Effect of Fenretinide and Low-Dose Tamoxifen on Insulin Sensitivity in Premenopausal Women at High Risk for Breast Cancer

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Abstract
The prevalence of metabolic syndrome is increasing along with breast cancer incidence worldwide. Because fenretinide improves insulin action and glucose tolerance in insulin-resistant obese mice and because tamoxifen has shown to regulate several markers involved in metabolic syndrome, we sought to investigate the effect of fenretinide or tamoxifen at low dose on features linked to insulin resistance in premenopausal women at risk for breast cancer. We randomized 235 women to low-dose tamoxifen (5 mg/daily), fenretinide (200 mg/daily), or their combination or placebo for 2 years. We used the homeostasis model assessment (HOMA; fasting insulin/glucose/22.5) to estimate insulin sensitivity. Women were considered to improve insulin sensitivity when they shifted from a HOMA ≥2.8 to <2.8. There was no effect of fenretinide or tamoxifen on HOMA overall, but overweight women (body mass index, >25 kg/m2) had a 7-fold greater probability to normalize HOMA after 2 years of fenretinide treatment [odds ratio (OR), 7.0; 95% confidence interval (95% CI), 1.2–40.5], with 25% of women improving their insulin sensitivity, whereas tamoxifen decreased insulin sensitivity by almost 7 times compared with subjects not taking tamoxifen (OR, 0.15; 95% CI, 0.03–0.88). In this group only, 5% improved their insulin sensitivity. Interestingly, women with intraepithelial or microinvasive neoplasia had higher HOMA (3.0) than unaffected subjects (2.8; P = 0.07). Fenretinide can positively balance the metabolic profile in overweight premenopausal women and this may favorably affect breast cancer risk. Furthermore, features of the metabolic syndrome should be taken into consideration before proposing tamoxifen for breast cancer prevention. The clinical implications of these results require further investigations. [Cancer Res 2008;68(22):9512–8]

Introduction
Tamoxifen is Food and Drug Administration approved for breast cancer risk reduction, but its use is associated with serious adverse effects (1). We have conducted several trials using lower doses of tamoxifen in an attempt to increase its therapeutic index (2, 3). Fenretinide is a synthetic vitamin A derivative that selectively accumulates in the breast tissue (4), exhibits apoptotic and anti-invasive properties in vitro and in vivo with a good toxicity profile (5, 6) that has shown a lower risk of second breast cancer in premenopausal women, which persists several years after treatment cessation (7).

Because the combination of tamoxifen and fenretinide is synergistic in rodent mammary tumor models and its safety has already been shown in clinical trials (8), we conducted a 2 × 2 chemoprevention trial in premenopausal women using the change in plasma insulin-like growth factor (IGF-I) and mammographic density as surrogate–end point biomarkers. Preliminary results (3) showed that the combination of low-dose tamoxifen and fenretinide is safe, that tamoxifen reduces IGF-I levels by 15%, and that no synergistic effect between the two drugs was observed on the primary study end points.

The prevalence of metabolic syndrome and obesity is rapidly increasing in the Western world and evidence points to a link with breast cancer incidence (9, 10). Strategies are being developed to trim down breast cancer incidence and recurrence through insulin-lowering drugs and dietary intervention combined with aerobic exercise programs to reduce insulin resistance. Interestingly, Yang and colleagues (11) showed an improvement in insulin action and glucose tolerance by fenretinide in insulin-resistant obese mice, a finding which prompted us to investigate the ability of fenretinide to improve insulin sensitivity in humans. We were also interested in assessing the effect of tamoxifen at a lower dose on the homeostasis model assessment (HOMA) index because previous studies were somewhat contradictory, tamoxifen being associated with a favorable profile of some lipids (2, 12, 13), but an increased risk of hypertriglyceridemia (14).

