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NON-THEMATIC REVIEW

Expression of estrogen and progesterone receptors across human malignancies: new therapeutic opportunities

J. Munoz · J. Wheler · R. Kurzrock

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Abstract Estrogen and progesterone receptors (ERs and PRs) are known for their prognostic as well as treatment predictive value in breast cancer. Although these receptors are differentially expressed in some other malignancies, and likely participate in the biology of those cancer types, the relevance to outcome and therapy is not well established. The use of ER as a highly effective therapeutic target in oncology was pioneered in breast cancer, and the lessons learned from its success could potentially benefit patients with several other malignancies in which hormone receptors are highly expressed. Indeed, there are several potent drugs available that target hormone receptors. These agents show incontrovertible evidence of benefit in patients with hormone receptor-positive breast cancer. It is conceivable that these drugs may have salutary effects in a variety of cancers other than those originating in the breast, based on the overexpression of hormone receptors in some patients, and the preclinical and clinical reports showing responses to these drugs in diverse cancers, albeit in small series or anecdotally. We therefore undertook a literature review in order to summarize the current data regarding the biologic and clinical implications of expression of estrogen and progesterone receptors in various malignancies and the possibilities for deployment of hormone manipulation beyond breast cancer.

Keywords Estrogen · Progesterone · Receptor · Therapy · Molecular · Phase I clinical trials

JM and JW share first authorship.

J. Munoz (✉)
Department of Hematology-Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ, USA
e-mail: jlmunoz@mdanderson.org

J. Wheler
Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX, USA

R. Kurzrock
Center for Personalized Cancer Therapy and Division of Hematology and Oncology, University of California San Diego Moores Cancer Center, San Diego, CA, USA

1 Introduction

Defining estrogen and progesterone receptor (ER and PR) status in tumor tissue is standard in patients suffering from breast carcinoma. Indeed, the expression of these receptors informs prognosis, and patients with breast cancer have shown excellent benefit from interrogating ER and PR status as a determinant of therapy. The exploration of ER and PR status and its relevance in other tumor types has, nonetheless, lagged behind breast cancer. Yet, ERs and/or PRSs have been documented in non-neoplastic tissues such as the skin [1–3], and multiple tumors have also been demonstrated to variably express ER and/or PR, including but not limited to the skin; cerebral meningioma; renal cell carcinoma, hepatocellular carcinoma, non-small cell lung carcinoma, and thyroid carcinoma; and breast, pancreatic, prostate, colon, and gastric adenocarcinoma (Table 1). The evidence is, however, not consistent, an issue perhaps attributable to a variety of factors: heterogeneous methods utilized to probe steroid hormonal status, differences between primary and metastatic tumors, intra-tumor heterogeneity, technical exigencies, and variability of interpretation by different pathologists [4, 5] (Table 2, Fig. 1). These issues have also been problematic for the breast cancer literature, but, despite

Table 1 Estrogen receptor (ER) and progesterone receptor (PR) expression across malignancies*

Neoplasm	Subtype	ER**	PR** **	Comment	References
Adrenocortical cancer	Not specified	47 %	Not reported		[122, 123]
Astrocytoma	Grade I/II	0 %	8 %		[124]
Astrocytoma	Anaplastic	0 %	45 %		[124]
Basal cell carcinoma	Not applicable	0–24 % (4/17)	0–29 % (5/17)		[64, 125]
Bladder cancer	Urothelial carcinoma	10.9 %	0 %		[72, 73, 71]
Cervical invasive carcinoma	Squamous adenocarcinoma	5 % 6 %	3 % 4 %		[103]
Colorectal	Adenocarcinoma	1.2 %	0.4 %		[72]
Desmoid		0–90 %	0–33 %	Variability in ER positivity rates may be due testing of ER-α versus ER-β, or to technique	[126–130]
Gastric/esophageal carcinoma	Not specified	0.4–100 %	0.5 %	Numbers varied widely, partially depending on whether ER-α or ER-β or both were assessed	[72, 95, 96]
Gastrointestinal stromal tumors	Not applicable	0 %	0 %	Only 19 patients assessed	[131]
Glioblastoma multiformis	Not specified	0 %	59 %		[124, 132]
Kaposi's Sarcoma	Not applicable	0 %	0 %		[131, 133–137]
Laryngeal cancer	Squamous	37–53 %	48–73 %		[58, 59]
Leiomyomata	Uterine	78 %	88 %		[138–140]
Leiomyosarcoma	Uterine	40 %	38 %		[138, 141]
Lung cancer	Adenocarcinoma	11.7 %	4 %	Rates may be different in other subtypes	[72]
Melanoma	Not applicable	46 %	18 %		[63, 64]
Mesothelioma	Peritoneal	80 %	100 %		[101]
Meningioma	Not specified	0 %	87.5 %		[142]
Nasopharyngeal angiofibroma (iuvenile)	Not applicable	0–25 %	0–58 %		[48, 49]
Nasopharyngeal carcinoma	Not applicable	94 %	44 %		[50, 51]
Osteosarcoma	Not applicable	40 %	32 %		[143–147]
Ovarian cancer		~66–89 %	~31–98 %	Percent positivity depends on subtype	[109–111, 148, 149]
Pancreatic cancer	Adenocarcinoma	0–33 %	3 %		[72]
Prostate cancer	High grade	80 %	83–92 %		[77–79, 150]
Renal cancer	Not specified	~1 %	~1 %		[151, 72]
Salivary gland, recurrent	Recurrent Pleomorphic adenoma	19 % Rare in other subtypes	96 %	ER and PR are rare in other subtypes of salivary gland tumors	[55, 57]
Testicular germ cell tumors	Not specified	0 %	0 %		[70, 69]
Thyroid	Various	0 to 31 %	0 to 7 %	ER-positive mainly in differentiated thyroid tumors	[32–34, 41, 42, 152]
Thymomas and thymic cancer	Not specified	38 to 83 %	~0 %	Rates may depend on ER-α versus ER-β	[44–47]
Uterine carcinoma	Endometrial adenocarcinoma	79.5 %	86.9 % (106/122)		[105]

