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Tumour biology of a breast cancer at least partly reflects the biology of the tissue/epithelial cell of origin at the time of initiation — a hypothesis

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Abstract

A hypothesis is presented suggesting that initiation of breast epithelial cell freezes the cell at least partly according to the development/differention of cell at the time of initiation. Tumour biology will mimic the physiology of normal cell development at the time of initiation and this is preserved at least partly onwards. Also preferentially, tumours will develop from the cell type that is proliferating at the time of initiation. This may explain the overrepresentation of different types of histology in breast cancer in relation to age of the woman. The development of each tumour may follow at least partly a distinct pathway of evolution.

Keywords: Tumour biology; Breast cancer; Tissue/epithelial cell; BRCA1; BRCA2; HRT and oral contraceptive use; Hormone receptors; Estrogen receptor; Progesterone receptor

1. Introduction

Carcinogenesis in hormone dependent organ as the breast may have a time sequence of promotion — initiation and promotion which is different from skin carcinogenesis, where initiation is followed by promotion [1,2]. The time of initiation of breast cancer is very seldom known except for a few cases of radiation induced breast tumours. A number of hormonal risk factors of breast cancer is known [3]. Recently some hereditary syndromes defined both through population genetics by dominant inheritance patterns from breast cancer prone pedigrees and by gene discoveries have been defined [4,5]. In order to better understand the tumour biology in an epithelial tissue such as the breast an attempt is made to present a unifying hypothesis relating at least partly the biology of the cell/tissue of origin at the time of initiation to tumour biological properties seen at tumour diagnosis. The situation in the breast would show similarities to tumour biology and evolution in hematological malignancies such as leukemias and lymphomas.

Various alternative hypotheses could be suggested as a cause or a reflection of the biology of a given tumour in relation to its normal epitelial counterpart. Firstly, the biology of a tumour could be dependent on the evolutionary age of the tumour, that is tumours which have been growing for a longer time have a larger chance of being less differentiated and show more genetic changes. Secondly, the biology of a tumour could be a chance event, being dependent on the initial genetic changes and their successive evolution. Genetic instable cells could have a larger chance of developing into high-grade tumours and have a survival benefit. Further the biology of the tumour and the development of tumour could be dependent on a faulty apoptotic mechanism preserving life of cells otherwise destined to die.

The biology of the tumour could at least partly reflect the biology of the originally initiated normal epithelial cell freezing the evolution to the developmental stage of the epithelial cell at the time of initiation. That reproductive and hormonal factors may have longstanding effects on normal and tumour tissue have been hypothezised before [6]. In general tumorigenesis occurs easier in tissue which is more undifferentiated and with a higher number of proliferating cells [7,8].

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Although all hypotheses may be plausible in the present paper arguments will be presented in support of the last hypothesis, suggesting that the tumour biology of a breast cancer at least partly reflect the biology of the tissue/epitelial cell of origin at the time of initiation.

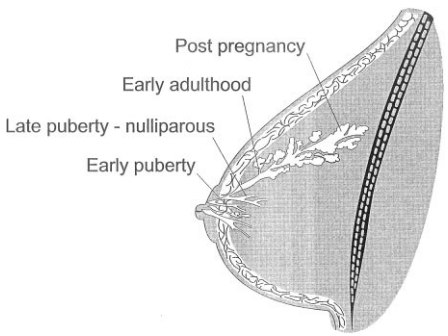

Fig. 1. The development of the mammary ductal tree is hypothetically described in relation to age and reproductive events. Note that the arrows only arbitrarily indicates the developmental age and differentiation of ducts.