Within our trial, we used the HOMA as a surrogate index of insulin resistance (15). Women were randomized to receive either low-dose tamoxifen (5 mg/daily), or fenretinide (200 mg/daily), or their combination or placebo for 2 years. We considered women to improve insulin sensitivity when they switched from a HOMA status of ≥2.8 to a HOMA status of <2.8. This cutoff value corresponds to the lower limit of the highest quintile in a population-based study conducted in 888 subjects randomly selected from the general population in Bruneck, Italy (16).

Patients and Methods
Eligibility criteria. Eligible subjects were premenopausal women with either an in situ breast cancer (n = 160) or a small invasive breast cancer of favorable prognosis (pT1mi or pT1a; n = 21) in the previous 3 y. Unaffected women (n = 54) were eligible if they had a Gall 5-y risk for breast cancer of ≥1.7%. The main subject characteristics and the preliminary data have been published elsewhere (3). All subjects signed a consent form approved by the local Institutional Review Board.
Study design. A 2 × 2 factorial design was adopted for this randomized double-blind placebo-controlled trial. Subjects were randomized to 2-y treatment of either low-dose tamoxifen (5 mg/day), or fenretinide (200 mg/day), or their combination, or placebo for 2 y. A monthly 3-d interruption of fenretinide was introduced to allow the partial recovery of retinal storage. Six-month follow-up continued after treatment completion for at least 5 y. There were two randomization strata: high-risk women identified from the Gail Model and affected women with in situ or pT1mic/pT1a breast cancer. The study was conducted in two centers: the European Institute of Oncology, Milan, where 91% of subjects were recruited, and the Division of Medical Oncology, Vicenza, Italy.

Assay methods. Fasting blood samples for circulating biomarkers were collected and stored at −80°C until centrally assayed. Serum glucose concentration and lipid profile were determined on fresh samples by enzymatic method with a Cobas Integra 800 (Roche Diagnostics S.p.A.). Circulating serum insulin levels were measured by RIA kits purchased from Diagnostic System Laboratories, Inc. (Webster). The sensitivity of the test was 1.3 μIU/mL, whereas intra-assay and interassay CV of our in-house pooled serum control sample (mean, 14.9 μIU/mL) were 11.5% and 15.2%, respectively. Plasma IGF-I was determined on EDTA by chemiluminescent immunometric assay method (Nichols Institute Diagnostics). The assay was performed on the automatic instrument LIAISON (DiaSorin SpA). The sensitivity of the test was 0.8 nmol/L, whereas intra-assay and interassay CV of our in-house pooled serum control sample were 5.4% and 8.2%, respectively. Total, high-density lipoprotein, low-density lipoprotein cholesterol, and triglycerides were measured by enzymatic luminescent methods with COBAS INTEGRA 880 (Roche Diagnostics). Plasma leptin concentrations were measured using a RIA kit for human leptin (Linco Research, Inc.). In this assay, the detection limit is 0.5 ng/mL; the in-house assay CV is 2.2% (5.9 ng/mL), 2.7% (25 ng/mL), and 5.9% (62.6 ng/mL); the interassay precision from 10 different runs of 3 patients serum samples was 4.3%, 4%, and 6.9% at the concentration of 5.1, 20.9, and 56.1 ng/mL, respectively. Plasma retinol levels were measured by high performance liquid chromatography using the method previously described (17).

We used the HOMA as a surrogate index of insulin sensitivity, i.e., [fasting insulinemia (mU/L)] × [glycemia (mmol/L)]/22.5 (15).

Statistical analysis. Descriptive statistics were first used to characterize the study population. The analysis was carried out for the whole population and separately for overweight/obese women [body mass index (BMI), ≥25] and normal weight subjects (BMI, <25). Spearman correlation coefficients (r) were calculated to study the relationships between circulating biomarkers and BMI. GLM models were also applied for the evaluation at baseline of the association between leptin and HOMA index, adjusting for BMI and randomization strata. Odds ratios (OR) were calculated to assess the probability of having an in situ or a pT1mic/pT1a breast cancer compared with unaffected high-risk women by unit of increase in HOMA index.

