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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/anti-apoptotic 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 to metabolically healthy normal weight women (hazard ratio [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*.

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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 anti-apoptotic 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] ≥ 25 kg/M²) 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 to that in metabolically healthy normal weight women.

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 aged 50-79 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 (HT), dietary modification, and vitamin D/calcium supplementation. All components were conducted at the same clinical centers and shared relevant methods including a standardized blood collection protocol. All WHI participants were aged 50-79 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 semi-annual 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 non-diabetic 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 were randomly selected subjects) is referred to, herein, as the subcohort. As in prior reports, women who were either diabetic or currently using hormone therapy (HT) 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 the current 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/m² and HOMA-IR-q1) to that in metabolically unhealthy overweight women (BMI ≥ 25 kg/m² and HOMA-IR quartiles 3 and 4 [HOMA-IR-q3+4]), metabolically healthy overweight women (BMI ≥ 25 kg/m² and HOMA-IR-q1), as well as metabolically unhealthy normal weight women (BMI 18-24.9 kg/m² 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 ($[\text{fasting insulin (IU/mL)} \times \text{fasting glucose (mg/dL)}] / 22.5$). 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 (HRs) 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 employed the Self-Prentice method for robust standard error 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 (10, 11–12[referent], or 13 years) and menopause (42 [referent], 43–48, 49–51, or 52 years), parity (0 [referent], 1, or 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 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, 18.75), as well as which of the two WHI studies each subject was enrolled in (observational study or clinical trial) and, 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 .05 were considered statistically significant. All analyses were performed using SAS statistical software (version 9.1, Cary, NC).

RESULTS

Table 1 shows selected baseline characteristics of the cases in the analysis as well as the non-cases 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 non-cases 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 ($HR_{HOMA-IR}=1.76$; 95% CI, 1.19-2.60; $P=0.005$) compared to metabolically healthy normal weight women (Table 2). Further, a similar association was observed for metabolically unhealthy normal weight though the relationship did not reach statistical significance ($HR_{HOMA-IR}=1.80$; 95% CI, 0.88-3.70; $P=0.11$). No relationship, however, was observed between breast cancer and metabolically healthy overweight ($HR_{HOMA-IR}=0.96$; 95% CI, 0.64-1.42; $P=0.83$) compared to metabolically healthy normal weight women. In addition, the hazard ratio 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. Further, 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) (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. Further, our sample size was not large enough to further stratify by breast cancer subtypes such as those defined by estrogen receptor expression. Given potential cross-talk 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, the current 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.

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References

1. Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT, Tehard B, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer*. 2004; 111(5):762–71. [PubMed: 15252848]
2. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000; 152(6):514–27. [PubMed: 10997541]
3. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002; 94(8):606–16. [PubMed: 11959894]
4. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003; 95(16):1218–26. [PubMed: 12928347]
5. Ish-Shalom D, Christoffersen CT, Vorwerk P, Sacerdoti-Sierra N, Shymko RM, Naor D, et al. Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor. *Diabetologia*. 1997; 40(Suppl 2):S25–31. [PubMed: 9248698]
6. Chappell J, Leitner JW, Solomon S, Golovchenko I, Goalstone ML, Draznin B. Effect of insulin on cell cycle progression in MCF-7 breast cancer cells. Direct and potentiating influence. *J Biol Chem*. 2001; 276(41):38023–8. [PubMed: 11500498]
7. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 2009; 101(1):48–60. [PubMed: 19116382]
8. Kabat GC, Kim M, Caan BJ, Chlebowski RT, Gunter MJ, Ho GY, et al. Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. *Int J Cancer*. 2009; 125(11):2704–10. [PubMed: 19588485]
9. Hvidtfeldt UA, Gunter MJ, Lange T, Chlebowski RT, Lane D, Farhat GN, et al. Quantifying mediating effects of endogenous estrogen and insulin in the relation between obesity, alcohol consumption, and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2012; 21(7):1203–12. [PubMed: 22564867]
10. Durward CM, Hartman TJ, Nickols-Richardson SM. All-cause mortality risk of metabolically healthy obese individuals in NHANES III. *J Obes*. 2012; 2012:460321. [PubMed: 23304462]
11. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med*. 2008; 168(15):1609–16. [PubMed: 18695074]
12. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk

- factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med.* 2008; 168(15):1617–24. [PubMed: 18695075]
13. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident Cardiovascular Disease Events in Metabolically Benign Obese Individuals. *Obesity* (Silver Spring). 2011
 14. Hosseinpanah F, Barzin M, Sheikholeslami F, Azizi F. Effect of different obesity phenotypes on cardiovascular events in Tehran Lipid and Glucose Study (TLGS). *Am J Cardiol.* 2011; 107(3): 412–6. [PubMed: 21257007]
 15. St-Pierre AC, Cantin B, Mauriege P, Bergeron J, Dagenais GR, Despres JP, et al. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ.* 2005; 172(10):1301–5. [PubMed: 15883404]
 16. Voulgari C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. *J Am Coll Cardiol.* 2011; 58(13):1343–50. [PubMed: 21920263]
 17. Group TWsHIS. Design of the Women’s Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998; 19(1):61–109. [PubMed: 9492970]
 18. Ligibel JA, Strickler HD. Obesity and its impact on breast cancer. *Am Soc Clin Oncol Educ Book.* 2013; 2013:52–9. [PubMed: 23714455]
 19. Prentice RL. A Case-Cohort design for epidemiologic studies and disease prevention trials. *Biometrika.* 1986; 73:1–11.
 20. Verheus M, Peeters PH, Rinaldi S, Dossus L, Biessy C, Olsen A, et al. Serum C-peptide levels and breast cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer.* 2006; 119(3):659–67. [PubMed: 16572422]
 21. Keinan-Boker L, Bueno De Mesquita HB, Kaaks R, Van Gils CH, Van Noord PA, Rinaldi S, et al. Circulating levels of insulin-like growth factor I, its binding proteins -1, -2, -3, C-peptide and risk of postmenopausal breast cancer. *Int J Cancer.* 2003; 106(1):90–5. [PubMed: 12794762]
 22. Toniolo P, Bruning PF, Akhmedkhanov A, Bonfrer JM, Koenig KL, Lukanova A, et al. Serum insulin-like growth factor-I and breast cancer. *Int J Cancer.* 2000; 88(5):828–32. [PubMed: 11072255]

