Hormone Replacement Therapy and Cancers: The Biological Roles of Estrogen and Progestin in Tumorigenesis are Different between the Endometrium and Breast

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ITO, K. Hormone Replacement Therapy and Cancers: The Biological Roles of Estrogen and Progestin in Tumorigenesis are Different between the Endometrium and Breast. Tohoku J. Exp. Med., 2007, 212 (1), 1-12 ——— Hormone replacement therapy (HRT) has become available over the past few decades, but the risk of breast cancer with HRT remains controversial. The Women’s Health Initiative Study has recently demonstrated that women receiving estrogen plus progestin (HRT) have an increased risk of invasive breast carcinoma, although women receiving estrogen alone (estrogen replacement therapy) exhibit no increased risk of breast carcinoma. By contrast, the risk of endometrial carcinoma increases with estrogen replacement therapy, while HRT reduces the risk of endometrial carcinoma. These clinical findings suggest that the biological roles of estrogen and progestin in tumorigenesis are certainly different between the endometrium and breast, although both are considered “estrogen-dependent tissues”. In this review, I summarize the recent studies and indicate that the enzymes responsible for intratumoral estrogen metabolism and biosynthesis are markedly different between human breast and endometrial carcinomas. 17β-hydroxysteroid dehydrogenases (17-HSDs) are enzymes estrogen replacement therapy involved in the formation of active sex steroids. Estrogens are interconverted by two enzymes, 17-HSD types 1 and 2. Type 1 converts estrone to estradiol, and type 2 catalyzes the reverse reaction. 17-HSD type 5 reduces androstenedione to testosterone. 17-HSD type 1 plays an important role in the regulation of high estradiol levels in breast carcinoma tissues, whereas 17-HSD types 2 and 5 appear to be essential for the maintenance of estradiol concentrations in endometrial carcinoma tissues. In addition, the biological significance of progesterone receptor isoforms differs between endometrial and breast carcinomas. These findings may provide new insights into the biology of “estrogen-dependent tissues”. ——— hormone replacement therapy (HRT); 17β-hydroxysteroid dehydrogenases; estrogen; progesterone; breast carcinoma; endometrial carcinoma

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Hormone replacement therapy (HRT) has become available over the past few decades. HRT is the most effective intervention to date for the relief of estrogen-deficiency symptoms after menopause. The use of HRT has increased among postmenopausal women worldwide. About 20 million women worldwide were using HRT in the late 1990s (Beral et al. 1999). However, the risk of breast cancer with HRT remains controversial. The Women’s Health Initiative (WHI) Study recently demonstrated the possible increased risk of breast cancer associated with HRT. The WHI study also showed that women receiving estrogen plus progestin (HRT) exhibited an increased risk of invasive breast carcinoma (hazard ratio [HR], 1.24; 95% CI, 1.01-1.54), although women receiving estrogen alone (estrogen replacement therapy [ERT]) exhibited no increased risk of invasive breast carcinoma (HR, 0.77; 95% CI, 0.59-1.01) (Rossouw et al. 2002; Chlebowski et al. 2003; Anderson et al. 2004). By contrast, the risk of endometrial carcinoma increased in a dose- and time-dependent manner with ERT, while HRT reduces the risk of endometrial carcinoma. These clinical findings suggest that the biological roles of estrogen and progestin in tumorigenesis are certainly different between the endometrium and breast, although both are considered “estrogen-dependent tissues”. The present review aims to summarize recent studies from this perspective.

**Metabolism and synthesis of estrogen**

*In situ estrogen metabolism and synthesis*

Estrogen is well recognized to play an important role in the development and progression of breast and endometrial carcinoma. However, the great majority of endometrial and breast carcinomas occur during the post-menopausal period, when ovaries cease to be functional. Recently, *in situ* estrogen metabolism and synthesis have been considered to greatly contribute to the genesis and progression of various human estrogen-dependent epithelial neoplasms, including breast and endometrial carcinoma (Lippman and Swain 1992). Several studies of tissue estrogen content in human breast carcinoma have been reported (van Landeghem et al. 1985; Pasqualini et al. 1996, 1999; Chetrite et al. 2000). In these studies, tissue concentrations of estrone (E1), estradiol (E2) and their sulfates were generally several times higher than those found in the plasma or in the area of the normal breast tissues of the same subjects, despite low levels of circulating estrogens. These findings indicated specific intratumoral biosynthesis and accumulation of these hormones.