We evaluated the frequencies of subjects with HOMA of ≥2.8 at baseline and HOMA of <2.8 at the first, second, and third year. Women were considered to improve insulin sensitivity when they passed from a HOMA of ≥2.8 to a HOMA of <2.8, using the cutoff value previously described (16). Frequency differences by treatment groups were assessed using χ² tests for independence of categorical variables, and risk analyses were done using logistic regression. ORs assessed the probability of improving insulin sensitivity status by fenretinide and tamoxifen treatment through logistic regression adjusting for treatment allocation.

Values of IGF-I, total cholesterol, HDL and LDL cholesterol, and triglycerides were analyzed through a repeated-measure ANCOVA model at I and II year of treatment. Because there was no statistically significant interaction between drugs, we compared the women who had taken fenretinide with those who did not, irrespective of the combination treatment (placebo or tamoxifen), and women on tamoxifen with those who were not, irrespective of the combination treatment (placebo or fenretinid). This allowed us to gain statistical power. Mixed effects models were adjusted for baseline value and included as fixed effects: time, treatment (tamoxifen and fenretinid as indicators variables), HOMA index, and interactions of treatment with HOMA index. Use of mixed-effect models and the Kenward-Roger technique for determining denominator degrees of freedom were adopted (PROC MIXED, SAS; ref. 18). Log transformations were used when necessary to achieve normality. Predicted values of the biomarkers were plotted against HOMA index when we found a significant interaction of treatment by HOMA index.

Data were analyzed using the SAS System Software for Windows, release 8.0. (SAS Institute; ref. 18).

Results

Table 1 shows descriptive statistics of the study population according to treatment allocation. In total, 171 (73%) women had...
a normal BMI, 47 (20%) were overweight (BMI, ≥25 kg/m²), and 16 (7%) were obese (BMI, >30 kg/m²). Of the women with a normal BMI, 49% had a HOMA index of ≥2.8, whereas those with a BMI of ≥25 showed a higher percentage of HOMA index ≥2.8 (59%). The frequencies of women at low and high insulin sensitivity were distributed evenly between treatment arms (P = 0.48). Likewise, there were no statistically significant differences between groups as regards circulating biomarkers linked to insulin resistance and retinol levels. Furthermore, we assessed the correlation between biomarkers (data not shown). HOMA index (r = 0.357), leptin (r = 0.688), HDL cholesterol (r = −0.266), and triglycerides (r = 0.228) were all significantly associated with BMI at baseline (P < 0.001).

Table 2 shows the biomarker levels after 2 years of treatment. Based on a previous analysis showing no interaction between tamoxifen and fenretinide (3), the effect of either agent was assessed separately (fenretinide versus no fenretinide and tamoxifen versus no tamoxifen). IGF-I levels were reduced by tamoxifen (r = 0.357), leptin (r = 0.573; P < 0.001), BMI (r = 0.357; P < 0.001), HDL cholesterol (r = 0.320; P < 0.001), and retinol (r = 0.177; P < 0.01).

Table 2. Median and interquartile ranges of biomarkers after 2-y treatment

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Tamoxifen+fenretinide</th>
<th>Tamoxifen+placebo</th>
<th>Fenretinide+placebo</th>
<th>Placebo+placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA index</td>
<td>2.9 (2.4–3.8)</td>
<td>3.0 (2.3–3.5)</td>
<td>2.6 (2.2–3.4)</td>
<td>2.5 (1.9–3.5)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>86 (83–93)</td>
<td>87 (81–93)</td>
<td>89 (80–93)</td>
<td>86 (82–93)</td>
</tr>
<tr>
<td>Insulin (mU/mL)</td>
<td>13.0 (11.1–16.4)</td>
<td>14.2 (10.6–16.1)</td>
<td>12.2 (10.3–15.4)</td>
<td>12.1 (8.9–15.3)</td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>121 (88–158)</td>
<td>118 (90–154)</td>
<td>141 (122–166)</td>
<td>140 (112–167)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>71 (57–81)</td>
<td>63 (52–78)</td>
<td>74 (64–82)</td>
<td>66 (58–73)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>112 (95–135)</td>
<td>117 (100–134)</td>
<td>126 (107–151)</td>
<td>126 (105–151)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>69 (54–103)</td>
<td>77 (66–111)</td>
<td>64 (53–82)</td>
<td>65 (52–90)</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>11.3 (7.2–15.2)</td>
<td>11.7 (8.4–16.5)</td>
<td>10.0 (6.5–14.0)</td>
<td>12.0 (7.0–15.3)</td>
</tr>
<tr>
<td>Retinol (ng/mL)</td>
<td>194 (117–495)</td>
<td>524 (484–608)</td>
<td>206 (120–491)</td>
<td>533 (444–610)</td>
</tr>
</tbody>
</table>

