Chapter 6

Triple-Negative Breast Cancer Risk in Women Is Increasing by the Loss of Estrogen Supply or by Defective Estrogen Signaling*

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Abstract

Many investigations propose that menopausal status, reproductive factors and exogenous hormone use may differently or even quite inversely affect the risk of TNBCs and steroid receptor positive cancers. Controversies concerning the exact role of even the same risk factor in TNBC development justify that the biological mechanisms behind the initiation of both TNBCs and non-TNBCs are completely obscure. The grade of defect in metabolic and hormonal equilibrium seems to be directly associated with TNBC risk for women during their whole life. Inverse impact of menopausal status or parity on the development of ER+ and ER- breast cancers is quite impossible; these erroneous results derive from the misinterpretation of statistical evaluations. There are fairly complex associations between excessive and defective estrogen signaling (multiparity and nullparity) and cancer development. The tumor suppressing effect of excessive and the deliberating effect of defective estrogen signaling have disproportional impact on ER+ and ER- breast cancers. Exogenous or parity associated excessive estrogen supply is highly defensive against all breast cancer subtypes, but ER- tumors; such as TNBCs are more resistant. The most important preventive strategy against breast cancers – included TNBCs – in women is the strict control and maintenance of hormonal equilibrium from early adolescence through a lifetime, particularly during the periods of great hormonal...

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changes. Effective breast cancer therapy requires complete conversion. Worldwide administration of antiestrogens for breast cancer treatment yielded thorough disappointment. By contrast, publications on successful estrogen treatment of advanced breast cancer cases are increasing in number and their results are encouraging.

**Introduction**

Triple-negative breast cancers (TNBCs) were first characterized in the literature in 2005 [1]. These tumors exhibit low histologic differentiation, lack the expression of steroid receptors for estrogen (ER), progesterone (PR) and the tyrosine kinase human epidermal growth factor receptor 2 (HER-2). TNBC is primarily a diagnosis of exclusion and its typical cytochemical features are upregulation of cytokeratins 5, 14 and 17 and increased expression of epidermal growth factor receptor (EGFR) [2, 3] Great studies have estimated that approximately 15-20% of breast cancers belong to this triple receptor negative group [4-6].

Clinically, TNBCs exhibit typically aggressive local growth, rapid progression and account for a high percentage of early metastases, most commonly to visceral organs including liver, lungs and central nervous system [7, 8]. TNBCs are also characterized by diagnosis at a later stage and the poorest survival of patients as compared with cases of any other breast cancer types [4, 9]. Pathologic features are high grade, infiltrative spread, high rates of mitotic figures and p53 mutations in addition to ER, PR and HER negativity [10].

Young age apparently exhibits closer correlation with the risk of triple negative breast cancer (TNBC) development as compared with such a risk in the postmenopausal, hormonally challenged period [7, 11]. In younger, premenopausal women, breast cancers more likely present an adverse prognostic profile; including steroid receptor negativity, rapid progression and poor outcome of disease as compared with the tumors of postmenopausal cases [4, 7, 9, 11-14].

Epidemiologic studies strongly support that TNBCs may be distinct entities as compared with steroid receptor positive tumors, suggesting that the etiologic factors, clinical features and therapeutic possibilities of breast cancers may vary by molecular subtypes [13-16]. However, many literary data refer to apparently common risk factors for TNBCs and non-TNBCs; such as metabolic syndrome, type-2 diabetes, obesity, BRCA gene mutations and the African-American race of women [8, 17-20]. Moreover, recent observations suggest that the stronger the risk factor for overall breast cancer the higher the risk for development of TNBC type [8, 21-24]. By contrast, further investigations propose that reproductive factors and exogenous hormone use may differently or even quite inversely affect the risk of TNBCs and steroid receptor positive cancers [13-15, 25-27].

There are many controversies and inconsistencies concerning the exact role of even the same breast cancer risk factor in TNBC development. This confusion justifies that the biological mechanisms behind the initiation of both TNBCs and non-TNBCs are completely obscure. A further puzzling question concerns the low incidence rate of overall breast cancer in young females, as opposed to the conspicuously high incidence rate of TNBC among these women. To arrive at a comprehensive understanding of the etiology of different breast cancer subtypes we should also reconsider our traditional concepts and beliefs regarding cancer risk factors.
The purpose of the current study is to analyze in detail the provoking and defensive factors as the players in mammary carcinogenesis based on the data of epidemiologic, clinical, experimental, biochemical, immunohistochemical and genetic studies. Our aim is to clarify, whether the different molecular subtypes of breast cancer also mean etiological differences, or they have quite common risk factors, differing only in intensity, exposure period and coexistence, while having a strengthening impact on each other. The current analysis would clarify the apparently misleading age related controversies in TNBC development as well.

Considering the puzzling processes behind TNBC development, the following questions are to be answered:

1. What is the explanation of the conspicuous changes in TNBC incidence rate during the different periods of life in women?
2. Is TNBC indeed a quite distinct entity, or is it a poorly differentiated variant of breast cancers induced by the same cancer risk factors?
3. How can similar breast cancer risk factors modify or define the development of TNBCs and non-TNBCs?
4. How can parity and exogenous hormone use affect breast cancer risk and is there any possibility for their quite inverse impact on the development of TNBCs and non-TNBCs?
5. Which are the proposed new strategies for primary prevention and therapy of TNBC?

**Difference in TNBC Incidence Rates between Young and Older Women**

Literary data support that young age in women is associated with an equivocally higher incidence rate of TNBCs as compared with older cases [12, 13]. The defining age border for the distinction of the two age groups of women is not identical. Some studies discern the age groups of breast cancer cases on the basis of the same principle, using the mean age at menopause, or the age around 50 [4]. Others define the critical limitation at a higher [Gaudet abstr] or lower age [9, 12, 14, 28, 29]. In spite of the different age groupings, hormonally mediated risk factors emerged as being essential in the higher TNBC incidence rate in young cases.

It was reported that 25.5% of breast cancer cases under the age of 40, exhibited TNBC and a conspicuously lower rate, 13.3% had highly differentiated luminal A type tumors [30]. Among breast cancer cases occurring in women less than 50 years of age, nearly half of the tumors (49%) were diagnosed as TNBCs in a Californian study [4]. In a population-based study of women 56 years or younger with breast cancer, this difference in incidences between molecular subtypes was more marked; 27.6% of breast tumors proved to be TNBC, whereas 8.1% was considered as luminal A [13].