On the other hand, information regarding tissue estrogen concentrations in endometrial carcinoma tissues has been limited and inconsistent (Bonney et al. 1986; Vermeulen-Meiners et al. 1986; Naitoh et al. 1989; Berstein et al. 2003). Berstein et al. (2003) recently examined 78 endometrial carcinomas and detected higher concentrations of E2 in cancer tissue specimens compared with macroscopically normal endometrium. The results of our recent study (Ito et al. 2006) are generally consistent with those in the previous investigations. In addition, we limited the subjects to postmenopausal patients with endometrioid type cancer in our evaluation of estrogen metabolism in postmenopausal cancer patients. In our study, E2, E1 and testosterone levels in the tumor tissue were several times higher than those in serum. It then becomes important to evaluate the mechanisms and/or conditions responsible for such an elevation of intratumoral estrogens in post-menopausal patients with endometrioid carcinoma. Numerous studies have demonstrated that human breast and endometrial carcinoma tissues contained the enzyme systems required for local biosynthesis of estrogen (Fig. 1). Among these enzymes, aromatase, 17β-hydroxysteroid dehydrogenases (17-HSDs) and steroid sulfatase (STS) are the three principal enzymes involved in the formation of biologically active estrogen, estradiol. Estrogen-dependent neoplasms, such as breast and endometrioid endometrial carcinoma, in which in situ conversion from serum androgen to biologically active estrogens occur, may be considered as “intracrine” tissues.

**Aromatase**

Aromatase catalyzes the conversion of circulating androgens, mainly androstenedione and
testosterone, into E1 and E2, respectively (Miller et al. 1982). Aromatase is a key enzyme in estrogen synthesis and the levels of expression in breast cancer tissues have been shown to be significantly higher than those in benign breast lesions (Suzuki et al. 2005). Expression of aromatase has also been detected in human endometrial carcinoma. Our laboratory has previously reported marked aromatase immunoreactivity and mRNA mainly in stromal cells of endometrioid endometrial carcinoma, but not in normal or hyperplastic endometrium (Watanabe et al. 1995). In addition, an aromatase inhibitor suppressed the proliferation of endometrial carcinoma cells, which exhibit aromatase activities in vitro (Sasano et al. 1999a).

**Steroid sulfatase (STS) and estrogen sulfotransferase (EST)**

STS hydrolyzes circulating estrone sulfate (E1S) to E1, whereas EST sulfonates E1 to E1S. STS immunoreactivity was not detected, whereas that of EST was observed in normal mammary glands. STS and EST immunoreactivities were detected in 74% and 44% of breast carcinomas (Suzuki et al. 2003). In normal endometrium, STS immunoreactivity was not detected but that of EST was observed in the secretory phase. STS and EST immunoreactivities were detected in 86% and 29% of endometrial carcinomas cases (Utsunomiya et al. 2004). Increased STS and decreased EST expression in human breast and endometrial carcinomas may result in increased availability of biological active estrogens.

**17-HSD**

17-HSD type 1 & 2. The 17-HSDs are enzymes involved in the formation of active sex steroids, including testosterone, E1 and E2 (Luu-The et al. 2001). The enzymes, 17-HSD types 1 and 2 catalyze the reversible interconversion of E1 and E2. Type 1 17-HSD catalyzes the 17β-reduction of biologically inactive E1 to E2 (Peltoketo et al. 1988; Luu-The et al. 1989; Gast et al. 1989), whereas the type 2 isozyme preferentially catalyzes the oxidation of E2 to E1 (Wu et al. 1993). Both type 1 and type 2 17-HSD regulate tissue levels of E2 and modulate estrogenic actions in estrogen target tissues, such as the breast and endometrium (Sasano et al. 2000).

Oxidative 17-HSD activity is the preferential reaction in normal breast tissues, but the reductive 17-HSD pathway predominates in breast carcinomas. 17-HSD type 1 mRNA levels and intratumoral E2/E1 ratios were significantly higher in postmenopausal compared with premenopausal
breast carcinomas (Miyoshi et al. 2001). 17-HSD type 1 immunoreactivity was detected in carcinoma cells in approximately 60% of breast carcinoma tissues, whereas 17-HSD type 2 was not expressed at all (Suzuki et al. 2000). In addition, breast carcinoma patients with high levels of expression of 17-HSD type 1 mRNA correlated with increased risk of developing a late relapse of breast carcinoma (Gunnarsson et al. 2001). Therefore, type 1 17-HSD is considered responsible for regulating the process leading to the accumulation of E2 in human breast carcinomas.

