Management of Breast Cancer in Older Women

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Editors

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Foreword

I was looking at Mrs T – all 45 kilos of her – with somewhat puzzled thoughts. I had prescribed her capecitabine at very prudent doses, in view of her 91-year-old kidneys and physiology. She had reduced my treatment even further, "because it was making her tired." As a result, she was taking a grand total of 500 mg of capecitabine a day. Yet, her metastatic, ER/PR-negative, Her2-positive breast cancer was undoubtedly responding. Her pain was improving and her chest mass was shrinking, as were her lung metastases… What was the secret of that response? Were Mrs T's kidneys eliminating even less drug than predicted by her creatinine clearance? Was her sarcopenia altering drug distribution? Was she absorbing more drug than average? Or was her tumor exquisitely sensitive to fluoropyrimidines? "Physicians," said Voltaire, "pour drugs they know little for diseases they know even less into patients they know nothing about." Medicine has made tremendous progress since the eighteenth century. Yet, there are fields where quite a lot remains to be learned. In developed countries, 25% of breast cancers occur in patients aged 75 years and older. Yet, these patients represent only 4% of the population of traditional clinical trials. That ought to let us wonder how relevant data acquired in patients in their 60s are to a nonagenarian. Fortunately, geriatric oncologists have been stepping up to the task and have generated data to help us to treat such patients.

Drs. Reed and Audisio have assembled in this book the results of their work. The readers will find in a condensed format data to help them to treat this important subgroup of breast cancer patients. They will find in this book data ranging from the impact of age on the biology of breast cancer to the psychosocial considerations. Two well-developed treatment sections will help the readers to practice personalized cancer care for our senior patients. The editors have assembled a remarkable panel of experts in breast cancer and geriatric oncology to contribute their knowledge in their respective field of expertise. This book will no doubt earn a well-deserved place as a reference in the office of oncologists treating older women with breast cancer. May it help us to know more about the drugs, the diseases, and the patients we treat.

Martine Extermann
Florida, USA

Preface

The aim of this book is to provide the readers with a comprehensive review of the important topic of the management of breast cancer in elderly women. The increasing prevalence of breast cancer in the aging population and the extended availability of screening have huge implications for health care services around the world. In the United Kingdom alone, these factors will contribute to an increased incidence of breast cancer of 20% over the next 10 years, representing a huge challenge for clinicians and researchers alike.

Although over half of the patients diagnosed with breast cancer are over the age of 70, there is a major lack of evidence based on randomised clinical trials to guide clinicians and patients in the selection of the best treatment options. Largely because of this failure to include these patients in clinical trials, there are very few evidence-based guidelines to guide treatment. All too often, older patients are managed in accordance with guidelines based on research trials that incorporated exclusively younger women. This deficiency often results in older patients failing to receive appropriate management in all aspects of their care, from screening through diagnosis, therapy, and follow-up.

Despite the real and recognised changes in physiology and functional status with age, assumptions are often made about treatments based on misconceptions in relation to patient's preferences and suitability for such therapies. This can result in under staging and inappropriate under- ,or in some cases, overzealous treatment.

In the face of this background, there is increasing recognition that this issue needs to be addressed and that there exists within the field of geriatrics the appropriate specialist skills to help oncologists to select the appropriate treatment for patients. The editors have an established research and clinical interest in this topic and have brought together a multidisciplinary team of contributors from the fields of epidemiology, oncology, and geriatrics to provide the readers with a comprehensive review of the field. The editors' and contributors' aim is to provide a detailed background to each topic along with clear and useful guidance based on the best available evidence. All the contributors are acknowledged experts in their field and the editors are grateful to them for the time and effort they have committed to this project. We have included relatively new areas such as breast reconstruction and the interpolation between age and race/ethnicity in order to cover the subject area comprehensively.

The editors acknowledge the support of SIOG (International Society of Geriatric Oncology) and the efficient and enthusiastic editorial support from Barbara Lopez-Lucio and our publisher, Springer.

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Part I
Background and Epidemiology

Chapter 1
Basic Science of Breast Cancer in Older Patients

Irmgard Irminger-Finger

1.1 Introduction

Breast cancer is the leading cancer for females in North America and Europe. Although the environment and cultural and ethical backgrounds have an impact on breast cancer frequency, two major risk factors arise above all doubt, namely, increasing age and estrogen exposures. It seems that a cumulative effect of both is leading to the peak of breast cancer incidence in postmenopausal women. In addition, molecular signaling pathways that change with aging might be involved in the predisposition setting. These aging-related signaling pathways and their relation to cancer-related signaling pathways will be discussed here. A second theme will be highlighted in different ways, namely the involvement of the breast cancer predisposition genes in age-dependent incidence of breast cancer.

1.2 Breast Cancer Risk Factors and the Biology of Breast Cancer

Breast cancer incidence and death rates increase with age (Fig. 1.1). About 95% of breast cancer cases in the US occurred in women aged 40 and older. The observed decrease in women aged 80 years and older might reflect the reduced rates of screening and incomplete detection. Today a woman's risk of developing breast cancer during her lifetime is 12.3%, or 1 in 8, while it was 1 in 11 in the 1970s. Mostly, this increase is thought to be due to increased life expectancy.

Hormone exposure is another risk factor, since early menarche, late menopause, and hormone replacement therapy are accepted risk factors (Hulka and Moorman 2001).

