



## Serum Insulin and Glucose Levels and Breast Cancer Incidence

### The Atherosclerosis Risk in Communities Study

Pamela J. Mink<sup>1</sup>, Eyal Shahar<sup>2</sup>, Wayne D. Rosamond<sup>3</sup>, Anthony J. Alberg<sup>4</sup>, and Aaron R. Folsom<sup>2</sup>

<sup>1</sup> Division of Cancer Prevention and Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.

<sup>2</sup> Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN.

<sup>3</sup> Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC.

<sup>4</sup> Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.

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The authors examined the association of breast cancer incidence with serum levels of insulin and glucose in a cohort of 7,894 women aged 45–64 years from four US communities. Anthropometric factors and fasting levels of insulin and glucose were measured at baseline (1987–1989). Over an average follow-up period of 7.1 years (1987–1995), 187 breast cancer cases were ascertained. Breast cancer was associated positively with body mass index but not with waist:hip ratio or serum insulin level. After adjustment for age, race, and study site, the incidence of breast cancer was 60% higher among diabetic women than among women with fasting glucose levels under 100 mg/dl, but this association was attenuated after further adjustment for body mass index and other covariates (adjusted rate ratio = 1.39, 95% confidence interval: 0.86, 2.23). Circulating insulin levels were not predictive of future breast cancer incidence, but there may be a weak association with type 2 diabetes, perhaps modulated via increased adiposity. *Am J Epidemiol* 2002;156:349–52.

breast neoplasms; glucose; insulin

Abbreviation: ARIC, Atherosclerosis Risk in Communities.

The associations of breast cancer with anthropometric and reproductive variables have implicated hormones, particularly estrogens, in the etiology of breast cancer (1, 2). Insulin also may play an etiologic role in the association of obesity and body fat distribution with breast cancer. Obesity increases insulin resistance, and women with abdominal obesity exhibit evidence of insulin resistance and hyperinsulinemia (3). Two case-control studies have reported higher serum C-peptide levels (a marker of insulin secretion) among breast cancer cases than among controls, even after adjustment for body mass index (weight (kg)/height (m)<sup>2</sup>) and waist:hip ratio (4, 5). However, another study found no difference in C-peptide levels or fasting insulin concentrations between breast cancer cases and controls (6). To our knowledge, no prospective study has documented whether fasting insulin level is associated with breast cancer incidence.

Type 2 diabetes has been hypothesized to be associated with breast cancer risk, because of its association with obesity and insulin. However, results from epidemiologic studies have been inconsistent (7–13).

The main purpose of this prospective study was to examine the association of breast cancer with fasting insulin level, fasting glucose level, and diabetes and to evaluate the role that these factors might play in breast cancer etiology.

#### MATERIALS AND METHODS

##### The Atherosclerosis Risk in Communities Study cohort

Participants came from the 8,710 women in the Atherosclerosis Risk in Communities (ARIC) Study cohort. The design and objectives of the ARIC Study have been

described elsewhere, including characterization of non-respondents (14, 15). Briefly, the ARIC Study is a longitudinal cohort study of 15,792 Black and White men and women aged 45–64 years at baseline from four US communities: suburban Minneapolis, Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi. Completion of a baseline clinic examination during 1987–1989 marked the enrollment of participants in the ARIC Study. An ancillary cancer study was implemented to establish the incidence of cancer as an endpoint in the ARIC cohort.

### Baseline measurements

Data on a wide range of physiologic and lifestyle factors, including anthropometric measures, were collected by trained staff. Interviewers collected information on age at menarche, menopausal status, age at menopause, number of pregnancies, number of livebirths, history (and age) of hysterectomy and/or oophorectomy, use of oral contraceptives, hormone replacement therapy, smoking, physical activity, usual alcohol intake, and previous cancer diagnoses. Participants were also asked whether they had ever been diagnosed with diabetes and whether they were taking medication to control diabetes.

A fasting blood sample was taken from each participant. Serum glucose level was assayed by a hexokinase/glucose-6-phosphate dehydrogenase method. Serum insulin level was assessed by nonspecific radioimmunoassay (<sup>125</sup>I-insulin Kit; Cambridge Medical Diagnostics, Inc., Billerica, Massachusetts). Reliability coefficients for insulin and glucose, obtained in subjects who were examined several times, were 0.81 and 0.84, respectively (16).