Figure 1. Effect of fenretinide (A, top; Fen, fenretinide+placebo or fenretinide+ tamoxifen) and tamoxifen (B, top; Tam, tamoxifen+placebo and tamoxifen+ fenretinide) and HOMA index. Histograms, the percentage of subjects improving their HOMA index from baseline, shifting from a HOMA of ≥2.8 to a HOMA of <2.8. Two-year treatment followed by 1-year follow-up.
treatment \( (P = 0.01) \) and retinol by fenretinide \( (P = 0.001) \). As retinol levels correlated with HOMA index, we checked for a possible interaction of HOMA index with retinol decline after fenretinide treatment, but this was not significant.

Figure 1 illustrates the changes over time in insulin sensitivity status by drug stratified by BMI. The findings, expressed as the percentage of women who shifted from a HOMA of \( \geq 2.8 \) to a HOMA of \( < 2.8 \), show that overweight women (BMI, \( \geq 25 \)) taking fenretinide for 2 years had a 7-fold greater probability to improve insulin sensitivity than women not taking fenretinide [OR, 7.6; 95% confidence interval (95% CI), 1.2–40.5; \( P = 0.029 \); Fig. 1A]. In contrast, tamoxifen decreased insulin sensitivity by nearly 7 times in overweight women (OR, 0.15; 95% CI, 0.03–0.88; \( P = 0.04 \); Fig. 1B). Neither agent showed any effect on insulin sensitivity in subjects with normal BMI. We also looked at the effect in each of the 4 allocated arms, and the insulin-sensitizing effect of fenretinide was particularly evident in the “fenretinide + placebo” arm, where the median HOMA levels decreased from 5.2 to 2.5 after 2 years of treatment in this group.

Figure 2 shows the differential effects of tamoxifen according to BMI category as regards the relationship between HOMA index and IGF-I \( \left( A \right) \) and HDL cholesterol \( \left( C \right) \). In women with normal BMI, IGF-I levels increased with increasing HOMA index and were significantly lowered by tamoxifen regardless of HOMA index values \( (P = 0.01; \text{Fig. 2A}) \). At variance, in overweight women, the decrease exerted by tamoxifen was much greater with increasing HOMA index \( (P = 0.004 \text{ for the HOMA } \times \text{ tamoxifen interaction}; \text{Fig. 2B}) \). In normal-weight women, tamoxifen improved HDL-C as HOMA increased \( (P = 0.02 \text{ for the HOMA } \times \text{ tamoxifen interaction}; \text{Fig. 2C}) \), whereas in overweight women, tamoxifen decreased HDL-C as HOMA increased \( (P = 0.001 \text{ for the HOMA } \times \text{ tamoxifen interaction}; \text{Fig. 2D}) \).

Figure 3 shows the different effects of the drugs according to BMI category on the relationship between HOMA index and triglycerides \( \left( A \right) \) or leptin \( \left( C \right) \). Tamoxifen increased triglyceride levels as HOMA increased irrespective of BMI \( (P = 0.01 \text{ for the HOMA } \times \text{ tamoxifen interaction}; \text{Fig. 3A}) \). In contrast, in normal-weight women, fenretinide blunted the increase in triglycerides associated with the HOMA increase \( (P = 0.01 \text{ for the HOMA } \times \text{ fenretinide interaction}; \text{Fig. 3B}) \). Finally, fenretinide had a different effect on leptin levels according to BMI, with a slight increase in leptin as HOMA increased in normal weight women \( (P = 0.05 \text{ for the HOMA } \times \text{ fenretinide interaction}; \text{Fig. 3C}) \), as opposed to a nonsignificant decrease in overweight women.