ER estrogen receptor, *NA* not available, *PR* progesterone receptor

*Data curated from references 1–154

**Many studies had small numbers of patients, using ranging from 15 to 100

the limitations, knowing ER and PR status has proven invaluable. Herein, we provide an overview of the literature on ER and PR expression in diverse tumors beyond breast cancer and implications for therapy.

Table 2 Limitations and primary reasons for discrepancies in rate of ER and PR positivity between studies

Non-standardized techniques
Different ER and PR subtypes studied
Grouping of ER-α/ER-β and PR-A/PR-B in earlier studies
Different types of antibodies used
Different concentrations of antibodies used
Non-selective (or unknown specificity) antibodies used
Histologic as well as epidemiologic different study populations within a particular malignancy
Variety of cutoff points for IHC used (1+ in >10 % of cells; 1+ in 1–25 % of cells; >50 % of cells; score 0–8, etc.)
Nuclear versus cytoplasmic staining of receptors
Different expressions of ER/PR depending on the area of the tumor that undergoes biopsy

1.1 The duality of estrogen receptors—ER-alpha and ER-beta

One of the first descriptions of the fate of steroidal estrogen in target tissues was reported in 1960 [6]. Since then, ERs have been discerned in a wide range of tumors (Table 1). When ERs were first cloned in 1986 [7], it was believed that only one receptor existed. However, a second gene coding for an ER was cloned in 1996 [8]. It was given the name of ER-beta (ER-β) due to the striking similarity of its sequence with the classic ER [8], which was then denoted as ER-alpha (ER-α) or "classic" ER (Fig. 1). Since that time, several ER-β isoforms have been identified in diverse malignancies.

ER-α and ER-β are distinct genes/proteins. They are encoded by separate genes known as ESR1 and ESR2, respectively. ER-α is localized on chromosome 6 and ER-β on chromosome 14. These genes have significant sequence