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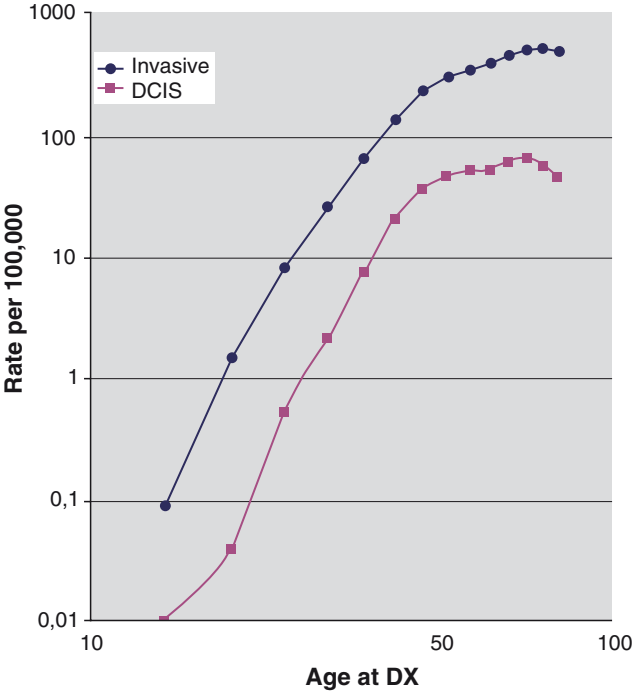

Fig. 1.1 Breast cancer incidence is correlated with age of patient at diagnosis. Breast cancer incidence rate at age of diagnosis (DX) is indicated for invasive and in situ cancers

Indeed, hormone replacement therapy prescription was reduced in the 1990s and led to a decline of breast cancer incidence in the US (Collaborative Group on Hormonal Factors in Breast Cancer 1997).

Interestingly, multiple pregnancies and breastfeeding are factors that decrease a woman's risk for breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2002; Shantakumar et al. 2007). This suggests that changes in hormone profiles might be beneficial for protection against the development of breast cancer.

Breast density, an increase of glandular tissue versus fatty tissue, is a strong risk factor for breast cancer (Barlow et al. 2006). Another risk factor is obesity, specifically for postmenopausal women (Eliassen et al. 2006), since fat tissue produces estrogens thus increasing the level of circulating estrogens. Alcohol consumption is strongly associated with increased breast cancer risk (Hamajima et al. 2002), and the mechanism is also based on the generation of increased estrogen and androgen levels through conversion of alcohol (Singletary and Gapstur 2001).

Risk factors include thus behavioral, social, and nutritional factors. However, the differences in breast cancer risk of women of different ethnic origin can only partially be attributed to lifestyle and environment, and a genetic component cannot be excluded.

1.3 Genetic Predisposition to Breast Cancer

Genetic predisposition to breast cancer is clearly associated with mutations in breast cancer predisposition genes BRCA1 and BRCA2. Women with a family history of breast cancer in first degree relatives have a strongly increased risk of developing breast cancer. As much as 5 to 10% of breast cancer cases are estimated to result from mutations in the genes for BRCA1 and BRCA2 (Ford et al. 1998).

Today mutations in these genes can be identified, but the prediction of risk is complicated and might be a combination of genetic susceptibility and lifestyle. Furthermore, while mutations in the BRCA1 and BRCA2 genes are correlated with increased breast cancer risk, the status of factors or other gene products that modulate their function, such as the BRCA1-associated protein BARD1 (Irminger-Finger and Jefford 2006), might also be implicated in what makes up the combined genetic susceptibility.

Mutations in genes other than BRCA1 and BRCA2 have also been identified, although to a lesser extent, in breast cancer patients, namely, TP53, PTEN (Palacios et al. 2008). Indeed, mutations in predisposition genes lead to earlier onset of breast cancer than observed for sporadic cancers, a fact generally attributed to less efficient repair and cell cycle control functions in heterozygous cells, which then permit loss of heterozygosity and a rapid progression to malignant transformation. However, the steps that make a heterozygous cell with one deficient allele of BRCA1 or BRCA2 transform into a malignant cell are not understood, nor has it been investigated why the heterozygous condition leads to early-onset breast cancer with a certain probability.

Thus, other mechanisms than mutations might exist that could be initiating or supporting factors toward a malignant transformation of mammary gland cells. Overexpression of MDM2, the protein responsible for rapid turnover of p53 in normal cells, overexpression of cyclin D, a factor driving mitosis, or overexpression of HER2, are examples often found in association with breast cancer, but the mechanisms that explain their role in the development and propagation and age-related risk of breast cancer are not understood.

1.4 Biology of Aging

Other factors that contribute to breast cancer initiation and proliferation might be factors that are related to aging. To investigate how aging could drive breast cancer risk, it is important to understand the molecular pathways that drive aging and secondly to investigate how they interfere with pathways relevant for breast cancer.