Tumors in younger women less than 40 years of age, showed significantly more frequently estrogen and progesterone receptor negativity (33.8% and 50.0%, respectively) than cancers in women over 40 (21.9% and 35.5%, respectively). Breast cancers in younger women exhibited a greater prevalence of Ki-67 (p<0.001) and higher levels of Her2/neu...
overexpression as well (p<0.05), suggesting a higher proliferative activity of tumors and a poorer outcome of disease as compared with older cases [9]. Moreover, tumors with the same histologic grade, exhibited lower expression of ERs and higher proliferative index in young cases than in postmenopausal women [12]. In young breast cancer cases, of all the examined tumor markers, estrogen receptor negativity was a crucial factor in defining biological aggressivity and fatal outcome [9, 12].

Graphic representation of estrogen receptor (ER) expression rate in breast tumors depending on patient’s age reveals new aspects concerning the numerical data of ER negative tumors in young cases (figure 1). A total of 306 breast cancer cases were examined and divided into two groups; 78 women under the age of 40 and 228 women aged 40 and over [9]. Mean age was 35 years among young and 59 years among older breast cancer cases. Numerical mean values of the overall, ER positive and ER negative breast cancer cases in the younger and older groups yielded some important observations. Although the percentage of ER negative breast tumors was higher in the young age group (33.8%) than among older women (21.9%), the numerical mean value of ER negative cancers among young cases was nearly the half as compared with the data of older cases (26 vs. 50). At the same time, the numerical mean value of ER positive tumors showed much higher, almost fourfold increase with aging (52 vs. 178) The overall breast cancer incidence rate was obviously, fairly suppressed in the group of young women (23.9%) as compared with the high value manifested among the older cases (76.1%), which is in concordance with the literary data.

Notes: Raw numbers show a close to twofold increase in ER- tumors and a much higher – almost fourfold – increase in ER+ tumors with aging, while the percentage of ER- cancers exhibits a decreasing trend. Data derived from Hartley et al.7. Abbreviations: BC, breast cancer; ER, estrogen receptor.

Figure 1. Age-related increases in overall, ER+ and ER- breast cancer incidences.
In the young, both ER- and ER+ tumor incidences were thoroughly suppressed by certain common factors and this suppression was particularly strong among ER+ breast cancers. The relatively high percentage of triple receptor negative breast cancers (TNBCs) among young cases may be attributed to the low incidence rate of more successfully repressed ER+PR+ cancers rather than to an excessive inclination to ER-PR- tumors. The latter tumor types are submitted only to a moderate suppression.

What can be the advantageous factor in young women suppressing strongly the ER+ breast cancers and moderately the ER- ones? As healthy or slightly defective synthesis of estrogen in young women supplies the ligand for ERs, inhibition of both initiation and progression of ER+ breast tumors may be more effective as compared with ER- cancers [31, 32]. Nevertheless, estrogen has alternative signaling pathways as well to overcome the ER- tumors (see later) but the efficacy of these latter possibilities is weaker, reflected by the relatively high percentage of ER- tumor survival in young women.

The antitumor capacity of preserved estrogen level in young women seems to be supported by the observation that ER negativity of breast cancers in young cases defines the poorest prognosis of the disease [9, 12]. Moreover, locoregional control after breast conserving therapy of young breast cancer cases (<40 yrs.) highlighted that the absence of CYP19-aromatase activity in these tumors carries a highly significant risk for locoregional tumor recurrence [33]. This result supports that lack of intratumoral estrogen synthesis means low differentiation of breast cancers, and correlates with weak tumor suppression and poor prognosis [32].

In conclusion, TNBC in the young is not a distinct entity with mysteriously unique etiology but a consequence of usual, strong and/or multiple risk factors for breast cancer. All risk factors, such as positive family history, metabolic syndrome, type 2 diabetes and BRCA gene mutation are particularly high risks for TNBCs. At the same time, these risk factors may disarm the cellular defense mechanisms by the derangement of estrogen surveillance even in young cases.

**Hormonal Factors Affecting the Changes in TNBC Risk during the Different Life Periods of Women**

Risk factors for breast cancer are usually evaluated when the tumors are clinically diagnosed. Nevertheless, cell kinetic studies of tumors justified that the clinical appearance of solid breast cancers requires at least a period of 6-8 years from their initiation to the development of palpable size [34]. Searching for the etiologic factors of breast cancer is hard as harmful noxae at the estimated time of first mutation in the past might be crucial instead of the momentary findings at the time of clinical diagnosis.

Great hormonal changes happening during a woman’s life might strongly define the inclination to initiate both overall breast cancer and TNBC. The stronger the hormonal imbalance characterized mainly by hyperinsulinism, hyperandrogenism and low estrogen exposure, the higher the breast cancer risk, particularly for the poorly differentiated TNBC type (Table 1).

Three main phases seem to be particularly dangerous for breast cancer initiation during the life of women [31]. Two of these are crucial periods inducing hormonal and metabolic storms in women; adolescence (14-18 years) and the perimenopausal phase (45-55 years).
Both periods present risks for overall breast cancer initiation if the biologic processes in the background become pathologic. The third, especially risky phase for breast cancer initiation is older age (over 60 years) when the hormonal and metabolic imbalance becomes stronger and the defense mechanisms against cancer initiation are debilitated.

The first challenges for the whole body of boys and girls are pubertal changes, since the abrupt somatic and sexual development means a real danger of developing insulin resistance and the associated imbalance of male-to-female sexual hormone ratio [35, 36]. When a young girl inherits genetic or acquires somatic anomaly; such as glucose intolerance or obesity, overproduction of androgens will develop at the expense of defective estrogen synthesis [31]. This hormonal disturbance may be insidiously symptom-free or may induce irregular anovulatory menstrual cycles [37]. In severe cases, polycystic ovary syndrome (PCOS) develops, which is the most prevalent hormonal alteration in young women.

Table 1. Lifelong changes in the sex hormone levels and insulin resistance of women and their correlations with TNBC risk

<table>
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<tr>
<th>Hormonal changes in the life periods of women</th>
<th>Estrogen level</th>
<th>Androgen level</th>
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Adolescent hyperandrogenism is usually preserved till the early thirties and leads to definite infertility or delayed childbirth [38, 39]. Low estrogen exposure and androgen excess at this young age may provoke anovulation and poses a risk for early breast cancer initiation. The clinical tumor appearance may also evolve in premenopause though both the exposition time to harmful factors and the latency period from cancer initiation to clinical diagnosis take several years. Thus, reproductive failures, such as nulliparity and delayed childbirth have sources common with breast cancer development; long lasting hyperandrogenism and defective estrogen synthesis associated with insulin resistance.

