Insulin, Macronutrient Intake, and Physical Activity: Are Potential Indicators of Insulin Resistance Associated with Mortality from Breast Cancer?

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Abstract

High levels of insulin have been associated with increased risk of breast cancer, and poorer survival after diagnosis. Data and sera were collected from 603 breast cancer patients, including information on diet and physical activity, medical history, family history, demographic, and reproductive risk factors. These data were analyzed to test the hypothesis that excess insulin and related factors are directly related to mortality after a diagnosis of breast cancer. The cohort was recruited from breast cancer patients treated at the British Columbia Cancer Agency between July 1991 and December 1992. Questionnaire and medical record data were collected at enrolment and outcomes were ascertained by linkage to the BC Cancer Registry after 10 years of follow-up. The primary outcome of interest was breast cancer-specific mortality (n = 112). Lifestyle data were analyzed using Cox proportional hazards regression models to relate risk factors to outcomes, controlling for potential confounders, such as age and stage at diagnosis. Data for biological variables were analyzed as a nested case-control study due to limited serum volumes, with at least one survivor from the same cohort as a control for each breast cancer death, matched on stage and length of follow-up. High levels of insulin were associated with poorer survival for postmenopausal women [odds ratio, 1.9; 95% confidence interval (CI), 0.7-6.6, comparing highest to lowest tertile, P trend = 0.10], while high dietary fat intake was associated with poorer survival for premenopausal women (relative risk, 4.8; 95% CI, 1.3-18.1, comparing highest to lowest quartile). Higher dietary protein intake was associated with better survival for all women (relative risk, 0.4; 95% CI, 0.2-0.8, comparing highest to lowest quartile). (Cancer Epidemiol Biomarkers Prev 2004;13(7):1163–72)

Introduction

Many North Americans are overweight, physically inactive, and eat excessive amounts of fat and high-glycemic-index carbohydrate, all of which are determinants of insulin resistance (tissue insensitivity to insulin) and hyperinsulinemia (excess circulating insulin; refs. 1-4). A diet high in refined carbohydrate and low in fiber causes rapid intestinal absorption of glucose. This glucose challenge, in the context of preexisting insulin resistance, can result in particularly high insulin levels because the muscle tissue does not take up the extra glucose and more insulin is produced to compensate. Chronically elevated insulin levels have been associated with several degenerative diseases, including heart disease, non-insulin dependent diabetes mellitus, and cancer (2, 5-7).

Although there is a genetic contribution to insulin resistance (8, 9), several modifiable lifestyle factors can have profound effects on an individual's insulin sensitivity. Obesity or weight gain (10, 11) and physical inactivity (12, 13) are two of the main environmental determinants of insulin resistance. A World Health Organization study reports that obesity and lack of exercise contribute to between one fourth and one third of all cancers of the colon, breast, kidney, and digestive tract (14), and that adiposity and inactivity seem to be the most important avoidable causes of postmenopausal breast cancer. Metabolic factors like hyperinsulinemia may mediate these relationships.

There are surprisingly few modifiable factors known to be associated with breast cancer mortality that might provide opportunities for risk reduction. High levels of insulin have been associated with breast cancer mortality, but only in one study to date (15). We recently reported an association between waist-to-hip ratio (WHR), an indicator of insulin resistance, and breast cancer mortality in this cohort (16), and we now report the results for serum insulin and related biological

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markers, for macronutrient intake, and for physical activity and the relationship of these factors with breast cancer mortality.

If insulin levels do increase risk of breast cancer mortality, their responsiveness to environmental changes is key to novel strategies for risk reduction. Such strategies may involve dietary changes, increases in physical activity, weight reduction, pharmacologic intervention, or some combination of these.

Materials and Methods

Study Participants. This cohort, described in detail elsewhere (16), is made up of female breast cancer patients, ages 19 to 75, who visited the Vancouver Cancer Centre (VCC) of the British Columbia Cancer Agency (BCCA) for a consultation between July 1991 and December 1992, an average of 2 months after surgery but before the start of adjuvant treatment. Of 700 consecutive patients presenting for initial assessment at the VCC during the study period, we excluded those for whom the reason for referral was not a new tumor, or who had had previous therapy other than surgery ($n = 7$), who did not speak English ($n = 4$), were stage IV at diagnosis ($n = 9$), or were more than age 75 ($n = 2$). Of 678 eligible patients, a response rate of 89% ($N = 603$) was achieved. Reasons for non-participation included not feeling well ($n = 12$), not interested ($n = 24$), unable to contact ($n = 4$), and contacted but questionnaire not returned ($n = 35$). Eligible non-participants ($n = 75$, 11%) did not differ from participants with respect to outcome ($P = 0.21$), but were slightly older than eligible participants (56.7 years versus 54.4, $P = 0.08$). Information on risk factors was not available for non-participants without patient consent. Eligible patients signed informed consent before participation, and the study was approved by the Clinical Screening Committee of Research involving Human Subjects of the University of British Columbia (UBC), the Clinical Investigations Committee and the Cancer Registry Director of the BCCA.

Blood Samples. A single non-fasting blood sample was obtained from eligible patients at the time of their second agency visit (a pre-therapy assessment), using the same venipuncture normally required for the standard clinical workup. Blood was allowed to clot, and the serum was separated, subdivided into four aliquots of approximately 1 mL each and immediately stored in liquid nitrogen, where they were maintained for the duration of the study period. Samples were stored at liquid nitrogen temperatures to minimize possible degradation and variability across samples. Frozen aliquots were removed from the liquid nitrogen, packaged with dry ice in approved 1A transport boxes and sent to Hospitals In-Common Laboratory (Toronto, Canada) for assay of insulin, C-peptide, fructosamine, and sex hormone binding globulin (SHBG).