### ARIC cancer questionnaire

In 1994, ARIC staff administered a supplemental questionnaire by telephone to collect data on additional cancer risk factors not measured as part of the ARIC Study. Of the 8,710 female ARIC participants, 8,140 (93 percent) responded to this questionnaire. Information requested included age at first birth and history of any cancer (including site and age of onset) in first-degree relatives.

### Ascertainment of incident breast cancer cases

Incident cancers diagnosed among ARIC cohort members between January 1, 1987, and December 31, 1995, were ascertained by two methods: linkage to a cancer registry and/or medical record review of potential cases identified through the annual follow-up of the ARIC cohort via telephone. Three of the four ARIC communities are covered by state and/or county cancer registries, including the Minnesota Cancer Surveillance System, the North Carolina Central Cancer Registry, the Washington County (Maryland) Cancer Registry, and the (statewide) Maryland Cancer Registry. To identify cases in Jackson, Mississippi, which has no cancer registry, and to identify additional missed cancer cases in the other three ARIC communities, staff retrieved medical records for participants who reported having a cancer-related

hospitalization during annual follow-up telephone calls. Information related to the cancer diagnosis, including primary site, date of diagnosis, and source of diagnostic information (e.g., a pathology report), was abstracted from the medical records by study staff.

### Data analysis

The cohort for this analysis included 7,894 Black and White female ARIC cohort participants who had fasted for at least 8 hours prior to the baseline clinic visit and did not report a history of cancer at baseline. An additional 817 women with prevalent diabetes or unknown diabetes status at baseline were excluded from analyses of insulin levels. Women were considered to have prevalent diabetes if they reported a history of diabetes or pharmacologic treatment for diabetes or if they had a fasting glucose level of at least 126 mg/dl or a nonfasting glucose level of at least 200 mg/dl (17).

Person-years at risk were calculated for each participant as time between the baseline examination date and December 31, 1995, or the date of breast cancer diagnosis, death, or loss to follow-up, whichever occurred first. We created quintiles for fasting insulin level. We created a three-level categorical variable for fasting glucose level, with the upper level comprising women who met our definition of prevalent diabetes. The SAS procedure PHREG (SAS Institute, Inc., Cary, North Carolina) was used to fit Cox proportional hazards regression models. The final multivariable model included factors that were associated with breast cancer incidence or that acted as confounders by influencing the parameter estimate for the independent variable of interest.

## RESULTS

Among the 7,894 eligible women, 187 breast cancers were diagnosed during 56,184 person-years at risk.

Breast cancer incidence in the ARIC cohort was associated with most accepted risk factors for breast cancer, including younger age at menarche, later age at first birth, family history of breast cancer, and alcohol intake (data not shown). There was no apparent association of body mass index with breast cancer among women aged 45–50 years at baseline; however, there were only 51 cases in this age group, and the 95 percent confidence intervals were wide. Multivariate-adjusted relative risks for increasing quintiles of body mass index among older women were 1.00 (referent), 1.82, 1.32, 1.59, and 1.79 (*p* trend = 0.28). There was no association of breast cancer incidence with waist:hip ratio.

Table 1 shows the prevalence of breast cancer risk factors across quintiles of fasting serum insulin level. Insulin levels were higher in women who were older, those who were younger at menarche, and those who were physically inactive; insulin levels were lower in women who were Caucasian, those who were more educated, and those who currently used hormone replacement therapy, drank alcohol, or smoked. Fasting insulin level increased across quintiles of body mass index and waist:hip ratio and was relatively constant across quintiles of height (data not

**TABLE 1. Prevalence (%) of selected breast cancer risk factors by quintile of fasting serum insulin level among nondiabetic women, Atherosclerosis Risk in Communities Study, 1987–1995**

Risk factor	Quintile of fasting serum insulin level				
	Q1* (<43 pmol/liter)	Q2 (43–51 pmol/liter)	Q3 (52–72 pmol/liter)	Q4 (73–108 pmol/liter)	Q5 (>108 pmol/liter)
Age, >50 years	59	64	66	66	66
Caucasian race	89	83	74	65	50
High school education or more	88	84	79	75	66
Nulliparity	2	2	2	1	2
Age at first birth, ≥30 years	6	5	7	5	4
Age at menarche, ≤11 years	15	15	18	18	19
Age at menopause, ≥50 years	20	21	23	22	22
Current estrogen use	27	23	21	17	12
Family history of breast cancer in a mother or sister	11	12	11	12	10
Current smoking	29	27	24	23	20
Current alcohol drinking	65	57	53	45	34
Physical inactivity (lowest category of the ARIC* Sports Index†)	15	16	20	21	22

\* Q, quintile; ARIC, Atherosclerosis Risk in Communities.

