852	0.0234
Insulin (pmol/L)	477/2,930		
<4.94		1.0	1.0
4.94–9.93		1.14 (0.91–1.43)	1.18 (0.94–1.49)
≥9.94		1.30 (1.04–1.62)	1.47 (1.15–1.88)
P-value[c]		0.0723	0.0075
Waist circumference (inches)[f]	597/3,577		
Category 1		1.0	1.0
Category 2		1.04 (0.81–1.32)	1.00 (0.76–1.30)
Category 3		1.06 (0.85–1.32)	1.06 (0.79–1.42)
P-value[c]		0.8641	0.8696

[a]Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and >30). Smoking status (never, past, and current smoker) was based on self-reported data from each exam.

[b]Impaired fasting glucose (IFG) is defined as >110 mg/dL by the Adult Treatment Panel III (27, 28).

[c]*P*-value associated with the Wald test that examines differences in association by category of the exposure variable.

[d]HOMA-IR >2.6 was considered abnormal in these analyses (38).

[e]Hemoglobin A1c values were used from exam 7.

[f]Waist circumference measurements were divided into categories (<31.5, 31.5–34.6, and >34.6 inches for women; <37, 37–40.2, and >40.2 inches for men) based on the World Health Organization cutoffs for normal, "increased," and "substantially increased" risk of metabolic complications (26).

in the United States: colorectal, breast, and prostate cancers (Table 5). For colorectal cancer, we noted robust evidence of >2-fold significant increased risk among persons with higher concentrations of all 4 biomarkers of glucose metabolism, but no association was observed for higher waist circumference. Although not always statistically significant, there was a suggestion of increased risk of breast cancer for all biomarkers with age-adjusted HR ranging from 1.23 to 1.95 after adjustment for age, sex, alcohol, smoking, and BMI. No associations were observed for the relationships between waist circumference and breast cancer. There was no strong evidence of associations with prostate cancer and biomarkers of insulin–glucose metabolism; however, nonsignificant HR > 1 (ranging from 1.10 to 1.52) were observed for all blood biomarkers and the direction of associations was consistent with the other cancer sites.

Discussion

The results of this prospective analysis provide support for the hypothesis that insulin–glucose dysregulation is an important underlying mechanism for the development of obesity-related cancers. Importantly, these analyses capture how timing of IFG exposure over defined periods influences cancer risk, a critical gap in the literature. We observed an increase in risk of obesity-related cancers among people with IFG exposure >10 years before the event. Our results emphasize that the strength of the association is likely moderated by the timing of exposure to a cancer-promoting biochemical environment. This may partially clarify the inconsistencies observed in previous studies that were conducted over shorter periods (8, 11, 13, 15, 18).

Hyperinsulinemia and hyperglycemia have pleiotropic effects on a number of cancer pathways (5). Insulin is a metabolic signal that serves as a "communicator of

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Table 4. Exposure to markers of insulin–glucose metabolism and risk of obesity-related cancers [HR (95%CI)][a,b] stratified by smoking status and sex

	By smoking status		By sex	
	Never smokers	**Ever smokers**	**Male**	**Female**
	***N* = 1,710**	***N* = 3,226**	***N* = 2,262**	***N* = 2,353**
Fasting glucose[c]				
$P_{interaction}$	0.09		0.98	
<110 mg/dL	1.0	1.0	1.0	1.0
>110 mg/dL	1.00 (0.72–1.39)	1.41 (1.13–1.76)	1.21 (0.95–1.53)	1.32 (0.99–1.77)
HOMA-IR[d]				
$P_{interaction}$	0.48		0.59	
<2.6	1.0	1.0	1.0	1.0
>2.6	1.62 (1.15–2.29)	1.36 (1.05–1.77)	1.34 (1.02–1.77)	1.54 (1.11–2.12)
Hemoglobin A1c (%)[e]				
$P_{interaction}$	0.27		0.33	
<5.25	1.0	1.0	1.0	1.0
5.25–5.72	1.62 (1.01–2.61)	0.96 (0.64–1.45)	1.39 (0.90–2.15)	1.14 (0.73–1.78)
≥5.73	1.64 (0.98–2.75)	1.43 (0.97–2.11)	1.38 (0.88–2.18)	1.80 (1.16–2.79)
P-value[f]	0.0876	0.0951	0.2543	0.0188
Insulin (pmol/L)				
$P_{interaction}$	0.19		0.76	
<4.94	1.0	1.0	1.0	1.0
4.94–9.93	1.18 (0.80–1.76)	1.18 (0.88–1.59)	1.08 (0.77–1.52)	1.27 (0.92–1.75)
≥9.94	1.92 (1.28–2.87)	1.27 (0.93–1.72)	1.28 (0.92–1.79)	1.66 (1.16–2.39)
P-value[f]	0.0037	0.2964	0.3184	0.0227
Waist circumference (inches)[g]				
$P_{interaction}$	0.14		0.96	
Category 1	1.0	1.0	1.0	1.0
Category 2	0.79 (0.51–1.22)	1.05 (0.76–1.46)	1.01 (0.698–1.473)	1.05 (0.701–1.562)
Category 3	0.88 (0.56–1.40)	0.97 (0.67–1.38)	1.22 (0.79–1.86)	1.00 (0.65–1.55)
P-value[f]	0.5558	0.8175	0.4968	0.9616