Table 1

Selected baseline characteristics of the study population

Variable[§]	Cases (N=497)	Subcohort (N=2,830)	P-value[¶]
<i>Age (years)</i>	65 (59 to 70)	63 (57 to 69)	<.0001
<i>Women's Health Initiative, N(%)</i>			
Observational Study Cohort	401 (80.7)	756 (26.7)	N/A
Clinical Trial Cohort	96 (19.3)	2074 (73.3)	
<i>Ethnicity, N (%)</i>			
White	394 (79.3)	1591 (56.4)	<.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)	
<i>Body mass index (BMI; Kg/M²), N(%)</i>			
Normal (BMI<25.0)	155 (31.2)	762 (26.9)	0.17
Overweight (25.0-<30.0)	165 (33.2)	998 (35.3)	
Obese (≥ 30.0)	177 (35.6)	1070 (37.8)	
<i>Age at Menarche, N (%)</i>			
10	41 (8.2)	193 (6.8)	0.44
11-12	203 (40.8)	1101 (38.9)	
13+	250 (50.3)	1523 (53.8)	
Missing	3 (0.7)	13 (0.5)	
<i>Age at Menopause, N(%)</i>			
42	72 (14.5)	541 (19.1)	0.001
43-48	106 (21.3)	629 (22.2)	
49-51	133 (26.8)	616 (21.8)	
52	142 (28.6)	675 (23.9)	
Missing	44 (8.8)	369 (13.0)	
<i>Parity, N(%)</i>			
0	79 (15.9)	334 (11.8)	0.04
1	39 (7.8)	254 (9.0)	
2	375 (75.5)	2223 (78.6)	
Missing	4 (0.8)	19 (0.6)	
<i>Family history of breast cancer, (N%),</i>			
Yes	138 (27.8)	440 (15.5)	<.0001
No	185 (37.2)	2164 (76.5)	
Missing	174 (35.0)	226 (8.0)	
<i>Smoking status, N (%)</i>			
Never	254 (51.1)	1519 (53.7)	0.001
Former	213 (42.9)	1021 (36.1)	
Current	22 (4.4)	250 (8.8)	
Missing	8 (1.6)	40 (1.4)	

Variable [§]	Cases (N=497)	Subcohort (N=2,830)	P-value [¶]
<i>Education history, N (%)</i>			<.0001
High school and less	144 (29.0)	1125 (39.8)	
College	203 (40.8)	982 (34.7)	
Postgraduate education	143 (28.8)	701 (24.8)	
Missing	7 (1.4)	22 (0.7)	
<i>Alcohol (servings per week)</i>	0.4 (0.0 to 3.5)	0.2 (0.0 to 1.4)	<.0001
<i>Physical activity (METs[‡])</i>	8.29 (2.00 to 17.50)	5.75 (0.50 to 15.00)	<.0001

P-values derived from Wilcoxon rank sum test for continuous data and Pearson's chi-square for categorical data.

[‡]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.

[§]Values are medians (inter-quartile range) unless otherwise stated.

Table 2

The Associations of Incident Postmenopausal Breast Cancer Risk with Metabolic Health Defined by HOMA-IR or Insulin Levels, Stratified by Body Mass Index (BMI) Category

<i>HOMA-IR based definition of Metabolic Health</i>						
BMI Category	N (Cases/Controls)	Age-adjusted HR (95% CI)	P-Value	Multivariate HR [†] (95% CI)	P-Value	P-Value
<i>Normal Weight (<25Kg/M²)</i>						
Metabolically Healthy ¹	113/356	1.00 (Referent)		1.00 (Referent)		
Metabolically Unhealthy ²	18/182	1.68 (0.85-3.33)	0.13	1.80 (0.88-3.70)		0.11
<i>Overweight (25 Kg/M²)</i>						
Metabolically Healthy ¹	87/339	0.93 (0.64-1.34)	0.68	0.96 (0.64-1.42)		0.83
Metabolically Unhealthy ²	169/1238	1.60 (1.12-2.28)	0.01	1.76 (1.19-2.60)		0.005
<i>Insulin based definition of Metabolic Health</i>						
BMI Category	N (Cases/Controls)	Age-adjusted HR (95% CI)	P-Value	Multivariate HR (95% CI)	P-Value	P-Value
<i>Normal Weight (<25Kg/M²)</i>						
Metabolically Healthy ³	108/352	1.00 (Referent)		1.00 (Referent)		
Metabolically Unhealthy ⁴	19/180	1.86 (0.95-3.65)	0.07	2.06 (1.01-4.22)		0.048
<i>Overweight (25 Kg/M²)</i>						
Metabolically Healthy ³	86/329	0.93 (0.64-1.35)	0.71	0.96 (0.64-1.42)		0.82
Metabolically Unhealthy ⁴	175/1250	1.86 (1.30-2.66)	0.001	2.01 (1.35-2.99)		0.001

¹ HOMA-IR (quartile 1);

² HOMA-IR (quartiles 3+4);

³ Insulin (quartile 1);

⁴ 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.