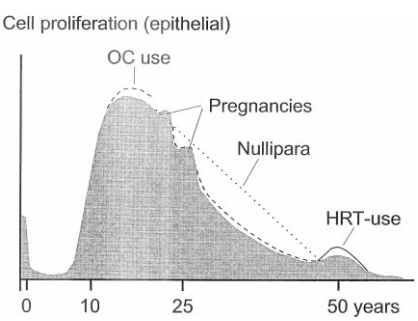

Fig. 2. A hypothetical curve describing the proportion of epithelial cells in proliferation in relation to the age of the woman and reproductive events. A parous and a nulliparous woman are seperately shown. Also the fetal development is indicated before age zero. OC-use, oral contraceptive use; HRT use, hormone replacement therapy. Patients with tumours initiated during early reproductive years are hypothesised to have a worse prognosis than patients with tumours initiated in late reproductive life or after menopause as the biology of the tumour partly would reflect the proliferation of the normal tissue.

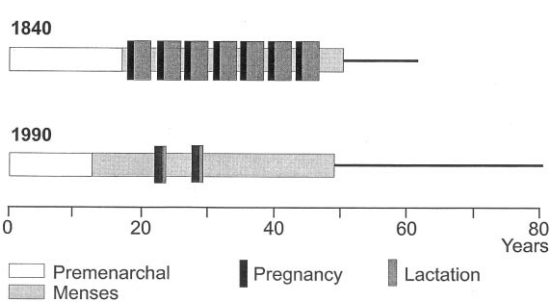

Fig. 3. Reproductive life 1840 and 1990 respectively. The fertile woman in 1840 had a later age at menarche, much more pregnancies and nursed each child for a longer time, while menopause occurred at a similar age as the woman in 1990.

2. Characteristics of the normal breast epithelium

The normal breast epithelium undergoes large changes in relation to fetal life, puberty and a pregnancy similar to changes that have been described in animal models [9,10]. Experimental studies suggest that the development of hormone receptors in breast tissue (estrogen alfa receptors and progesterone receptors) follows a pattern in relation to age and tissue differentiation, where first estrogen receptors are detected and later progesterone receptors appear especially after having completed a pregnancy [11,12].

In general undifferentiated tissue show a higher proliferation and low hormone receptor content. The differentiation of breast parallels the development of different types of duct structures suggested by Russo et al. [9,10]. In Fig. 1 the hypothetical stage of development of the breast epithelial tree is indicated in relation to the reproductive age of the woman.

In Fig. 2 a hypothetical curve of the proportion of breast epithelial cells in proliferation in relation to age is shown. Further important reproductive events such as a pregnancy, exogenous hormone use and menopause is depicted and may have profound effect on cell proliferation and differentiation [13–19]. The proliferation of the breast epithelium is highest in the second half of the menstrual cycle [17,19] and therefore thought to be both estrogen and progesterone dependent contrary to the endometrium where the proliferation to a high degree is estrogen dependent [20]. Initially, a pregnancy increases breast epithelial proliferation while later in pregnancy and during lactation proliferation is reduced and permanently lowered compared with the situation of a nulliparous woman. Use of exogenous hormones, such as high dose oral contraceptives before first full term pregnancy and in early reproductive years increases breast proliferation compared to hormone use in other time periods [19]. Although data is scarse a family history of breast cancer may be associated with a higher proliferation if the woman at the same time is exposed to exogenous hormones [19]. Hormone stimulation from a large number of menstrual cycles has been considered a very important risk factor of breast cancer [21–23]. The great change in female reproduction between the last centuries has been suggested to be the most important factor underlying the high incidence of breast and gynecological tumours nowadays (see Fig. 3). While the number of children and the lactation time per woman greatly have been reduced women also have experienced an earlier age at menarche. Indirect evidence that estrogen receptor alfa levels also could be lowered in normal tissue by early high dose oral contraceptive use

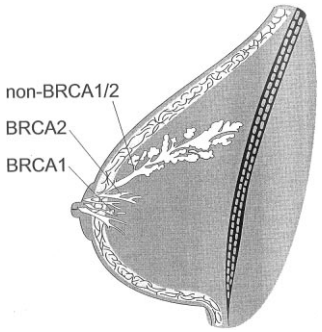

Fig. 4. Hypothetical origin in the mammary duct tree of tumours from BRCA1, BRCA2 and non-BRCA1/2 cases. The tumours of BRCA1 cases may develop from duct structures that are more early and immature in their development. Most breast cancers are thought to originate from terminal end buds of the ductal tree and this picture do not exact depict the location of the end buds and responsible cells for the origin of each hereditary syndrome.

has been found in studies of receptor content in endometrial tissue [24] and breast tissue [18,25].

