

Research Article

Risk of Breast Cancer Recurrence Associated with Carbohydrate Intake and Tissue Expression of IGFI ReceptorJennifer A. Emond¹, John P. Pierce¹, Loki Natarajan¹, Laarni R. Gapuz¹, John Nguyen¹, Barbara A. Parker¹, Nissi M. Varki², and Ruth E. Patterson¹**Abstract**

Background: The insulin-like growth factor-I (IGFI) receptor is a potential target for breast cancer treatment and may be influenced by dietary intake.

Methods: Nested, case-control study of 265 postmenopausal breast cancer survivors; primary breast cancer tissue was stained to determine IGFI receptor status. Change in carbohydrate intake from baseline to year 1 of study was estimated from 24-hour dietary recalls. Breast cancer recurrence cases (91) were matched to two controls ($n = 174$) on disease and study characteristics and counter matched on change in carbohydrate intake. Weighted conditional logistic regression models fit the risk of recurrence on IGFI receptor status and dietary change.

Results: Half of the tumors were IGFI receptor positive. Increased risk of recurrence was associated with IGFI receptor-positive status [HR 1.7; 95% confidence interval (CI), 1.2–2.5] and, separately, with a stable/increased intake of carbohydrates (HR 2.0; 95% CI, 1.3–5.0). There was a borderline significant interaction between those two variables ($P = 0.11$). Specifically, carbohydrate intake had no significant impact on risk of recurrence among women who were receptor negative, yet increased the risk of recurrence by more than 5-fold among women who were receptor positive (HR 5.5; 95% CI, 1.8–16.3).

Conclusions: Among women whose tumor tissue is positive for the IGFI receptor, reducing carbohydrate intake after diagnosis could reduce the risk of breast cancer recurrence. These findings need replication in a larger sample.

Impact: This is the first study to suggest that it may be possible to personalize dietary recommendations for breast cancer survivors based on molecular characteristics of their primary tumor tissue. *Cancer Epidemiol Biomarkers Prev*; 23(7); 1273–9. ©2014 AACR.

Introduction

The number of breast cancer survivors is predicted to increase to 3.4 million by 2015 (1). Despite suggestive evidence from observational studies, randomized controlled trials have provided no convincing evidence that changing dietary patterns following a diagnosis of breast cancer can impact prognosis (2, 3). However, the effects of dietary intake on breast cancer recurrence may be limited to subpopulations defined by prognostic profile, molecular subtype, or exposures to treatment.

On the basis of new evidence and hypotheses about the association of obesity and diabetes with cancer risk (4, 5), the insulin/insulin-like growth factor-I (IGFI) system has

been proposed as a potentially valuable target for breast cancer treatment. In particular, activation of the IGFI receptor gives strong proliferation and survival signals that implicates this receptor system in growth and survival of cancer cells (6). The IGFI receptor is commonly (though not always) overexpressed in breast cancer and its expression has been associated with poor prognosis (7–10), possibly due to treatment resistance and treatment evasion. Steroid hormones and growth factors regulate the expression of the IGFI receptor. There is also evidence that nutrition (such as high-energy diets) affects receptor levels directly or indirectly (e.g., via changes in circulating IGFI concentrations; refs. 11, 12).

Our objective was to investigate the association of IGFI receptor status, dietary intake, and breast cancer risk. Specifically, we hypothesized that there would be an interaction between expression of the IGFI receptor in the primary breast cancer tumor tissue, postdiagnosis changes in carbohydrate intake, and breast cancer recurrence. The hypothesis was tested in a nested case-control analysis of postmenopausal breast cancer survivors who participated in the Women's Healthy Eating and Living (WHEL) Study. The trial results for the WHEL study were null (2); however, the dietary intervention resulted in

Authors' Affiliations: ¹Cancer Prevention and Control Program, Moores UCSD Cancer Center, Department of Family and Preventive Medicine; and ²Department of Pathology, University of California, San Diego, La Jolla, California

Corresponding Author: Ruth E. Patterson, Program Leader, Cancer Prevention and Control Program, Moores Cancer Center, University of California, San Diego, 3855 Health Sciences Drive #0901, La Jolla, CA 92093. Phone: 858-534-2563; Fax: 858-822-2399; E-mail: repatterson@ucsd.edu

doi: 10.1158/1055-9965.EPI-13-1218

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considerable changes in macronutrient intake (13). We are not aware of any studies that have investigated whether an interaction of diet with molecular characteristics of the tumor tissue can alter the risk of breast cancer recurrence.