In healthy premenopausal women, breast cancer development is rare. Preserved ovulatory menstrual cycles are defensive as even a slightly defective estrogen synthesis may counteract to cancer initiation [31]. However, increasing grades of insulin resistance associated with
enhanced severity of sexual hormone imbalance mean high risk for overall breast cancer even in young cases and particularly for poorly differentiated TNBC initiation.

In case of mild hyperinsulinemia and hyperandrogenism, preserved circulatory female sexual steroid levels and regular menstrual cycles may usually be enough to protect against breast tumor initiation. With aggravation of insulin resistance in young women, the associated moderate decrease in circulating estrogen level may cut off the ovulatory estrogen peak resulting in anovulatory infertility. Even this slightly estrogen deficient milieu may confer preferential risk for breast cancer as well as for endometrial and ovarian malignancies in anovulatory women. These female organs have the highest estrogen demand so as to preserve their structural and functional integrity [31, 40].

Among premenopausal cases, the metabolic syndrome is associated with particular increase in the risk for ER-PR- cancers and TNBCs [8] parallel with decreasing estrogen exposure. In young premenopausal cases with type-2 diabetes, progressive insulin resistance and blocked aromatase activity inhibit the conversion of androgens to estrogen in both the ovaries and peripheral tissues [41]. The low estrogen exposure is incapable of defending the cellular functions against the strong insulin resistance and hyperandrogenism [31, 42, 43]. This breakdown leads to the preponderance of early initiation and rapid clinical appearance of poorly differentiated, aggressive breast tumors; such as TNBCs.

The second risky period for breast cancer initiation may be the perimenopausal phase, when there is a slow or steep decline in ovarian female sexual steroid synthesis and the last menstrual cycle approaches. Breast cancer initiation is relatively frequent in these hormonally challenged women between the ages of 45 and 55. Tumors, initiated in the period of perimenopausal hormonal changes are predominantly hormone receptor positive, which is attributed to the inequalities of decreasing estrogen supply [40, 44].

In perimenopause, breast and other peripheral tissues may exhibit rapid compensatory hormone production for the completion of decreasing ovarian estrogen synthesis in an amount sufficient to kill or differentiate breast tumor cells initiated by chance. In this case menopausal women are generally complaint free and do not require medical help. In further cases, the gradual hormonal adaptation to ovarian senescence is defective and the beginning of tissular estrogen synthesis in the breast is late. This delay may result in tumor initiation, but later the increasing extraovarian estrogen synthesis promotes the differentiation of early cancers, which will predominantly be hormone receptor positive [45]. These women, with transitorily insufficient estrogen level frequently have strong menopausal complaints.

Postmenopausal hormone replacement therapy (HRT) is typically associated with highly differentiated, receptor positive tumors, which are initiated in the late premenopausal or perimenopausal hormonal failure period much earlier than the beginning of hormone treatment [46]. Estrogen administration may help to differentiate the already existing subclinical tumors; however the dose of hormone replacement is not always enough to kill them. The clinical diagnosis is always postmenopausal in case of tumors initiated in the perimenopausal phase due to the long latency period.

Breast cancers diagnosed in elderly women over 65, are typically initiated in the postmenopausal period over 60. These patients are generally non HRT users and exhibit deepening estrogen deficiency and insulin resistance, even a high prevalence of type-2 diabetes and obesity. Both obesity and highly elevated fasting blood glucose level were found to be especially dangerous for mammary malignancies in elderly cases over 65 years of age [47, 48]. The TNBC ratio among breast cancers is increasing in elderly cases attributed to
their low circulatory and tissular estrogen levels, hyperandrogenism and the associated insulin resistance. Since women from the elderly population are much fewer than middle aged postmenopausal cases, pooled examination of breast tumors diagnosed after menopause may give a blurred value with predominance of hormone receptor positive cases.

Taken together, risk for breast cancer and particularly for TNBC is directly associated with the grade of defects in metabolic and hormonal equilibrium during the whole life of women. Although breast cancer is multicausal having diverse inherited and acquired etiologic factors, lack of sufficient estrogen surveillance seems to be a crucial risk for the development of mammary tumors, particularly for TNBCs in both young and older cases.

**Common Risk Factors for ER Positive and ER Negative Breast Cancers**

The majority of breast cancer risk factors seem to be common to both ER positive and ER negative tumors. Moreover, the stronger the risk factors, the higher the danger of TNBC development. The well-known risk factors of breast cancer, such as metabolic syndrome, type 2 diabetes, obesity, African-American race and BRCA gene mutation all proved to be particularly strong for poorly differentiated, steroid receptor negative tumors, such as TNBCs [8, 20-24, 49, 50].

**Metabolic Syndrome and Type-2 Diabetes As Risk Factors for Overall Breast Cancers and TNBCs in Particular**

Today, the correlation is widely accepted that the higher the grade of insulin resistance with or without obesity in women, the higher the risk for more aggressive breast cancer [21, 22, 49]. The *metabolic syndrome* is a phase of insulin resistant state characterized by a quartet of elevated fasting glucose, dyslipidemia, hypertension and visceral obesity [51]. Each of these symptoms alone is a risk factor for cancer and together they mean a multiple risk [52, 53].

Metabolic syndrome is associated with increased overall breast cancer risk, higher tumor aggressivity and poorer prognosis [8, 54, 55]. Positive correlations were found between metabolic syndrome and breast cancer incidence, due primarily to positive associations with serum glucose and serum triglyceride levels, as well as diastolic blood pressure [56]. In a prospective study, elevated fasting glucose level proved to be a high risk for breast cancer. Women in the highest glucose quartile showed a significantly greater risk than those in the lowest quartile (RR = 1.63). This association was significant separately in both pre- and postmenopausal women [57].