Questionnaire. The self-administered questionnaire gathered information on lifestyle factors, including diet, cigarette smoking, alcohol consumption, exercise, height, weight, hip and waist measurements, education, ethnicity, family history, and medical history. It included a validated semi-quantitative Block food frequency questionnaire (17). A common standardized protocol was used for questionnaire coding and data entry.

Patient and Outcome Data. Abstracting of clinical charts was done at enrolment to obtain patient and tumor information, including the following: size and stage of tumor at diagnosis, histologic type of tumor, pathologic nodal status, estrogen receptor (ER) status of tumor, age and menopausal status of the patient, and primary treatment information. Outcome data from diagnosis to June 30, 2001, including vital status, date of death, primary and secondary cause of death if applicable were obtained from BCCA patient records, which are updated monthly from Statistics Canada and the Canadian Cancer Registry with national death certificate information, so follow-up included current national data. BCCA's Surveillance and Outcomes Unit gets a death list every month from the British Columbia Vital Statistics Agency. On average each month's list consists of deaths for the previous month with stragglers from other months. A year's deaths are usually considered totally complete by the following June. BCCA also participates in a national death clearance through the Canadian Cancer Registry which allows them to pick up BC residents dying in other provinces. Also, BC Cancer Registry death information is compared with a national mortality database that is comprised of death information sent to Statistics Canada from each provincial Vital Statistics Agency. We estimate that only about 1% to 2% of patients die in other provinces. Any discrepancy in death information is investigated and resolved.

Variables. The questionnaire variables included daily intake of calories, fiber, carbohydrate, protein, saturated and total fat, and physical activity, including how often (per week, month, or year) the participant does each of the following: physical exercise, active sports, jogging or running, swimming or taking long walks, and gardening or fishing or hunting, as well as blocks walked and flights of stairs climbed on average each day. In addition, a variable for total number of times engaged in activity per year was calculated, summing the individual activity frequencies. From this, the number of activities per week was calculated and used to create a categorical variable to represent frequency of ''regular exercise'' (>3 times/wk, 3+ times/wk).

For fat, protein, and carbohydrate calculations, both plant and animal sources were included, and any food that is a member of the alcohol food group was ignored. The food grouping for ''Sweets'' included ice cream, doughnuts, cookies, cake, pastry, pie, chocolate candy, other candy, jelly, honey, and sugar. Biological variables were derived from laboratory assays of serum insulin, C-peptide, fructosamine, and SHBG. Variables entered in the models as potential confounders were: age, stage at diagnosis, menopausal status, body mass index, WHR, education, employment status, ethnicity, marital status, family history, local and systemic treatment, cigarette smoking, alcohol consumption, age at menarche, parity, and age at menopause (where applicable). Local treatment values were lumpectomy alone, complete mastectomy alone, lumpectomy plus radiation therapy, complete mastectomy plus radiation therapy, and other (e.g., a combination of these). The values for the systemic

treatment variable were chemotherapy, tamoxifen, both, other hormone, none. Menopausal status was classified as ''pre'' if menstruation had occurred within the previous year or if the patient had had a hysterectomy (ovaries not removed) and no menopausal symptoms were present; ''post'' if the last menstruation was more than 1 year previous to assessment.

Data on menopausal status, an important stratification variable, were missing for 50 (8%) of the cohort members. Menopausal status was imputed for these patients using the median age at menopause for the cohort, age 50, as the cut-off (up to and including 49, premenopausal; 50 and up, postmenopausal).

Biomarkers. Four biological variables were examined: serum insulin, C-peptide, fructosamine, and SHBG. A measure of insulin secretion over approximately the previous 3 months, C-peptide can serve as a valuable index to insulin secretion (18), though it still shows significant variability in relation to food intake. Fructosamine was assayed in place of glucose because plasma was not available to do a glucose assay. The concentration of fructosamine reflects the average of the continuously varying blood glucose concentrations during the previous 1- to 3-week period, serving as a blood glucose ''memory'' (19). Fructosamine was required to calculate the C-peptide-to-fructosamine ratio, an approximate measure of insulin sensitivity. SHBG was assayed to address one possible mechanism of insulin action, through effects on sex steroid availability. Additional assays were not possible due to limited sera.

All assays were done by Hospitals In-Common Laboratories (Toronto, Canada), the largest network of medical laboratories in Ontario, and a leading provider of reference testing services to hospital in Canada. C-peptide was assayed using Immulite solid-phase competitive chemiluminescent enzyme immunoassay from Diagnostic Products Corporation (Los Angeles, CA) (18). There is no detectable cross-reactivity with insulin and 13% cross-reactivity with proinsulin. Fructosamine was assayed using Spectrophotometry (Cobas Integra) from Roche (Nutley, NJ) (19), using a colorimetric test by reaction with nitroblue tetrazolium. Insulin was measured using the Immunolite immunometric assay from Diagnostic Products (20). There is no detectable cross-reactivity with C-peptide and 11.9% cross-reactivity with proinsulin. SHBG was assayed using Immunolite immunometric assay from Diagnostic Products (21). There is no detectable cross-reactivity with estradiol or testosterone. Replicate assays were not possible due to very small sera volumes, so an estimate of intra-assay variation is not available. The within-run coefficient of variation (intra-assay, or replicates done in a single run) established in laboratory standards testing ranged from 3.8% to 5.4% for insulin (20), 6.5% to 10.3% for C-peptide (18), 0.65% to 0.92% for fructosamine (19), and 4.1% to 7.7% for SHGB (21).