17-HSD type 1 immunoreactivity was not detected in any of the cases of normal endometrium, endometrial hyperplasia and endometrioid endometrial carcinoma (Ito et al. 2001; Utsunomiya et al. 2001). 17-HSD type 1 mRNA expression and enzymatic activity were also absent in all carcinoma cases. In normal endometria, 17-HSD type 2 immunoreactive protein was detected only in the cytoplasm of glandular cells in the secretory phase. 17-HSD type 2 mRNA was also markedly expressed in the endometrial glandular epithelial cells of the luteal phase, but 17-HSD type 1 mRNA was not detected in any of the phases of the examined endometrium (Casey et al. 1994). 17-HSD type 2 immunoreactivity was detected in 75% and 37% of endometrial hyperplasia and endometrioid endometrial carcinoma cases, respectively. 17-HSD type 2 expression was decreased from normal endometrium (secretory phase) to hyperplasia and finally carcinoma (Utsunomiya et al. 2001). In addition, there was a statistically significant inverse correlation between the intratumoral E2 concentration and the level of 17-HSD type 2 mRNA in endometrial carcinoma (Ito et al. 2006). These results suggest that type 2 17-HSD contributes to the regulation of “intratissue” estrogen levels in normal endometrium and that disruption of the control mechanism of intratissue estrogen levels may be related to the development of endometrial disorders.

Type 5 17-HSD. Since 17-HSD type 1 expression is negligible in endometrioid endometrial carcinoma tissues, intratumoral E2 concentration may be maintained primarily by aromatization of testosterone in endometrial carcinoma. Recently, 17-HSD type 5, which reduces androstenedione to testosterone, was cloned (Dufort et al. 1999). 17-HSD type 5 is expressed in various peripheral tissues, liver, prostate, ovary and has been also detected in prostate and breast carcinoma tissues (Luu-The et al. 2001; Suzuki et al. 2001; Vihko et al. 2004). 17-HSD type 5 immunoreactivity was detected in normal mammary gland and breast carcinoma cells in 53% of the cases. Immunoreactivity of 17-HSD type 5 correlated significantly with that of 5α-reductase, which catalyzes the reduction of testosterone to the biologically active and potent androgen, 5α-dihydrotestosterone (DHT). 17-HSD type 5 is considered to be involved in DHT production in breast carcinomas in situ (Suzuki et al. 2005).

In normal endometria, 17-HSD type 5 immunoreactive protein was detected only in the cytoplasm of glandular cells but not of stromal cells (Pelletier et al. 1999; Ito et al. 2006). 17-HSD type 5 immunoreactivity was detected in 19% and 25% of proliferative phase endometrium and secretory phase endometrium, respectively. 17-HSD type 5 immunoreactivity was detected in 50% and 69% of endometrial hyperplasia and endometrioid endometrial carcinoma cases, respectively. 17-HSD type 5 expression was increased significantly throughout normal endometrium, hyperplasia and finally carcinoma. In addition, there was a statistically significant inverse correlation between intratumoral testosterone concentration and aromatase mRNA level in endometrial carcinoma (Ito et al. 2006). Testosterone produced by 17-HSD type 5 in the tumor tissue may be finally aromatized to E2 by aromatase, which is overexpressed in endometrial cancer tissues. Therefore 17-HSD type 5 is considered one of the key enzymes for estrogen concentrations in endometrial malignancy.