[a]Adjusted for age, sex, alcohol, smoking (excluding when analyses were stratified by smoking status), and BMI (<25, 25–30, and >30).
[b]Smoking status (never, former, current) was determined via self-report at each exam.
[c]Impaired fasting glucose (IFG) is defined as >110 mg/dL by the Adult Treatment Panel III and World Health Organization (27, 28).
[d]HOMA-IR >2.6 was considered abnormal in these analyses (38).
[e]Hemoglobin A1c values are from exam 7.
[f]*P*-value associated with the Wald test that examines differences in association by category of the exposure variable.
[g]Waist circumference measurements were divided into categories (<31.5, 31.5–34.6, and >34.6 inches for women; <37, 37–40.2, and >40.2 inches for men) based on the World Health Organization cutoffs for normal, "increased," and "substantially increased" risk of metabolic complications (26).

nutritional state" (6) and influences carcinogenesis through its ability to support cell differentiation and survival (5, 39, 40). Insulin increases the production of free insulin-like growth factor-1 (IGF-1), a mitogenic agent (5), and adipocyte-derived VEGF, a critical angiogenic factor, which influences cell survival and migration (41). Hyperinsulinemia also promotes inflammation, which is an established factor in carcinogenesis (40). Furthermore, glucose upregulates cell growth through activation of cell proliferation factors and delays apoptosis (42–44). Stimulation of the insulin-signaling network affects activity of several genes that support cell survival and antiapoptotic activities (45, 46).

In the site-specific cancer analyses, significant detrimental associations persisted for colorectal cancer for multiple biomarkers of glucose metabolism and for earlier exposure to elevated glucose. Our findings are congruent with the literature that generally report detrimental associations with abnormalities in the insulin–glucose axis and colorectal cancer (47–49). For instance, in the large,

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Table 5. Exposure to markers of insulin–glucose metabolism and risk of commonly diagnosed obesity-related cancer sites