Statistical Analysis. Overall mortality and breast cancer-specific mortality were examined in relation to covariates of interest. The tables present data on breast cancer mortality (n = 112, or 77% of total mortality), and any differences for all-cause mortality (n = 146) are noted in the text. Lifestyle data, including dietary intake and leisure-time physical activity, were analyzed using Cox proportional hazards models to relate the prognostic markers to outcomes, controlling for potential confounders, such as age, tumor stage, and menopausal status. For analysis of biological variables only, a nested case-control design was used to accommodate limited serum resources. Breast-cancer deaths (n = 91 of the original 112) were frequency-matched to survivors from the original cohort (n = 170), on stage at diagnosis and length of follow-up such that controls had at least as long a period of follow-up as cases. A variable for ''time since last meal'' was calculated as the difference between ''time of blood draw'' and ''time of last meal.'' Cases and controls were not additionally matched on time since last meal as has been done in at least one other study (22), but the two groups did not differ significantly (P = 0.50) in that regard. Time since last meal is only a rough approximation of effects of eating on serum insulin levels, but the rationale for ensuring comparability is based on the biological relationship between dietary intake and serum insulin.

We excluded the following deaths from the analysis of biological variables: diabetics (n = 6), those with no matched survivor (n = 9), and those with no sera available (n = 6). To avoid selection bias introduced by matching in the design, the matching factor, stage at diagnosis, was controlled in the analysis. Insulin and C-peptide continuous variables were log-transformed before analysis, to compensate for skewed distributions.

For both proportional hazards and logistic regression analyses, clinical prognostic factors, such as age and stage at diagnosis, were included first. Other potential confounders were then added and their significance assessed by both their effect on the −2LogLikelihood of the model, and by their effect on the relative risk (RR) associated with the primary variable. To conserve degrees of freedom, only variables with a statistically significant ($P < 0.1$) effect on both mortality and the RR for insulin were retained for the multivariate models, and they were represented in continuous form where possible.

Results

The Study Population. Of the 603 participants, 235 were classified as premenopausal, and 368 as postmenopausal. The average age for the premenopausal women was 43.1 years, and for the postmenopausal women, 61.8 years (Table 1). By current standards (23), the average woman in the study was overweight (body mass index = 26), with a WHR of 0.8, the point in which risk of mortality may increase for women (24). Not surprisingly, there is a difference between pre- and postmenopausal women in percentage employed ($P < 0.001$) and marital status ($P < 0.001$). The cohort was mainly Caucasian (88.4%), with a small Asian component that is somewhat larger among the premenopausal women (10.2% for premenopausal women, 5.2% for postmenopausal women, P = 0.003).

The data for tumor size, grade, and nodal status demonstrate a higher percentage of poorly differentiated tumors among premenopausal women (53.5% versus 41.3%, P = 0.005). Of those tested (n = 423), 76.4% had ER-positive tumors, and there was a significant difference by menopausal status (69.0% for pre, 81.3% for post,

Table 1. Selected characteristics of the study population at diagnosis

	All cases (N = 603) mean (SD)	Premenopausal (n = 235) mean (SD)	Postmenopausal (n = 368) mean (SD)
Personal variables			
Age (y)	54.5 (11.0)	43.1 (5.7)	61.8 (6.8)
Family history of breast cancer*	15.9%	11.3%	18.8%
Number of children	2.4 (1.8)	1.8 (1.2)	2.8 (2.0)
Age menstruation began	12.9 (1.7)	12.6 (1.4)	13.0 (1.8)
Body size and shape variables			
Body mass index†	26.0 (4.6)	25.3 (4.7)	26.4 (4.5)
Waist-to-hip ratio‡	0.80 (0.07)	0.79 (0.06)	0.82 (0.07)
Demographic variables (%)			
Employed	46.7%	70.2%	31.6%
Marital status			
Single	5.3%	9.8%	2.4%
Married	68.3%	70.6%	66.8%
Widowed	11.6%	1.3%	18.2%
Divorced	14.8%	18.3%	12.5%
Ethnicity			
Caucasian	88.4%	83.4%	91.6%
Asian	7.1%	10.2%	5.2%
E. Indian	2.2%	1.7%	2.4%
Black	0.3%	0.9%	0.0%
Other	2.0%	3.8%	0.8%
Prognostic variables (%)			
Tumor grade			
Well differentiated	7.6%	8.8%	6.8%
Moderately differentiated	46.4%	37.8%	51.9%
Poorly differentiated	46.0%	53.5%	41.3%
Tumor size (cm)			
0-1.0	20.6%	16.3%	23.8%
1.1-2.0	23.5%	20.9%	25.4%
2.1-5.0	47.1%	54.7%	41.7%
5.1-9.9	8.7%	8.1%	9.2%
Nodal status			
No axillary dissection	11.1%	13.6%	9.5%
No positive nodes	57.5%	53.2%	60.3%
Positive nodes	27.9%	29.4%	26.9%
Unknown	3.5%	3.8%	3.3%
Estrogen receptor positive	76.4%	69.0%	81.3%
Systemic treatment			
None	40.1%	32.7%	44.7%
Tamoxifen only	21.9%	4.0%	33.1%
Chemotherapy only	14.7%	31.8%	3.9%
Both	21.4%	28.7%	16.9%
Other hormone	1.9%	2.6%	1.4%
Local treatment			
Lumpectomy alone	4.6%	5.3%	4.2%
Lumpectomy + RT	14.6%	11.9%	16.3%
Complete mastectomy alone	59.6%	59.3%	59.8%
Complete mastectomy + RT	10.0%	10.6%	9.6%
Other§	11.2%	12.8%	10.1%

Abbreviation: RT, radiation therapy.
*Family history is defined as breast cancer in any first-degree relative.
†kg/m^2.
‡Missing values: WHR (17), family history (10), employment status (1), estrogen receptor status (180).
§For example, a lumpectomy followed by a complete mastectomy.