**Estrogen and progesterone receptor**

**Estrogen receptor**

The cellular actions of estrogen are mediated through the estrogen receptors (ER). Estrogen receptors are members of the steroid receptor superfamily and act as transcription fac-
tors, affecting target organs, including the breast and endometrium. ER is also expressed in a great majority of breast and endometrial carcinoma tissues. To date, two ERs (ERα and ERβ), encoded by different genes, have been detected (Pearce and Jordan 2004). ERα and ERβ differ markedly in the N-terminal A/B domains, exhibiting only about 20% amino acid identity. They also differ substantially in the hormone-binding domain. The differences in the A/B domains suggest that the transcriptional activation of different estrogen-responsive genes by ERα and ERβ may play different roles in carcinogenesis. It is well known that the presence of ERα in breast and endometrial carcinoma is associated with a less aggressive phenotype (Rose 1996; Pearce and Jordan 2004; Ito et al. 2005). However, the role of ERβ in the development and growth of these tumors has not been as fully elucidated as that of ERα. The ratio of ERα/ERβ differed between normal and cancerous tissues and a higher ERα/ERβ ratio was observed in breast and endometrial carcinoma (Sasano et al. 1999b; Utsunomiya et al. 2000; Bardin et al. 2004). ERβ mRNA was detected in 36% of endometrial carcinomas cases, whereas ERα mRNA hybridization signals were detected in 80% of those cases. ERβ was coexpressed with ERα and the estrogenic effects were considered to occur predominantly through ERα in endometrial carcinomas (Utsunomiya et al. 2000).

**Progesterone receptor**

Progesterone receptor (PR) is present in two isoforms, termed PRA and PRB. These isoforms are translated from the same gene, following initiation of transcription from different promoters (Kastner et al. 1990). There have been several studies addressing the individual effects of PR isoforms. PRA can repress PRB activity in cells in which PRA was not transcriptionally active, and PRA might be associated with a cell- and promoter-specific repressor of PRB (Vegeto et al. 1993). In addition, microarray analyses of human breast cancer cells expressing either PRA or PRB have confirmed that each of the PR isoforms has a unique set of target genes, with little overlap (Richer et al. 2002). These functional and transcriptional differences suggest that the development, invasiveness, and metastatic potential of carcinoma cells can be influenced by the PR status of the tumor cells. In breast carcinoma, a significant proportion of tumors expressed very low levels of PRB and consequently exhibited a high PRA/PRB ratio (Graham et al. 1996). PRA predominated in invasive ductal carcinoma (Ariga et al. 2001). In addition, breast carcinoma patients with PRA-rich tumors were generally associated with poorer disease-free survival rates (Hopp et al. 2004). PRA overexpression was also associated with alterations adhesive properties.

In endometrial carcinoma, reduced expression of either one or both of the PR isoforms has been observed in the majority of endometrial tumors, compared with hyperplastic or normal endometrium (Arnett-Mansfield et al. 2001). Several studies have demonstrated that PRB was more common than PRA in endometrial carcinoma (Miyamoto et al. 2004; Saito et al. 2006) (Fig. 2). Very recently, we reported that cases that were negative for either one or both of the PR isoforms were significantly associated with shorter disease-free and overall survival of the patients (Saito et al. 2006) (Fig. 2). In addition, multivariate analysis demonstrated that an absence of PRA immunoreactivity was an independent risk factor in disease-free survival of the patients. The results of our study indicate that the loss of expression of PR isoforms, especially expression of PRA, may result in aggressive biological characteristics in human endometrioid endometrial carcinoma that can play important roles in the prognosis and/or recurrence, in these patients.

In summary, these results indicate that the biological significance of PR isoforms differs markedly between endometrial and breast carcinomas.

**Hormone replacement therapy**

The possible increased risk of endometrial carcinoma associated with exogenous estrogen in postmenopausal women was suggested in the 1970s. Several reports suggested the increased incidence of endometrial carcinoma in patients who used unopposed estrogen (Creasman 2002;
Hale et al. 2002). This risk of endometrial carcinoma increases in a dose- and time-dependent manner with ERT. High levels of estrogens and for a long-term, elevated the risk of endometrial carcinoma 5-fold and beyond (Schneider 2002). Thus, estrogen-induced endometrial carcinoma tends to be well-differentiated and superficially invasive form of cancer, with an excellent long-term survival (Creasman 2002; Schneider 2004).