1.4.1 Damage by Oxidative Stress

A fundamental mechanism of aging is based on the production of reactive oxygen species (ROS) and free radicals (Ramsey and Sharpless 2006). ROS and free

radicals can be generated by environmental circumstances or can have inherent cellular origins, a consequence of cellular respiration, in summary termed oxidative stress. ROS can activate transcription of genes implicated in inflammatory and other disease-associated processes, or cause damage on DNA, proteins, and lipids (Langen et al. 2003). In response to this accumulation of damage, cells might undergo apoptosis or become senescence (Fig. 1.2), leading to a decrease in viable cells. Prevention of oxidative stress is therefore an important contribution to a general slowing of the aging process (Song et al. 2005). Evidently, oxidative stress production of ROS can be influenced by nutrition and lifestyle.

1.4.2 Replicative Senescence Controlled by Telomere Length

It is well-established that in vitro cells undergo a limited number of cell divisions dictated by the length of telomeres (Allsopp et al. 1995; Hayflick 1985). Critical shortening of telomeres leads to cell cycle arrest and cellular senescence (Fig. 1.2), a phenomenon termed replicative senescence. A causal relationship between reduction of replicative potential and induction of cellular senescence and the shortening of telomeres has been established in vitro, and the diminishing of telomere length during aging has been demonstrated in vivo (Artandi and DePinho 2000; Kajstura et al. 2000). Telomere shortening and loss has been associated with genetic changes, and experimental data in mouse models support the link between telomere length and cancer susceptibility (DePinho 2000; Ferron et al. 2004; Metcalfe et al. 1996).

1.4.3 Cellular Senescence and Apoptosis

Aging is thought to be the result of genetically programmed and environmentally inflicted accumulation of damage to tissues and cells. Mechanisms of decline of active cells are apoptosis and cellular senescence. Cellular senescence is the irreversible exit of the cell cycle and can be caused by various stimuli. Senescence occurring at the end of the proliferative life span of normal cells is a response to telomere shortening (Fig. 1.2).

Senescence therefore contributes to tumor suppression, but also to tissue insufficiency. Senescence does not happen in cancer cells, and so it does not deviate cancer cells (Campisi 2001).

Apoptosis, the induced, regulated cellular suicide is an important mechanism for tissue homeostasis and renewal. Apoptosis can be triggered by a variety of signals. These signals can be a response to genomic insults (Amundson et al. 1998; Jiang et al. 2005), to telomere erosion (Zhang et al. 1999), or to developmental or tissue regulatory signals.

Apoptosis signals might be important in all proliferative tissues and counterbalanced by replenishing with functional cells by tissue-specific stem cells (Rizo et al. 2006).

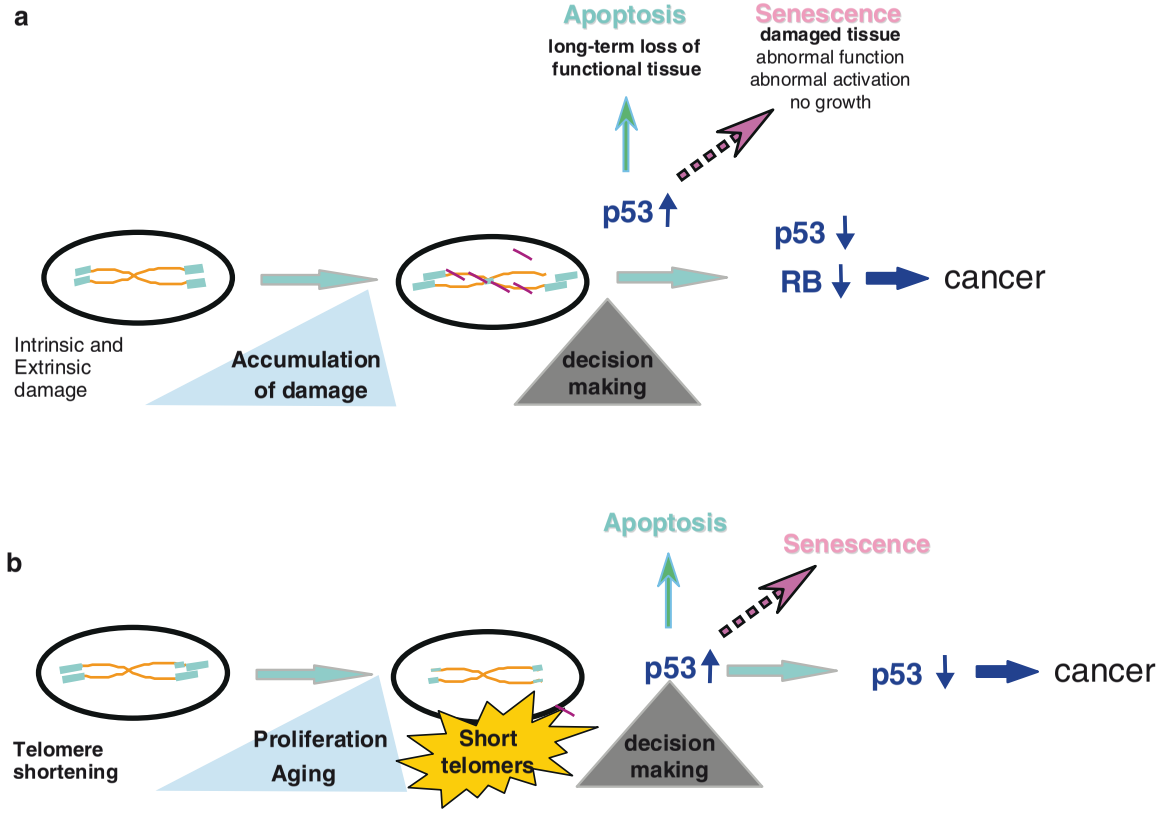

Fig. 1.2 Mechanisms contributing to aging and cancer. (**a**) DNA damage signaling requires p53 or retinoblastoma (RB) to induce cell cycle arrest and apoptosis or senescence. (**b**) Telomere shortening leads to a DNA damage response signal towards p53. Elimination of cells by apoptosis and reduction of functional cells by senescence leads to tissue aging