Metabolic syndrome was highly associated with overall breast cancer in patients of advanced age and belonging to the African-American race of cases. Among breast cancer cases 26% were considered obese, 16% hyperglycemic, 54% hypertensive and 30% dyslipidemic. When the data were adjusted for age, race and tumor stage, the metabolic syndrome was only marginally associated with estrogen receptor positive tumors [49].
In a study conducted in Ireland, metabolic syndrome was established in 39% of all newly diagnosed breast cancer cases. Patients with advanced pathologic stage (II-IV) at diagnosis had metabolic syndrome in 51% of cases, whereas among early stage cases this ratio was only 12% [55]. These data suggest that metabolic syndrome may be associated with more aggressive tumor biology.

In 2007, a meta-analysis of twenty studies estimated a 20% increased risk of breast cancer for women with type-2 diabetes (RR = 1.20) [58]. A review of epidemiologic studies on the association between type 2 diabetes and breast cancer risk revealed moderate association appearing to be more consistent among postmenopausal than premenopausal women [59]. Breast cancer incidence in women diagnosed at or after the age of 65 was strongly associated with highly elevated fasting blood glucose (> or =7.0 mmol/l) [48].

In young premenopausal women a wide range of insulin resistant states may occur from mild hyperinsulinism to diabetes mellitus, which are associated with different stages of androgen excess as well as defective estrogen synthesis [31]. Polycystic ovarian syndrome (PCOS) is the most frequent endocrine disorder in young women with insulin resistance and androgen excess [60]. In PCOS cases, the coexistence of anovulatory infertility and insulin resistance represents common risk for the cancers of highly hormone dependent breast, endometrium and ovary [61].

In women with PCOS, oral contraceptive (OC) administration improves anovulatory disorders and has favorable impacts on carbohydrate and lipid metabolism as well [62]. OC therapy regularizes the menses, ameliorates hirsutism and acne and is protective from the development of endometrial carcinoma [63].

In the mildly hyperandrogenic syndromes, only the ovulatory estrogen peak is missing, which results in occult anovulatory infertility and preferential cancer risk for the female organs with high estrogen demand [31, 42, 45]. Nevertheless, the preserved, but slightly defective estrogen level may be enough for the killing or differentiation of randomly initiated breast cancer cells. Accidental failures of estrogen defense in these cases yield biologically milder, ER+ cancer development. Taken together, the lower incidence rate of highly differentiated ER+ breast cancers in young cases with low grade insulin resistance may be attributed to the relatively preserved estrogen surveillance [31].

In young women, another extremity of insulin resistance is advanced visceral obesity and/or type-2 diabetes conferring high breast cancer risk attributed to the concomitant hyperinsulinism, hyperandrogenism, defective aromatase activity and a failure of estrogen synthesis [31]. Low estrogen supply cannot counteract the severe dysmetabolism and hyperandrogenism in premenopausal women, which explains the relatively increased incidence rate of poorly differentiated ER- breast cancers, preferentially TNBCs.

Postmenopausal aging in women seems to exhibit close correlation with an increased prevalence of metabolic syndrome [64]. In a case control study the risk of postmenopausal breast cancer was significantly increased in case of women with metabolic syndrome (OR = 1.75) with the risk being much higher above the age of 70 years (OR =3.04) [54].

Metabolic syndrome and type 2 diabetes seem to be preferential risk factors for TNBC as compared with the ER+ breast cancer risk. In a sample of 176 individuals, 58 % of TNBC patients exhibited the comorbid condition of metabolic syndrome as compared with 37% of the non-TNBC cases, using the metabolic syndrome criteria of the National Cholesterol Education Program. Similar differences were established using the criteria of the American
Association of Clinical Endocrinologists; 52% of TNBC cases, whereas only 34% of non-TNBC cases exhibited the criteria of metabolic syndrome [22].

The risk for TNBC is equally high for women with severe metabolic and hormonal derangement in either their pre- or postmenopausal phases. However, in premenopausal women, their preserved estrogen levels may successfully counteract moderate dysmetabolism and can overcome differentiated, ER+ cancers. Low incidence rate of ER+ breast cancers in young cases explains the apparent accumulation of more resistant ER- cancers, such as TNBCs.

Taken together, insulin resistant states, such as metabolic syndrome and type-2 diabetes are risk factors for breast cancer [54, 57], preferentially for poorly differentiated, biologically more aggressive tumors, like TNBCs [8, 22, 55]. The vast majority of literary data support that the more advanced the insulin resistance associated dysmetabolism and sexual hormone imbalance the higher the risk for TNBC development.

Obesity Mediated Risk for Overall Breast Cancer and for TNBC

Both clinical and experimental evidences prove that obesity, particularly visceral fatty tissue deposition leads to insulin resistance associated with diverse immunologic, metabolic and hormonal alterations mediating breast cancer risk [65, 66].

Distribution of fat deposition is thoroughly affected by male to female sexual steroid equilibrium [67]. In young premenopausal obese women, the overall breast cancer risk is low, as in their majority adipose tissue deposition is predominantly subcutaneous resulting in mild insulin resistance counteracted by their preserved hormonal cycle [31]. However, male-like central obesity and dysmetabolism in young obese women are associated with a decrease in serum estradiol levels, particularly in the follicular phase of the cycle [68]. Increased breast cancer risk in obesity may be attributed particularly to this hormonal imbalance [31, 42, 69].

In postmenopausal estrogen deficient, obese women the regional distribution of fat deposition near uniformly affects the visceral region in close correlation with their dysmetabolism and high breast cancer risk [47]. By contrast, in obese, HRT user postmenopausal women the improvement of hormonal and metabolic balance may equivocally reduce the incidence of breast cancer [70].

Body mass index (BMI) or body weight in kilograms reflects general adiposity and may not correctly refer to correlations among fat distribution, hormonal disorders and overall breast cancer risk in young cases [71]. In certain studies BMI defined obesity was reported as being inversely correlated with breast cancer risk in premenopausal women [47, 72, 73] showing that general obesity is not always reliable in the estimation of tumor risk.