Several studies have found that the addition of progestin to estrogen reduced the increased incidence of endometrial carcinoma associated with unopposed estrogen (The Whiting Group for the PEPI Trial 1996; Creasman 2002; Hale et al. 2002; Schneider 2004). For example, the Postmenopausal Estrogen/Progestin Interventions trial (PEPI) (The Whiting Group for the PEPI Trial 1996) clearly showed the effects of hormone replacement therapy on endometrial histology in postmenopausal women, in a 3-year multi-center,
randomized trial. They concluded: 1. Among the 119 women in the conjugated equine estrogen-only group (CEE), 74 developed some type of endometrial hyperplasia during follow-up, with 41 women displaying the more serious diagnoses of complex or atypical hyperplasia; 2. At a dosage of 0.625 mg, daily administration of CEE enhanced the development of endometrial hyperplasia; 3. Combining CEE with continuous or cyclic progestin protected the endometrium from the hyperplastic changes associated with estrogen-only therapy. In general, current management of postmenopausal hormone therapy is based on continuous application of estrogens with additional cyclical or continuous combination of progestins, especially medroxyprogesterone acetate (MPA). The WHI study randomized 16,608 women to HRT (CEE and MPA; 8,506 patients) and placebo (8,102 patients) (Rossouw et al. 2002). Endometrial carcinomas were observed in 22 patients of the HRT group (0.05%) and in 25 patients of the placebo group (0.06%), corresponding to a hazard ratio of 0.83 (95% CI, 0.47-1.47) (Anderson et al. 2003). Similar results were obtained in the Heart and Estrogen/Progesterin Replacement Study (HERS) and the Million Women Study (MWS) (Hulley et al. 1998; Beral et al. 2005). Taking the recent results of the WHI-, HERS-, and MWS-study into account, the available data show that combined HRT reduced the risk of endometrioid endometrial carcinoma.

Several epidemiologic studies have specifically addressed the formulation of hormone replacement therapy utilized, and the risk of breast carcinoma (Schneider 2002; Colditz 2005). In addition, the WHI study and the MWS recently reported an increasing risk of breast cancer in a group of HRT-users (Rossouw et al. 2002; Beral 2003). The findings of the WHI- and the MWS-studies are summarized in Table 1. The WHI study showed that women receiving estrogen plus progestin exhibited an increased risk of invasive breast carcinoma (HR, 1.24; 95% CI, 1.01-1.54), but not an increased risk of in situ breast carcinoma (HR, 1.18; 95% CI, 0.77-1.82) (Chlebowski et al. 2003). However, the WHI study also showed that women receiving estrogen alone did not exhibit an increased risk of invasive breast carcinoma (HR, 0.77; 95% CI, 0.59-1.01) (Anderson et al. 2004). The WHI study clearly showed that breast carcinoma risk was not increased in patients treated only with estrogen, but was significantly increased in those with both estrogen and progestin. In addition, subgroup analyses of this study recently revealed that first time exposure to estrogen treatment during the trial was associated with significantly fewer cases of breast cancer, compared to placebo (HR, 0.76; 95% CI, 0.58-0.99; p < 0.05); women who received estrogen treatment exhibited significantly fewer breast cancers with localized disease and significantly fewer breast cancers with ductal carcinoma (HR,

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<td>HR (95% CI)</td>
<td>0.83 (0.47-1.47)</td>
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<td>HR (95% CI)</td>
<td>1.45* (1.02-2.06)</td>
<td>0.71* (0.56-0.90)</td>
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WHI, Women’s Health Initiative; MWS, Million Women Study; HR, hazard ratio.
0.71; 95% CI, 0.52-0.99) (Stefanick et al. 2006). The international menopause society assessed this study and suggested that ET for postmenopausal women does not increase the risk of breast cancer and may even be protective, in certain subgroups of hormone users. These clinical data suggest that the risk and mechanism(s) for estrogen and progestin in tumorigenesis are certainly different between the endometrium and breast.

Progestin is important in opposing the proliferative actions of estrogen. Many of the clinical studies described above support the fact that progestin stimulates cell differentiation and growth suppression of endometrial glandular cells. However, the molecular mechanisms that negatively regulate the growth of endometrial cells are not fully understood. Growth suppression of endometrial glandular cells by progestin has been explained by several hypotheses. Progestin decreases the expression of ERs via an increase in the rate of ER breakdown and a decrease in the rate of ER synthesis (Takeda and Leavitt 1986). Up-regulation of p27, a tumor suppressor that inhibits cyclin E/cdk2 activity, by progestin was found to be involved in the growth suppression of normal and malignant human endometrial glandular cells (Shiozawa et al. 2001). In addition, progestin stimulates the expression of 17-HSD type 2, which catalyzes the conversion of the potent estrogen, E2, to the inactive form, E1, in epithelial cells of human endometrial tissue (Yang et al. 2001). We also demonstrated that 17-HSD type 2 was detected only in the cytoplasm of glandular cells in the secretory phase, but that this expression did not occur in the proliferative phase endometrium (Utsunomiya et al. 2001; Ito et al. 2006).