3. Biologic characteristics of the tumours in relation to exogenous risk factors, possible time at initiation and age at diagnosis of the woman

The age of the woman and the hormonal/reproductive status of the woman at the time of the initiation will have a profound effect on the tumour biology. Malignant breast tumours originating from less differentiated tissue in younger women will show evidence of lower hormone receptor levels, higher proliferation rates and generally have a worse prognosis than tumours being diagnosed at later ages [26–29].

A relationship between the cell proliferation and age at higher risk for tumour initiation exists such as pre- and pubertal ages being more vulnarable for radiation carcinogenesis [30–32].

Breast tumours possible induced by radiation after a full term pregnancy more often is progesterone receptor positive while tumours possibly being induced before a pregnancy or in nulliparous women more often are either estrogen receptor positive/negative and progesterone receptor negative tumours [33].

Breast tumours occurring in young women after teenage high dose oral contraceptive use more often are hormone receptor negative, ERBB-2 positive, DNA non-diploid with a high percentage of tumour cells in cell proliferation compared to breast tumours developing in later users or non-users of oral contraceptives [34–36]. Breast cancer diagnosed during pregnancy generally is high proliferating with a low hormone receptor content [37]. However high levels of hormones may block receptor content and give false negative values and therefore results in pregnant women is difficult to interpret. Breast cancer developing in women after HRT use in general have been found to less adverse prognostic signs than in women of similar age that have never used HRT [38,39]. Breast cancer in men are diagnosed late in life (in general ≥ 70 years of age) are rich in receptor content and have a deficit in lobular structures [40–42].

The histologic type of breast cancer also show some age patterns [43] possibly reflecting the state of cell of origin at the time of initiation. Thus atypic medullar carcinomas and comedocarcinomas are diagnosed at rather early ages while tubuloductal and lobular carcinomas often are found in middle aged or older women and mucinous tumours are common in elderly women.

4. Biologic characteristics of the tumours in relation to genetic risk factors, possible time at initiation and age at diagnosis of the woman

Various genetic syndromes may predispose to breast cancer [4,44]. Although very rare syndromes as women having germline mutation in the p53 and p16 gene occasionally are found in a clinical setting the most common aggregation of families with a dominant inheritance of breast cancer includes families with germline mutations of the BRCA1 or BRCA2 genes [45]. Another large group, constitute women from breast cancer prone families where no BRCA1/2 mutation is found (non-BRCA1/BRCA2 families). These three different syndromes display more or less distinct tumour and clinical phenotypes that may be used to support the above presented hypothesis (see hypothetical Fig. 4 of development of BRCA1, BRCA2 and non-BRCA1/2 tumours from different parts of the breast epithelium).

Tumours developing in BRCA1 carriers are low differentiated tumours, that often are estrogen and progesterone receptor negative, ductal carcinomas of the 'atypic medullary type', rich in lymphocytes, nuclear grade III, highly proliferating and the tumours grow with pushing borders [46,47]. The tumours show rarely in situ components. Also the tumour evolution follows a distinct CGH pattern [48]. Median age at tumour presentation is 40 years. It is very rare that male mutation carriers develop breast cancer.

The BRCA2 associated tumours are both low and well differentiated, both estrogen and progesterone receptor positive and negative, have various histologic types and grow with pushing borders [47]. Again tumour evolution follows a distinct CGH pattern [49]. Median age at tumour presentation is 44 years. Men carrying the BRCA2 mutation can also develop breast cancer up to a frequency of 5–10% [50].

Tumours occurring in breast cancer prone families negative for BRCA1 or 2 are often well differentiated, and estrogen and progesterone receptor positive with a low proliferation rate and of various histologic types

[51]. Often in situ components are seen and median age at presentation is 55 years.