By contrast, body circumference measurements; such as hip (HC), waist (WC) and waist to hip ratio (WHR) give better information on abdominal fat accumulation and dysmetabolism related cancer risk [74]. Among obese young women, visceral obesity related high WC and WHR values exhibited direct correlations with increased risk for premenopausal breast cancer [71, 74-76]. Conversely, in a further study, high circumference measurement data did not show exact correlation with overall breast cancer risk [24]. The contradictory results indicate that these simple circumference measurements may not always discern the metabolically inert subcutaneous and dangerous visceral fat deposition.
Obesity raises an overall risk for breast cancer even in premenopausal women showing apparently ambiguous behavior as regards the development of different molecular subtypes. Slight or moderate insulin resistance in obese young women may be associated with still sufficient estrogen signaling capable of killing the majority of developing ER+ tumors, but the more resistant, aggressive ER- cancers may escape, leading to an increase in their incidence rate. Particularly strong insulin resistance in young obese women may defeat the partially preserved estrogen surveillance, which is especially advantageous for the increased prevalence of ER-PR- tumors and TNBCs. In the meantime, there may be an unchanged or increased risk of ER+ tumors in young obese cases, depending on the preserved suppressive capacity of hormonal forces.

Considering these diverse correlations among obesity, grade of insulin resistance, level of estrogen surveillance and its different killing capacities in relation to ER+ and ER- cancers, one can understand the deceiving, apparently controversial clinical and epidemiologic findings. The above mentioned schemes are sometimes difficult to follow, as breast cancer is multicausal and the possibilities are diverse for both the mistakes and failures, which can be encountered during the complex examinations.

BMI defined general obesity is typically associated with increased TNBC risk, particularly in premenopausal women. In young cases, overweight and obesity seems to be in consistent direct correlation with the development of TNBC and other ER- types of breast tumors [11, 17, 19, 77]. Similarly, among cases with TNBC, obesity was established in 49.6%, whereas in only 35.8% of those with non-TNBCs [19]. A further study also confirmed that in premenopausal women with TNBC, obesity and overweight is much more likely as compared with cases with ER+PR+ tumors [78].

The impact of high BMI on ER+, as well as non-TNBC tumors is not uniform, depending on the hormonal status of obese women. In case of a severe defect of hormonal surveillance, ER+ cancer risk may exhibit only somewhat lower increase as compared with ER- ones [13, 19]. By contrast, when the estrogen defense is relatively preserved in obese young cases, ER+PR+ and other non-TNBC tumor incidence rate may be markedly suppressed [19, 79, 80].

Nevertheless, in a further study, high BMI was associated with similarly increased risk for luminal B type cancers (OR=1.73) and TNBCs (OR=1.67) in women 56 years or younger [13]. Explanation to the near equally weak tumor suppression rate on ER+ and ER- tumors may be the extension of the study for hormonally challenged perimenopausal and postmenopausal women. Such cases have hormonal imbalance and/or defective estrogen synthesis resulting from both their obesity and menopausal changes.

Each of the three measurements for abdominal fat (WC, HC and WHR) was statistically significantly associated with increased incidence of ER- breast cancer in premenopausal cases [24]. Hazard ratios of ER- breast cancer for the highest versus lowest quintile of body fat distribution measures were 2.75 for WC, 2.40 for HC and 1.95 for WHR. These correlations justify that central obesity is strongly associated with increased risk for ER- breast cancers. In a further study, among different obesity related factors hip circumference was directly associated with increased breast cancer risk [18]. After adjustment for BMI, both ER+PR+ breast cancers (HR=1.65) and ER-PR- tumors (HR=2.65) showed directly increased risk with central obesity when comparing the highest to lowest HC tertile. These remarkable results justified that in premenopausal women, even visceral obesity associated defective estrogen synthesis may be more suppressive for ER+PR+ tumors than ER-PR- ones.
In conclusion, obesity is a multifaceted disease associated with different grades of dangerous dysmetabolism and sexual hormone imbalance promoting breast cancer development. Obesity associated defective estrogen surveillance allows easier escape for steroid receptor negative tumors than for ER+ ones, resulting in conspicuous accumulation of ER- cancers and TNBCs in obese patients.

Role of Light Deficiency in Disparities between African-American and White American Women in TNBC Incidence Rate

Population-based data demonstrated that African-American women have breast cancer at an earlier age, diagnosed in a more advanced stage and exhibiting higher incidence rates for poorly differentiated steroid receptor negative and TNBC types than white American women [11, 50, 81]. Triple negative tumor cases tended strongly to be African American (OR: 3.14) as compared with race distribution among differentiated luminal A cases [78]. Black race was strongly associated with ER PR tumors regardless of HER2 status [11] and TNBC incidence was significantly higher in black women at all ages as compared with white women [82]. Tumor recurrence rate, metastatic spread and mortality are all disadvantageous in black American women as compared with either Caucasian or Asian groups in America [81, 83-85].

Comprehensive analysis of epidemiologic results suggests that poor light exposure in Northern regions is a marked cancer risk factor for their inhabitants, for women in particular [86]. Moreover, dark skinned immigrants have an excessive cancer risk as compared with the natives of Northern adoptive countries and the diagnostic age of breast cancer was found to be earlier [87, 88]. Excess cancer risk, rapid progression of poorly differentiated cancers and worse prognosis in black skinned American women may be conferred by poor natural light exposure and increased melatonin synthesis mediated by their high pigmentation [86].

Till now, melatonin was regarded as an anticancer agent, being presumably protective against hormone dependent tumors by its antiestrogenic impact [89, 90]. Melatonin does indeed suppress the estrogen signaling pathways, as it interferes with the activation of nuclear estrogen receptors [91] and inhibits the expression and activity of aromatase enzymes, which are responsible for estrogen synthesis [92]. Nevertheless, the well documented antiestrogenic effects of melatonin administration do not justify its protective effect against the cancers of highly hormone dependent female organs [86, 93]. By contrast, excessive melatonin exposure seems to be rather carcinogenic conferred by the defective estrogen signaling, the associated insulin resistance as well as the thyroxin and vitamin D deficiencies.

Defective estrogen signaling in black skinned American women is justified by their disproportionately impaired fertility [94]. Anovulatory disorders and early natural menopause before age 40 in African-American women are conferred by ovarian failure and associated with a higher rate of all-cause and cancer-specific mortality [95]. Infertility and ovarian failure are high risk factors for breast cancer in young women, being congruent with the health disadvantage of African-American women [86].

Melatonin excess in young tumor-free African-American women is associated with obesity, hyperinsulinism, and high free testosterone level resulting in increased breast cancer risk [86, 96, 97]. African-American women with breast cancer exhibit metabolic syndrome, type-2 diabetes and central obesity more frequently than white cases with similar tumors [98, 99].
A population based study revealed wide-spread hypothyroidism among African-American women as compared with whites [100]. As melatonin administration suppresses the thyroid function in animal experiments and clinical examinations [101, 102], disproportional hypothyroidism in black skinned American women may also be attributed to their low light exposure. In a prospective study, hypothyroidism and low FT4 values exhibited direct correlation with increased breast cancer risk [103].