Materials and Methods

Study participants and study design

The WHEL study was a multisite, dietary intervention trial that enrolled 3,088 breast cancer survivors. Eligibility criteria included diagnosis of a primary operable invasive breast carcinoma categorized using American Joint Committee on Cancer (edition IV) criteria as stage I–IIIA, no current or planned chemotherapy, no evidence of recurrent disease or new breast cancer, and no other cancer in the past 10 years. In addition, all participants were non-diabetic (unless treated with only diet and physical activity). Participants provided written, informed consent for all aspects of the WHEL study, including tissue acquisition. Women were enrolled from 6 months to 4 years after their primary diagnosis [mean (SD) of 1.9 (1.0) years]. At baseline, half of the participants were assigned to a dietary pattern high in fruits, vegetables, fiber, and low in total fat; half were given a printed copy of the United States Department of Agriculture (USDA) dietary guidelines. The intervention did not target weight loss or total carbohydrate intake. As reported in 2007, the intervention had no effect on breast cancer recurrence or mortality (2).

For this nested case–control analysis, cases were confirmed breast cancer recurrence over a median of 7.3 years of follow-up in the WHEL study. Recurrence included local, regional, or distant invasive metastasis or new primary breast cancer. Cases and controls were selected from 2,111 postmenopausal WHEL Study participants who had complete dietary intake data at baseline and year 1 and remained recurrence free for at least 18 months after randomization. Participants were limited to postmenopausal women to reduce potential confounding by monthly fluctuations in estrogen and other sex hormone concentrations that are known (or postulated) to impact the insulin/IGF axis and stimulate IGF1 receptor expression (11). There were 247 women who experienced a recurrence, and 91 of these had archived primary cancer tissue. Two controls for each case with tissue were selected from eligible participants who remained recurrence free 1 year after the index case's date of recurrence. Controls were matched to cases based on stage of primary cancer (exact match based on American Joint Committee on Cancer staging, version IV), age at diagnosis (within 5 years), and time from diagnosis to enrollment (within 1 year). In addition to the matching criteria, controls were also counter-matched on change in carbohydrate intake over the first year of the WHEL study as described below. Controls were allowed to be resampled, and less than 5% of controls were matched on the basis of relaxed criteria for age at diagnosis (within 10 years) or time from diagnosis to enrollment (within 2 years).

Counter-matched design

The hypothesis of this study was that the protective effect of a decrease in carbohydrate intake would be most pronounced among participants with IGF1 receptor expression in the primary cancer, an analysis that required the inclusion of an interaction term between each main effect. However, nested case–control studies are typically too small with respect to sample size to be appropriately powered to detect a significant interaction term. Therefore, to increase the power of this nested case–control study to detect an interaction term, we used a counter-matching design in addition to the matched design (14–16). Specifically, for each case, two controls were selected from participants matched on stage of primary cancer, age at diagnosis, and time from diagnosis to enrollment as described above; and counter-matched on change in carbohydrate intake over the first year of the WHEL study. For cases who had a decreased carbohydrate intake, two controls were selected from participants who had a stable or increased carbohydrate intake, and vice versa. Counter matching increases the variation in a known predictor variable, increasing the power to detect an interaction between two main effects.

Dietary intake

Dietary intake was assessed using the mean of three or four dietary recalls collected at baseline and again at year 1. Data were collected and analyzed using Nutrition Data System for Research software version 4.03 developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN. Details about the dietary assessment procedures are published (2).

For each participant, change in mean carbohydrate intake (g/day) over the first year of the WHEL study was computed as year 1 minus baseline intake. Using data from the full WHEL cohort of eligible postmenopausal women, change in carbohydrate intake was categorized into tertiles: < –26.8, –26.8 to 22.2, and >22.2 g/day. Preliminary analyses indicated that a change in carbohydrate intake, adjusted for both baseline and year 1 change in total energy intake influenced the risk of recurrence with the main effect confined to the group that decreased their intake. Specifically, a decreased intake over 1 year appeared protective. Therefore, to increase study power, postdiagnosis change in carbohydrate intake was dichotomized into decreased intake (tertile 1) versus stable (tertile 2) or increased intake (tertile 3).