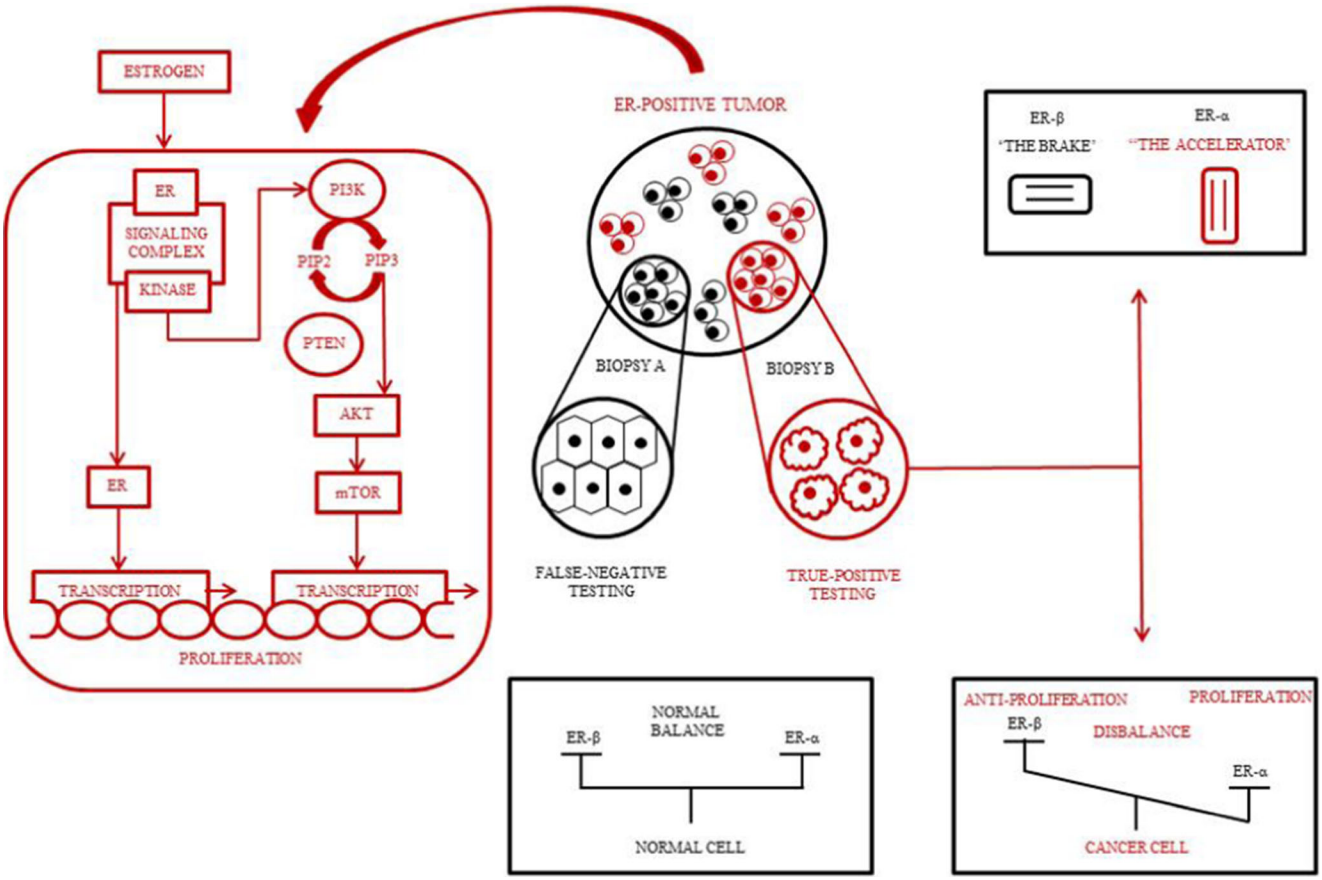

Fig. 1 Sampling issues and ER-α/ER-β pathways. *Center*: sampling pitfalls regarding interpretation of IHC for hormonal estrogen receptors (ER) in solid tumors. *Right*: diagram representing the imbalance between ER-α and ER-β that results in estrogen-dependent malignant progression. ER-β has been designated as "the brake" of estrogen-mediated proliferation. *Left*: after estrogen binding, ER will function as a ligand-activated transcription factor that translocates to the nucleus and triggers gene expression. These hormone-attached receptors form dimers and bind to specific DNA sequences named estrogen response elements, removing DNA co=repressors, and enlisting co-activator proteins, with subsequent gene expression. ER will also be activated via a ligand-independent path as growth factor receptors may activate specific kinases that will directly phosphorylate ER triggering gene expression. Finally, a third signaling path involves a subpopulation of cell membrane-associated ER that, after activation by estrogen, forms a signaling complex that results in rapid activation of specific kinases. Possible relationship between ER and the PI3K pathway is also shown. Upon estrogen binding, signaling complexes assemble and sequentially activate tyrosine kinases (i.e., src), the serine/threonine kinase PI3K that produces phosphatidylinositol (3,4,5)-triphosphate (PIP3), and the subsequent interaction between Akt and mTOR

homology. ERs function as ligand-activated transcription factors. Hormone-activated ERs form dimers, including ER-αα or ER-ββ homodimers, or heterodimers. At least three ER-α and five ER-β isoforms have been identified.

The potent tumor growth-promoting activities of estrogens in target tissues are well established and are achieved in part by increased transcription of cell cycle genes via ER-α. Although ER-α activates transcription at the activator protein-1 site, ER-β might also inhibit gene transcription induced by ER-α. It is thus believed that ER-α is pro-proliferative, whereas ER-β is anti-proliferative, and that these antagonist forces co-exist in a finely tuned homeostatic balance [9]. Based on this concept, several studies suggested that an increase in the ER-α / ER-β ratio (Fig. 1) might have a possible role in tumor growth [10, 11]. Thus, it has been suggested that ER may have a dual role in cancer proliferation [12]. In a paradoxical fashion, however, estrogens and ER can also inhibit cancer cell invasiveness in experimental models [12]. Estrogens are proliferative signals in ER-positive cells, whereas anti-estrogens are effective weapons in our armamentarium against such hormone-fueled tumors. Nonetheless, estrogens can also apparently protect against cancer cell invasiveness through different mechanisms, which might explain why ER-driven tumors are usually well differentiated and less invasive than their ER-negative counterparts [12].

1.2 The good, the bad, and the ugly: ER-beta subtypes 1, 2, and 5

ER-β has a putative overall protective role against carcinogenesis and, in the world of hormonal receptors, has been named "the brake pedal" of tumor progression [13]; nevertheless, current identification of several other ER subtypes complicates this matter. Recently, Leung et al. [14] identified the ER-β isoforms, particularly in prostatic cancer samples, as well as distinct roles for ER-β1, ER-β2, and ER-β5. ER-β2 was the most common isoform, followed by ER-β1. The least common of the three isoforms was ER-β5. ER-β2 and ER-β5 have been observed most frequently in the cytoplasm, whereas ER-β1 is located primarily in the nucleus. The seminal contribution of this report stems from the fact that metastasis-promoting ER-β2 and ER-β5 were associated with a poor prognosis in prostate cancer [14]. Both isoforms, separately or together, enhanced cancer invasiveness, whereas ER-β5 promoted migration. Shaaban et al. [15] found that different forms of ERβ were relevant in breast cancer; specifically, their report showed that nuclear and cytoplasmic expression of ERβ1, ERβ2, and ERβ5 were associated with distinct prognostic outcomes for breast cancer patients. Most studies have however concentrated primarily on the "classical" wild-type ER-β (now called ER-β1), as the presence and roles of the new isoforms have yet to be validated across different malignancies.

1.3 The duality of progesterone receptors, PR-A and PR-B

A dichotomy similar to that discovered for ERs exists for PRs [16]. Indeed, there are two distinct isoforms of PR: PR-A and PR-B [17]. PR-B contains an additional 164 amino acids at the amino-terminus, possibly due to transcription from alternate promoters within the same gene [18]. PR-A seems to be a robust repressor of PR-B-mediated transcription in a hormone-dependent manner, which would suggest a specific role for the PR-A isoform as a regulator against uncontrolled stimulation by its PR-B counterpart. In the search for a biologic rationale for the existence of two almost identical forms of receptors, which nonetheless behave in an antagonistic fashion, the duality of the roles of PR as an activator or repressor of transcription serves to explicate the potential mechanism by which cells can signal opposite responses after being challenged by a single hormone [19].