Correlations between the epidemiology of vitamin D deficiency, cancer incidence and mortality were studied in the United States [104]. The African-American population exhibits a particularly widespread vitamin D deficiency. This observation suggests that adequate vitamin D replacement may be an important measure for reduction of race related health disparities including breast cancer incidence [105, 106].

In conclusion, the racial disadvantage of black skinned American women in the incidence, progression and outcome of TNBCs may largely be attributed to their defective estrogen signaling and further hormonal disturbances associated with insufficient light exposure.

**BRCA Gene Mutations Induce Particularly High TNBC Risk by Defective Estrogen Signaling**

Inherited mutations in BRCA1 or BRCA2 genes predispose to breast, ovarian, and other cancers. Their ubiquitously expressed protein products are implicated in processes fundamental to all cells, including DNA repair and recombination, checkpoint control of cell cycle, and transcription [107]. BRCA gene mutations lead to a defect of DNA double-strand break repair through homologous recombination. Disruption of BRCA proteins in mutation carriers can induce susceptibility to specific types of cancer [108].

Studies have shown that breast cancers in women with germline BRCA1 mutation are more likely to be triple negative presenting with a high grade histologically [109]. Among BRCA1 mutation carrier women with breast cancer, 48% exhibited TNBC, whereas non-carriers showed only 12% [110]. Among women with breast cancer, TNBC was established in 57.1% of BRCA1-mutation positive and in 23.3% of BRCA2-mutation positive cases, whereas in only 13.8% of BRCA-negative women [20].

Strong correlation between BRCA mutations and high TNBC risk proposes certain mediators between germline mutations and the risk for poorly differentiated breast cancers. All justified risk factors for TNBC development seem to be in close correlation with estrogen loss or defective estrogen signaling as well as further associated hormonal disorders. It is worthwhile to examine, whether any correlation exists between BRCA mutations and defective estrogen signaling, or BRCA dysfunction leads to breast cancer and preferentially TNBC development by quite different pathways.

Estradiol-mediated transcriptional activity of ERs exhibited a relative decrease in BRCA1 gene deficient human ovarian cancer cells [111]. At the same time, in these tumor cells ERα showed an unexpected ligand independent transcriptional activity that was not observed in BRCA1-proficient cells [112]. Increased estrogen independent and slight or no estrogen dependent stimulations of ERs in BRCA1-deficient ovarian cancer cells suggest that this gene mutation may confer high cancer risk by the defect of ligand activated ER signal. The observed ligand independent activation of ERα in tumor cells seems to be a compensatory
mechanism of omnipotent estrogen signal in emergency situations. Considering these data the possibility of an excessive estrogen administration emerges as a breakthrough of the gene defect induced blockage of ligand activated ER signaling in BRCA mutation carriers.

Correlations between BRCA1 mutation and low response to fertility treatments were examined, as both germline mutations in BRCA genes and anovulatory infertility are associated with high susceptibility for breast and ovarian cancers [113]. In BRCA1 mutation positive women, the low response rate of ovaries to fertility treatment was significantly increased (33.3%) as compared with BRCA1 mutation negative patients (3.3%). These results support that BRCA1 mutations are associated with defective estrogen signaling reflected by increased rate of ovulatory failure.

In women with BRCA1/2 mutation, earlier age at natural menopause, under 40 years, was observed significantly more frequently than among unaffected cases (p<0.001) [114, 115]. The high risk of premature ovarian failure among BRCA1/2 carriers reflects the disturbances in estrogen synthesis or estrogen receptor signaling pathways. As both infertility and early menopause are in close correlation with general health risk and breast cancer development [31], disorders of estrogen signaling may at least partially confer the risk of tumors associated with BRCA1/2 mutation.

Hyperestrogenism (71.7 pg/ml) was observed in BRCA2 mutation carrier patients compared to the estrogen levels of women with BRCA1 mutations (45.5 pg/ml) and cases without BRCA mutation (38.5 pg/ml) [116]. Estrogen overproduction may be a contraregulatory effect against defective estrogen signaling in germline mutation. In BRCA2 mutation carriers, increased estrogen level may mediate their markedly lower cancer risk as compared with the high risk of BRCA1 mutation carriers with slightly elevated estrogen level. Excessive estrogen synthesis was also described in a single publication on a male patient with lack of ERα function [117]. Despite his elevated estrogen level, this men presented glucose intolerance, hyperinsulinemia, obesity and premature coronary artery disease attributed to the missing ERα signaling. These valuable observations raise the possibility of breast cancer prevention by high dose estrogen administration in cases with BRCA1/2 mutations instead of the prophylactic mutilation of the breast and ovaries.

Literary data support the fact that in BRCA gene mutation carriers, the elevated estrogen levels of high parity, artificial hormonal cycle created by oral contraceptives and estrogen administration may decrease the high cancer risk. Parity in BRCA1 mutation carriers significantly reduced the risk for ovarian cancer [118], moreover, the risk was reduced with each additional full-term pregnancy in women with germline mutation [119]. Furthermore, parity with its highly elevated estrogen level seemed also to be protective against TNBC similarly as against the predominant ERα tumors [25].

Use of oral contraceptives (OCs) was found to highly reduce the risk of ovarian cancers in women with both BRCA1 (OR: 0.56) and BRCA2 mutations (OR: 0.39) [118]. Ovarian cancer risk decreased with each year of long term contraceptive use in women carrying BRCA1 or BRCA2 mutations [120]. Protective effect of OC can be used as chemoprevention against ovarian cancers in young women with BRCA mutation [121].

Consumption of phytoestrogen-rich foods such as soy emerged as preventive measure against breast cancer. Soy consumption may be beneficial in early life before puberty or during adolescence, according to results of immigrant and epidemiological studies [122]. In animal experiments, prepubertal administration of 17β-estradiol reduced the later risk of breast cancer by inducing a persistent up-regulation of BRCA1 gene [123].
As intact estrogen signaling has a significant role in glucose uptake and energy expenditure, defective estrogen synthesis and/or disorders in estrogen receptor signaling play a great role in the development of diverse insulin resistant states [43, 124]. In BRCA mutation carrier women, breast cancer development is frequently associated with high BMI and type-2 diabetes [125, 126]. These observations justify the close correlation between defective estrogen signaling and insulin resistance in the development of breast cancer [42].

