Multiple epidemiologic and animal studies have established the link between obesity and increased risk for postmenopausal breast cancer. Because obesity is referred to as the epidemic of the 21st century with around 36% of the adult United States women defined as obese and another one third as overweight (1), this disease has a dramatic effect on quality of life as well as on life expectancy in the United States. The estimated increased risk for breast cancer is around 1.3- to 2-fold for obese postmenopausal women as compared with normal-weight postmenopausal women (2, 3). Several mechanisms have been proposed as being responsible for this increased risk for breast cancer. Among those, a well-studied mechanism is altered estrogen biosynthesis, mainly involving increased aromatase expression (4). Aromatase catalyzes the last steps of estrogen biosynthesis from androgens. Estrogen executes its effect mostly by binding to estrogen receptors (ER). Nuclear ERs function as transcription factors and regulate gene transcription by binding to specific DNA sequences called estrogen response elements (ERE). In clinical practice, selective ER modulators including breast cancer, showing a beneficial effect (12, 13). For example, several in vivo studies showed that PPARγ inhibited breast cancer growth (14–16). The inhibitory effects of PPARγ on mammary tumorigenesis occur through inducing terminal differentiation, cell-cycle arrest, and apoptosis of human breast cancer cells (17–19) as well as on life expectancy in the United States. The estimated increased risk for breast cancer is around 1.3- to 2-fold for obese postmenopausal women as compared with normal-weight postmenopausal women (2, 3). Several mechanisms have been proposed as being responsible for this increased risk for breast cancer. Among those, a well-studied mechanism is altered estrogen biosynthesis, mainly involving increased aromatase expression (4). Aromatase catalyzes the last steps of estrogen biosynthesis from androgens. Estrogen executes its effect mostly by binding to estrogen receptors (ER). Nuclear ERs function as transcription factors and regulate gene transcription by binding to specific DNA sequences called estrogen response elements (ERE). In clinical practice, selective ER modulators and aromatase inhibitors are commonly and successfully used for breast cancer prevention and treatment. Aromatase is expressed mainly in undifferentiated adipose fibroblasts (also referred to as visceral preadipocytes) but not in mature adipocytes (5). Indeed, undifferentiated breast adipose fibroblasts have been shown to play a major role in aromatase expression leading to breast cancer development (6–8). Therefore, in obese or overweight women, a larger mass of breast adipose tissue with a correspondingly high number of fibroblasts may result in increased local production of aromatase.

PPARγ is a member of the PPAR family, including PPARα, β, and γ, which belongs to the superfamily of nuclear hormone receptors. PPARγ is a ligand-activated transcription factor, which along with retinoid X receptors (RXR) forms heterodimers that activate transcription of its target genes by binding to PPAR response elements (PPRE) located in the promoter region. In addition to the role of PPARγ in glucose and lipid metabolism, PPARγ stimulated adipocyte differentiation (9, 10), and inhibition of PPARγ attenuated adipocyte differentiation induced by breast cancer epithelial cells (11). Furthermore, PPARγ ligand therapy was tested in many preclinical studies of solid tumors, including breast cancer, showing a beneficial effect (12, 13). For example, several in vivo studies showed that PPARγ inhibited breast cancer growth (14–16). The inhibitory effects of PPARγ on mammary tumorigenesis occur through inducing terminal differentiation, cell-cycle arrest, and apoptosis of human breast cancer cells (17–19) as well as inhibiting invasion (20) and angiogenesis in vitro and in vivo (21, 22). In this issue of the journal, Subbaramaiah and colleagues (23) report for the first time that pioglitazone, a PPARγ agonist, inhibited aromatase expression via inhibiting prostaglandin E2 (PGE2) signaling and upregulation of BRCA1. Their findings provide potential targets for preventing or treating obesity-related breast cancer. Cancer Prev Res; 5(10); 1169–72. ©2012 AACR.
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pathway (24, 25, 27). Another pathway that regulates aromatase expression in breast cancer is through the BRCA1 tumor-suppressor gene. Mutations in the BRCA1 gene lead to breast and/or ovarian cancer with increased aromatase expression (30). Several studies have shown that BRCA1 inhibits aromatase expression in human adipose fibroblasts and malignant breast epithelial cells (31–33). Moreover, adipose-specific PPARγ knockout mice exhibited decreased BRCA1 expression in mammary stromal adipocytes (34). Interestingly, PGE2 inhibited BRCA1 expression in human visceral preadipocytes and breast cancer cells (24), suggesting a link between these two pathways. Because PPARγ agonists were shown to inhibit PGE2 (35, 36) and upregulate BRCA1 (37), it is conceivable that PPARγ agonists inhibit aromatase expression through both the PGE2 and BRCA1 pathways.