1.4 Localization of hormonal receptors: plasma membrane, cytoplasm, or nuclear compartments

Immunohistochemistry (IHC), despite its shortcomings, remains the method of choice for the assessment of ER expression. The method has certain advantages in that the number of cancer cells and the presence of non-malignant cells in the specimen can be co-ascertained. Moreover, low-grade ER-positive (currently known in breast cancer literature as luminal A) cancer cells must be differentiated from high-grade ER-positive cancer cells as they might respond to therapy in a different way. These characteristics differentiate IHC from tissue-grinding methods that delineate receptor-binding activity or determination of messenger RNAs [20].

Hormonal receptors may be localized in the nucleus, plasma membrane, cytoplasm, and mitochondria, where they mediate the distinct physiological actions of estrogens. The subcellular localization of ERs determines the particular functionality of the ER, which is disturbed in several malignancies. The classical hormonal receptors, in addition to having a well-documented transcriptional potential, can also mediate the activation of intracellular signaling pathways (Fig. 1), including the rapid effects of estrogen on vasodilation and protection of endothelial cells against injury [21]. However, in spite of overlapping expression and functionality in multiple tissues, the precise mechanisms and consequences of their subcellular localization remain largely unclear.

1.5 Co-expression of and interaction with androgen receptors

The literature suggests that androgen receptors (AR) expression is widespread among malignancies. Furthermore, some tumors, such as salivary gland ductal tumors, have AR positivity rates approaching 100 % in some subtypes [22]. Of interest, breast [23] and gynecologic tumors also have high

rates of AR positivity [24]. The latter may have special clinical relevance since agents such as anastrozole, an aromatase inhibitor used to suppress estrogen levels in patients with ER-positive breast tumors, can elevate androgen levels [25]. The interaction of estrogen or progesterone or their inhibitors with androgen receptors may also be important. For instance, Mobbs et al. [26] studied the concentration of free and total androgen receptors (ARs) in prostate neoplasia. In untreated carcinoma samples, the occupancy of cytoplasmic AR by endogenous androgens was high. Orchiectomized patients had AR levels consistent with androgen deprivation as total cellular AR was depleted. However, samples obtained from patients who had received chronic diethylstilbestrol (DES) (a synthetic nonsteroidal estrogen) showed high total cellular AR levels, and most of the AR was present as free cytoplasmic AR [26]. The interaction of estrogens, progesterone, and androgens and their receptors may therefore be of importance to protean malignancies that co-express these receptors and for the potential of effective hormonal manipulation (Fig. 2).

1.6 Expression and biology of hormone receptors in diverse cancers

A subset of patients with multiple different tumor types can express ER and/or PR receptors (Table 1). Furthermore, both preclinical and clinical evidence suggests that these receptors participate in the biology of some of these malignancies. Indeed, patients with cancers other than those derived from the breast that are hormone receptor-positive have been shown to respond to anti-estrogen agents, though the number of patients reported is generally small.

2 Head and neck malignancies

2.1 Thyroid carcinoma

Thyroid cancer is the most common endocrine neoplasm. Premenopausal women have the highest risk for developing papillary and follicular thyroid carcinoma, which suggests a hormonal influence [27]. In the thyroid microenvironment, estrogen seems to be anti-apoptotic via Bcl expression [28] and pro-angiogenic via ER and vascular endothelial growth factor signaling [29]. Preclinical data show that there is evidence of cross talk between estrogen and the PI3K [30] and/or ERK1/2 pathway [31].

In earlier studies that did not distinguish between ER-α and ER-β [32], the incidence of ER-positive cases was 24 % (31/130) for nodular goiters, 22 % (8/37) for follicular adenomas,