Tissue samples and immunohistochemical analysis

The WHEL Coordinating Center at the University of California, San Diego Moores Cancer Center (San Diego, CA) collected paraffin blocks of tissue samples of the primary breast cancer (17). The Cancer Center's Histology Shared Resource prepared ten unstained slides from each block. The study pathologist reviewed each slide to confirm that tissue samples were consistent with pathology reports. Sections on the slides were coated in

paraffin wax for long-term preservation and stored at room temperature.

To quantify differences in IGFI receptor within the breast carcinoma samples, the immunohistochemical (IHC) assays were first optimized on sections of breast carcinoma controls from the Moores Cancer Center Histology Shared Resource. The primary antibody, IGFI receptor antibody, was a mouse monoclonal, clone 24-31, purified without bovine serum albumin and Azide and supplied at 20 $\mu\text{g}/\text{mL}$ (Thermo Scientific #MS-641-PABX). Antibody epitope was the amino acid sequence 283-440 on the α -subunit of the IGFI receptor. Mouse immunoglobulin G (IgG; Dako #N1698) was used as a negative control against the primary antibody; mouse anti-vimentin (Dako #N1521) was used as a positive control. In-house tissue samples of breast cancer were used as positive controls for breast cancer tissue. The IHC assay steps included deparaffinization as well as blocking of endogenous peroxidases and nonspecific endogenous collagen-binding sites. Antigen retrieval was performed with proteinase K treatment and the primary antibody (diluted 1:100) was overlaid overnight in a humid chamber at 40°C, followed by buffer washes and treatment with the secondary antibody (Dako EnVision+ System, HRP Dako K4001) buffer washes. The same procedure was repeated before substrate color development (AEC substrate kit for peroxidase, Vector Labs SK4200) was applied for 40 minutes at room temperature. Samples were mounted in aqueous mounting medium (Vectamount H-5501) for viewing and digital photomicrographs were taken using an Olympus BH2 microscope equipped with MagnaFire software.

Slides were scored by a pathologist who was blind to case and control status. A subset of slides ($n = 30$) was scored twice by the pathologist to assess intra-rater agreement, which was high (Pearson $\rho = 0.91$). Slides were scored on the basis of total membrane staining and intensity: 0 (no staining for membrane staining in <10% of cancer cells); 1+ (faint membrane staining in $\geq 10\%$ of cancer cells); 2+ (weak to moderate complete membrane staining $\geq 10\%$ of cancer cells); 3+ (strong complete membrane staining in >30% of cancer cells). Cancers with no evidence of staining were considered negative and cancers with positive staining (1, 2, 3) were considered positive. Eight samples from controls were unreadable due to poor tissue integrity, resulting in a final sample size of 265 participants.

Statistical analyses

Primary tumor characteristics, treatment history and baseline demographics were compared by case status and by IGFI receptor status (i.e., negative versus positive). Bivariate analyses were completed with unweighted χ^2 or t tests. Weighted conditional logistic regression modeling was used to determine the main effects of receptor status and dietary intake on breast cancer recurrence. Weighting in the conditional logistic regression models accounted for the counter-matching design (16). Regres-

sion models were adjusted for *a priori* covariates related to change in dietary carbohydrate intake (i.e., baseline carbohydrate intake; baseline and change in fiber and energy intake) and for covariates that were not balanced by IGFI receptor status ($P < 0.10$). To test the interaction, the logistic model was fitted to case status (i.e., breast cancer recurrence) on the cross product of a decreased carbohydrate intake and receptor status. The dietary intervention was not statistically significant in any models and inclusion of an intervention indicator variable did not appreciably change the results. Therefore, intervention status was not included in the models.

As described above, two controls were selected for each case, with each control counter matched to a case on change in carbohydrate intake category. To incorporate conditional weights for the counter-matched design, one control from each pair was randomly selected from the set of 2 counter-matched controls, resulting in a sample of 182 case-control pairs. An adjusted conditional logistic regression model was run on that sample and point estimates were saved for analysis. The process of randomly selecting 1 control and fitting a conditional logistic model was repeated 5,000 times; results were used to empirically estimate the distribution of point estimates. The final HRs were computed by exponentiation of the mean of the model coefficients over the 5,000 runs, and 95% confidence intervals (CI) were computed by exponentiation of the 2.5th and 97.5th percentiles of the model coefficients over the 5,000 runs. The median P value (along with the interquartile range) is presented for the results from likelihood ratio tests used to assess the significance of the overall interaction between change in carbohydrate intake and IGFI receptor status. Specifically, for each conditional logistic regression model, a likelihood ratio test compared two nested models, 1 with the main effects of a change in carbohydrate intake and receptor status and 1 with main effects along with an interaction term. All analyses were computed using the R Language and Environment for Statistical Computing, version 2.15.2 (18).