In this issue of the journal, Subbaramaiah and colleagues elegantly address the complicated pathways that mediate pioglitazone inhibition of aromatase expression in vitro and in vivo. First, pioglitazone inhibits early growth response factor-1 (Egr-1), known to induce Snail, a repressive transcription factor that in turn inhibits the expression of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the enzyme responsible for PGE2 degradation. Therefore, this derepression of 15-PGDH reduces PGE2 levels. Moreover, by using silencing of 15-PGDH and overexpression of Snail, they show for the first time that both these factors mediate pioglitazone inhibition of aromatase. Notably, previous studies showed that PPARγ ligands reduce PGE2 level by downregulating the PG synthase microsomal prostaglandin E synthase-1 (mPGES1) via inhibiting its activators Egr-1 and IL-1β (35, 38). Therefore, PPARγ ligands could affect PGE2 level through both mPGES1-dependent biosynthesis and 15-PGDH-dependent degradation pathways. Subbaramaiah and colleagues also show for the first time that pioglitazone can inhibit aromatase in vivo in murine mammary glands, along with inducing 15-PGDH and BRCA1, further substantiating the link between the pioglitazone, the PGE2, and BRCA1 pathways in mediating aromatase inhibition in vivo.

Although aromatase inhibitors are indeed beneficial in breast cancer prevention and treatment, their systemic side effects include musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture. One way to reduce these systemic side effects without interfering with treatment efficacy would be to specifically inhibit aromatase levels in breast cancer tissue. In normal adipose tissue, aromatase expression is driven by its promoter I.4. However, in breast cancer and adipose fibroblasts surrounding breast tumors, aromatase expression is driven by its promoters I.3 and II (39, 40). Indeed, both PGE2 signaling and BRCA1 were shown to regulate aromatase expression through the I.3/II promoters (24, 27, 31, 32). Therefore, inhibition of aromatase expression via both inhibition of PGE2 and upregulation of BRCA1 provides an opportunity for a highly tissue-specific endocrine therapy that targets the estrogen required for tumor growth, whereas sparing other important sites of estrogen action, such as bone. Hence, using PPARγ agonists to inhibit aromatase via the PGE2 and BRCA1 pathways is expected to reduce aromatase-related systemic side effects.

PPARγ can also regulate the estrogen signaling through aromatase-independent pathways by inhibiting ER expression through either the PTEN pathway (15, 41) or inducing proteasome-dependent degradation of ER (42). Furthermore, the PPARγ/RXR heterodimer binds to the ERE, which inhibits ER transactivation (43). By the same token, ER was shown to bind PPREs and negatively interfere with PPARγ signaling in breast cancer cells (44, 45). This cross-talk further supports the possible benefit from combination therapy of ER antagonists or aromatase inhibitors along with PPARγ agonists.

In conclusion, Subbaramaiah and colleagues have meticulously delineated the pathways that mediate pioglitazone inhibition of aromatase expression. Their findings suggest that PPARγ agonists may hold promise as potent agents in breast cancer prevention and treatment, with possibly fewer aromatase-related systemic side effects. In addition, their work provides several novel drug targets, such as the transcription factor Snail, for the prevention and treatment of breast cancer. In the clinical setting, 2 small-scale and short-term clinical trials of PPARγ agonists in early (46) and metastatic (47) breast cancer have failed to show positive results. It would be interesting to see the results from a small-scale trial completed in August 2012, which was designed to determine whether the addition of the PPARγ agonist rosiglitazone, along with metformin, could improve the efficacy of the aromatase inhibitor exemestane in postmenopausal obese women with ER positive metastatic breast cancer (NCT00933309). Further large-scale and long-term clinical trials using PPARγ agonists in combination with ER antagonists or aromatase inhibitors may be considered.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: O. Margalit, D. Wang
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PPARγ Agonists Target Aromatase Via Both PGE2 and BRCA1

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