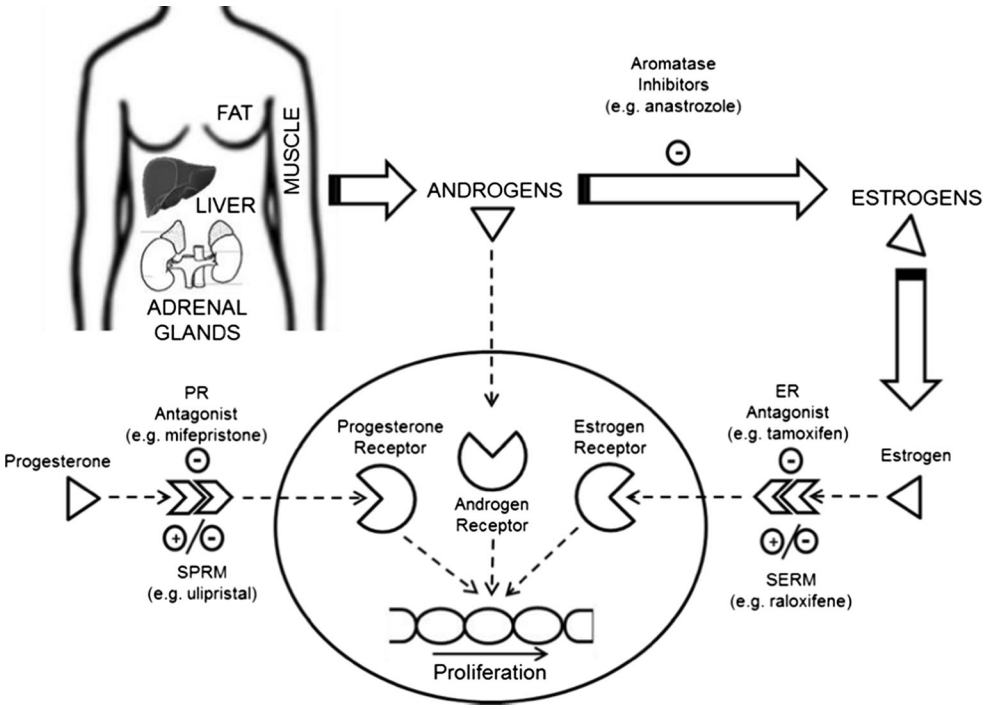

Fig. 2 Simplified mechanism of action of estrogen receptor (ER) antagonists, selective estrogen receptor modulators (SERM), progesterone receptor (PR) agonists, and selective progesterone receptor modulators (SPRM). SERMs are a class of compounds that act on the estrogen receptor; they are distinguished from pure estrogen receptor agonists or antagonists in that their action is different in various tissues, thereby permitting selective inhibition or stimulation of estrogen-like action in various tissues. Examples include raloxifene, which acts as an estrogen antagonist in uterine and breast tissue and as an agonist in bone (see also Table 3). Similarly, SPRMs are agents that act of the progesterone receptor in a selective fashion, being agonist in some tissues and antagonists in others. An example of an SPRM is ulipristal. In contrast, progesterone is a full progesterone receptor agonist, and aglepristone is a full antagonist

11 % (2/18) for follicular carcinomas, 31 % (37/119) for papillary carcinomas, 0 % (0/35) for medullary carcinomas, and 0 % (0/12) for undifferentiated carcinomas, suggesting that the incidence of ER reactivity is higher in well-differentiated thyroid lesions. Similar findings have been reported by others [33, 34] though, when isoforms of ER were examined, there was more inconsistency in results [35–37] [38] [39].

In regard to PR, Kansakar et al. [40] found significantly higher PR in tumors compared to normal tissue (N=104 patients), while in a smaller study, no PR positivity was found [41]. Bléchet et al. [42] reported that 7 % of medullary thyroid cancers (2/28) expressed PR.

The clinical implications of these results merit investigation. As an example, albeit an anecdotal one, Khalil et al. [43] reported a 29-year-old woman with non-resectable papillary thyroid cancer who had a dramatic response to anti-estrogen therapy with tamoxifen.

2.2 Thymoma and thymic carcinoma

Early studies that did not distinguish between ER-α and ER-β showed ER positivity in 37.5 % (3/8) cases of thymoma; PR was not detected in any of the cases (0/8) [44]. Ishibashi et al. [45] found positive nuclear immunoreactivity for ER-α in 66 % of cases, for ER-β in 7 %, for PR-A in 4 %, and for PR-B in 49 %. Mimae et al. [46] found a high rate of ER-β expression in thymomas (82.9 %) and thymic carcinomas (76.4 %), whereas the expression rates for other hormonal receptors were low, including ERα (13.6 %) and PR-A (0.71 %). Interestingly, intra-tumoral estradiol apparently abrogates cell proliferation via ER-α in human thymoma epithelial cells, leading some authors to speculate that estradiol could be an effective therapy for thymoma [47].

2.3 Nasopharyngeal carcinoma and juvenile nasopharyngeal angiofibroma

Juvenile nasopharyngeal angiofibroma is a benign hormone-driven tumor that primarily afflicts adolescent males and expresses ER (0–25 %) and PR (0–58 %) [48, 49]. Looking at malignant tumors, particularly nasopharyngeal carcinomas, Xu et al. [50] found ER in 94.3 % (67/71) and PR in 43.6 % (31/71). A retrospective study by Mo et al. [51] suggested that positive expression, particularly strong reactivity, of ER and PR correlated with poor prognosis and development of metastasis. We were unable to find studies of hormonal manipulation in nasopharyngeal carcinoma despite the high degree of ER/PR expression in this tumor.

2.4 Salivary gland tumors

Salivary gland tumors seem to be hormonally driven [22, 52] in a similar fashion to that of breast cancer, and some salivary tumors such as adenoid cystic carcinomas and salivary ductal cancers portray microscopic similarities to primary lesions of the breast [53].

Nasser et al. [22] reported a series of 78 formalin-fixed, paraffin-embedded salivary gland tumors: ER and PR reactivity were seen in only a few cases of salivary gland tumors, and all 26 benign salivary gland tumors were negative for ER and PR. AR reactivity is also seen in 20 % (2/10) of acinic cell carcinomas, 20 % (2/10) of mucoepidermoid carcinomas, and 20 % (2/10) of adenoid cystic carcinomas [22]. Fan et al. [54] reported that salivary duct carcinoma expresses AR in nearly all cases. Therefore, receptor reactivity might differ depending on the type of salivary gland tumor [55]. As another example, patients with recurrent pleomorphic adenomas of the parotid gland showed a high PR expression (96 %) compared to a control group (61 %) with primary pleomorphic adenoma, whereas ER expression was present but relatively low in those groups (19 and 17 %, respectively) [55].

Despite the morphologic similarity of adenoid cystic salivary gland tumors and breast cancer, the former have been shown to either not express ERs [52] or to express only ER-β as in the case of salivary adenocarcinoma cells [56]. Even so, an anecdotal report by Shadaba and colleagues [57] described treatment with tamoxifen in a patient with adenoid cystic carcinoma of the parotid gland with an 18+-month partial remission achieved.

2.5 Laryngeal cancer

ERs were present in 37 % (17/46) and PRs in 48 % (22/46) of patients with laryngeal squamous cell carcinoma [58]. A different study evaluated samples from 15 laryngeal carcinomas assayed both by mRNA and protein levels for ER (53.3 %) and PR (73.3 %), finding greater immunopositivity in malignant cells than in normal adjacent tissue [59]. However, Urba et al. [60] treated 12 patients with recurrent laryngeal carcinoma with tamoxifen, reporting no clinical responses, although only two samples were assayed for ER and PR. In other squamous head and neck tumors, functional ER may be present in 40.3 % of cases [61], while PR positivity may be low [62].