As for breast and progestin, there are many controversies as to whether progestins protect against or enhance the risk of breast carcinoma development (Santen et al. 2001; Santen 2003). In the normal breast, breast cell mitotic activity changes due to the menstrual cycle (Anderson et al. 1982). The mitotic activity of breast epithelium varies markedly during the normal menstrual cycle, with peak activity occurring during the luteal phase. This result demonstrated that a close correlation existed between the mitotic activity of breast epithelium and progestin. This pattern is quite different from the endometrium, in which mitotic activity is virtually restricted to the follicular phase. Hofseth et al. (1999). Benign breast biopsies have been analyzed using proliferative cell nuclear antigen (PCNA) and Ki-67 antibodies to measure the relative risk of cell proliferation among the users of estrogen plus progestin, estrogen only and no HRT. Treatment with estrogen plus progestin had a significantly higher index of PCNA and Ki-67 compared with treatment with estrogen alone. They showed that postmenopausal HRT with estrogen plus progestin was associated with greater breast epithelial cell proliferation and density than with estrogen alone or no HRT.

Even if progestin may exhibit proliferative effects on normal breast tissue, a big question remains as to whether or not progestin also exhibits a proliferative effect on breast carcinoma tissue. If progestin exhibits anti-proliferative actions on breast carcinoma tissue, carcinoma cells would not grow or at least grow very slowly. Indeed, the WHI study revealed the increased risk of invasive breast carcinoma, but not of in situ breast carcinoma in the patients treated with estrogen and progestin (Chlebowski et al. 2003). Little is known about the function of progestin, especially the combined function of estrogen and progestin, in breast carcinoma tissue. Recently, Lofgren et al. (2006) reported that among women using HRT at the time of diagnosis, breast carcinoma tissue showed higher values for both PRA and PRB, compared to women without such treatment, and suggested that increased PR expression could possibly be related to breast carcinoma risk during estrogen/progestin treatment. This particular group also demonstrated that different treatments, estrogen only and estrogen/progestin therapy, exhibited a different impact on PRA and PRB expression in the normal breast tissue from surgically postmenopausal Cynomolgus macaques and thus on the PRA/PRB balance (Isaksson et al. 2003). We previously demonstrated that MPA increased the level of 17-HSD type 1 mRNA in a breast carcinoma cell line (Sasano et al. 2000). In addition, breast carcinoma cells express only 17-HSD type 1, which converts estrone to estradi-
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ol (Suzuki et al. 2000). These results suggest that progestin induces 17-HSD type 1 expression and eventually, tissue concentrations of estradiol may be increased, contrary to the expectation. Further investigation will be necessary to determine the combined function of estrogen and progestin, in breast carcinoma tissue.

**Conclusion - differential expressions of 17-HSD and PR isoforms between endometrial and breast carcinomas**

This review suggests that the enzymes responsible for intratumoral estrogen metabolism and biosynthesis are markedly different between human breast and endometrial carcinoma, although both are considered “estrogen-dependent malignancies” (Fig. 3). 17-HSD type 1 plays an important role in the regulation of high E2 levels in breast carcinoma tissues, while 17-HSD type 1 is not detectable and 17-HSD types 2 and 5 are essential for the maintenance of E2 concentrations in endometrial carcinoma tissues. In addition, the biological significance of PR isoforms differs between endometrial and breast carcinomas.

These basic and clinical investigations will help to understand the biology and provide the new knowledge for prevention, diagnosis and

**Fig. 3.** The possible cascades of local production of testosterone and estrogen in “estrogen-dependent malignancies”.
A: Schema illustrating the possible cascade of local production of testosterone and estrogen in breast carcinoma. B: Schema illustrating the possible cascade of local production of testosterone and estrogen in endometrioid endometrial carcinoma.
treatment of “estrogen-dependent tissues”. However, this awaits further investigations for clarification.

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References


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