P = 0.003). Local treatment did not differ by menopausal status, but systemic treatment, as expected, was more likely to be chemotherapy if the participant was premenopausal at diagnosis, and tamoxifen if postmenopausal at diagnosis.

Average 10-year survival for the cohort was 75.8%, strongly affected by stage at diagnosis (Table 2). The survival by stage was DCIS—90.4%, stage I—86.5%, stage II—68.6%, stage III—40.4%, stage IV—excluded. For survivors (n = 457), the median length of follow-up by stage was 8.1, 8.3, 7.9, and 8.2 years for DCIS, stage I, II, and III, respectively.

Biological Markers. A strong positive correlation was observed between insulin and C-peptide levels (r = 0.78, $P < 0.001$), as expected (Table 3). Insulin level was also weakly correlated with WHR (r = 0.19, $P < 0.001$) and body mass index (r = 0.29, $P < 0.001$), and weakly negatively correlated with SHBG levels ($r = -0.17$, $P < 0.01$). Insulin level was not correlated with fructosamine

Table 2. Average survival time from enrolment

	Alive		Survival time (y)		
	N	%	Mean	Median	SD
DCIS	47	90.4%	5.2	3.9	3.0
Stage I	224	86.5%	6.3	6.7	2.0
Stage II	165	68.6%	4.6	4.3	2.4
Stage III	21	40.4%	3.7	3.4	2.3
	457	75.8%			

levels, stage at diagnosis, tumor grade, ER status, or systemic treatment. Insulin also was not correlated with dietary intake of energy, fat, protein, alcohol, or carbohydrate (data not shown).

Odds ratios (OR) by tertile for each serum biomarker are shown for all women, and separately by menopausal status, in Table 4. Though not statistically significant at the 0.05 level, the data suggest that the risks associated with high insulin, C-peptide, and C-peptide-to-fructosamine ratio were greater for postmenopausal women than for premenopausal women. For example, the OR for the third (highest) tertile of insulin, compared with the first (lowest) tertile was 1.9 [95% confidence interval (CI), 0.7-6.6, *P* trend = 0.10] for postmenopausal women, and 0.9 (95% CI, 0.3-2.9, *P* trend = 0.75) for premenopausal women. Similarly, postmenopausal women in the highest tertile of C-peptide (OR, 2.3; 95% CI, 0.7-7.5) and C-peptide-to-fructosamine ratio (OR, 2.7; 95% CI, 0.9-8.5) may be at higher risk of dying from breast cancer than those in the lowest tertile, but this was not observed in premenopausal women. Although the point estimates for insulin and C-peptide are not identical, the CIs are similar. For fructosamine alone, there was no consistent relationship with mortality for premenopausal or postmenopausal women (data not shown). The results for SHBG levels were not statistically significant, but they suggested a possible reversal of association at menopause, such that higher SHBG levels may be protective for premenopausal women (OR, 0.4; 95% CI, 0.1-1.7 for third tertile compared with first tertile), but may confer risk for postmenopausal women (OR, 1.3; 95% CI, 0.5-4.1).

Macronutrient Intake. RRs for each 1% increase in energy derived from fat, protein, carbohydrate (excluding alcohol), alcohol, and the sweets food group are presented in Table 5. These RRs are adjusted for age and stage at diagnosis, and for total energy intake. The only macronutrient with statistically significant results was protein, with an RR of 0.87 (95% CI, 0.82-0.93) for all women, seen for both pre- and postmenopausal subgroups. No significant association with mortality was observed for carbohydrate, fat, fiber, or alcohol intake. Intake of beer, wine, and liquor, when analyzed separately, also showed no association with breast cancer mortality (data not shown). The only food group associated with elevated risk was the sweets group, with an RR of 1.05 (95% CI, 1.03-1.08) for each 1% increase in percentage of total energy derived from sweets.

When the macronutrients were analyzed by quartile of intake (Table 6), the risk associated with high intake of fat was restricted to premenopausal women (RR, 4.8; 95% CI, 1.3-18.1 for fourth quartile of total fat compared with first quartile, *P* trend = 0.08), while no risk was observed for postmenopausal women as a result of high intake of dietary fat (RR, 0.7; 95% CI, 0.2-2.2). An inverse association with dietary protein intake was observed for pre- and postmenopausal subgroups, while the dose-response relationship was most apparent when all women were considered together (*P* trend = 0.07). Intake of energy (calories), carbohydrate, fiber, and e-carb (carbohydrate excluding fiber) were not associated with mortality in this cohort. For intake of total energy, there was a suggestion that very low intake was associated with more risk than moderate intake (RR, 0.6; 95% CI, 0.3-1.0 for second quartile compared with first or lowest quartile), which may indicate a non-linear relationship, probably due to the cachectic and anorexic effects of the cancer, despite controlling for stage at diagnosis. A quadratic term was tested but not found to be statistically significant.