The pathways of apoptosis might be triggered by extracellular signals (Kari et al. 2003; Rizo et al. 2006; Smith et al. 2003), activating receptors, or intra cellular signals activating specific kinases (Watters 1999). A key player in apoptosis signaling is the tumor suppressor TP53. The p53 protein is stabilized by phophorylation by stress response kinases at various sites (Chao et al. 2006; Feki et al. 2005; Feng et al. 2006). In cells growing normally, p53 is rarely detectable, due to its rapid turnover controlled by MDM2 (Kubbutat et al. 1997; Yin et al. 2002).

Once p53 is stabilized and activated, it assumes tumor suppressor functions through its role as transcription factor, activating transcription of p21, to induce cell-cycle arrest, and bax, to induce apoptosis (Megyesi et al. 1996; Yamaguchi et al. 2004). The factors regulating the decision between these two pathways are not completely clear, but might involve a quantitative threshold mechanism (Moll and Zaika 2001) or implicate other posttranslational regulation, such as acetylation (Kaneshiro et al. 2007).

1.4.4 Tissue Aging Through Stem Cell Aging

Aging of stem cells can be influenced by extrinsic changes or by the accumulation of mutations or changes occurring in the *stem cell niche,* those cells nourishing the *stem cells,* which are responsible for replenishing an organ or tissue with functional cells. Tumor suppressor pathways, which comprise signaling from telomere shortening to p53 and p16/INK4a actions (Fig. 1.3), whilst important for the control of cancer cell growth, have the negative action of reducing the replicative function of stem cells. Indeed, with advancing age, p16 expression increases in stem cells (Janzen et al. 2006) suggesting that tissue aging is due to stem cell exhaustion.

1.5 Molecular Crossroads of Cancer and Aging

Telomere shortening could be an important cancer-predisposing mechanism in tissues with high proliferation, mostly of epithelial cells. Indeed, epithelial-cell-derived cancers happen to be frequent in old age and rare in children (DePinho 2000).

1.5.1 Cellular Senescence: A Double-Edged Sword

Aging is thought to be the result of genetically programmed and environmentally inflicted accumulation of damage to tissues and cells. Mechanisms that contribute to the decline of active cells are apoptosis and cellular senescence. Thus, senescence, like apoptosis, contributes to tumor suppression, but also to tissue insufficiency. Interestingly, oncogene-induced senescence is observed as a form of

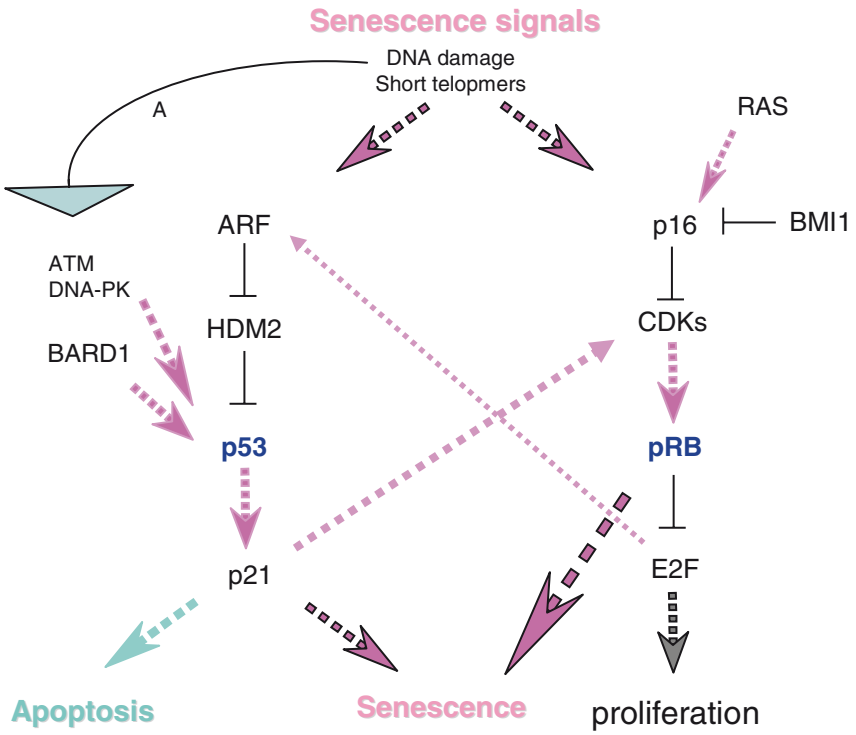

Fig. 1.3 Senescence signaling, a double edged sword: the p53-pRB pathway of senescence control. Senescence signaling induces ARF and p16. ARF inhibits HDM2, a down-regulator of p53. Activation of p53 by HDM inhibition or ATM, or DNA-PK and BARD1 (Feki et al. 2005) results in p21 induction and cell cycle arrest. Both p21 and p16 inhibit CDKs. Without phosphorylation of pRB by cyclins, E2F is repressed. Active E2F can induce transcription of ARF. RAS signaling can induce p16. BMI1 acts as inhibitor of p16-induced senescence signaling

response to excessive replicative stimuli. One example for an oncogene-inducing senescence is RAS (Serrano et al. 1997), suggesting that oncogenic events can finally lead to proliferation arrest (Fig. 3.3). Importantly, the senescence pathway can be activated in cells that are resistant to apoptosis, the programmed cell death. Furthermore, manipulating genes that are regulators of apoptosis can cause cells to undergo senescence and vice versa (Campisi 2003).