3 Cutaneous malignancies

3.1 Melanoma

Hormone receptors have been implicated in melanoma [63]. ER positivity has been found in 46 % (16/35) [63] and PR in 18 % of 45 cases of malignant melanoma [64]. Even so, Creagan et al. [65] showed no responses to the anti-estrogen tamoxifen in 25 patients. In contrast, however, Karakousis

et al. [66] showed that three women had objective responses (of 17 patients with melanoma treated with tamoxifen). Quencez et al. [67] also showed responses in two of four patients treated with tamoxifen for cutaneous ER-positive metastases from melanoma. Cocconi et al. [68] reported that dacarbazine plus tamoxifen is more effective than dacarbazine alone (response rate of 28 % versus 12 %, P=0.03, and median survival of 48 versus 29 weeks, P=0.02).

4 Genitourinary malignancies

4.1 Testicular germ cell tumors

Preclinical data suggest that estrogens might fuel human testicular germ cell cancer proliferation via membrane-mediated activation of extracellular regulated kinase (ERK)1/2 and cAMP-dependent protein kinase A (PKA) [69]. The expression of hormone receptors differs by tumor type [70]. ER-α was absent in all of the testicular germ cell cancers studied by Pais et al. [70]; ER-β expression was markedly diminished in seminomas, embryonal cell carcinomas, and in mixed germ cell tumors [70].

4.2 Bladder cancer

Urothelial carcinoma of the urinary bladder, unlike prostate and breast cancer, is currently not considered as a hormone-driven malignancy [71]. Wei et al. [72] pooled data from five different studies (N=651 patients) regarding ER expression in bladder urothelial carcinoma, finding it in 10.9 % (71/651) of cases. None of the specimens containing urothelial carcinoma of the bladder exhibited PR expression [73]. However, Shen et al. [74] documented that only 0.8 % (2/224) of human bladder cancers weakly expressed ER-α, whereas ER-β was expressed in 63 % (141/224) of samples. Estradiol modestly enhanced growth in cancer cell lines, while anti-estrogens, such as hydroxytamoxifen and raloxifene, halted the growth of cancer cell lines [74]. Treatment with tamoxifen leading to resolution of cutaneous metastatic implants from transitional cell carcinoma has been documented in a case report [75].

4.3 Prostate cancer

The roles of androgens in prostate cancer are well known. Even so, it may be the balance between androgens and estrogens that is critical to prostate health and disease. Serum testosterone decreases in aging men, while estradiol remains stable or even increases slightly with aging. The variation in the androgen to estrogen ratio has been hypothesized to be responsible for the transition from benign to malignant prostate tissue [76]. The normal stromal tissue in the prostate expresses some aromatase, whereas malignant epithelial tissue in prostate cancer induces aromatase levels, which ultimately alters the ratio between androgens and estrogen [76]. Estrogen, in addition to androgens, may be a candidate therapeutic target.

In this regard, epithelial ER-α immunostaining was present in 80 % of prostatic carcinoma cells, whereas approximately 15 % of stromal cells were positively immunostained for ER-α [77]. PR was found in 92 % (12/13) of prostate cancers [78]. On the other hand, Asgari et al. [79] found ER-β expression in 100 % (29/29) of low and intermediate prostatic carcinomas and in 83 % (19/23) of high-grade tumors. Leav et al. [80] also found that prostatic carcinogenesis was characterized by a loss of ER-β in high-grade dysplasia. Differences between studies may be in part accountable to the anatomic location of the specimens within the prostate (Table 2). For instance, the ratio of AR to PR in the central zone of the prostate is 1.5 to 2.0 while the same ratio in the peripheral zone of the prostate is 0.3 to 0.5 [81]. In a phase II trial of tamoxifen (41 evaluable patients), there was one durable complete remission (1+ year) [82].

5 Lung malignancies

5.1 Non-small cell lung cancer

Wei et al. [72] reported ER expression in 11.7 % (89/760; denominator from pooled data) of lung adenocarcinomas; PR expression was found in 4 % (19/479) of lung adenocarcinomas. A more recent study by Rades et al. [83] reported 20.6 % (12/58) ER-α and 8.4 % (5/59) PR positivity. ER-α was a harbinger of a negative prognosis for men and women, whereas PR status was not associated with outcome. Mauro et al. [84] found total cytoplasmic and/or nuclear immunostaining in 77.6 % (45/58) for ER-α and 75.9 % (44/58) for ER-β; lack of nuclear ER-β and loss of EGFR expression were independently associated with a worse prognosis [84]. Sun et al. [85] reported that EGFR mutation was independently associated with female gender, negative PR expression, and negative aromatase expression, all of which were statistically significant.

Shen et al. [86] illustrated the fact that dual exposure with tamoxifen, an anti-estrogen, and gefitinib, an EGFR tyrosine kinase inhibitor, in non-small cell lung cancer cell lines showed synergistic anti-proliferative effects likely due to functional cross talk between such pathways. Hormonal manipulation in non-small cell lung cancer has been paired with chemotherapy in the clinic with acceptable toxicity, although it remains unclear whether or not the addition of hormonal manipulation would be superior to chemotherapy alone. Perez et al. [87] showed anti-tumor activity in 4 out of 10 patients

with non-small cell lung cancer in a phase I trial of high-dose tamoxifen plus cisplatin. Lara et al. [88] showed an overall response rate of 18 % with a median overall survival of 8.1 months in a phase II trial of high-dose toremifene (an oral selective estrogen receptor modulator) in combination with cisplatin. Chen et al. [89] showed that five out of 25 patients (20 %) had a partial response after 2 cycles with a median survival of 7.7 months in a phase II trial of tamoxifen added to a regimen that included ifosfamide, epirubicin, and cisplatin.