Physical Activity. Indicators of leisure-time physical activity are shown in Table 7, adjusted for age, stage, and total energy intake. No relationship was observed between any of the activity variables and breast cancer mortality. To account for women doing several activities, the total number of times engaged in physical activity per year was summed from the individual activities and analyzed as a total activity measure, but was not associated with breast cancer mortality (data not shown). A categorical variable to represent ''regular exercise'' was derived from this total (less than 3 times per week, versus 3 or more times per week), but no significant difference was found with respect to breast cancer mortality by comparing these two categories (data not shown). A few individual results shown in Table 7 reached statistical significance, notably those representing activity done only a few times per year, for example, sports for postmenopausal women (RR, 2.5; 95% CI, 1.0-5.9, compared with doing no sports), or exercise for premenopausal women (RR, 2.9; 95% CI, 1.1-7.3, compared with doing no exercise). These may be chance results, or they may be indicative of risk associated with sporadic physical activity. Overall, the cohort seems to be fairly sedentary, at least in terms of leisure-time activity, and

Table 3. Insulin, C-peptide, fructosamine, and SHBG

	Level			Correlations*
	Mean	SD	Median	Insulin
Insulin	92.9	77.9	68.0	—
C-peptide	579.0	432.1	483.0	0.78***
Fructosamine	254.3	33.8	250.5	0.03
SHBG	61.3	31.9	55.0	−0.17**
WHR	0.8	0.07	0.8	0.19***
Body mass index	26.0	4.60	25.0	0.29***
Stage	—	—	—	−0.04
Tumor grade	—	—	—	0.001
ER status†	—	—	—	−0.047
Treatment‡	—	—	—	−0.031

NOTE: Missing values: insulin (1), C-peptide (2), fructosamine (4), SHBG (11). *, means $P \leq 0.05$; **, means $P \leq 0.01$; ***, means $P \leq 0.001$.
*Spearman correlation coefficients.
†ER = estrogen receptor (missing values, 180).
‡Systemic treatment: chemotherapy, tamoxifen, both, other hormone, or none.

Table 4. Insulin, C-peptide, C-peptide-to-fructosamine ratio, SHBG, and breast cancer mortality

	All women				Premenopausal women				Postmenopausal women			
	Cases/Controls	OR*	95% CI	*P*	Cases/Controls	OR*	95% CI	*P*	Cases/Controls	OR*	95% CI	*P*
Insulin, pmol/L†												
Tertile 1 (lowest)	31/60	1.0		0.69	20/28	1.0		0.75	11/32	1.0		0.10
Tertile 2	32/58	1.4	0.7-2.8		12/23	0.7	0.2-2.0		20/35	3.0	1.0-9.5	
Tertile 3 (highest)	28/52	1.3	0.6-2.9		10/24	0.9	0.3-2.9		18/28	1.9	0.7-6.6	
C-peptide, pmol/L†												
Tertile 1 (lowest)	26/68	1.0		0.43	14/30	1.0		0.77	12/38	1.0		0.35
Tertile 2	36/54	1.5	0.7-3.2		18/23	1.3	0.4-3.8		18/31	1.7	0.6-5.4	
Tertile 3 (highest)	29/48	1.6	0.7-3.6		10/23	0.8	0.2-2.8		19/25	2.3	0.7-7.5	
C-peptide/Fructosamine ratio†												
Tertile 1 (lowest)	27/66	1.0		0.45	15/30	1.0		0.28	12/36	1.0		0.17
Tertile 2	32/51	1.4	0.7-3.1		17/19	1.8	0.6-5.7		15/32	1.3	0.4-3.9	
Tertile 3 (highest)	31/52	1.6	0.7-3.5		10/26	0.6	0.2-2.2		21/26	2.7	0.9-8.5	
SHBG, nmol/L†												
Tertile 1 (lowest)	27/53	1.0		0.99	12/19	1.0		0.49	15/34	1.0		0.87
Tertile 2	31/57	1.0	0.5-2.1		13/26	0.7	0.2-2.3		18/31	1.2	0.4-3.4	
Tertile 3 (highest)	29/55	1.0	0.4-2.2		15/28	0.4	0.1-1.7		15/28	1.3	0.5-4.1	

*OR adjusted for age and stage at diagnosis, treatment, estrogen receptor status, WHR, and family history of breast cancer.
†Tertile cutpoints: Insulin: Q1 (<54), Q2 (54-91), Q3 (92+). C-peptide: Q1 (<330), Q2 (330-666), Q3 (667+). SHBG: Q1 (<45), Q2 (45-66), Q3 (67+). Diabetics excluded from insulin and C-peptide analyses.

there is no clear dose-response pattern of association with mortality.

Discussion

Non-fasting serum insulin level was directly associated with 10-year mortality in postmenopausal women with non-metastatic breast cancer, but the association was not statistically significant at the 0.05 level. Levels of physical activity and energy intake at diagnosis were not associated with breast cancer mortality. Dietary intake of fat was associated with premenopausal breast cancer mortality, and intake of protein was inversely associated with outcome for all women. No association with mortality was observed for total carbohydrate, fiber, or alcohol intake.