	Number of cases/*N*	Age-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Colon cancer			
Fasting glucose[b]	136/4192		
<110 mg/dl		1.0	1.0
>110 mg/dl		2.21 (1.53–3.19)	2.20 (1.48–3.27)
HOMA-IR[c]	71/3428		
<2.6		1.0	1.0
>2.6		2.39 (1.49–3.85)	2.36 (1.40–4.00)
Hemoglobin A1c (%)[d]	45/2881		
<5.25		1.0	1.0
5.25–5.72		0.80 (0.34–1.89)	0.78 (0.33–1.86)
≥5.73		2.10 (1.05–4.22)	2.18 (1.06–4.51)
P-value[e]		0.0206	0.0159
Insulin (pmol/L)	71/3433		
<4.94		1.0	1.0
4.94–10.08		1.01 (0.53–1.91)	1.11 (0.58–2.13)
≥10.09		2.02 (1.15–3.55)	2.10 (1.12–3.93)
P-value[e]		0.0157	0.0354
Waist circumference (inches)[f]	93/3610		
Category 1		1.0	1.0
Category 2		1.05 (0.55–2.03)	0.91 (0.44–1.88)
Category 3		1.36 (0.76–2.43)	1.08 (0.50–2.35)
P-value[g]		0.4486	0.8566
Breast cancer			
Fasting glucose[b]			
<110 mg/dL	217/2152	1.0	1.0
>110 mg/dL		1.33 (0.93–1.92)	1.23 (0.82–1.83)
HOMA-IR[c]			
<2.6	135/1810	1.0	1.0
>2.6		1.28 (0.87–1.89)	1.44 (0.94–2.22)
Hemoglobin A1c (%)[d]			
<5.25	77/1525	1.0	1.0
5.25–5.71		1.42 (0.78–2.58)	1.37 (0.76–2.50)
5.72–14.57		2.03 (1.14–3.62)	1.95 (1.07–3.54)
P-value[e]		0.0545	0.0877
Insulin (pmol/L)			
<1.4	135/1814	1.0	1.0
1.4 to <8.56 Tertile 2		1.30 (0.85–1.99)	1.28 (0.83–1.97)
>8.59 Tertile 3		1.31 (0.85–2.02)	1.41 (0.88–2.24)
		0.3749	0.3293
Waist circumference (inches)[f]			
Category 1	164/1953	1.0	1.0
Category 2		1.04 (0.63–1.73)	0.88 (0.52–1.50)
Category 3		1.08 (0.69–1.68)	0.68 (0.38–1.23)
P-value[e]		0.9407	0.4049
Prostate cancer			
Fasting glucose[b]	219/2042		
<110 mg/dL		1.0	1.0
>110 mg/dL		1.07 (0.79–1.45)	1.11 (0.80–1.52)

(Continued on the following page)

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Table 5. Exposure to markers of insulin–glucose metabolism and risk of commonly diagnosed obesity-related cancer sites (Cont'd)

	Number of cases/*N*	Age-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
HOMA-IR[c]	152/1492		
<2.6		1.0	1.0
>2.6		1.05 (0.75–1.46)	1.19 (0.84–1.70)
Hemoglobin A1c (%)[d]	75/1215		
<5.25		1.0	1.0
5.25–5.72		1.33 (0.78–2.27)	1.52 (0.88–2.62)
≥5.73		0.90 (0.49–1.64)	1.10 (0.59–2.04)
P-value[e]		0.3621	0.2811
Insulin (pmol/L)	152/1493		
<5.65		1.0	1.0
5.65–11.80		1.25 (0.85–1.84)	1.35 (0.91–2.00)
≥11.81		1.01 (0.67–1.53)	1.21 (0.78–1.88)
P-value[e]		0.4285	0.3256
Waist circumference (inches)[f]	193/1725		
Category 1		1.0	1.0
Category 2		1.18 (0.80–1.76)	1.22 (0.76–1.96)
Category 3		1.09 (0.74–1.60)	1.35 (0.78–2.32)
P-value[e]		0.6918	0.5658

[a]Adjusted for age, sex, alcohol, smoking, and BMI (<25, 25–30, and >30). Smoking status (never, past, and current smoker) was based on self-reported data from each exam.

[b]Impaired fasting glucose (IFG) is defined as >110 mg/dL by the Adult Treatment Panel III and World Health Organization (27, 28).

[c]HOMA-IR >2.6 was considered abnormal in these analyses (38); HOMA-IR was calculated using the following equation: fasting glucose (mg/dL) × fasting insulin (μU/mL)/405 (29).

[d]Hemoglobin A1c values are from exam 7.

[e]*P*-value associated with the Wald test that examines differences in association by category of the exposure variable.

[f]Waist circumference measurements were divided into categories (<31.5, 31.5–34.6, and >34.6 inches for women) based on the World Health Organization cutoffs for normal, "increased," and "substantially increased" risk of metabolic complications (26).

prospective Nurse's Health Study, risk associations ranged from 1.43 to 2.39 for colon and rectal cancers among diabetic women (47), while a Norwegian study found risk estimates that approached 2, among women with a diabetes history or abnormal blood glucose control (48). Interestingly, our study noted strong associations for colorectal cancer among persons with early exposure to elevated blood glucose. Similarly, in the Nurse's Health Study, women whose diabetes had been diagnosed for 11 to 15 years had >2-fold increased risk of colorectal cancer. These documented associations suggest that earlier exposures to insulin and glucose perturbations may shape the risk profile for subsequent colorectal tumorigenesis.

