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A hypothesis about tumour development and the clinical features of hereditary breast cancers

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Abstract

A unifying hypothesis is presented about tumour biology in hereditary breast cancer in relation to the epithelial origin and the degree of differentiation of the normal epithelium at the time of tumour initiation. By using different breast cancer syndromes as examples, it is possible to, at least partly, predict the tumour biology, clinical presentation and therapeutic response. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: *TP53*; *TP16*; *BRCA1*; *BRCA2*; *BRCAX*; *ATm*; *Pten*; Oestrogen receptor; Progesterone receptor

1. Introduction

Population genetic studies suggest that 5–10% of all breast cancers are due to single gene disorders [1]. Already, some genes (*TP53*, *BRCA1*, *BRCA2*, ataxia teleangiectasia (ATm), protein tyrosine phosphotase with homology to tensin (Pten)) have been identified and linked with specific syndromes where breast cancer is the only tumour disease among mutation carriers or where breast cancer occurs together with other tumours in predisposed families [2–8]. The disease penetrance identified in mutation-carrying families is incomplete rendering the life-time risk of breast cancer to between 40 and 90% [9]. The reason for the incomplete penetrance is unknown, but could be due to interaction with both environmental and other genetic factors. It is conceivable that in families with a very high penetrance of breast cancer, other breast cancer predisposing genes may be at work and raise the disease risk leading to a higher risk of breast cancer than in the general population, even among the non-mutation-carrying members of the family.

Knowledge from the hereditary breast cancer syndromes can be used to construct a unifying hypothesis about the tumour biology in breast cancer in relation to the epithelial origin and the reproductive age of the individual at the time of tumour initiation. I have previously proposed a hypothesis in relation to age at initiation and tumour biology in breast cancer [10,11]. The proposal suggests that the age and differentiation of the breast epithelium at the time of initiation, at least partly, reflects the tumour biology at diagnosis. The development of this hypothesis has been stimulated by our research findings about tumour biology and prognosis in hereditary breast cancer and in women exposed to hormonal risk factors.

2. Patients and methods

In the present paper, the recent knowledge acquired in hereditary breast cancer has been used to propose a hypothesis about how age, reproductive status and breast epithelium at tumour initiation affects the biology in seven syndromes associated with hereditary breast cancer (*TP53*, *TP16*, *BRCA1*, *BRCA2*, *Pten*, *ATm* and non-*BRCA1/2* families). Families with mutation in the *TP16/CDKN2* gene were included as we have recently found that they experience a high incidence of breast cancer [12]. Furthermore, it has been recognised that a large proportion of hereditary breast cancer (here named *BRCAX*) is not explained by mutations in any of the above genes, and we have recently linked a subgroup among these patients to a new gene location on chromosome 13 [13]. *BRCAX* families are characterised by rather late tumour onset and often receptor-positive

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tumours [14]. Controversy surrounds the hypothesis that heterozygotes of mutations in the *Atm* gene may have an increased risk of breast cancer and what proportion of hereditary breast cancer such mutations may explain [15–17]. It is believed that an increased risk exists, but that the proportion of hereditary cases explained by *ATm* mutations is rather low. Patients with Cowden's syndrome with germline mutations in the *Pten* gene also have an increased risk of breast cancer [18]. Again, the proportion of cases with hereditary breast cancer explained by such mutations is low. Germline mutations in the *TP53* gene are also rare events and explain only a small proportion of hereditary breast cancers, especially those occurring at a very young age [9].

The present hypothesis focuses, in particular, on the age at initiation, cellular origin, hormone receptor status, prognosis, possible effects of pregnancy, lactation and chemoprevention for each syndrome.

The hypothesis is built on a number of postulates: first, that breast carcinogenesis originating in more immature, less differentiated breast epithelium would lead to a more aggressive tumour behaviour, second, that the hormone receptor content would be lower in tumours originating from a tissue with a higher proliferation rate [19] (as is the case in normal tissues) or from a less differentiated tissue before a pregnancy [20] and third, that tumour initiation in a more immature epithelium would lead to a disease presentation in more organs than when the disease originates in a more differentiated tissue. This hypothesis may generate research aimed at validating or refuting its postulates and, if it is supported by epidemiological and experimental evidence, it may assist clinicians in their work with individuals from hereditary cancer families.

3. Results

3.1. The hypothesis

In Table 1, the features of each syndrome are presented. The following features of each disease/syndrome are discussed: cell of origin of the breast epithelium, age at tumour initiation and diagnosis, tumour type, associated tumour disease, bilaterality and multifocality, tumour prognosis, interaction with hormonal risk factors, possible effects from chemoprevention, founder mutations and new mutations and disease penetrance.