Our insulin findings are consistent in both direction and magnitude with a previous cohort study (15), which reported an adjusted hazard ratio for the upper versus lower insulin quartile of 3.3 (95% CI, 1.5-7.0) for mortality and 2.1 (95% CI, 1.2-3.6) for distant recurrence. The insulin results are also consistent with our previously reported association of WHR and breast cancer mortality in postmenopausal women (16), and together these findings support the study hypothesis that hyperinsulinemia and related factors may predict higher breast cancer mortality. The association between insulin and breast cancer mortality was modified by menopausal status, in the same way as the WHR and breast cancer mortality relationship. It is not clear why this relationship only applies to postmenopausal women, but it may be related to tumor subtype, because the proportion of ER-positive tumors differs significantly by menopausal status in this cohort. Due to missing values and small subgroup sizes, it was not possible to stratify on ER status, but the adjustment of the insulin model for ER status resulted in a strengthened association of insulin with breast cancer mortality. A mechanism involving estrogen is consistent with insulin's role in estrogen production and bioavailability. The apparently contradictory results observed for pre- and postmenopausal women with respect to insulin levels may be related to insulin-estrogen interactions that would be modified by postmenopausal reduction in estrogen. Because insulin resistance and hyperinsulinemia are sometimes

Table 5. Percent of energy at diagnosis and breast cancer mortality

	All women (*N* = 603)			Premenopausal (*n* = 235)			Postmenopausal (*n* = 368)		
	RR*	95% CI	*P* value†	RR*	95% CI	*P* value	RR*	95% CI	*P* value
Percent energy from:									
Fat	1.02	0.99-1.04	ns	1.02	0.99-1.07	ns	1.00	0.96-1.04	ns
Protein	0.87	0.82-0.93	<0.0001	0.81	0.73-0.90	<0.0001	0.91	0.84-0.99	0.03
Carbohydrate w/o alcohol	1.00	0.99-1.03	ns	1.00	0.97-1.04	ns	1.02	0.99-1.05	ns
Alcohol	0.99	0.94-1.04	ns	0.96	0.90-1.04	ns	1.00	0.93-1.07	ns
Sweets	1.05	1.03-1.08	<0.0001	1.08	1.03-1.13	0.002	1.04	1.01-1.08	0.01

*Adjusted for age, stage at diagnosis, and total caloric intake. RR is for each 1% increase.
†Two-sided. ns = not significant, or >0.1.

Table 6. Macronutrient consumption at diagnosis and breast cancer mortality by menopausal status

		All women				Premenopausal women				Postmenopausal women			
		N	RR*	95% CI	*P* trend†	*N*	RR*	95% CI	*P* trend	*N*	RR	95% CI	*P* trend
Total fat	Quartile 1 (lowest)‡	150	1.0		0.35	55	1.0		0.08	95	1.0		0.49
	Quartile 2	151	1.0	0.6-1.8		50	2.3	0.9-5.7		101	0.6	0.3-1.2	
	Quartile 3	151	1.1	0.6-2.4		61	2.0	0.7-6.1		90	0.7	0.3-1.6	
	Quartile 4 (highest)	151	1.8	0.9-4.8		69	4.8	1.3-18.1		82	0.7	0.2-2.2	
Saturated fat	Quartile 1 (lowest)‡	150	1.0		0.07	51	1.0		0.06	99	1.0		0.54
	Quartile 2	151	1.4	0.8-2.4		53	2.7	1.0-6.8		98	0.9	0.5-1.9	
	Quartile 3	151	1.3	0.7-2.5		60	2.5	0.8-7.8		91	0.8	0.3-1.9	
	Quartile 4 (highest)	151	2.5	1.2-5.3		71	4.9	1.4-17.0		80	1.5	0.5-4.0	
Protein	Quartile 1 (lowest)‡	150	1.0		0.07	52	1.0		0.14	98	1.0		0.12
	Quartile 2	151	0.6	0.4-1.0		57	0.5	0.2-1.3		94	0.7	0.3-1.3	
	Quartile 3	151	0.5	0.3-0.9		59	0.6	0.2-1.7		92	0.3	0.1-0.8	
	Quartile 4 (highest)	151	0.4	0.2-0.8		67	0.2	0.1-0.9		84	0.6	0.2-1.6	
Total carbohydrates	Quartile 1 (lowest)‡	150	1.0		0.69	62	1.0		0.73	88	1.0		0.47
	Quartile 2	151	1.1	0.6-1.8		59	0.8	0.3-1.8		82	1.4	0.7-2.9	
	Quartile 3	151	1.1	0.6-2.0		57	1.2	0.4-3.7		94	1.1	0.5-2.5	
	Quartile 4 (highest)	151	1.5	0.7-3.4		57	1.3	0.3-5.1		94	2.0	0.7-5.7	
Fiber	Quartile 1 (lowest)‡	150	1.0		0.34	72	1.0		0.26	78	1.0		0.74
	Quartile 2	152	1.2	0.7-2.0		61	1.5	0.7-3.0		91	1.1	0.5-2.2	
	Quartile 3	150	1.0	0.6-1.8		59	1.0	0.4-2.2		91	1.1	0.5-2.4	
	Quartile 4 (highest)	151	0.7	0.4-1.3		43	0.7	0.2-1.6		108	0.8	0.3-1.8	
E-carb	Quartile 1 (lowest)‡	150	1.0		0.59	60	1.0		0.53	90	1.0		0.81
	Quartile 2	151	1.0	0.6-1.8		59	0.9	0.4-2.2		92	1.2	0.6-2.5	
	Quartile 3	151	1.3	0.7-2.4		58	1.5	0.5-4.8		93	1.4	0.6-3.0	
	Quartile 4 (highest)	150	1.7	0.7-3.8		57	2.1	0.5-8.6		93	1.7	0.6-4.9	
Energy	Quartile 1 (lowest)‡	150	1.0		0.26	57	1.0		0.85	93	1.0		0.25
	Quartile 2	151	0.6	0.3-1.0		48	0.7	0.3-1.8		103	0.5	0.2-0.9	
	Quartile 3	151	0.8	0.5-1.3		62	0.8	0.4-1.7		89	0.8	0.4-1.5	
	Quartile 4 (highest)	151	0.8	0.5-1.3		68	0.7	0.3-1.6		151	0.8	0.4-1.6	

