

# Adjuvant Diet to Improve Hormonal and Metabolic Factors Affecting Breast Cancer Prognosis

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**ABSTRACT:** Western lifestyle, characterized by reduced physical activity and a diet rich in fat, refined carbohydrates, and animal protein is associated with high prevalence of overweight, metabolic syndrome, insulin resistance, and high plasma levels of several growth factors and sex hormones. Most of these factors are associated with breast cancer risk and, in breast cancer patients, with increased risk of recurrences. Recent trials have proven that such a metabolic and endocrine imbalance can be favorably modified through comprehensive dietary modification, shifting from Western to Mediterranean and macrobiotic diet.

**KEYWORDS:** breast cancer; hormonal and metabolic factors; diet

## METABOLIC, ENDOCRINE, AND DIETARY CORRELATES OF INCREASED BREAST CANCER

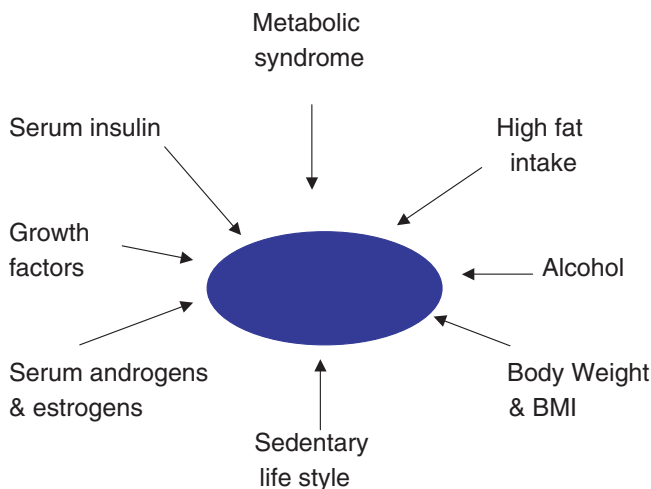
The metabolic, endocrine, and dietary correlates of increased breast cancer risk and of increased risk of recurrence in breast cancer patients are summarized in FIGURE 1.

Overweight and obesity are associated with an increased risk of breast cancer after menopause.<sup>1,2</sup> The association decreases markedly when adjusted for serum levels of endogenous estrogens,<sup>3</sup> suggesting that most of the effect of overweight is due to the aromatization of androgens into estrogens in the adipose tissue. Epidemiological studies of breast cancer and obesity showed either no association or slightly reduced breast cancer risk before menopause.<sup>2</sup> The reason for this paradoxical effect is not clear. As menstrual cycles in obese premenopausal women are frequently anovulatory, it has been hypothesized that the lack of endogenous progesterone production could be responsible for

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**FIGURE 1.** Hormonal, metabolic, and dietary correlates of breast cancer risk and recurrences.

the increased risk.<sup>4</sup> This hypothesis, however, has been shown to be false by the results of prospective studies showing that high endogenous progesterone levels are associated with significantly decreased breast cancer risk.<sup>5,6</sup> Anovulatory cycles are characterized by lower levels of both progesterone and estrogens, but studies measuring estrogens before menopause have not been able to find any clear association with the risk of breast cancer. Also, women who were overweight at the age of menarche experience a lower breast cancer risk in adulthood, independent of menstrual cycle characteristics.<sup>7</sup> Even if associated with early menarche, a moderate risk factor for breast cancer, early overweight might reflect well-functioning ovaries stimulating early breast epithelial cell differentiation. Preventing weight gain in adulthood, however, would decrease the overall burden of breast cancer,<sup>8</sup> as well as other “Western” diseases and premature mortality. Obese breast cancer patients appear to have a higher risk of lymph node metastasis and larger tumors, and many observational studies showed that, after adjustment for disease stage, overweight is associated with poorer prognosis.<sup>9,10</sup> Several studies, in particular, showed that weight gain in the course of adjuvant chemotherapy is a negative prognostic factor.<sup>11–13</sup>

Epidemiological studies consistently showed that a sedentary lifestyle is associated with increased risk of breast cancer, both before and after menopause.<sup>1</sup> Women who practice regularly at least some physical activity decrease their breast cancer risk by 30% or more.<sup>1</sup> There is evidence that physical activity may also protect against cancer recurrence. Daily physical activity corresponding to about half an hour of brisk walking may reduce breast cancer recurrences by 50%. More intense activity does not seem to add any benefit.<sup>14</sup>

