Priority Report

Cancer Research

Breast Cancer Risk in Metabolically Healthy but Overweight Postmenopausal Women

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Abstract

Adiposity is an established risk factor for postmenopausal breast cancer. Recent data suggest that high insulin levels in overweight women may play a major role in this relationship, due to insulin's mitogenic/antiapoptotic activity. However, whether overweight women who are metabolically healthy (i.e., normal insulin sensitivity) have elevated risk of breast cancer is unknown. We investigated whether overweight women with normal insulin sensitivity [i.e., homeostasis model assessment of insulin resistance (HOMA-IR) index, or fasting insulin level, within the lowest quartile (q1)] have increased breast cancer risk. Subjects were incident breast cancer cases ($N = 497$) and a subcohort ($N = 2,830$) of Women's Health Initiative (WHI) participants with available fasting insulin and glucose levels. In multivariate Cox models, metabolically healthy overweight women, defined using HOMA-IR, were not at elevated risk of breast cancer compared with metabolically healthy normal weight women [$HR_{HOMA-IR}$, 0.96; 95% confidence interval (CI), 0.64–1.42]. In contrast, the risk among women with high (q3-4) HOMA-IRs was elevated whether they were overweight ($HR_{HOMA-IR}$, 1.76; 95% CI, 1.19-2.60) or normal weight ($HR_{HOMA-IR}$, 1.80; 95% CI, 0.88–3.70). Similarly, using fasting insulin to define metabolic health, metabolically unhealthy women (insulin q3-4) were at higher risk of breast cancer regardless of whether they were normal weight ($HR_{insulin}$, 2.06; 95% CI, 1.01–4.22) or overweight ($HR_{insulin}$, 2.01; 95% CI, 1.35–2.99), whereas metabolically healthy overweight women did not have significantly increased risk of breast cancer ($HR_{insulin}$, 0.96; 95% CI, 0.64–1.42) relative to metabolically healthy normal weight women. Metabolic health (e.g., HOMA-IR or fasting insulin) may be more biologically relevant and more useful for breast cancer risk stratification than adiposity *per se*. *Cancer Res; 75(2); 270–4. ©2014 AACR.*

Introduction

Excess body weight is a well-established risk factor for breast cancer in postmenopausal women.(1, 2) Until recently, this relationship was largely thought to be attributable to the prevalence of higher estrogen levels in overweight women, which is an established risk factor for postmenopausal breast cancer (3, 4). However, being overweight is also associated with high levels of insulin, which has mitogenic and antiapoptotic activity (5, 6), and recent cohort data have linked insulin levels with breast cancer risk (7, 8). A large prospective study, for example, reported a highly significant 2.4-fold increased risk of breast cancer among postmenopausal women with insulin levels in the highest relative to the lowest quartile, after adjusting for multiple breast cancer risk factors, including serum estradiol (7). In subsequent analyses using mediation analysis methods, it was reported that the obesity–breast cancer association is more greatly attributable to insulin than to estradiol levels (9).

These observations lead to an important but yet untested clinical corollary to the insulin–breast cancer association, namely, that those overweight women with high insulin levels but not those with normal insulin levels will be at increased risk of breast cancer relative to healthy normal weight women. Indeed, a metabolically healthy obese phenotype has been posited to be relevant for cardiovascular disease risk (10–12), and there is accumulating evidence that individuals who are overweight [body mass index (BMI) $\geq$25 kg/m^2], but who have normal insulin sensitivity [e.g., a low quartile of homeostasis model assessment of insulin resistance (HOMA-IR) index] have little, if any, excess risk of cardiovascular events (13–16). Therefore, we compared the risk of incident postmenopausal breast cancer among metabolically healthy overweight women with that in metabolically healthy normal weight women.

Patients and Methods

Study population

The data analyzed were from two separate prospective studies of incident postmenopausal breast cancer and fasting serum insulin and glucose levels based in the Women's Health Initiative (WHI), a large prospective cohort study of postmenopausal women ages 50 to 79 years at enrolment (17). WHI has both an observational component ($N = 93,676$) and a clinical trial component ($N = 68,132$) with three arms: hormone therapy, dietary modification, and vitamin D/calcium supplementation.

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doi: 10.1158/0008-5472.CAN-14-2317

All components were conducted at the same clinical centers and shared relevant methods, including a standardized blood collection protocol. All WHI participants were ages 50 to 79 years at baseline and were recruited at 40 clinical centers across the United States between October 1, 1993 and December 31, 1998. At baseline, a physical examination that included measurement of height and weight, and collection of fasting blood, was conducted. Incident cancer was then ascertained through annual or semiannual self-administered questionnaires or by self-report, and were subsequently confirmed through centralized review of all pathology reports, discharge and consultant summaries, operative and radiology reports, and tumor registry abstracts.

