

# *The Ecology of Breast Cancer*

## *The Promise of Prevention and the Hope for Healing*

*By Ted Schettler MD, MPH*



October 2013

This work is licensed under a Creative Commons Attribution Non-Commercial NoDerivs 3.0 Unported License.



## Appendix A: Breast cancer, body weight, insulin resistance, and diabetes

Diet, physical activity levels, and body weight are major determinants of blood glucose levels, baseline insulin levels, insulin sensitivity, and general metabolic profiles.<sup>1,2,3,4,5,6</sup> Other factors that contribute to insulin resistance include stress and sleep deprivation. Newly emerging data also find an association between insulin resistance and exposure to certain environmental chemicals.<sup>7,8</sup>

Obesity is associated with increased risk of post-menopausal breast cancer as well as cancers of the colon, uterus, esophagus, gallbladder, pancreas, kidney, and thyroid.<sup>9</sup> Obesity is also a risk factor for diabetes among other disorders. Epidemiologic studies have found an increased risk of several kinds of cancer in association with diabetes, including liver, pancreatic, colorectal, gynecologic, and breast.

Type 2 diabetes is characterized by elevated blood glucose caused by insulin resistance and ultimate defects in insulin secretion. Early in the development of the disorder as insulin resistance develops, increased secretion of insulin helps to keep blood glucose levels relatively normal.<sup>10,11</sup> Ultimately  $\beta$ -cell function in the pancreas declines, insulin levels fall, and blood glucose begins to rise.

Insulin increases the biologic activity of insulin-like growth factor I (IGF-I) by stimulating IGF-1 production and decreasing some IGF binding proteins. Both insulin and IGF-1 can promote tumor development and/or progression by stimulating cell proliferation and inhibiting apoptosis (programmed cell death).<sup>12</sup> Insulin and IGF-1 also decrease levels of sex hormone binding globulin (SHBG), thereby increasing bioavailable levels of testosterone and estrogen. Insulin also stimulates sex hormone production in the ovary, primarily androgens.<sup>13</sup> Solid tumors are able to utilize glucose for energy production, even in the presence of relatively low oxygen levels.<sup>14</sup> For these reasons, there is considerable interest and concern about the role of elevated blood glucose, insulin, and IGF-1 levels in breast cancer development, progression, and outcomes, whether or not clinical diabetes is present and recognized. A number of large prospective studies report increased risk of breast cancer with elevated levels of fasting blood glucose, although associations with insulin and IGF levels are mixed.

### *Studies of glucose metabolism and breast cancer occurrence*

In the Italian (ORDET) cohort of 10,673 participants, after an average follow up of 13.5 years, women with the highest glucose levels at baseline had a significantly greater risk of breast cancer than those in the lowest. (RR 1.63)<sup>15</sup> This association remained significant when data from pre- and post-menopausal cases were analyzed separately. Highest insulin resistance was also significantly associated with higher risk. In women over 55 years old at

diagnosis, the relative risk was more than 2-fold higher in those with the highest quartile of glucose levels compared to the lowest.

In a population based study of 33,293 women and 31,304 men in Sweden, total cancer risk in women increased by 26 percent with higher fasting blood sugar compared to lowest. Pre-menopausal breast cancer risk was increased 2-fold with higher fasting blood sugar.<sup>16</sup>

In a population cohort study of 140,000 Austrian adults, after an average 8.4 yrs follow up highest fasting blood sugar was associated with an increased likelihood of all cancers combined (HR 1.20 in men; 1.28 in women). In post-menopausal women over 65, higher fasting blood sugar was associated with increased breast cancer risk (HR 1.38).<sup>17</sup>

A pooled cohort study of 290,000 women from Austria, Norway, Sweden identified increased risk of breast cancer incidence and mortality with increased glucose (RR=1.57) and BMI in women over 60 after 11 years of follow up. In women less than 50, breast cancer risk decreased with higher BMI but increased with higher levels of blood glucose.<sup>18</sup>

A nested case control study of 10,786 women who were 35-69 years old found significantly increased risk of breast cancer in premenopausal and heavier post-menopausal women with higher levels of fasting blood glucose after 5.5 years of follow up. With longer follow up, (see the ORDET study above; the same cohort) breast cancer risk was increased for all post-menopausal women with higher blood glucose. The findings were independent of insulin and IGF-1 levels<sup>19</sup>