The detrimental relationships observed for colorectal cancer in this study may be attributed to other mechanisms driven by metabolic dysregulation including imbalances in gut microbiota (50), elevated levels of fecal bile acids (51), and slower gut transit time (52), which have been hypothesized as underlying mechanisms in colorectal cancer etiology. Furthermore, the observed detrimental associations partially reflect the confluence of unhealthy lifestyle factors that cluster with insulin–glucose abnormalities, which may not be fully captured in observational studies (4).

Our data also suggested an increased risk for breast cancer, albeit not always statistically significant. Our results are consistent with existing evidence (53); however, the strength of associations remains moderate for breast cancer in the literature (1.2- to 1.5-fold increased risk; ref. 16), making it difficult to detect these associations in studies with limited power. Progesterone and estrogen receptor status are known to modify risk associations for breast cancer (54, 55), which we were unable to investigate in these analyses, and therefore expect our results to be biased toward the null.

We did not observe associations for prostate cancer, although the majority of HR > 1. We speculate that the risk associations of prostate cancer may be attenuated, in part, due to misclassification related to prostate cancer diagnosis. Diagnosis of prostate cancer is routinely based on biopsies driven by abnormal serum prostate-specific antigen (PSA) concentrations (56). Evidence within 2 national populations reported that both obesity and aberrations in blood glucose lowered PSA concentrations that influence

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PSA production in the prostate, partially because of reduced testosterone and sex hormone binding globulin concentrations (57, 58). Subsequently, the rate of PSA-induced biopsies is lower (56), leading to possible underdetection of prostate cancer among obese and prediabetic individuals (56, 58). This phenomenon may have attenuated the observed risk associations. Findings in the literature are inconsistent for prostate cancer and perturbations in insulin–glucose axis, although the mechanisms are not clearly understood (17).

It is important to note that we observed stronger and more significant associations between IFG and overall obesity-related cancers among adults who were either past or current smokers. Smoking is an independent risk factor of diabetes and several cancers (16, 59–61). Our results suggest the potential integrated effects of multiple risk factors. There was also some suggestion of stronger relationships of cancer risk among women for the majority of the exposures. In part, this may be because of attenuated associations between insulin–glucose perturbations and prostate cancer, in men. However, some evidence suggests that estrogen may play a protective role in the etiology of diabetes-related cancer (62). We speculate that loss of this protective role of estrogen may adversely influence obesity-related cancer risk in older women.

The FHS study has several novel aspects with clinical relevance. The study has a long follow up period of approximately 37 years, with in-person exams conducted by trained personnel, on an average every 4 years. Cancer diagnostic information was provided by the participant's doctor. Cancer status was queried at every study visit and was updated in between exams. Differently from most previous studies that use fixed values, this analyses capture changes in the exposure values over time by using time-dependent variables. The availability of comprehensive dietary, medication, anthropometric, physical activity, and demographic data made it possible to control for major risk factors of cancer. We acknowledge that there may be other underlying mechanisms beyond the hypothesized obesity-related pathways that we are unable to disentangle. In addition, we were unable to consider family history of cancer in these analyses as this information was not available for the majority of the population. Finally, the FHS participants are predominantly Caucasian, therefore studies in ethnically diverse cohorts are warranted.

In conclusion, these data support the procarcinogenic role of insulin–glucose axis dysregulation in cancer development and contribute to essential missing mechanistic information necessary to identify critical cancer control points. Our study provides evidence of the importance of early glycemic control during adulthood, which may reduce later risk of colorectal and possibly other obesity-related cancers. This research provides the impetus to further investigate unanswered questions related to critical time periods of IFG exposure during the life course and the cumulative impact of prolonged exposures to metabolic dysregulation of the insulin–glucose axis on cancer risk.

Disclosure of Potential Conflicts of Interest

Grace L. Lu-Yao is a consultant for Merck Research Laboratory, which does not contribute funding or play any role whatsoever in the design, interpretation, or drafting of our manuscript. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Vadiveloo
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Metabolic Dysregulation of the Insulin–Glucose Axis and Risk of Obesity-Related Cancers in the Framingham Heart Study-Offspring Cohort (1971 –2008)

Niyati Parekh, Yong Lin, Maya Vadiveloo, et al.

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