1.5.2 Actors at the Crossroads of Senescence and Cancer

A common regulator of apoptosis and senescence is p53. Senescence is associated with the expression of the cyclin-dependent kinase (CDK) inhibitors p21 and p16, components of the p53 and retinoblastoma (RB) tumor suppressor pathways, which

are frequently disrupted in cancer. Both pathways can establish and maintain growth arrest and senescence (Fig. 3.3).

Upon damage signals, p53 is phosphorylated by DNA damage sensors, in particular ATM and DNA-PK, which results in its stabilization and activation. Activated p53 induces expression of p21, a CDK inhibitor. Inhibition of CDKs results in transient growth arrest (when accompanied by repair) or senescence. Alternatively, senescence signaling toward p53 is transmitted via ARF (Kamijo et al. 1999), an inhibitor of MDM2 (HDM2 in humans), which is a ubiquitin ligase targeting p53 for degradation and keeps p53 protein levels low in proliferating cells (Sherr and McCormick 2002).

The RB pathway of senescence is induced by p16. Since CDKs phosphorylate RB in a cell-cycle-dependent fashion, their inhibition leads to hypophosphorylation of RB. In its hypophosphorylated state RB halts cell proliferation by suppressing the activity of the transcription factor E2F, which stimulates expression of genes required for cell-cycle progression. Thus activation of p16 leads to cell-cycle arrest or senescence.

There is cross talk between the p53 and RB pathways. p21 action on CDKs inhibits RB phosphorylation. The RB pathway links to the p53 pathway through induction of ARF by E2F. An important regulator of senescence is BMI-1, an oncogene and a repressor of p16 (Park et al. 2004), with anti-aging activity in mice (Itahana et al. 2003). Interestingly, p16 expression in tissues increases with age. Mice without p16 live longer, show better tissue regeneration, but are more cancer prone (Janzen et al. 2006). Similarly, hyperactive p53 prevents cancer but provokes premature aging (Sharpless and DePinho 2002; Tyner et al., 2002). Thus the senescence pathways represent a trade-off between tumor suppression and aging. Importantly, some of the factors involved in these pathways are associated with and are targets for treatment of breast cancer.

1.6 Biomarkers for Breast Cancer Change with Age

Biomarkers of breast cancer are indicators of the number of mitosis or apoptosis in tissues, the mitotic index or Ki-67 positivity and apoptotic index thus reflecting tumor growth. Other markers are linked to the invasive potential and include VEGF, or proteases such as cathepsin D. Another generally used biomarker for breast cancer is p53 positivity, reflecting a stabilized aberrant p53 and suggesting a certain loss of cell-cycle control (Benz et al. 2003).

The estrogen receptor (ER) is probably the most powerful predictive marker in breast cancer management, both in determining prognosis and in predicting response to hormone therapies. Progesterone receptor (PR) is also a widely used marker, although its value is less well established. HER-2 status has become a routine prognostic and predictive factor for treatment in breast cancer.

Interestingly, biomarkers indicative of invasive behavior of breast cancers do not correlate with patient age at diagnosis, but hormone receptor status is correlated

with age (Eppenberger-Castori et al. 2002; Quong et al. 2002). Factors that are indicative of tumor proliferation are in general inversely correlated with age (e.g., HER2); this observation is consistent with the observation of slower growth rates of breast tumors in older patients.

Importantly however, ER, but not PR, expression is correlated with patient age at diagnosis (Benz et al. 2003; Eppenberger-Castori et al. 2002; Quong et al. 2002). In summary, breast cancers in older women are more likely to be ER positive, but less likely to be HER2 or p53 positive.

ER has transcription activation function for a large variety of ER response genes, including PR, Bcl-2, cathepsin D, also expressed in normal and malignant mammary gland cells. Co-overexpression of ER and ER-response genes indicates an intact ER signaling pathway. Consequently, PR expression, when not co-expressed with ER, is indicative of defective ER signaling (Petz and Nardulli 2000). Thus, it is unclear whether inhibition of ER by anti-estrogens is an effective treatment of these types of cancer.

1.6.1 Oxidative Stress and Estrogen Receptor Pathways

Among several ER-α [alpha] response genes are the PR, Bc12, and cathepsin D. Tumors that are overexpressing ER are thought to activate the full ER-response gene set. However, age-specific comparison of the expression levels of ER and ER-response genes showed, that, while ER upregulation in breast tumors is clearly correlated with increasing age, the expression levels of the respective response genes, namely PR, Bc12, AP1, and the oxidative stress-activated kinase Erk5, are not (Quong et al. 2002). This is consistent with previous observations of ER-positive/PR-negative breast cancers increased with patient age. The results of this study suggest that age-dependent oxidative stress is a modulator of the responsiveness of ER-response genes.