In conclusion, BRCA1 and BRCA2 mutations seem to increase the breast cancer risk, particularly that of TNBC by defective estrogen signaling. Upregulation of these genes by means of increased estradiol exposure may be a promising measure against mammary carcinogenesis.

Correlation between Reproductive History and the Risk of Different Breast Cancer Subtypes

Correlations between reproductive capacity and breast cancer risk represent the greatest challenge for epidemiologists and scientists for a long time. Revolutionary molecular characterization of breast cancer subtypes yielded further paradigms and contradictions. The apparently controversial results concerning correlations between parity and the development of breast cancer subtypes suggested a striking presumption; hormonally mediated factors might be differently or quite inversely related to the development of ER+ and ER- breast cancers [15, 26, 27].

It has been hypothesized that risk for ER+ breast cancer is positively associated with a woman’s lifetime exposure to endogenous ovarian hormones; thus reproductive history may strongly influence the risk by affecting the number of ovulatory cycles over lifetime [127, 128]. By contrast, as triple-negative breast cancers are steroid hormone receptor negative, risk factors operating through hormonal mechanisms are presumed to be less important in the etiology of these tumors as compared with ER+ cancers [15].

Multiparity in women, and risk for malignancies at several sites exhibit a strong inverse correlation [129-131]. High parity shows tumor protective effect even against the cancers of highly hormone dependent female organs including overall breast cancer, endometrial and ovarian tumors [127, 132]. In anovulatory patients, a significantly decreased overall cancer risk was reported after in vitro fertilization assisted childbirth, mainly due to a lower than expected incidence of breast cancer [133].

In experimental animals, pregnancy equivalent high estrogen administration could consequently prevent the development of transplanted or chemically induced mammary tumors [134-137]. In ovariecтомized, female mice, alcohol consumption and obesity enhanced the growth of experimental mammary tumors, while estrogen supplementation triggered the loss of body fat, improved insulin sensitivity and suppressed tumor growth [137, 138].

Parity and particularly multiparity are associated with a decreased risk of the predominant ER+ breast cancer type, which is in consistent correlation with the literary data [11, 15, 26, 27, 78, 139]. Among parous women, even the number of births was inversely associated with the risk of ER+ breast cancer (HR=0.88) [15]. A strongly decreased risk of ER+ breast cancer
(OR=0.55) was reported among women who had at least four pregnancies as compared with nulligravid women [25].

Conversely, TNBC incidence exhibited an apparently unchanged ratio in parous women [11, 14, 25], whereas in certain studies even an increased risk of TNBC was reported in multiparous cases [16, 140, 141]. In a recent study the number of births was found to be directly associated with the risk of TNBC [15]. Obviously, apparently unchanged or relatively increased TNBC incidence rate in parity may be explained by the weaker killing capacity of high estrogen level against ER- than ER+ breast cancers.

Nulliparity is generally in strong correlation with anovulatory disorders, thus these hormone deficient cases may be regarded as opposite extremes as compared with multiparous women [31]. Delayed first childbirth is usually also associated with prolonged defective estrogen synthesis and ovulatory failures. Nulliparity and delayed first childbearing are well-known risk factors for overall breast cancer among premenopausal women [142, 143], which may be associated with their postpubertal, prolonged sexual hormone imbalance and fertility disorders [144]. High overall breast cancer risk in correlation with defective estrogen synthesis and anovulatory disorders justifies the role of physiologic estrogen level in preservation of mammary health [31].

Some studies suggested that nulliparity plays quite inverse role in the risks of ER+ breast cancer and TNBC as compared with multiparity [26]. Nulliparous status of women was associated with a 35% higher risk of ER+ breast cancer (HR=1.35), whereas with a 39% lower risk for TNBC (HR=0.61) [15]. Delayed first childbirth was also directly associated with risk for ER+ cancers but did not affect risk for TNBCs [15].

Considering these contradictory results, if women undertake more childbirth they may be exposed to strong TNBC risk, conversely, if they remain nulliparous they are exposed to higher risk for ER+ cancers. So what should they do?

Deceivingly inverse correlations between the prevalence of ER+ and ER- cancer subtypes in parous and non-parous women are similar to the paradigm experienced in premenopausal young and postmenopausal cases. Good hormonal equilibrium is represented among parous and premenopausal women, while defective estrogen exposure is characteristic among nulliparous and postmenopausal cases.

In multiparous women, good fertility associated estrogen supply and excessive estrogen levels during pregnancies strongly and equivocally reduces the development of overall breast cancers and the predominant ER+ tumors in particular. An obvious explanation is that estrogen, being the specific ligand for ERs, may preferentially block the development and progression of ER+, more vulnerable cancers through their available receptors. By contrast, the tumor killing capacity of estrogen against ER- cancers is slower and weaker as the specific receptors are missing. In an abundantly estrogen rich milieu, the weaker killing effect on ER- tumors and strong destructive capacity on ER+ cancer cells may result in a deceivingly higher or unchanged ratio of poorly differentiated ER- cancers.

By contrast, in nulliparous, hormone-deficient women, the weakness of estrogen surveillance results in enhanced overall breast cancer risk with strong persistence of both the predominant ER+ and uncommon ER- tumors. The defective estrogen supply in nulliparous women may weakly kill even the predominant, ER+ breast cancer cells resulting in an apparently high incidence rate of surviving ER+ tumors. In the meantime, the incidence rate of the considerably more resistant, unsuppressed ER- cancer cells remains unaffectedly low.
There is a plausible proposal for perplexed women to choose parity either by natural way or by in vitro fertilization to prevent the development of both TNBC and non-TNBC type tumors.

**Some Aspects of the Molecular Mechanism of Estrogen Surveillance on the Cell Proliferation**

The classic genomic mechanism of estrogen binding activates ERs in the nucleus and they act as transcriptional modulators in the promoter region of target genes. ERs can also regulate gene expression without direct binding to DNA through interaction with transcription factor proteins in the nucleus [145]. Estrogen action also has non-genomic signaling cascades through cell membrane associated ERs [146]. Finally, genomic and non-genomic pathways of estrogen receptor signaling converge on the target genes.