5.2 Small cell lung cancer

Figueredo et al. [90] reported an encouraging phase I/II study of verapamil and tamoxifen added to the initial chemotherapy of small cell lung cancer that documented 24 % complete and 34 % partial response rates with a median survival of 46 weeks. Chen et al. [91] assessed the feasibility of a regimen containing tamoxifen, ifosfamide, epirubicin, and cisplatin for patients with extensive-disease small cell lung cancer; nevertheless, median survival in chemotherapy-naive patients did not increase when compared to the results of a previous trial of ifosfamide plus etoposide. A phase III trial [92] testing a regimen of cisplatin, etoposide, and radiotherapy, with or without tamoxifen, in patients with limited-stage small cell lung cancer failed to show improved survival in the tamoxifen group (88 % for 154 patients treated without tamoxifen and 84 % for 153 patients treated with tamoxifen), although it was an unselected population in terms of ER status.

6 Gastrointestinal malignancies

6.1 Gastric and esophageal carcinomas

Data pooled from 19 previous studies evaluating ER expression and 10 studies evaluating PR expression, irrespective of the antibody used, documented ER expression in 15.9 % (155/972) of cases; however, that number dropped to 0.4 % (2/467) when studies utilizing seldom used older antibodies were excluded [72]. By the same token, when more stringent criteria was used to screen studies that did not specify the type of antibody used, PR expression was found only in 0.5 % (2/383) of cases. A randomized, controlled trial of adjuvant tamoxifen in gastric cancer, in which 55.8 % of tumors were ER positive by an immunohistologic method (ERD5), showed that tamoxifen did not influence survival, although ER receptor status was an independent prognostic factor [93]. Again, discrepancies between the rates of ER expression may be explained by different immunohistologic methods used in older studies (Table 2). Mifepristone, an anti-progestin, abrogates proliferation of PR-positive human gastric cancer cells *in vitro* and *in vivo* mice xenografts [94]. Matsuyama et al. [95] further divided ER into ER-α and ER-β, finding positivity in 0 % (0/29) and 100 % (29/29), respectively. Ryu et al. [96] obtained more conservative numbers, showing that 45.3 % (67/148) of gastric cancer patients displayed ER-β positivity.

6.2 Pancreatic adenocarcinomas

Wei et al. [72] found that ER was found in 0 % (0/276) cases, while PR expression was found in 3 % (2/64) (pooled data from nine studies). Of interest, Lamy et al. [97] reported a complete response to tamoxifen in a patient with metastatic pancreatic adenocarcinoma. Hormonal modulation in advanced pancreatic cancer has been added to chemotherapy too. Tomao et al. [98] showed a partial response in 11 % of patients while 48 % experienced stable disease lasting at least 8 weeks. Eckel et al. [99] showed similar results. Sun et al. [100] suggested that curcumin-induced upregulation of microRNA-22 expressions in pancreatic cells suppressed the expression of the target gene estrogen receptor 1 (ESR1).

6.3 Malignant peritoneal mesothelioma

Chua et al. [101] described ER and PR positivity in 80 and 100 %, respectively, in patients with malignant peritoneal mesothelioma. A phase III randomized trial of surgery with or without intraoperative photodynamic therapy and postoperative immunochemotherapy (cisplatin, interferon alpha-2b, and tamoxifen) showed that the addition of intraoperative photodynamic therapy failed to improve local control or survival in malignant pleural mesothelioma [102]. The role of tamoxifen was not clarified.

7 Gynecologic malignancies

7.1 Cervical cancer

Kwasniewska et al. [103] reported weak immunoreactivity (+/+++) across multiple hormonal receptors including ER expression in 5 % (10/200) of squamous cell carcinoma of the cervix and in 6 % (3/50) of adenocarcinoma of the cervix. In the same study, PR expression was seen in 3 % (6/200) of squamous cell carcinoma of the cervix and in 4 % (2/50) of adenocarcinoma of the cervix. A trial of tamoxifen in patients with recurrent non-squamous cell cancer of the cervix [104] revealed an objective response rate of 11.1 % (two partial and one complete response).

7.2 Uterine cancer

IHC analysis of 144 patients with primary endometrial cancer demonstrated ER positivity in 79.5 % (97/122) and PR positivity in 86.9 % (106/122) of patients [105]. A phase II study of fulvestrant in patients with recurrent endometrial cancer performed by the Gynecologic Oncology Group revealed that one (3 %) patient had a complete response and four (13 %) had partial responses out of 31 ER-positive patients [106]. Interestingly, Xie et al. [107] showed *in vitro* that metformin stimulated PR expression. Ramondetta et al. [108] led a phase II clinical trial of the anti-progesterone mifepristone (RU-486) in patients with PR-positive advanced endometrioid adenocarcinoma or low-grade endometrial stromal sarcoma; no partial or complete responses were observed [108].