In a study of 7,894 women aged 45-64 years from four U.S. communities, authors examined the association of breast cancer incidence with serum levels of insulin and glucose over an average follow-up period of 7.1 years. 187 breast cancer cases were identified. Breast cancer risk increased with higher BMI but not with serum insulin level. After adjustment for age, race, and study site, the incidence of breast cancer was 60 percent higher among diabetic women than among women with normal fasting glucose levels, but this increase was no longer statistically significant after adjustment for body mass index.<sup>20</sup>

A study of 5,450 participants enrolled in the Women's Health Initiative examined the relationship between glucose, insulin, and insulin resistance measures at baseline and the risk of breast cancer with an average 8-year follow-up period. All participants were post-menopausal (age 50-79 at entry); it included black, Hispanic, Asian-Pacific, and white women; during the follow up period 153 cases of invasive and 37 cases of carcinoma in situ were diagnosed. Mean serum glucose and insulin levels were measured at baseline and at years 1, 3, and for some at year 6 of follow up. Glucose levels were higher in women who developed

breast cancer than in those that did not, and this relationship was significantly greater in black women. Baseline insulin levels and insulin resistance were both significantly higher in women who developed breast cancer.<sup>21</sup>

One prospective study of 9738 women, however, with up to 24 years follow up, found no association of breast cancer with fasting blood sugar in pre- or post-menopausal women.<sup>22</sup>

### *Effect of diabetes on breast cancer outcome/prognosis*

A meta-analysis of 8 studies showed a 49 percent increased risk of all cause mortality in women with diabetes and breast cancer during the follow up period that ranged from 1-12 years. The authors noted that women with diabetes tend to be diagnosed at a more advanced stage of breast cancer than non-diabetics and the presence of diabetes appeared to modify treatment choices in varying ways.<sup>23</sup>

A more recent study of 3003 early stage breast cancer survivors, not included in this meta-analysis, also found that chronically elevated blood sugar was associated with a shorter disease-free period and two-fold increased risk of all cause mortality compared to participants with normal blood sugar levels.<sup>24</sup>

A study of 331 African American and 257 white women with stage I, II, or III breast cancer found that diabetes significantly shortened the period of disease-free survival following initial treatment, adjusted for age, stage, nodal involvement, ER/PR status, and co-morbidities.<sup>25</sup>

A prospective cohort study of 527 multiethnic women diagnosed with stage I-III breast cancer evaluated the association between adiponectin, insulin, glucose, and insulin resistance levels and breast cancer mortality and all-cause mortality, over an average six years of follow-up. Most participants did not have diabetes. Increasing insulin resistance was associated with reduced breast cancer survival and reduced all-cause survival when all participants were considered as a group. When the data were analyzed by subsets, this relationship remained significant for African-American women and for women with ER positive tumors, but not for Hispanic/non-Hispanic white women or women with ER negative tumors. Higher levels of adiponectin were associated with longer breast cancer survival.<sup>26</sup>

Together, these studies show a less favorable prognosis in women with breast cancer who also have diagnosed or undiagnosed diabetes or patients with different forms of glucose intolerance, as measured by insulin resistance or elevated fasting blood glucose levels. As noted in an editorial in the *Journal of Oncology*:

“The findings...highlight the influence of insulin resistance on breast cancer progression. In the era of treatment selectivity and molecular-targeted anti-cancer drugs, the accumulating evidence of common pathways linking breast cancer and impaired glucose intolerance or diabetes is increasingly pointing the way forward. The time has come to overcome the conventional tunnel vision that results in two diseases being treated by separate clinicians, and to move towards a comprehensive approach that ideally integrates oncologists, internists, nutritionists, and other health care professionals in an attempt to improve breast cancer prognosis in a significant proportion of patients.”<sup>27</sup>

A number of plausible biologic pathways link obesity, insulin resistance, and diabetes to increased breast cancer risk, particularly post-menopausal, and less favorable outcomes after diagnosis and treatment regardless of menopausal status. These biologic pathways are favorably influenced by adoption of healthy dietary patterns, weight control, and regular exercise, and their benefits are demonstrated in epidemiologic studies.<sup>28</sup> They should be routinely included in the daily lives of individuals and encouraged via public health policy decisions.