1.6.2 Metabolism and Oxidative Stress

As discussed above, the generation of intracellular ROS through the metabolism of glucose and production of ATP is inevitable and can act as a constitutive tumor promoter by inducing mutations in genes and defects on proteins and lipids. However, tumor cells have also constitutively activated glycolysis and produce increased levels of lactic acid (Gatenby and Gillies 2007).

Although the glycolysis pathway is activated in tumors even in normoxia (Warburg effect), hypoxia could play a role in the initial switch to glycolysis. Stimulators other than hypoxia can be loss of p53 function or activation of the phosphoinositide-dependent kinase 1 (PDK1)/Akt pathway, which is an important regulator of multiple biological processes including cell growth, survival, and

glucose metabolism (Young and Anderson 2008), and is negatively regulated by the tumor suppressor PTEN (Fig. 1.4).

These pathways might be of particular importance in breast cancer since PTEN is often mutated in breast cancer. Furthermore, epidermal growth factor (EGF) and human EGF receptor (HER2) downstream signaling pathways are via Raf/MEK/ERK and PI3K/PDK1/Akt (Schlessinger 2004). Thus nutrition and accumulation of damage, as an inevitable consequence are linked to pathways involved with breast cancer predisposition.

1.7 Drugs and their Molecular Targets for the Treatment of Breast Cancer

There are several molecular tools under investigation and a few already applied today in the treatment of breast cancer. The types of molecules that are being developed or tested and which target cellular signaling pathways are either small molecules, inhibitors of protein–protein interactions, kinase inhibitors, small molecules inhibiting specific kinases, histone deacetylase inhibitors acting on DNA and gene expression, or monoclonal antibodies.

Another class of treatments comprises cytotoxins acting on the microtubule cytoskeleton, as is the case for taxols, or on the structure and packaging of DNA with topoisomerase inhibitors. A third group of treatment tools are hormone or hormone-induced pathway inhibitors, such as somatostatin analogues for inhibition of somatostatin, aromatase inhibitors, or tamoxifen, an antiestrogen modulating ER activity.

Many targeted drugs in use for breast cancer treatment are directed against HER-2. HER-2 is a member of the (EGFR) family, composed of EGFR (ErbB1), HER-2 (ErbB2), HER-3 and HER-4. HER-2, overexpressed in many breast cancers, is targeted by either ectodomain-binding monoclonal antibodies (mAb) or by small molecule tyrosin kinase inhibitors (TKIs) competing with ATP for the cytoplasmic tyrosine kinase domain. The efficiency in anticancer treatment by the mAb transtuzumab and by the IKI lapatinib, both inhibiting HER-2 signaling, is investigated in many trials (Widakowich et al. 2007). Similarly, mAb cetuximab and TKIs gefitinib, canertinib, and erlotinib target the EGFR. Downstream effectors of this signaling pathway are also targets for inhibition, namely mTOR with rampamycin analogues (Fig. 1.4).

Interestingly, with the exception of aromatase inhibitors and tamoxifen and its analogues, none of the drugs in use or under trial have a functional link to estrogen or estrogen signaling pathways.

1.7.1 The Multi-Target Player Genistein

An important biological effect on the incidence of breast cancer is observed by the soy isoflavone genistein. The concentration of plasma genistein was inversely