Results

Table 1 presents participants characteristics overall, by case status and IGFI receptor status. Mean age at diagnosis was 57 years and most participants (84%) were non-Hispanic White. Mean (SD) body mass index (BMI) was 28.7 (6.2) kg/m^2 and baseline carbohydrate intake was 243 (60.4) g/day . Median time from diagnosis to enrollment was 1.8 years. Primary cancers were mostly early stage and positive for the estrogen or progesterone receptors. The majority of participants had received chemotherapy, radiation therapy, and used tamoxifen.

There were 91 cases matched (1:2) from a pool of 174 controls as detailed above. Cases and controls were well balanced on demographic, lifestyle, and clinical characteristics with one exception: cases were significantly more

Table 1. Characteristics of postmenopausal breast cancer survivors in a nested case-control analysis of IGFI receptor status, carbohydrate intake, and breast cancer recurrence

Characteristic	Overall N = 265	Case status		IGFI receptor status of breast tumor tissue	
		Control N = 174 (65.7%)	Case N = 91 (34.3%)	Negative N = 132 (49.8%)	Positive N = 133 (50.2%)
Age at diagnosis, y (mean, SD) ^b					
Non-Hispanic White	221 (83.4%)	144 (82.8%)	77 (84.6%)	116 (87.9%)	105 (79.0%)
College graduates	115 (43.4%)	76 (43.7%)	39 (42.9%)	62 (47.0%)	53 (39.9%)
BMI, kg/m ² (mean, SD)	28.7 (6.2)	28.7 (6.2)	28.6 (6.2)	28.4 (6.5)	29.0 (5.9)
Physical activity, METs (mean, SD)	12.3 (12.2)	12.2 (11.9)	12.4 (12.9)	13.0 (13.0)	11.6 (11.4)
Carbohydrate intake, g (mean, SD)					
Baseline	243 (60.4)	^a	^a	246 (58.6)	240 (62.2)
Change (year 1 – baseline)	–32 (59.0)	^a	^a	–31.4 (59.2)	–31.7 (58.9)
Years from diagnosis to study enrollment (mean, SD) ^b	1.9 (1.0)	2.0 (1.0)	1.9 (1.0)	1.9 (0.9)	2.0 (1.0)
Stage of primary cancer ^b					
I	66 (24.9%)	43 (24.7%)	23 (25.3%)	28 (21.2%)	38 (28.6%)
II	175 (66.0%)	115 (66.1%)	60 (65.9%)	90 (68.2%)	85 (63.9%)
IIIA	24 (9.1%)	16 (9.2%)	8 (8.8%)	14 (10.6%)	10 (7.5%)
Number of positive nodes					
0	122 (46.0%)	86 (49.4%)	36 (39.6%)	55 (41.7%)	67 (50.4%)
1–3	76 (28.7%)	53 (30.5%)	23 (25.3%)	40 (30.3%)	36 (27.1%)
>3	67 (25.3%)	35 (20.1%)	32 (35.2%)	37 (28.0%)	30 (22.6%)
Estrogen receptor positive	190 (72.8%)	121 (70.8%)	69 (76.7%)	67 (51.2%)	88 (69.3%)
Progesterone receptor positive	155 (60.1%)	97 (57.7%)	58 (64.4%)	103 (78.0%)	82 (62.1%)
Chemotherapy	185 (70.1%)	121 (70.8%)	69 (76.7%)	103 (78.0%)	82 (62.1%)
Radiation therapy	168 (63.4%)	97 (57.7%)	58 (64.4%)	88 (66.7%)	80 (60.2%)
Ever tamoxifen use	199 (75.1%)	121 (70.8%)	69 (76.7%)	93 (70.5%)	106 (79.7%)

NOTE: $P < 0.05$ for differences in number of positive nodes by case-control status and for differences in progesterone receptor status and chemotherapy by IGFI receptor status.

Abbreviation: METs, metabolic equivalent hours per week.

^aAs detailed in the Materials and Methods, cases were counter matched on decreased versus stable/increased carbohydrate intake to increase power to detect an interaction. Therefore, baseline intake for cases [254 (56.4)] versus controls [222 (62.3)] and change in intake among cases [–46.1 (54.3)] versus controls [–3.7 (57.8)] are a function of the study design.