The first of the two WHI breast cancer studies used was a case–cohort investigation of nondiabetic women based in the observational component of WHI that included 835 incident cases diagnosed over a mean of 8.2 years of follow-up and a randomly selected subcohort of 816 women present at the baseline visit (7). The second study was a conventional cohort investigation involving a random sample of approximately 1% of women in the observational ($N = 1{,}054$) and 6% in the clinical trial component ($N = 4{,}396$), who were asked to provide extra blood for serologic studies (8). A total of 190 incident breast cancer cases in this second study were diagnosed over 8 years of follow-up. The combined comparison group from both studies (each of which was randomly selected subjects) is referred to, herein, as the subcohort. As in prior reports, women who were either diabetic or currently using hormone therapy were excluded, due to the impact of these factors on insulin levels (7, 18), leaving 497 cases and a subcohort of 2,830 women. All subjects included in this analysis had fasting insulin and glucose levels available.

Categorization of metabolic health

We compared the risk of incident postmenopausal breast cancer among metabolically healthy normal weight women (BMI 18–24.9 kg/m^2 and HOMA-IR–q1) with that in metabolically unhealthy overweight women [BMI $\geq$25 kg/m^2 and HOMA-IR quartiles 3 and 4 (HOMA-IR–q3+4)], metabolically healthy overweight women (BMI $\geq$ 25 kg/m^2 and HOMA-IR–q1), as well as metabolically unhealthy normal weight women (BMI 18-24.9 kg/m^2 and HOMA-IR–q3+4)—similar to the design of prior studies of cardiovascular disease (14, 16). HOMA-IR–q2 was excluded to make the two strata discrete (non-abutting) categories. HOMA-IR is a standard measure of insulin resistance and is defined by a formula that incorporates both insulin and glucose levels [(fasting insulin (IU/mL) $\times$ fasting glucose (mg/dL))/22.5]. However, as our hypotheses focused particularly on the impact of insulin on breast cancer risk, we also *a priori* used insulin quartile itself to distinguish metabolically healthy from unhealthy women.

Statistical analyses

Hazard ratios (HR) and 95% confidence intervals (CI) for the association of metabolic health subtypes with incident breast cancer were estimated using Cox proportional hazards regression modeling that used the self-prentice method for robust SE estimates (to account for the case–cohort design), with time from study enrollment as the underlying time metric (19). Statistical analyses adjusted for established breast cancer risk factors, namely, age [50–54 (referent), 55–59, 60–64, 65–69, 70–74, or 75–79 years], ethnicity [white (referent), black, Hispanic, or Asian/other], age at menarche [$\leq$10, 11–12 (referent), or $\geq$13 years], and menopause [$\leq$42 (referent), 43–48, 49–51, or $\geq$52 years], parity [0 (referent), 1, or $\geq$2 live births], first-degree relative with breast cancer (yes or no), education [high school or lower (referent), college, or postgraduate education], alcohol consumption (assessed as the number of servings per week during the preceding 3 months [none (referent), <3, or $\geq$3], physical activity [assessed as metabolic equivalent tasks per hour per week (METs; defined as the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest) and categorized as quartiles (<3.75, 3.75–9.82, 9.83–18.74, $\geq$18.75)], as well as which of the two WHI studies each subject was enrolled in (observational study or clinical trial) and,