## References

1. Strasser B. Physical activity in obesity and metabolic syndrome. *Ann NY Acad Sci.* 2013; 1281:141-159.
2. Boule N, Haddad E, Kenney G, et al. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA.* 2001; 286:1218–1227.
3. Boule N, Weisnagel S, Lakka T, et al. Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. *Diabetes Care.* 2005; 28:108–114.
4. Andersen C, Fernandez M. Dietary strategies to reduce metabolic syndrome. *Rev Endocr Metab Disord.* 2013; Aug 13 [Epub ahead of print]
5. Weiss R, Bremer A, Lustig R. What is metabolic syndrome, and why are children getting it? *Ann NY Acad Sci.* 2013; 1281:123-140.
6. Frassetto L, Schloetter M, Mietus-Synder M, Morris R, Sebastian A. Metabolic and physiologic improvements from consuming a Paleolithic, hunter-gatherer type diet. *Eur J Clin Nutr.* 2009; 63(8):947-955.
7. Alonso-Magdalena P, Quesada I, Nadal A. Endocrine disruptors in the etiology of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2011; 7(6):346-353.
8. Lee D. Persistent organic pollutants and obesity-related metabolic dysfunction: focusing on type 2 diabetes. *Epidemiol Health.* 2012;34:e2012002. doi: 10.4178/epih/e2012002. Epub 2012 Jan 27.
9. Ligibel J, Strickler H. Obesity and its impact on breast cancer. *Am Soc Clin Oncol Educ Book.* 2013; 2013:52-59.
10. Cavaghan M, Ehrmann D, Polansky K. Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. *J Clin Invest.* 2000; 106(3):329-333.
11. Mahler R, Adler M. Clinical review 102: Type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment. *J Clin Endocrinol Metab.* 1999; 84(4):1165-1171.

12. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? *Cancer Causes Control*. 1996; 7(6):605-625.
13. Poretsky L, Cataldo N, Rosenwaks Z, Giudice L. The insulin-related ovarian regulatory system in health and disease. *Endocrin Rev* 1999 20(4):535-538.
14. Gatenby R. The potential role of transformation-induced metabolic changes in tumor-host interaction. *Cancer Res* 1995; 55:4151-4156.
15. Sieri S, Muti P, Claudia A, Berrino F, et al. Prospective study on the role of glucose metabolism in breast cancer occurrence. *Int J Cancer* 2011; doi: 10.1002/ijc.26071. [Epub ahead of print]
16. Stattin P, Bjor, O, Ferrari, P, Lukanova, A, Lenner, P, Lindahl, B, Hallmans, G, Kaaks, R. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007; 30: 561-567.
17. Rapp, K, Schroeder, J, Klenk, J, Ulmer, H, Concin, H, Diem, G, Oberaigner, W, Weiland, S. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia* 2006; 49: 945-952.
18. Bjorge, T, Lukanova, A, Jonsson, H, Tretli, S, Ulmer, H, Manjer, J, Stocks, T, Selmer, R, Nagel, G, Almquist, M, Concin, H, Hallmans, G et al. Metabolic syndrome and breast cancer in the mecan (metabolic syndrome and cancer) project. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1737-1745.
19. Muti, P, Quattrin, T, Grant, BJ, Krogh, V, Micheli, A, Schunemann, HJ, Ram, M, Freudenheim, JL, Sieri, S, Trevisan, M, Berrino, F. Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 1361-1368.
20. Mink P, Shahar E, Rosamond W, Alberg A, Folsom A. Serum insulin and glucose levels and breast cancer incidence: the atherosclerosis risk in communities study. *Am J Epidemiol* 2002; 156: 349-352.
21. Kabat, GC, Kim, M, Caan, BJ, Chlebowski, RT, Gunter, MJ, Ho, GY, Rodriguez, BL, Shikany, JM, Strickler, HD, Vitolins, MZ, Rohan, TE. Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. *Int J Cancer* 2009; 125: 2704-2710.
22. Manjer, J, Kaaks, R, Riboli, E, Berglund, G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo Preventive Project. *Eur J Cancer Prev* 2001; 10: 33-42.
23. Peairs K, Barone B, Snyder C, Yeh H, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol* 2011; 29(1):40-46.
24. Erickson K, Patterson R, Flatt S, Natarajan L, et al. Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. *J Clin Oncol* 2011; 29(1):54-60.
25. Du W, Simon M. Racial disparities in treatment and survival of women with stage I-III breast cancer at a large academic medical center in metropolitan Detroit. *Breast Cancer Res Treat* 2005; 91(3):243-248.
26. Duggan C, Irwin M, Xiao L, Henderson K, et al. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J Clin Oncol* 2011; 29(1):32-39.
27. DeCensi A, Gennari A. Insulin breast cancer connection: confirmatory data set the stage for better care. *J Clin Oncol* 2011; 29(1):7-10.
28. Ligibel J, Strickler H. Obesity and its impact on breast cancer. *Am Soc Clin Oncol Educ Book*. 2013; 2013:52-59.