^bMatching factor.

likely to have had node positive cancers than controls ($P = 0.025$; Table 1).

Half of the primary cancers showed IGFI receptor expression (Table 1). The majority of tissues that showed IGFI receptor expression were given a score of 1 ($N = 87$, 65.4%) compared with a score of 2 ($N = 40$, 30.1%) or 3 ($N = 6$, 4.5%; data not shown). Participant characteristics were generally balanced by IGFI receptor status. However, non-Hispanic White women were less likely to have a primary cancer that was receptor positive ($P = 0.074$). Specifically, 105 of 221 (47.5%) White women, 11 of 19 (57.9%) Latina women, and 11 of 12 (91.7%) African American women had IGFI receptor-positive breast cancers. Cancers that were receptor positive were also significantly more likely to be positive for the progesterone receptor ($P = 0.004$) and to have been treated with adjuvant chemotherapy ($P = 0.007$).

In separate conditional logistic regression models, both expression of the IGFI receptor postdiagnosis and change in carbohydrate intake were significantly associated with breast cancer recurrence (Table 2). A primary cancer positive for IGFI receptor was associated with an increased likelihood of recurrence [HR 1.7; 95% CI, 1.2–2.5] in a model adjusted for race/ethnicity, number of positive nodes, progesterone receptor status of primary cancer, and chemotherapy treatment. Stable/increased change in carbohydrate intake increased the risk of recurrence (HR 2.0; 95% CI, 1.3–5.0) in a model adjusted for baseline carbohydrate, energy, and fiber intake as well as change in energy and fiber intake.

Results from the likelihood ratio test suggested an interaction of change in carbohydrate intake and IGFI receptor status with breast cancer recurrence ($P =$

Table 2. Breast cancer recurrence by IGFI receptor status and carbohydrate intake among postmenopausal breast cancer survivors in a nested case–control analysis

IGFI receptor status of breast tumor tissue	Postdiagnosis change in carbohydrate intake ^a			HR (95% CI) breast cancer recurrence
		Cases	Controls	
Main effect models				
Negative		40	92	1.0
Positive		51	82	1.7 (1.2–2.5) ^b
	Decreased	25	129	1.0
	Stable/increased	66	45	2.0 (1.3–5.0) ^c
Interaction model ^d				
Negative	Stable/increased	27	26	1.0 (Referent)
Negative	Decreased	13	66	0.7 (0.2–1.7)
Positive	Decreased	12	63	0.6 (0.2–1.3)
Positive	Stable/increased	39	19	5.5 (1.8–16.3) ^e

^aDecreased intake reflects lowest tertile of postdiagnosis change in carbohydrate intake (<–26.7 g/day) and stable/increased intake reflects upper two tertiles of change.

^bAdjusted for race/ethnicity, number of positive nodes, progesterone receptor status of primary cancer, and chemotherapy treatment.

^cAdjusted for carbohydrate and energy intake at baseline as well as change in postdiagnosis energy and fiber intake.

^dLikelihood ratio test $P = 0.110$.

^eAdjusted for all covariates listed above.

0.110). Therefore, we fit recurrence status on the cross-product of change in carbohydrate intake and IGFI receptor status, adjusted for covariates. As shown in Table 2, among women who were receptor negative, dietary intake had no statistically significant impact on the risk of recurrence. However, compared with the reference group, the risk of recurrence was more than 5-fold (HR 5.5; 95% CI, 1.8–16.3) among women who were receptor positive and had stable/increased carbohydrate intake.

Discussion

These results suggest that the impact of postdiagnosis changes in dietary intake on breast cancer recurrence may vary depending on the molecular characteristics of the original tumor. We know of no studies with which to compare our findings.

Our finding that expression of the IGFI receptor was predictive of a poor prognosis is consistent with most published studies (8,19–22), although others concluded that expression of this receptor was a favorable prognostic indicator (23). Published data about associations of IGFI receptor expression with breast cancer clinical characteristics are conflicting (8, 19,21–24).

These data also indicated that African American and Latina postmenopausal breast cancer survivors were more likely to have a primary cancer that was positive for the IGFI receptor, although the sample sizes were small. However, a recently published study of tumor tissue ($n = 47$) found no difference in IGFI receptor protein expression between non-Hispanic White and African American women (25). Larger studies of

IGFI receptor status by race/ethnicity are needed to determine whether differences in this receptor could explain the poor breast cancer prognosis seen among African American and Latina breast cancer survivors (26).