3.2. Breast cancer in TP53 patients (<<1% of all breast cancers)

Breast cancer is a part of the Li–Fraumeni syndrome [21]. The tumours originate in very immature breast tissue, and diagnoses are made at a very early age (1/3 below the age of 30 years) [22]. Tumour initiation occurs at a very young age. As the tumour retains at least part of the features of the tissue of origin, it is poorly differentiated, low in oestrogen receptor (ER), and progesterone receptor (PGR) content. Cancer *in situ* is uncommon. Prognosis is poor. There is an associated tumour risk in many organs (soft tissue, brain, lung, adrenal and haematopoetic tissue). Relative to the syndromes occurring at a later age, bilaterality and multifocality are less common. Hormonal risk factors do not interact. New mutations are common, while founder mutations are rather rare. No effect from chemoprevention is anticipated. Disease penetrance is high [21].

3.3. Breast cancer in TP16 patients (<<<1% of all breast cancers)

Recently, we have reported that breast cancer is increased in *TP16* mutation carriers [12]. The tumours also have their origin in immature or partly differentiated breast tissue and diagnosis is often made between 30 and 70 years. Tumour initiation occurs at a variable age. Tumours are often poorly differentiated and low in ER and PGR content. Cancer *in situ* is uncommon. Prognosis is moderately poor. Mutation carriers have an associated tumour risk in the skin (melanoma) and pancreas [12]. Relative to syndromes occurring at a later age, bilaterality and multifocality are less common. Hormonal risk factors do not interact. New mutations are uncommon, while founder mutations are common. No effect from chemoprevention is anticipated. Disease penetrance is not known.

3.4. Breast cancer in BCRA1 patients (approximately 1–2% of all breast cancers)

Breast cancer is the most common tumour seen in *BRCA1* mutation carriers [23,24]. The tumours have their origin in an immature breast tissue, and diagnoses are made at a rather early age (average 40 years). Tumour initiation occurs at a rather young age. As the tumour retains at least part of the features of the tissue of origin, it is poorly differentiated and low in ER and PGR content [25,26]. Survival is slightly worse than age-matched women with breast cancer [27,28]. The tumour grows as an atypical medullary breast cancer rich in lymphocytes and demonstrates pushing borders [26,29]. Its cellular origin probably represents the epithelial site for Ig-A lymphocyte secretion of Ig-A into the milk. The common lymphocyte phenotype in medullary breast cancer is a plasma cell with Ig-A in the cytoplasm and as a secretory component [30]. Cancer *in situ* is uncommon. The incidence of other tumours are increased, especially ovarian tumours [23,24]. Bilaterality and multifocality are common [31]. Pregnancies increase the risk of breast cancer [32,33]. New mutations

Table 1

	TP53	*TP16*	*BRCA1*	*BRCA2*	*Pten*	*BRCAX*	*ATm*
Origin/type of breast epithelium	Immature	Immature	Immature	Partly differentiated	Well differentiated	Well differentiated	Well differentiated?
Age at tumour initiation	Very young	Varying age	Rather early	Moderately early	Rather late	Rather late	Rather late
Age at tumour diagnosis (years)	<40	<30–70	Average 40	Average 48	Average 60	30–80	50+
Tumour type	Ductal, low differentiated, ER−, PGR−?	Ductal, low differentiated, EG−, PGR−?	Atypic medullary, low differentiated, ER−, PGR−, lymphocyte rich (epithelial site for lymphocyte Ig-A secretion)	Ductal/lobular moderately differentiated ER±, PGR±, *in situ*	Ductal, well differentiated ER+, PGR+? cystic benign disease, hyalinisation, *in situ*	Ductal/lobular, well differentiated ER+, PGR+ *in situ*	Ductal/lobular, well differentiated ER+?, PGR+? *in situ*
Associated tumour disease	Sarcoma brain tumours leukaemia lung cancer adrenal tumours	Melanoma pancreas cancer	Ovarian cancer	Ovarian cancer (male breast cancer)	Thyroid cancer	−?	−
Bilateral/multifocal breast tumour	?	?	High	Moderately high	High	?	High
Tumour prognosis	Bad	Moderate	Bad–moderate	Moderate	Good	Good	Good?
Interaction with hormonal risk factors	No	No	Pregnancy increased risk, lactation?	Pregnancy increased risk, lactation?	?	Pregnancy reduced risk lactation reduced risk	?
Possible effect of chemoprevention	−?	−?	−?	±	+?	+?	+?
Founder mutations	Less common	Common	Common	Less Common	?	?	?
New mutations	Common	Uncommon	Uncommon	Uncommon	?	?	?
Disease penetrance	High1	?	High	Slightly lower than *BRCA1*	Lower than *BRCA1/2*?	Lower than *BRCA1*	Lower than *BRCA1*

ER, oestrogen receptor; ATm, ataxia teleangiectasia; PGR, progesterone receptor. Each disease/syndrome is presented by cell origin of the breast epithelium, age at tumour initiation and diagnosis, tumour type, associated tumour disease, bilaterality and multifocality, tumour prognosis, interaction with hormonal risk factors, possible effects from chemoprevention, founder mutations and new mutations and disease penetrance. It needs to be emphasised that the table includes both results supported both by direct studies and by indirect reasoning. Question marks indicate areas were information is especially poor.

are uncommon, while founder mutations are common. No effect from chemoprevention is anticipated. Disease penetrance is high [9].