Table 1. Selected baseline characteristics of the study population

Variable[a]	Cases ($N = 497$)	Subcohort ($N = 2{,}830$)	*P*
Age, y	65 (59–70)	63 (57–69)	<0.0001
WHI, *N* (%)			
Observational study cohort	401 (80.7)	756 (26.7)	N/A
Clinical trial cohort	96 (19.3)	2,074 (73.3)	
Ethnicity, *N* (%)			
White	394 (79.3)	1,591 (56.4)	<0.0001
Black	60 (12.1)	634 (22.4)	
Hispanic	22 (4.4)	340 (12.0)	
Asian/other	19 (3.8)	263 (9.2)	
Missing	2 (0.4)	2 (0.1)	
BMI (kg/m^2), *N* (%)			0.17
Normal (BMI < 25.0)	155 (31.2)	762 (26.9)	
Overweight (25.0 $\leq$ 30.0)	165 (33.2)	998 (35.3)	
Obese ($\geq$30.0)	177 (35.6)	1,070 (37.8)	
Age at menarche, *N* (%)			0.44
$\leq$10	41 (8.2)	193 (6.8)	
11–12	203 (40.8)	1,101 (38.9)	
13+	250 (50.3)	1,523 (53.8)	
Missing	3 (0.7)	13 (0.5)	
Age at menopause, *N* (%)			0.001
$\leq$42	72 (14.5)	541 (19.1)	
43–48	106 (21.3)	629 (22.2)	
49–51	133 (26.8)	616 (21.8)	
$\geq$52	142 (28.6)	675 (23.9)	
Missing	44 (8.8)	369 (13.0)	
Parity, *N* (%)			0.04
0	79 (15.9)	334 (11.8)	
1	39 (7.8)	254 (9.0)	
$\geq$2	375 (75.5)	2,223 (78.6)	
Missing	4 (0.8)	19 (0.6)	
Family history of breast cancer, *N* (%)			<0.0001
Yes	138 (27.8)	440 (15.5)	
No	185 (37.2)	2,164 (76.5)	
Missing	174 (35.0)	226 (8.0)	
Smoking status, *N* (%)			0.001
Never	254 (51.1)	1,519 (53.7)	
Former	213 (42.9)	1,021 (36.1)	
Current	22 (4.4)	250 (8.8)	
Missing	8 (1.6)	40 (1.4)	
Education history, *N* (%)			<0.0001
High school and less	144 (29.0)	1,125 (39.8)	
College	203 (40.8)	982 (34.7)	
Postgraduate education	143 (28.8)	701 (24.8)	
Missing	7 (1.4)	22 (0.7)	
Alcohol (servings/week)	0.4 (0.0–3.5)	0.2 (0.0–1.4)	<0.0001
Physical activity (METs[b])	8.29 (2.00–17.50)	5.75 (0.50–15.00)	<0.0001

NOTE: *P* values derived from the Wilcoxon rank-sum test for continuous data and Pearson χ^2 for categorical data.

[a]Values are medians (interquartile range) unless otherwise stated.

[b]MET, metabolic equivalent tasks (defined as the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest) per hour per week.

Table 2. The associations of incident postmenopausal breast cancer risk with metabolic health defined by HOMA-IR or insulin levels, stratified by BMI category

BMI category	*N* (cases/ subcohort)	Age-adjusted HR (95% CI)	*P*	Multivariate HR[a] (95% CI)	*P*
HOMA-IR–based definition of metabolic health					
Normal weight (<25 kg/m^2)					
Metabolically healthy[b]	113/356	1.00 (Referent)		1.00 (Referent)	
Metabolically unhealthy[c]	18/182	1.68 (0.85–3.33)	0.13	1.80 (0.88–3.70)	0.11
Overweight (≥25 kg/m^2)					
Metabolically healthy[b]	87/339	0.93 (0.64–1.34)	0.68	0.96 (0.64–1.42)	0.83
Metabolically unhealthy[c]	169/1238	1.60 (1.12–2.28)	0.01	1.76 (1.19–2.60)	0.005
Insulin-based definition of metabolic health					
Normal weight (<25 kg/m^2)					
Metabolically healthy[d]	108/352	1.00 (Referent)		1.00 (Referent)	
Metabolically unhealthy[e]	19/180	1.86 (0.95–3.65)	0.07	2.06 (1.01–4.22)	0.048
Overweight (≥25 kg/m^2)					
Metabolically healthy[d]	86/329	0.93 (0.64–1.35)	0.71	0.96 (0.64–1.42)	0.82
Metabolically unhealthy[e]	175/1250	1.86 (1.30–2.66)	0.001	2.01 (1.35–2.99)	0.001

[a]Variables that are included in the multivariate model.
[b]HOMA-IR (quartile 1);
[c]HOMA-IR (quartiles 3+4);
[d]Insulin (quartile 1); and
[e]Insulin (quartiles 3+4); adjusted for age, ethnicity, age at menarche and menopause, parity, first-degree relative with breast cancer, education, alcohol consumption, physical activity, which of the two WHI studies each subject was enrolled in and, among those who participated in the clinical trials, which specific clinical trial arm they were assigned to and whether they were a member of the placebo or treatment group.

among those who participated in the clinical trials, which specific clinical trial arm they were assigned to [hormone therapy (estrogen-alone, estrogen plus progestin), calcium/vitamin D and dietary modification] and whether they were a member of the placebo or treatment group. In addition, caloric intake, total carbohydrate, saturated fat, and glycemic load and index were also considered as potential confounding variables in the analysis but their inclusion in the multivariable model did not meaningfully alter the regression coefficients, and were therefore not included in the final models. Individuals were censored at diagnosis of breast cancer, death, or at the end of follow-up. Data from each of the two contributing WHI studies of insulin, glucose, and breast cancer were combined and were analyzed using a case–cohort approach with each study permitted to retain its individual baseline hazards function (19). The proportionality of the data was verified by graphical inspection and by Schoenfeld residuals. All tests of statistical significance were two sided, and *P* values less than 0.05 were considered statistically significant. All analyses were performed using SAS statistical software (version 9.1).