Our data indicated that compared with decreased carbohydrate intake, stable/increased intake approximately 2 years postdiagnosis was associated with increased risk of recurrence. Decreasing carbohydrate intake after diagnosis may have a protective effect by limiting the availability of glucose as an energy source for malignant cells (27), reducing circulating insulin, a mitogen of breast cancer growth (28), or by reducing levels of systemic inflammation (29). We are not aware of any studies reporting on postdiagnosis change in carbohydrate intake and breast cancer outcomes. However, in a study of 539 nondiabetic breast cancer survivors, Goodwin and colleagues found that baseline insulin-related variables and adverse prognostic associations were significant only during the first 5 years postdiagnosis (e.g., insulin quartile 4 vs. 1: HR 2.3; 95% CI, 1.4–3.9 for distant disease-free survival; ref. 30). The authors concluded that insulin-related factors may influence prognosis to the greatest extent during the first 5 years after diagnosis, whereas obesity-related factors (e.g., leptin) continue to be important with longer follow-up.

A strength of this study is the use of immunohistochemistry to determine IGFI receptor status in the breast tumors. However, IGFI and insulin are ligands for the insulin/IGFI receptor hybrid receptors, which also trigger breast cancer proliferation (7, 28, 31). Given that our

antibody was not specific for the insulin or IGFI receptor hybrid receptors, it is possible that decreased carbohydrate intake influenced breast cancer progression by limiting activation of receptors other than the IGFI receptor. An additional strength of this study was the use of counter matching, which provided increased power for detecting an interaction in this nested case-control study (16). Other strengths include the use of multiple 24-hour dietary recalls, as several studies have reported that food record and recalls can provide more precise estimates of macronutrient intake compared with food frequency questionnaires (32–34). The major limitation of this study is the modest sample size. We are not able to address the impact of potential effect modifiers such as antiestrogen treatments or estrogen receptor status of the primary cancer without losing a considerable proportion of matched case/control pairs for analysis. In addition, to maximize study power, we only investigated decreased intake of carbohydrates in comparison with a stable or increased intake of carbohydrates combined.

To our knowledge, this is the first study to demonstrate that a personalized dietary prescription based on molecular characteristics of the primary tumor tissue could improve breast cancer prognosis. These results also contribute to the growing evidence linking the insulin/IGF axis to breast cancer prognosis. In future, more highly powered studies should compare the association of IGFI receptor expression and changes in dietary intake with prognosis in view of the impacts of race/ethnicity of the survivors, clinical characteristics such as the estrogen receptor status of the primary cancer, and the impacts of treatment.

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Disclosure of Potential Conflicts of Interest

N.M. Varki has ownership interest (including patents) and is a consultant/advisory board member of Sialix Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.A. Emond, L. Natarajan, R.E. Patterson
Development of methodology: J.A. Emond, L. Natarajan, L.R. Gapuz, N.M. Varki, R.E. Patterson

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.P. Pierce, B.A. Parker, N.M. Varki, R.E. Patterson

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.A. Emond, L. Natarajan, J. Nguyen, B.A. Parker, R.E. Patterson

Writing, review, and or revision of the manuscript: J.A. Emond, J.P. Pierce, L. Natarajan, B.A. Parker, N.M. Varki, R.E. Patterson

Acknowledgments

The authors thank Susan Wancewicz, Cancer Prevention Program, UCSD, for her assistance in identifying the archived tissue samples used in this study.

Grant Support

J.P. Pierce, B.A. Parker, L. Natarajan, and J.A. Emond were funded by a donation from the Walton Family Foundation, from National Cancer Institute (CA-69375), and the General Clinical Research Centers, NIH (M01-RR00070, M01-RR00079, and M01-RR00827). J.A. Emond was supported by an Institutional training grant from the National Institute of General Medical Sciences (5 T32-GM084896) and the National Cancer Institute Centers for Transdisciplinary Research on Energetics and Cancer (1U54CA155435-01). L. Natarajan was also partially funded by National Cancer Institute (1R01CA166293-01A1). Finally, J.A. Emond and J.P. Pierce received funding from Ms. Carol Vassiliadis and her family in the form of philanthropic support for these analyses.

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Received December 12, 2013; revised March 10, 2014; accepted April 6, 2014; published OnlineFirst April 22, 2014.

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Cancer Epidemiol Biomarkers Prev 2014;23:1273-1279. Published OnlineFirst April 22, 2014.

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