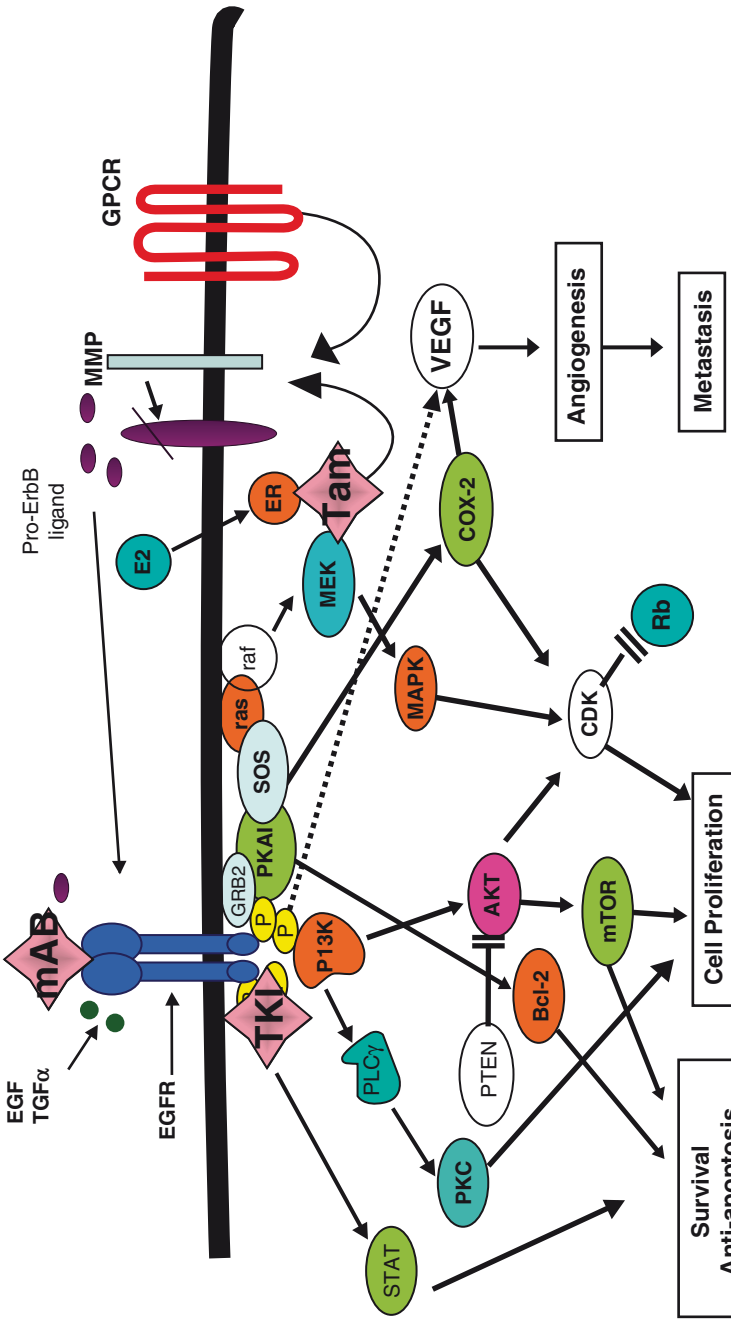

Fig. 1.4 Converging pathways of epidermal growth factor receptor (EGFR)/HER2 and estrogen signaling. Inhibitory drugs, such as mAB against the extracellular domain of EGFR or HER2, tyrosin kinase inhibitor (TKI) against the intracellular kinase domain, and Tamoxifen (Tam), inhibiting estrogen receptor (ER), are indicated. (Bianco et al. 2007)

correlated with the risk of developing breast cancer in Asian women (Lampe et al. 2007). Interestingly genistein has anticancer properties due to its antioxidant properties but also by interfering with signaling pathways that are activated in cancer and by activating apoptotic pathways.

Genistein binds to ER-α [alpha] and β [beta] and competes with more potent estrogens, such as β[beta]-estradiol. Interestingly, genistein inhibits the growth of both estrogen positive and negative breast cancer cells in vitro, presumably based on other interactions with cancer signaling pathways, namely by inhibiting protein-tyrosine kinase (PKT) and HER2 phosphorylation (Sakla et al. 2007). Importantly, genistein inhibits activation and nuclear localization of NF-KB (Davis et al. 1999) by inhibiting phosphorylation of the IkB, by IkB kinase a (IKKa) and b (IKKb), which when unphosphorylated sequesters NF-KB in the cytoplasm. Finally, genistein interferes with Akt signaling, which interferes with multiple survival pathways (El Touny and Banerjee 2007). Thus genistein acts by interfering with signaling in multiple ways, including those of inhibitory drug targets.

1.8 A Possible Link Between the Breast Cancer Predisposition Genes and Estrogen

The breast cancer predisposition genes BRCA1 and BRCA2 both collaborate in DNA repair and cell-cycle control. Both BRCA1 and BRCA2 bind to the repair protein RAD51, but, although linked to similar functions, BRCA1 and BRCA2 are structurally different and do not directly interact.

An important binding partner for BRCA1 is the BRCA1-associated protein BARD1 (Irminger-Finger and Jefford 2006). Indeed BARD1 stabilizes BRCA1, and most functions of BRCA1 depend on the formation of a BRCA1-BARD1 heterodimer, which has E3 ubiquitin ligase activity.

BARD1, although seemingly important in BRCA1-dependent tumor suppressor functions, is relatively rarely mutated in breast cancer. However, in all types of gynecological cancer isoforms of BARD1, derived from differential splicing, were detected (Li et al. 2007; Wu et al. 2006). These isoforms lack the BRCA1-interaction domain, are proproliferative, and their inhibition can block cancer cell growth, which defines them as oncogenic.

Since its cloning in 1994, research on BRCA1 has generated knowledge on its fundamental cellular functions involved in cell-cycle control and DNA repair, but the link between BRCA1 and estrogen signaling in breast tumorigenesis has remained uncertain.

Some studies indicate that BRCA1 physically interacts with ER-α [alpha] and inhibits its transcriptional activity (Fan et al. 2001) and inactivation of BRCA1 (by mutation or knockdown) confers activation of ER-α in the absence of ligand (Ma et al. 2006). It was thought for a long time that the presence of functional BRCA1 is important for keeping estrogen-signaling related cell proliferation under control. This thought is substantiated with the recent finding that the BRCA1–BARD1

heterodimer E3 ligase activity can target the ER-a, providing an explanation for a protective role of BRCA1 in breast cancer (Eakin et al. 2007).

Interestingly, BARD1 is an ER-response gene and induced by estrogen (Creekmore et al. 2007). However, the BRCA1 gene lacks a consensus estrogen response element (Hockings et al. 2008), but BRCA1 protein upregulation can be due to BARD1 up-regulation in response to estrogens.