Results

Table 1 shows selected baseline characteristics of the cases in the analysis as well as the noncases in the subcohort. The two groups did not differ significantly by ethnicity, BMI or age at menarche. However, cases (median age = 65) were on average older than noncases in the subcohort (median age = 63), more likely to be college educated, to be nulliparous, have a later age at menopause, to have a first-degree relative with breast cancer, and also consumed more alcohol and engaged in more physical activity.

In multivariate Cox proportional hazards models, metabolically unhealthy overweight was associated with a significantly increased risk of incident breast cancer ($HR_{HOMA\text{-}IR}$, 1.76; 95% CI, 1.19–2.60; $P = 0.005$) compared with metabolically healthy normal weight women (Table 2). Furthermore, a similar association was observed for metabolically unhealthy normal weight, though the relationship did not reach statistical significance ($HR_{HOMA\text{-}IR}$, 1.80; 95% CI, 0.88–3.70; $P = 0.11$). No relationship, however, was observed between breast cancer and metabolically healthy overweight ($HR_{HOMA\text{-}IR}$, 0.96; 95% CI, 0.64–1.42; $P = 0.83$) compared with metabolically healthy normal weight women. In addition, the HR directly contrasting breast cancer risk in overweight women who were metabolically unhealthy versus healthy was HR, 1.84 (95% CI, 1.38–2.45; $P < 0.0001$).

We additionally used insulin quartile to differentiate metabolically healthy (q1) versus unhealthy (q3+q4) women. Statistically significant associations between breast cancer risk and metabolic health were observed, regardless of whether women were normal weight ($HR_{insulin}$, 2.06; 95% CI, 1.01–4.22; $P = 0.048$) or overweight ($HR_{insulin}$, = 2.01; 95% CI, 1.35–2.99; $P = 0.001$), whereas metabolically healthy overweight women did not have significantly increased risk of breast cancer ($HR_{insulin}$, = 0.96; 95% CI, 0.64–1.42; $P = 0.82$) relative to metabolically healthy normal weight women. Furthermore, the HR directly contrasting cancer risk in overweight women who were metabolically unhealthy versus healthy (based on insulin) was HR, 2.11 (95% CI, 1.58–2.81; $P < 0.0001$).

Conclusion

Overall, the results from this study suggest that metabolic health status (as defined by HOMA-IR or fasting insulin levels), and not adiposity *per se*, may be the relevant factor associated with risk of postmenopausal breast cancer. These findings are consistent with recent reports that overweight individuals with normal insulin sensitivity are not at increased risk of cardiovascular disease, and collectively provide further evidence of the existence of a healthy obese phenotype (10–12). Our findings also support the hypothesis that hyperinsulinemia is a significant risk factor for breast cancer, independent of adiposity and that insulin, or a closely related mechanism, may be driving development of breast tumors. Several prospective studies have now reported significant, positive associations between fasting insulin or C-peptide (a marker of insulin secretion; refs. 7, 8, 20–22), and there is evidence that insulin plays a significant role in mediating the obesity–breast cancer relationship (7, 9).

We note that our conclusions are limited by the fact that only a single insulin and glucose measurement were available from the study participants and that multiple measurements over time would enable a more precise assessment of long-term metabolic health. Furthermore, our sample size was not large enough to further stratify by breast cancer subtypes such as those defined by estrogen receptor expression. Given potential crosstalk between estrogen and insulin signaling, it is possible that the association of metabolic health with breast cancer varies by breast tumor estrogen receptor subtype, and future studies should be of sufficient sample size to examine this hypothesis with adequate precision.

In conclusion, these findings raise the possibility that HOMA-IR or fasting insulin levels may be useful in combination with other predictors of breast cancer risk in efforts to individualize breast cancer screening practices.

Disclosure of Potential Conflicts of Interest

S. Wassertheil-Smoller is a consultant/advisory board member for Ologen study in ophthalmology. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Acknowledgments

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Grant Support

This study was funded by National Cancer Institute grant R01-CA93881-01 (H.D. Strickler). The WHI program is funded by the National Heart, Lung, and Blood Institute, NIH, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

Received August 8, 2014; revised October 27, 2014; accepted November 3, 2014; published online January 15, 2015.

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Cancer Res 2015;75:270-274.