7.3 Ovarian cancer

Sinn et al. [109] found PR immunostaining positivity in 31.5 % (45/143) of patients with ovarian carcinoma associated with a favorable prognosis. De Stefano et al. [110] demonstrated positive nuclear ER-α in 74 % of 58 primary advanced serous carcinomas, whereas there was ER-β positivity in 89 % of the same population. Of note, cytoplastic immunopositivity was the main pattern seen in malignant cases although nuclear staining was the norm when normal ovarian tissue was assessed. Farinola et al. [111] reported PR and ER-α positivity in 98 and 66 % of granulosa cell tumors, respectively, and in Sertoli-Leydig cell tumors of 86 and 79 %, respectively. Although epidemiologic studies as well as animal experiments and receptor studies demonstrate that many malignant ovarian tumors are endocrine related and hormone dependent, the place of hormonal therapy in the management of patients with ovarian cancer remains unsettled. Most trials of hormonal treatment in ovarian cancer have been retrospective, involved only limited numbers of patients, and utilized a variety of hormonal preparations with different degrees of potency at different dosages. Overall, in advanced disease, response to hormonal therapy is modest, with about an 8 % objective response rate, albeit with almost no side effects. In a similar patient setting, more toxic agents do not yield a better outcome [112].

8 Lessons from erα-positive breast cancer

The use of ER as a highly effective therapeutic target in oncology was pioneered in breast cancer (Table 3), and the lessons learned from its success could potentially benefit patients across malignancies. The frequency of ER and PR positivity varies widely, from 0 % in triple-negative breast cancer to ~60 % in patients with other types of breast cancer [113]. Ng et al. [114] stratified subgroups of breast cancer patients depending on their hormonal receptor phenotype and found the following percentages: 46.8 % (1230/2629), ER+/PR+; 11.6 % (306/2629), ER+/PR-; 4.6 %, (122/2629), ER-/PR+; and 37 % (972/2629), ER-/PR-. The mechanism of action of drugs (Table 3, Fig. 2) used in the management of ER-positive metastatic breast cancer includes competitive antagonists of the ER, molecules that act as antagonists or agonists depending on the target tissue, receptor down-regulators, and aromatase inhibitors that block estrogen synthesis (Table 3) [115].

The most critical steps for initiation and progression of ERα-positive breast cancers are thought to be upregulation of ERα expression. There are several mechanisms implicated in ER upregulation: increased promoter activity of the ERα gene (ESR1) at the transcriptional level, changes in miRNAs that control ESR1 level, ESR1 gene amplification, and diminished degradation of ERα protein through ubiquitination and proteasomal pathways. Other mechanisms may also be operative, albeit incompletely elucidated. For instance, it has been suggested that ERα (ESR1) gene amplification is frequent in breast cancer [116] and identifies those individuals with high ERα expression. More recently, however, it has been posited that the clustered FISH signals interpreted as ESR1 amplification may be due to the accumulation of transcripts, rather than amplification [117].

Table 3 Examples of Food and Drug Administration (FDA)-approved estrogen and progesterone inhibitors. [Data from www.fda.gov (Accessed August 18th 2014)]

Drug name	Mechanism of action	Indication
Exemestane	Aromatase inhibitor Decreases estrogen production	Breast cancer treatment
Letrozole	Aromatase inhibitor	Breast cancer treatment
Anastrozole	Aromatase inhibitor	Breast cancer treatment
Fulvestrant	Selective estrogen receptor down-regulator	Breast cancer treatment
Tamoxifen	Estrogen receptor antagonist Tamoxifen is metabolized into compounds that bind estrogen receptor but do not activate it (competitive antagonism) Acts as agonist at bone and uterus, antagonist at breast	Breast cancer treatment and prevention
Raloxifene	Selective estrogen receptor modulator (SERM) Acts as an estrogen antagonist in uterine and breast tissue and as an agonist in bone	Breast cancer prevention
Mifepristone	Progesterone receptor antagonist	Medical termination of pregnancy
Ulipristal	Selective progesterone receptor modulator (SPRM)	Emergency contraception

Several different point mutations in the ligand-binding domain of *ESR1* have also been identified in tumor samples from patients with ER-positive metastatic breast cancer. They are discerned after treatment with anti-estrogen therapy, but are rare in primary untreated cancers [118, 119]. Some of these mutations have also been seen in endometrial tumors. In functional modeling of molecular dynamics, these mutations confer constitutive ligand-independent activation of ER and may mediate anti-estrogen resistance.

In addition to deregulation of the components of the ER pathway itself, multiple other mechanisms responsible for endocrine resistance have been proposed: alterations in cell cycle and cell survival signaling molecules and the activation of escape pathways including, but not limited to, EGFR/HER2 (in breast cancer). Activation of the PI3K/AKT/mTOR pathway is also known to attenuate the effects of hormone therapy; combining aromatase inhibitors with mTOR inhibitors has shown efficacy in breast cancer [120] as well as ER-positive ovarian and uterine cancer [121].

9 Conclusions

The determination of ER and PR status in breast cancer proved to be crucial for predicting response to endocrine therapy. While high ER and PR expression have been found in a subgroup of patients with many other malignancies (Table 1), in the majority of cases, they are not being routinely tested as possible targets for therapy. Furthermore, there is a dearth of therapeutic studies using standardized ER or PR assessment and targeting outside of breast cancer, though anecdotal reports and small studies suggest efficacy with minimal toxicity in several cancers including, but not limited to, gynecologic, pancreatic, and lung neoplasms. The biology of ER and PR is however complex with several receptor subtypes that may act to either stimulate or inhibit cell growth. Co-expression of androgen receptors is also found in many malignancies, and these receptors and their ligands may be impacted by hormonal modulation targeted at ER or PR. The differential expression of ER and PR across tumors, and the availability of potent agents that can manipulate hormone status, suggests that interrogation and prosecution of these targets warrant more robust evaluation beyond breast cancer.

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