Table 3 shows the median and interquartile ranges of HOMA index according to disease status. The median HOMA index value

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Relationship between HOMA index and IGF-I \( \left( A \right) \) or HDL cholesterol \( \left( C \right) \) by BMI category according to treatment. Lines, fitted values of the interaction between HOMA index and treatment, obtained from repeated-measure analysis of year I and II, after adjusting for baseline value, time, HOMA index, and treatment. Women allocated to tamoxifen were compared with those who were not, irrespectively of combination treatment (placebo or fenretinide).
of unaffected high-risk women overlapped the HOMA index reference value of 2.8, whereas women with intraepithelial or microinvasive breast cancer had a median HOMA index equal to 3.0. This translated into a 24% increased risk of bearing an intraepithelial or microinvasive breast cancer by unit increase in HOMA index ($P = 0.07$).

**Discussion**

The metabolic syndrome, which is characterized by visceral obesity, glucose intolerance, hyperinsulinemia, hypertension, and dyslipidemia, has become a worldwide problem, and the mechanisms by which it promotes breast cancer development have recently been elucidated (19). Increased levels of insulin and IGF-I have been causally linked to breast cancer (20, 21), with hyperinsulinemia, which in turn amplifies the bioavailability of IGF-I (22). Insulin resistance develops as a metabolic adaptation to increased levels of circulating nonesterified fatty acids released from intra-abdominal adipose tissue that forces liver, muscles, and other tissues to shift toward storage and oxidation of fats (9).

In our study, we found that overweight and obese women taking fenretinide improved their HOMA-based insulin sensitivity...
score. This benefit was associated with a decrease in plasma leptin concentrations in overweight women as HOMA index increased. Moreover, fenretinide prevented triglyceride increase associated with HOMA increase in normal weight women. Leptin is mainly produced by the adipocytes, conveys information to the hypothalamus on the amount of energy stored in fat, and suppresses appetite. It is a mitogen for various cell types, including normal and transformed breast epithelial cells (23, 24). We found a highly positive correlation between leptin levels and BMI in our cohort of premenopausal women. The relationships between obesity, leptin, insulin resistance, and mammary tumor development are not fully understood. Genetically obese, leptin-deficient mice, or mice lacking a functional leptin receptor fail to develop oncogene-induced mammary tumors (25, 26), but a direct association between high-circulating leptin levels and breast cancer risk has not unequivocally been confirmed (27).

Interestingly, the insulin-sensitizing effect of fenretinide was observed only after the second year of treatment, with a 7-fold greater probability to improve insulin sensitivity compared with women not taking fenretinide. We have no clear explanation for this time lag, which suggests a gradual activity of the drug on reversal of insulin-resistance and its persistence after treatment cessation. Fenretinide and N-(4-methoxyphenyl)retinamide, the most abundant metabolite in human plasma, are lipophilic and therefore accumulates in the adipose tissue where they are retained for several months after drug cessation (17). Fenretinide may enhance nuclear receptor heterodimerization promoting the synthesis of lipids and carbohydrates possibly favoring insulin sensitivity (28).

A putative link between fenretinide and insulin sensitivity may be ascribed to the likely reduction in retinol-binding protein 4 (RBP4) levels after the decrease in retinol levels. RBP4 is an adipocyte-secreted molecule that vehicles retinol in the blood through a specific binding site and is associated with several features of the metabolic syndrome (29). Improvement in insulin action in insulin-resistant subjects after exercise training is associated with a drop in serum RBP4 (30). Plasma concentrations of RBP4 decrease proportionally with retinol (31), and their decrease is highly correlated (r = 0.96) during fenretinide administration (32). In our study, plasma retinol levels underwent a 50% decrease at the first and second year of treatment, then almost virtually recovered back to baseline values at the third year. Although we were unable to measure RBP4 levels, we considered the retinol decrease as a surrogate marker of serum RBP4 drop. Serum levels of RBP4 are increased in insulin-resistant states (11, 30, 33), although the correlation is attenuated with increasing age (34), and experiments in mice suggest that elevated RBP4 levels cause insulin resistance by reducing IRS-1 tyrosine phosphorylation (11).