Prospective studies with biological repositories have proven beyond reasonable doubt that the endogenous levels of serum sex hormones are associated with breast cancer risk. After menopause high serum levels of both estrogens and androgens predict the risk of breast cancer.<sup>15,16</sup> Women in the upper quintile of estradiol or testosterone showed the risk of breast cancer to be 2 to 3 times higher than women in the lower quintile, and the risk of androgens persisted after adjustment for estrogens and *vice versa*. Before menopause, the hormonal pattern at high risk of breast cancer is characterized by high serum levels of androgens and low levels of progesterone in the luteal phase of the menstrual cycle.<sup>5,6</sup> The risk of breast cancer in women with increased androgenic activity and luteal insufficiency may increase by 3 to 7 times.<sup>6</sup> Premenopausal estrogen levels do not seem associated with a subsequent risk of breast cancer, either because a single blood sample, as used in these prospective studies, may be insufficient to properly classify the hormonal pattern of premenopausal women, or because any level of estrogens, before menopause, is sufficiently high to promote breast cancer growth. Estrogen levels capable of promoting breast cancer after menopause, in fact, are still one order of magnitude lower than normal premenopausal levels. A recent prospective study, however, suggested that premenopausal breast cancer risk is associated with high serum levels of estrogens in the early follicular phase.<sup>49</sup> The role of estrogens in sustaining breast cancer cell proliferation, moreover, is clearly demonstrated by the efficacy of anti-estrogen therapies for treating and preventing recurrences.<sup>17</sup> Also, androgens proved to be strong predictors of recurrence. Patients with localized breast cancer with high testosterone levels show an increased risk of metastasis, local recurrence, and contralateral breast cancer.<sup>18</sup> Serum estradiol was also associated with recurrences, but the association became insignificant upon adjustment for testosterone.<sup>18</sup> Measuring testosterone levels, therefore, seems to be the most parsimonious endocrine examination to select women at high risk of breast cancer or patients at high risk of recurrence. Consistent with the elevation in risk by increasing endogenous testosterone level, women using estrogen plus testosterone therapies for menopausal symptoms have a significantly greater risk of invasive breast cancer than do women using estrogen only.<sup>19</sup>

Besides the synthesis of estrogens and androgens in the adipose tissue the association of obesity with breast cancer may be mediated by insulin resistance. Several epidemiological studies inconsistently showed an association between serum insulin or C-peptide and the risk of breast cancer.<sup>20,21</sup> This association is quite clear after menopause, while in young women it seems to be in the opposite direction.<sup>22</sup> Elevated serum insulin levels, however, are associated with an increased risk of recurrences in breast cancer patients.<sup>23</sup> IGF (insulin-like growth factor)-I is also likely to be involved in breast cancer incidence and prognosis. Several prospective cohort studies have suggested a strong association, especially for young premenopausal women.<sup>24-28</sup> (Some studies, however, failed to confirm such a strong association in young women).<sup>29,30</sup>

Insulin resistance and hyperinsulinemia are a feature of the so-called metabolic syndrome, defined by at least three of five metabolic factors, each of which has been found to be associated with breast cancer incidence: high plasma levels of glucose ( $>110$  mg/100 mL),<sup>26</sup> high levels of triglycerides ( $>150$  mg/100 mL),<sup>31</sup> low levels of HDL cholesterol ( $<50$  mg/100 mL),<sup>32</sup> large waist circumference ( $>88$  cm),<sup>33</sup> and hypertension (SBP  $>130$  mmHg or DBP  $>85$  mmHg).<sup>34</sup> We examined the presence of metabolic syndrome in breast cancer patients and found that patients with metabolic syndrome have the worst prognosis, especially if it is associated with increased androgenic activity.<sup>35</sup>

The relationship between fat consumption and breast cancer risk is a highly controversial subject: several case-control studies suggested an association, but most prospective cohort studies did not. The WHI (Women's Health Initiative) randomized trial of dietary prevention, however, showed a borderline significant 9% decrease in breast cancer incidence in the low-fat arm.<sup>36</sup> Subgroup analyses showed a larger and significant effect in women characterized by high fat consumption at baseline, high white blood cell count, large waist circumference, hypertension, or diabetes, suggesting that women with markers of metabolic syndrome may be more likely to gain an advantage by dietary fat restriction. On the other hand, most observational studies analyzing the prognostic association of fat consumption at the time of diagnosis have found that fat intake negatively affects prognosis,<sup>9</sup> especially total and saturated fat,<sup>37</sup> whereas omega-3 might be protective.<sup>38</sup> Only a few observational studies considered the effect of diet after diagnosis with inconsistent results.<sup>38</sup> The WINS (Women's Initiative on Nutrition Study) randomized trial, however, showed that reducing fat consumption down to about 20% of calories significantly decreased the occurrence of recurrences by 22%.<sup>39</sup>

Most of the effect was due to the reduction of recurrences in estrogen receptor (ER)-negative patients, possibly because ER-positive patients were treated with tamoxifen, which may have conferred all the achievable preventive effect.