*Adjusted for age, total caloric intake, and stage at diagnosis. Referent category is first quartile.
†Two-sided. ns = not significant, or >0.1.
‡Quartile cutpoints: Fat, in grams/day: Q1 (<43), Q2 (44-57), Q3 (58-75), Q4 (76+). Protein, in grams/day: Q1 (<52), Q2 (53-67), Q3 (68-82), Q4 (83+). Carbohydrate, in grams/day: Q1 (<146), Q2 (147-181), Q3 (182-223), Q4 (224+). Total energy, in kilocalories: Q1 (<1,262), Q2 (1,263-1,555), Q3 (1,556-1,899), Q4 (1,890+).

associated with anovulation, as in polycystic ovary syndrome (6, 25, 26), for premenopausal women, the benefit of fewer ovulation cycles may outweigh possible risks. Such a benefit would be expected to disappear with menopause. Associations of ER positivity and endogenous hormone-related variables like WHR have been reported in our study (16), as well as in the Iowa Women's Health Study cohort (27), but in the latter, the association was further modified by progesterone receptor (PR) status. Despite the lack of progesterone receptor status information in our study, the effect of ER status on the insulin association is consistent with the hypothesis of distinct risk factors for tumor subtypes.

Although similar to the insulin results in direction, order of magnitude, and menopausal modification, the C-peptide and C-peptide-to-fructosamine ratio results were not statistically significant (*P* trend > 0.1). SHBG levels at diagnosis were not significantly associated with breast cancer mortality, but the point estimates suggest a different effect for pre- and postmenopausal women.

With respect to dietary fat intake, the literature suggests that a high fat diet reduces insulin sensitivity, but the pattern of consumption of fatty acids may be a more significant factor than total quantity consumed (28). The effect of dietary fat intake on insulin resistance may come about via changes in membrane lipid composition (28), affecting membrane fluidity and activity of the insulin receptors. Our results on dietary fat intake are consistent with this, but our observation of an association only in premenopausal women is somewhat puzzling, and it suggests that dietary risk factors may be modified by hormonal environment, though in what way is not yet clear.

Protein intake, whether measured in grams per day or percentage of total energy, was associated with a protective effect, for both pre- and postmenopausal subgroups. Our results are consistent with previous studies looking at dietary protein intake and breast cancer mortality which, though few in number, have reported improved breast cancer outcomes with increased protein intake (29, 30). Goodwin et al. (31) reported evidence of an inverse linear association with breast cancer mortality of borderline statistical significance when protein intake was expressed as grams per day.

Our null results for total carbohydrate, fiber, and e-carb do not support a relationship with breast cancer mortality, possibly due to a combination of small effect size compared with other variables, and modest sample size. The highly significant risk associated with percentage of total calories derived from sweets, however, is consistent with Sevak et al. (4), Daly et al. (32), and others. Sevak et al. (4) studied the relationship of hyperinsulinemia to dietary intake in South Asian and European men residing in London. The results suggested that a high intake of carbohydrates, especially sucrose, may worsen metabolic disturbances associated with

Table 7. Physical activity at diagnosis and breast cancer mortality

		All women			Premenopausal women			Postmenopausal women		
		N	RR*	95% CI	*N*	RR*	95% CI	*N*	RR	95% CI
Climbing stairs	None	100	1.0		30	1.0		70	1.0	
	1 to 4 flights	250	1.2	0.7-2.2	90	4.0	0.9-16.9	160	0.8	0.4-1.6
	5 to 8 flights	148	1.4	0.8-2.6	62	4.1	0.9-17.9	86	1.0	0.5-2.2
	9+ flights	104	1.1	0.5-2.2	53	2.8	0.6-13.4	51	1.0	0.4-2.3
Walking	None	77	1.0		30	1.0		47	1.0	
	1 to 4 blocks	245	1.1	0.6-1.9	98	0.8	0.3-1.7	147	1.6	0.6-3.8
	5 to 8 blocks	122	1.0	0.5-1.9	50	0.7	0.3-1.8	72	1.5	0.5-4.0
	9+ blocks	159	1.0	0.5-1.9	57	0.5	0.2-1.4	102	1.7	0.7-4.2
Sports	None	449	1.0		143	1.0		306	1.0	
	A few times a year	63	1.1	0.6-2.0	42	0.6	0.3-1.4	21	2.5	1.0-5.9
	A few times a month	27	1.2	0.4-2.6	21	0.9	0.3-2.5	6	4.2	0.6-32.2
	About once a week	34	0.7	0.3-1.7	19	0.6	0.2-1.6	15	0.9	0.2-3.8
	More than once a week	30	1.0	0.5-3.2	10	0.9	0.2-3.7	20	1.1	0.3-3.6
Exercise	None	263	1.0		88	1.0		175	1.0	
	A few times a year	60	1.4	0.7-2.6	22	2.9	1.1-7.3	38	0.8	0.3-2.2
	A few times a month	68	2.2	1.2-4.0	36	1.6	0.7-4.1	32	3.6	1.6-7.9
	About once a week	69	1.3	0.7-2.3	31	1.7	0.7-3.9	38	1.1	0.4-2.3
	More than once a week	142	1.0	0.6-1.6	58	1.4	0.6-3.0	84	0.8	0.4-1.5
Jogging	None	555	1.0		202	1.0		353	1.0	
	A few times a year	19	1.5	0.5-4.1	11	1.6	0.5-5.2	8	1.1	0.2-8.0
	A few times a month	10	1.9	0.7-5.4	9	1.4	0.4-4.5	1	10.2	1.4-75.9
	About once a week	6	1.8	0.4-7.5	4	1.0	0.2-7.5	2	6.2	0.8-46.8
	More than once a week	13	1.8	0.4-7.5	9	1.1	0.2-8.2	4	4.4	0.6-33.3
Swimming	None	116	1.0		33	1.0		83	1.0	
	A few times a year	82	1.2	0.6-2.4	48	2.4	0.8-7.5	34	0.6	0.2-1.9
	A few times a month	91	1.0	0.5-2.0	39	1.6	0.5-5.3	52	0.9	0.4-2.0
	About once a week	96	1.2	0.7-2.3	43	2.3	0.7-7.1	53	0.8	0.3-1.9
	More than once a week	218	0.9	0.5-1.5	72	1.1	0.4-3.4	146	0.8	0.5-1.5
Gardening	None	219	1.0		78	1.0		141	1.0	
	A few times a year	100	1.0	0.6-1.8	46	1.3	0.6-2.9	54	0.7	0.3-1.8
	A few times a month	82	1.6	0.9-2.7	44	1.5	0.7-3.1	38	1.6	0.7-3.8
	About once a week	82	1.0	0.6-1.7	28	0.9	0.4-2.3	54	1.0	0.5-2.0
	More than once a week	120	0.8	0.5-1.4	39	0.5	0.2-1.6	81	1.0	0.5-1.8