In contrast to fenretinide, low-dose tamoxifen was associated with increased HOMA index in overweight women. Moreover, tamoxifen worsened circulating levels of HDL-cholesterol and triglycerides in overweight women as HOMA index increased. Although several reports suggest that the predominant effects of tamoxifen on lipids are favorable, especially on LDL cholesterol (2, 12, 13), hypertriglyceridemia during tamoxifen 20 mg/day has been observed mostly in patients with family history of dyslipidemia and high pretreatment triglyceride levels (35–37). Tamoxifen has also been associated with an increased risk of developing nonalcoholic steatohepatitis in overweight-obese women in association with abnormal elevations of alanine aminotransferase (38). In our study, we found that low-dose tamoxifen exerted a greater increase of triglyceride levels with increasing HOMA index, whereas there was no association between triglycerides and HOMA index in women not taking tamoxifen. Tamoxifen is known to reduce the hepatic production in IGF-I (2, 3). The drug also interacts with the IGF-I receptor signaling pathway, down-regulating the downstream cascade in breast cancer cells, including insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation (39, 40). One of the primary defects underlying insulin resistance is an impairment in postreceptor pathways of insulin action, bringing to a down-regulation of IRS-1 signaling by excess free fatty acids (41). In addition, the active metabolite 4-OH-tamoxifen may induce a marked inhibitory action on pancreatic β-cell function in a rat model (42).

Given the information above, we suggest that tamoxifen may increase insulin requirement in women carrying features of the metabolic syndrome. Although circulating SHBG and IGFBP-1 increase with tamoxifen treatment (2), a phenomenon expected to positively influence insulin sensitivity, our data suggest that in overweight women the insulin resistant effect of tamoxifen is predominant.

We observed a border-line significant association between HOMA index at baseline and disease status, which translated into a 24% increased risk of having intraepithelial or microinvasive breast cancer by every unit of increase in HOMA index relative to unaffected high-risk women (P = 0.07). This finding is in line with the observation that postmenopausal breast cancer patients with metabolic syndrome or type 2 diabetes have an increased risk of recurrence (43, 44), and that premenopausal women with features of the metabolic syndrome (hyperandrogenism and luteal insufficiency) have an increased breast cancer risk (45–47). As the prevalence of metabolic syndrome is increasing steadily in the developing countries, intervention aimed at preventing insulin-resistance and obesity represent important health issues also for breast cancer prevention.

In conclusion, our results suggest that fenretinide positively balance the metabolic profile in obese women, offering some clues toward its evaluation in the treatment of metabolic syndrome. In contrast, tamoxifen, even at a lower dose, worsened insulin sensitivity in obese subjects, providing further support to its careful use as a preventive agent in these women, where most serious adverse events tend to occur, including endometrial cancer (48, 49) and deep-vein thrombosis (50).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Received 2/14/2008; Revised 8/8/2008; Accepted 8/20/2008.

Grant support: National Cancer Institute grant number CA-77188, a contract from the Italian Foundation for Cancer Research, and a regional grant (1068/2005) on second tumors from the Associazione Italiana per la Ricerca sul Cancro.

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We thank Loredana Quadro for her technical expertise in the preparation of the manuscript. Fenretinide was manufactured by and a gift from the RW Johnson Pharmaceutical Research Institute, Spring House, PA, USA. Tamoxifen was a gift from Laboratori MAG, Garbagnate, and manufactured by Cosmo SpA, Lainate, Italy.
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Cancer Res 2008; 68: (22), November 15, 2008 9518 www.aacrjournals.org

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