The consumption of alcoholic beverages has been consistently found to be associated with increased risk of breast cancer.<sup>40</sup> Only a few studies, however, examined its association with breast cancer prognosis, without significant associations with survival.<sup>9</sup>

## MECHANISTIC CONSIDERATIONS

Various mechanisms by which diet and lifestyle may promote increased risk for and progression of breast cancer have been previously reviewed.<sup>1,20,41</sup> In short, sedentary lifestyle, overweight, and a fat-rich diet are major determinants of metabolic syndrome, which in turn is associated with insulin resistance and increased androgenic activity. Physical activity improves insulin sensitivity and decreases testosterone levels, and in the long term, IGF-I levels. Insulin

**TABLE 1. DIANA-1: Hormonal changes after 5 months of diet in healthy postmenopausal women**

	Change (%)	<i>P</i>		Change (%)	<i>P</i>
Testosterone	-18	**	Glucose	-6	*
Estradiol	-18	ns	Insulin	-10	ns
Free testosterone	-29	**	Insulin area	-8	*
Free estradiol	-23	*	C-peptide	-19	*
SHBG	+25	**	IGF-I	-6	ns
Triglycerides	-1	ns	IGFBP-1	+12	**
Total cholesterol	-14	**	IGFBP-2	+30	**
BMI	-6	**	Waist	-5	**

Note: See Berrino *et al.*<sup>44</sup> and Kaaks *et al.*<sup>45</sup>

\**P* < 0.05.

\*\**P* < 0.01

stimulates the synthesis of androgens in the ovary and the expression of GH receptors, and inhibits the liver production of SHBG and IGFBP1 and 2, thus increasing the bioavailability of both sex hormones and IGF-I. IGF-I is increased by a diet rich in protein, in particular, milk protein.<sup>42</sup> Alcohol intake increases the synthesis of androgens and estrogens.<sup>43</sup> Postmenopausal overweight is associated with increased peripheral conversion of androgens into estrogens, decreased SHBG, and increased insulin levels. A newer hypothesis suggests a critical role for the adipocyte production of adipokines, which may affect tumorigenesis through the upregulation of genes involved in proliferation, invasion, and metastasis.

## THE DIANA STUDIES

The DIANA (DIet and ANDrogens) intervention trials demonstrated that a sustainable dietary modification aimed at lowering insulin levels, based on Mediterranean and macrobiotic dietary principles, can reduce body weight,

**TABLE 2. DIANA-2: Hormonal changes after 12 months of diet in breast cancer patients**

	Change (%)	<i>P</i>		Change (%)	<i>P</i>
Testosterone	-10	*	Glucose	-5	*
Estradiol	-6	*	Insulin	-17	*
SHBG	+5	*	IGF-I	-4	ns
Triglycerides	-14	*	PDGF	-38	**
Total cholesterol	-11	*	Systolic BP	-1	*
BMI	-5	**	Waist	-4	**

Note: Berrino *et al.*<sup>18</sup> and unpublished material.

\**P* < 0.05.

\*\**P* < 0.01.

metabolic syndrome, and the bioavailability of sex hormones and growth factors.<sup>18,44,45</sup> TABLES 1 and 2 summarize the results of these trials, showing the percentage of change in several metabolic and endocrine parameters after 5 months and 12 months, respectively, of dietary intervention. The prevalence of metabolic syndrome also decreased significantly. As a consequence of the highly satiating diet, women lost weight (about 4 kg) in both these studies. Part of the metabolic effects could have been just a consequence of this weight loss. Interestingly, however, the participating women lost weight just by changing the composition of the diet, without any recommendation to eat less. Together with other studies showing that a Mediterranean diet can reverse metabolic syndrome,<sup>46,47</sup> these results suggest that there is room for proposing adjuvant dietary changes both for breast cancer prevention and treatment. Patients with metabolic syndrome and high serum levels of testosterone, in particular, should be advised to modify their diet and to increase physical activity. Testosterone levels above 0.4 ng/mL (the upper tertile in our study populations) are associated with a significant increased risk. The prevalence of metabolic syndrome in adult Western populations ranges from 2 to 3% at 25 years of age to 25% above 70 years.<sup>48</sup> Metabolic screening for these two variables may identify subgroups of women and of breast cancer patients likely to benefit from dietary counselling.

### **DIETARY RECOMMENDATIONS FOR BREAST CANCER PATIENTS**

At present our recommendations include:

1. Reduce calorie intake, through the preferred consumption of highly satiating foods, such as unrefined cereals, legumes, and vegetables.
2. Reduce high glycemic index and high insulinemic index food, such as refined flours, potatoes, white rice, corn flakes, sugar, and milk, using instead whole grain cereals (unrefined rice, barley, millet, oat, buckwheat, spelt, quinoa), legumes (any type, including soy products), and vegetables (any type, except potatoes).
3. Reduce sources of saturated fat (red and processed meat, milk, and dairy products) preferring instead unrefined vegetable fats, such as olive oil, nuts, and oleaginous seeds.
4. Reduce protein intake, mainly animal proteins (except fish).

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