*Adjusted for total caloric intake, age, and stage at diagnosis. First category (None) is reference category.

insulin resistance. Some evidence suggests that a high carbohydrate diet worsens glucose tolerance and increases insulin levels in normal as well as non-insulin dependent diabetes mellitus subjects (1). The effect seems strongest for high levels of sucrose and fructose consumption (4, 32).

The lack of association we observed for alcohol intake and mortality is not consistent with other studies, such as Hebert et al. (30), who reported that beer drinking increased the risk of mortality in early stage breast cancer. That study, however, suffered from even smaller numbers of breast cancer deaths than our study (73 compared with 112), so their result may have been a spurious finding. In studies of breast cancer incidence, the association with alcohol has been observed to differ by ER and progesterone receptor status, and increased risk of mortality may also be limited primarily to women with particular tumor subtypes (33, 34).

Dietary energy intake is one area in which risk factors for mortality from breast cancer may differ from those for developing breast cancer. The importance of adequate nutrition during treatment and recovery suggests a possible U-shaped or even inverse relationship between energy intake and risk of mortality. This has been shown in recently published data from a Canadian cohort, in which midrange intake of the major sources of energy was associated with optimal survival, as compared with both high and low extremes of intake (31). Our null result for high levels of energy intake might be partly explained by differences in physical activity, but adjustment for activity variables did not appreciably alter the result.

The data on leisure-time physical activity do not support the study hypothesis, in that physical activity was not inversely related to mortality from breast cancer in this cohort. In this study, sample size is adequate for effects of 2-fold or larger, but the RRs associated with physical activity may be smaller, as shown in the literature on physical activity and breast cancer incidence. Luoto et al. (35) reported no statistically significant association of leisure-time physical activity with breast-cancer incidence in a Finnish cohort of 30,548 women, whereas McTiernan et al. (36), in a case-control study, found a slightly decreased non-significant risk of breast cancer in women who exercised more than 1.5 hours per week or engaged in at least some high-intensity physical exercise (OR, 0.7; 95% CI, 0.4-1.1). Moore et al. (37) reported an RR of 0.92 (95% CI, 0.80-1.05) for women in the highest level of physical activity at baseline, in the Iowa Women's Health Study. A recent Canadian randomized controlled trial showed that exercise training had no significant effect on fasting insulin or insulin resistance in 53 postmenopausal breast cancer survivors (38). Moreover, the lack of occupational physical activity data would likely further weaken any observed relationship. A true null finding for physical activity in a female cohort would not be entirely surprising, however, if

WHR is related to mortality, since Trichopoulou et al. (39) reported that physical activity was not an independent predictor of WHR in women, although it is in men. Also, if the risk of mortality is mediated by insulin resistance, the results of the Oslo Trial (40) are relevant, in that exercise alone did not significantly improve insulin resistance although diet alone, or diet and exercise combined did result in improvement.

The results of this study must be interpreted with caution because the data are from an urban, largely Caucasian cohort, and the results may not generalize to a more mixed population. Variables selected from questionnaire data were subject to possible recall errors, and for insulin and C-peptide, non-fasting measurements would likely increase measurement error. This potential error may have biased the results toward the null, and attenuated the insulin effect size seen in postmenopausal women, so the association may be stronger than that reported. Potential misclassification of menopausal status may have attenuated observed differences between pre- and postmenopausal women. Confounding by hormone replacement therapy use and progesterone receptor status cannot be ruled out.

The strengths of this study include the use of prospective data with up to 10 years of follow-up which provided, in our view, strong observational evidence. An 89% participant response rate decreased the likelihood of selection bias. A well-characterized cohort and excellent follow-up, record keeping, infrastructure, and resources were critical success factors.

In summary, our research suggests a prognostic association between serum insulin and breast cancer mortality. These results contribute information on the importance of menopausal status and possibly ER status to the relationship between insulin and breast cancer mortality. The responsiveness of insulin levels to environmental changes is key to novel strategies to improve breast cancer outcomes. Such strategies may involve dietary changes, increases in physical activity, weight reduction, pharmacologic intervention, or some combination of these. The available evidence, however, does not yet support a causal relationship between serum insulin and breast cancer mortality.

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