† An index of physical activity ranging from 0 (low) to 5 (high) that was based on the Baecke questionnaire (Am J Clin Nutr 1982;36:936–42).

shown). There was no association of fasting insulin with breast cancer incidence (table 2). However, the age-, race-, and center-adjusted relative risks of breast cancer were 1.32 (95 percent confidence interval: 0.96, 1.81) for fasting glucose levels of 100–125 mg/dl and 1.60 (95 percent confidence interval: 1.02, 2.50) for diabetic women in comparison with the referent level (<100 mg/dl). These associations, not unexpectedly, were attenuated after body

mass index was added to the regression model, and they were attenuated further with the addition of other breast cancer risk factors. After multivariable adjustment, including adjustment for body mass index, the relative risk for diabetic women versus the referent women was 1.39 (95 percent confidence interval: 0.86, 2.23). There was no evidence of effect modification by age group (≤50 years vs. >50 years) for either insulin or glucose.

**TABLE 2. Age-, race-, and center-adjusted and multivariate-adjusted relative risks for associations of fasting serum insulin and glucose levels with breast cancer incidence, Atherosclerosis Risk in Communities Study, 1987–1995**

	No. of cases	Person-years at risk	RR*,†	95% CI*	RR‡	95% CI	RR§	95% CI	p trend
Quintile of insulin level (pmol/liter)									
<43	40	11,347	1.00¶		1.00¶		1.00¶		
43–51	22	9,437	0.67	0.40, 1.13	0.67	0.40, 1.13	0.66	0.39, 1.13	
52–72	50	10,724	1.41	0.93, 2.15	1.40	0.91, 2.14	1.38	0.89, 2.14	
73–108	26	9,697	0.88	0.53, 1.45	0.86	0.50, 1.46	0.89	0.52, 1.54	
>108	27	9,449	1.07	0.64, 1.76	1.03	0.57, 1.84	1.01	0.55, 1.86	0.87
Glucose level (mg/dl)									
<100	93	32,221	1.00¶		1.00¶		1.00¶		
100–125	68	17,527	1.32	0.96, 1.81	1.27	0.92, 1.76	1.23	0.88, 1.71	
Diabetic	26	6,436	1.60	1.02, 2.50	1.48	0.93, 2.36	1.39	0.86, 2.23	

\* RR, relative risk; CI, confidence interval.

† Adjusted for age, race, and study center.

‡ Adjusted for age, race, study center, and body mass index.

§ Adjusted for age, race, study center, body mass index, age at menarche, age at menopause, age at first livebirth, family history of breast cancer in a mother or sister, number of sisters, alcohol intake, and pack-years of smoking.

¶ Referent.

## DISCUSSION

We found no association between fasting insulin level and breast cancer incidence, but we did observe a higher incidence of breast cancer among women with diabetes compared with women with fasting glucose levels below 100 mg/dl. These positive associations were attenuated after adjustment for body mass index and other covariates, but the pattern of increasing relative risks remained.

Laakso (18) has reported that fasting insulin level is a moderately good measure of insulin resistance among subjects with normal glucose tolerance ( $r = 0.66$ ). Because insulin resistance is a characteristic of type 2 diabetes and has been implicated in the promotion of breast cancer cell proliferation in vitro and in increased insulin-like growth factor activity in breast tissue, diabetes may be associated with increased breast cancer risk (9, 10, 12). Results from epidemiologic studies of breast cancer and diabetes have not provided strong support for this hypothesis (9), although in two recent studies investigators reported modest positive associations of breast cancer with type 2 diabetes (11, 12). However, in one of those studies, researchers could not adequately take into account the contribution of obesity (12). In the ARIC Study, we found that the age-, race-, and center-adjusted relative risk for the association between diabetes and breast cancer decreased from 1.60 to 1.48 after additional adjustment for body mass index, and the risk was further attenuated to 1.39 by further multivariate adjustment (table 2).

Strengths of the ARIC Study include the ability to identify women with undiagnosed (or unreported) diabetes, to fully adjust for body mass index, and to examine dose-response for fasting glucose and breast cancer incidence. However, data from this study did not support our main hypothesis that serum insulin level is associated positively with breast cancer incidence. Although there was no association of fasting insulin level with breast cancer incidence, a modest positive, independent association of diabetes with the disease cannot be ruled out entirely.

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