According to the above, it could be hypothesised that breast cancers develop from different epithelial structures in these three settings reflecting the differentiation and development of breast ducts and lobuli (see Fig. 4). According to this hypothesis BRCA1 tumours develop from the early duct system which is less differentiated than in BRCA2 and non-BRCA1/2 carriers. Tumours in BRCA2 carriers on the other hand develop from less developed duct structures than tumours in non-BRCA1/2 women.

Experimental data regarding the BRCA1 gene indicates that conditional knock out of both alleles of BRCA1 in breast tissue leads to underdeveloped breast epithelium and with tumour formation while in heterozygous animals no clear effect on epithelium and no increase in tumour formation is seen [52]. The expression of the BRCA1 protein is increased in relation to rapid proliferation of the breast tissue and stimulated by estrogen and progesterone [53,54]. The normal protein therefore could in a protective way be upregulated at times of rapid proliferation to counteract neoplastic transformation [55]. The protein is further involved in repair of DNA double strand breaks [56].

Initial studies on humans lend some support of biological effects in BRCA1 heterozygous individuals. First newborn BRCA1 carriers are small for gestational age compared with sister non-carriers [57]. Carriers further show a shorter lactation time due to an involuntary drain of milk production during lactation [58]. Cancer risk is not decreased by a pregnancy in BRCA1 or BRCA2 carriers, instead an increased risk is seen for each succeeding pregnancy [59,60]. Preliminary data may also indicate that oral contraceptive use among BRCA1 carriers increase the risk of breast cancer development [61].

Human findings may support the hypothesis that there is ''underdeveloped breast tissue in BRCA1 and BRCA2 carriers'' and that this is reflected in the breast cancer tumour biology that is seen. If the receptor content of the tumour reflects the time of initiation a protective effect from antiestrogens could mainly be postulated for non-BRCA1/2 carriers with their receptor rich and highly differentiated tumours occuring later than tumours in the two other groups.

5. The prognosis of the tumour in relation to the time of initiation

A difference in prognosis between BRCA1, BRCA2 and non-BRCA1, BRCA2 hereditary breast cancer is postulated. Already data suggest that women with BRCA1 tumours have similar or worse prognosis than age matched patients [62]. Breast cancer diagnosed during pregnancy has a poor prognosis [63]. Breast cancer diagnosed in women having used high dose oral contraceptives during teenage years or before the first full term pregnancy has a worse prognosis than other young women with breast cancer [34,64].

Women with breast cancer and a history of previous HRT use have a better prognosis than other women of similar age with breast cancer regardless of their tumours are estrogen or progesterone receptor positive or negative or if the tumour is detected by mammography screening [65].

6. Conclusion

In the present paper arguments have been presented in support of a hypothesis in breast cancer that the tumour biology and then indirectly the prognosis of a breast cancer at least partly reflect the biology of the tissue/epitelial cell of origin at the time of initiation. The hypothesis argues that at least part of the function/development of the normal cell is 'frozen' and retained in the tumour cell. Initiation would be much easier in time periods when the epithelial cell is undifferentiated and in a proliferative state. Further, tumours initiated from a more undifferentiated epithelial cell would show rapid growth characteristics and a more adverse biology reflected in a worse prognosis compared with tumours initiated from a more differentiated tissue. Tumour evolution would also occur in this situation and at least in the beginning follow distinct pathways related to cell of origin while later turn into a more chaotic genetic pattern.

Examples in support of the hypothesis have been given from radiation induced breast cancer, breast cancer diagnosed during pregnancy, breast cancer in BRCA1, BRCA2 germ line mutation carriers and non-BRCA1/BRCA2 hereditary cases, and breast cancer diagnosed in relation to previous oral contraceptive- and HRT-use.

Studies of breast cancer histiogenesis with use of old and new epithelial markers, possibly through array systems, would help to further assess the truth of the hypothesis. Especially studies of the new estrogen hormone receptor beta in the context of breast cancer tumour biology and epidemiologial risk factors would be of great interest.

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