The BRCA1 action on ER-α [alpha] requires BRCA1 binding to BARD1, but BARD1 expression is repressed in most breast and ovarian cancer and oncogenic isoforms, incapable of interacting with BRCA1 are expressed (Fig. 1.5). Since

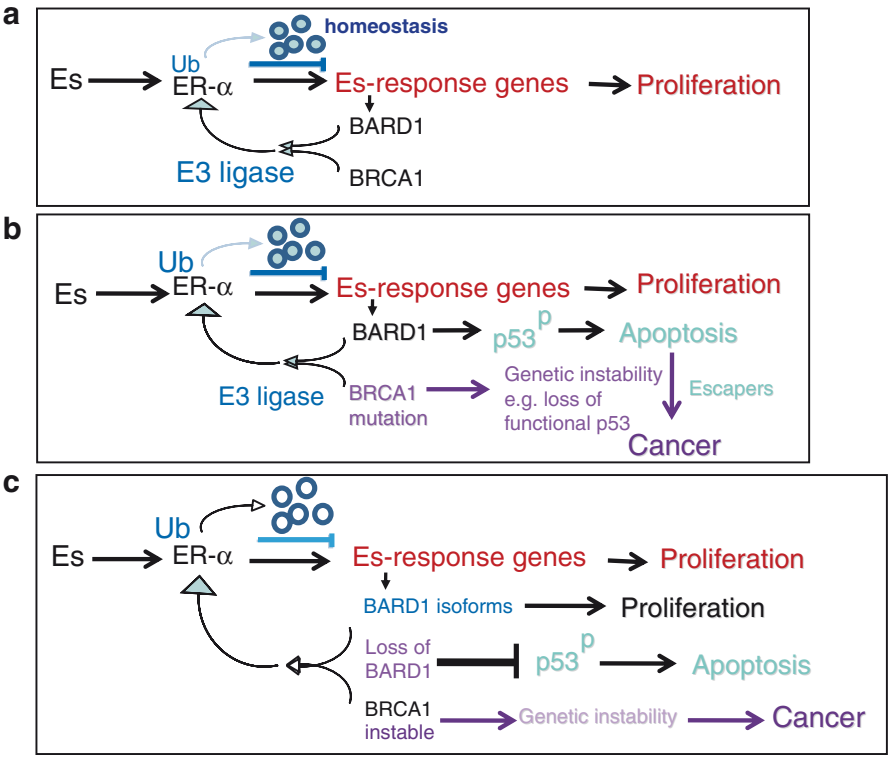

Fig. 1.5 Modulation of estrogen-ER signaling by BRCA1 and BARD1. (**a**) BARD1 and BRCA1 could act as E3 ligase in degradation of ER-α [alpha] (Eakin et al. 2007). BARD1 is induced by ER-α [alpha] (Creekmore et al. 2007), which could create a regulatory loop to control tissue homeostasis. (**b**) BRCA1 mutations lead to deficiency of E3 ligase function, but an increase of BARD1 over BRCA1, which could induce apoptosis (Irminger-Finger et al. 2001). However, genetic instability in the absence of BRCA1, permits cells to escape from apoptosis, consistent with loss of functional p53 in *BRCA1* knockout cells. (**c**) In breast and ovarian cancer loss of full length BARd1 and expression of isoform is observed, this should result in BRCA1 instability, loss of E3 ligase activity, loss of ER-α [alpha] degradation, loss of BARD1 apoptotic functions, increased expression of BARD1 isoforms, which are oncogenic (Li et al. 2007)

these isoforms are proproliferative, they might play an important role in ER-positive breast cancers.

A switch from FL BARD1 to BARD1 isoforms would lead to BRCA1 degradation, without affecting BRCA1 gene structure, upregulation of ER-α [alpha], in consequence up-regulation of PR, und proliferation.

This hypothesis puts in question genetic testing for BRCA1 mutations in tumors, which might be misleading. It also suggests that BARD1 isoforms might be important novel targets for treatment, since their inhibition provokes cell-proliferation arrest.

1.9 Conclusion

A strong link exists between breast cancer risk and estrogen exposure. As estrogens act as growth factors for hormone-dependent tissues, it is important to characterize the molecular signaling pathways involved. With increasing age and time of exposure to estrogen the associated breast cancer risk increases, but also the accumulating damage due to the exposure to oxidative stress. In addition, the biology of breast tissue itself changes with age, and the molecular pathways relevant for tissue aging will influence the impact of risk factors and might even represent additional risk factors.

Thus, what drives cancer might ultimately come down to a few genes, and what promotes cancer might be specific for the organ.

This was nicely shown with the comparison of specific breast cancer gene signatures that converge on signaling hubs (Shen et al. 2008). High concordance of several breast-cancer gene signatures for predicting disease recurrence despite minimal overlap of the gene lists was shown. Interestingly, the signatures did not identify the same set of genes but converged on the activation of a similar set of oncogenic and clinically relevant pathways. A clear and consistent pattern across the four breast cancer signatures is the activation of the estrogen-signaling pathway. Other common features include BRCA1-regulated pathway, extracellular matrix protease inhibitor (RECK) pathways, and insulin signaling associated with the ER-positive disease signatures, all providing possible explanations for the prediction concordance (Shen et al. 2008).

Finally, the notion of age-dependent differences is not integrated in these studies, but signaling pathways involved in aging are comprised in the common signature. Thus, analyses that pay attention to and integrate information for dissecting senescence/cancer pathways remain to be performed.

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