Two receptor isoforms were identified; estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), which belong to the steroid-thyroid hormone nuclear receptor supergene family [147, 148]. ERα and ERβ regulates by means of thorough interplay the metabolic processes, the cell growth and proliferation of mammalian cells. They may oppose each other’s activities eliciting sometimes quite opposite reactions in the presence of estradiol [149], which may be crucial for the dynamism of regulatory mechanisms.

Agonistic and antagonistic cross talk of estrogen receptors and their thorough interplay with other hormonal and growth factor signals ensure that estrogen orchestrates the gene regulation of cell proliferation with high safety [145, 146]. Crosstalk of estrogen receptor isoforms provide a momentary equilibrium of cell growth and mitotic activity defined by tissue type, functional activity and environmental influences. Physiologic equilibrium of estradiol induced mitotic activity and apoptotic cell death was observed in mouse mammary cell line, HC11, the cells of which expressed both estrogen receptors and showed no proliferative activity [150]. Embryonic development justifies the importance of the omnipotent actions of estrogen. High estrogen level in the fetoplacental unit may ensure explosion-like cell proliferation, the silencing of mitotic activity, or even apoptotic cell death if it is necessary [32].

As estrogen and ER signals are essential players for harmonizing the regulation of all cellular functions, sufficient hormone exposure and available intact receptors are indispensable for the health of mammalians [43]. Separated activation or blocking of each ER isoform may produce thorough alterations and disturbances. It is quite impossible to interfere with or even improve this highly controlled safeguard of estrogen on cellular mechanisms.

It is a well-known fact that the higher the proliferative activity of a cell population, the stronger the danger of mutagenic failures and tumor initiation. Following conception, 17β-estradiol level increases exponentially from a level of 0.1 ng/ml in the follicular phase of cycle up to 30 ng/ml at term, which means a 300 fold elevation [151]. During pregnancy, extreme increase in the estrogen supply of fetoplacental unit serves as an exquisite safeguard for the abundant, explosion-like cell proliferation of embryonic structures. If estrogens would have even the slightest carcinogenic capacity, tumor birth would be a typical event instead of childbirth, attributed to the overwhelming estrogen supply in pregnancy.
In animal experiments, the administration of high doses of estradiol before or after carcinogen treatment was equally protective against mammary carcinogenesis [152]. Different mechanisms emerged as explanations for hormone-induced refractoriness to carcinogenesis. Target cells in the mammary gland may become non susceptible by excessive hormone treatment through DNA protection [152], or chemically initiated tumor cells may undergo differentiation [153]. As a further possibility, the tumor cell killing capacity of excessive estradiol administration may also reduce the mammary cancer incidence [154].

There are literary data on the supposed roles of membrane associated ER signaling pathways in human cancer induction [155], particularly in breast cancer cases [156, 157]. Obvious interactions of estrogen and growth factor receptors (GFRs) in various cancers have been regarded as revelation of the cancer provoking effect of estrogen. The presumed synergistic carcinogenic capacity of ERs and GFRs would mean a constant danger for cancer initiation without contraregulatory impact. Nevertheless, in human breast epithelial cells both growth inhibition and growth stimulation by estradiol were observed depending on the rate of ERs and GFRs [158].

A dynamic inverse relationship was justified between the expressions of GFRs and membrane associated ERs in malignancies. Excessive epithelial growth factor (EGF) administration on the human breast cancer cell line MCF-7 resulted in persistent decreases in ERα protein concentration, in estradiol binding sites, and in ERα gene transcription [159]. Alternatively, high estrogen dose could inhibit lung carcinogenesis by reducing the level of insulin-like growth factor-I (IGF-I), which is a potent mitogenic agent for several malignant tumors, including lung and breast cancers [21, 160].

There are plausible possibilities for the anticancer effect of estrogen even on receptor negative cancers. In apparently ER-negative breast tumor cells, inhibition of growth factor signaling yielded a potential restoration of ER expression [161]. Abundant estradiol administration may also counteract the growth factor signaling and the concomitant restoration of estrogen receptor expression yields possibility for the apoptotic killing of tumor cells. This may be one of the possible secrets of the antitumor capacity of pregnancy equivalent estrogen level even in case of receptor negative breast cancer cells.

In conclusion, pregnancy associated high estrogen level is protective against the initiation and progression of all breast cancer subtypes. However, the intensity of this defense strongly depends on the molecular subtype of the tumors; the higher the ER expression of cancers the stronger the tumor suppressive effect of estrogen.

**Answers to the Unanswered Questions**

1. Malignancies are multicausal but the disturbance of proper estrogen signaling seems to be a crucial risk for the development of mammary cancers. The grade of defect in metabolic and hormonal equilibrium is directly associated with TNBC risk for women during their whole life.

2. TNBC is not a distinct entity with unique etiology, but rather its development is mediated by usual cancer risk factors, which at the same time destroy the estrogen defense of cellular mechanisms.
3 Usual but strong and/or multiple breast cancer risk factors may provoke the development of poorly differentiated tumors, such as TNBCs in particular.

4 Exogenous or parity associated excessive estrogen supply is highly defensive against all breast cancer subtypes, but ER- tumors and TNBCs are more resistant. Inverse impact of parity on ER+ and ER- breast cancers is quite impossible; these erroneous results derive from the misinterpretation of statistical evaluations.

5 The most important preventive strategy against breast cancers – included TNBCs – in women is the strict control of hormonal equilibrium from early adolescence through a lifetime, particularly during the periods of great hormonal changes. Screening of symptom-free anovulatory disorders, cycle irregularities and infertilities as well as estrogen treatment of all hormonal defects may be lifesaving. In the peri- and postmenopausal periods, menopausal complaints and tumor risk factors such as; hysterectomy, obesity, metabolic syndrome and type 2 diabetes are absolute indications for estrogen substitution therapy. In regard to inherited inclinations for breast cancer, exogenous hormone treatment and parity are indicated.

Effective breast cancer therapy requires a complete conversion. Worldwide administration of antiestrogen compounds for breast cancer treatment yielded thorough disappointment. Antiestrogens are strong cytostatic agents blocking the most important regulatory mechanisms in mammalian cells, in turn resulting toxic effects and powerful cancer induction at several sites. Nevertheless, publications on the successful, high dose estrogen treatment of advanced breast cancer cases are increasing in number and their results are encouraging.

Widespread estrogen use in the primary prevention and therapy of breast cancer may help to eradicate this dreadful, torturing disease around the world.

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