3.5. *Breast cancer in* BRCA2 *patients (approximately 1% of all breast cancerss)*

Breast cancer is the main feature of the *BRCA2* syndrome as well [24,34,35]. The tumours have their origin in a partly differentiated breast tissue, and diagnoses are made at an average age of 48 years. Tumour initiation occurs at a moderately early age. As the tumour retains at least part of the features of the tissue of origin, it is both ductal and lobular and moderately differentiated and low or high in ER and PGR content [14]. Cancer *in situ* is not uncommon. Prognosis is moderately poor [36,37]. There may be an associated tumour risk in the ovary. While studies from large research families suggest an increased risk for ovarian cancer in mutation carriers, population-based studies which excluded the nuclear family which was the basis for the research ascertainment, argue against a large risk for ovarian cancer [24]. Bilaterality and multifocality are common. Pregnancies increase the risk of breast cancer [32,33]. New mutations are uncommon and while founder mutations are present, they are not as common as in *BRCA1* [38]. Chemoprevention may prevent disease in a proportion of the risk population. Disease penetrance is slightly lower than in *BRCA1* [34,39].

3.6. *Breast cancer in Cowden's disease (Pten) patients (<<<<1% of all breast cancers)*

Women with Cowden's syndrome are also at increased risk for breast cancer [18], but the syndrome's overall importance in familial breast cancer is low [40]. The tumours have their origin in a well differentiated breast tissue, and diagnoses are made at an average age of 60 years (range: 30–80 years). Tumour initiation occurs rather late. As the tumour retains at least part of features of the tissue of origin, tumours are both ductal and well differentiated and presumably high in ER and PGR. The breasts often show cystic benign disease and hyalinisation and cancer *in situ* is common [41,42]. Prognosis is good. There is an associated tumour risk in the thyroid. Bilaterality and multifocality are common. It is unknown whether hormonal risk factors interact. Chemoprevention may prevent disease in a proportion of the risk population. Disease penetrance is lower than in *BRCA1/2* and may be as low as 30% [21,43].

3.7. *Breast cancer in* BRCAX *patients (approximately 2–4% of all breast cancers)*

A strong familial breast cancer risk is also seen in women presenting with breast cancer at a rather late age. The phenotype of tumours in these patients has been described by us [14] and a linkage to a possible new breast cancer gene on chromosome 13 has recently been presented [13]. *BRCAX* has been used to designate a number of mainly pure breast cancer family syndromes, presenting late in life, where so far the responsible genes have not been cloned.

The tumours have their origin in well differentiated breast tissue, and diagnoses are made at an average age of 60 years. Tumour initiation occurs at a rather late age. As the tumour retains at least part of the features of the tissue of origin, tumours are both ductal and lobular and well differentiated and high in ER and PGR content. Cancer *in situ* is common. Prognosis is very good. Risk for tumours in other organs is low. Bilaterality and multifocality are probably common. Pregnancies probably strongly reduces the risk of breast cancer. New mutations are probably uncommon, while founder mutations are probably common. Chemoprevention may to a large extent prevent the disease. Disease penetrance is proposed to be lower than in *BRCA1*.

3.8. *Breast cancer in* ATm *mutation carriers (heterozygotes) (<1% of all breast cancer?)*

Women who are heterozygous carriers of a mutation in the *ATm* gene have been found to have an increased risk of breast cancer [44,45]. Its overall importance for hereditary breast cancer is controversial [46].

The tumours have their origin in a well differentiated breast tissue, and diagnoses are often made in women who are aged 50 years and over [15]. Tumour initiation occurs rather late. As the tumour retains at least part of the features of the tissue of origin, tumours are both ductal and lobular and well differentiated and probably high in ER, and PGR content. Cancer *in situ* is common. Prognosis is good [47]. The risk of tumours in other organs is low. Bilaterality is common [47]. It is unclear if hormonal risk factors interact. New mutations are probably uncommon, while founder mutations are probably common (1% of the population are heterozygous carriers [48]). Chemoprevention may to a large extent prevent the disease. Disease penetrance is lower than in *BRCA1*.

4. General implications for the management of patients with hereditary breast cancer

The hypothesis presented here would imply that breast cancer presenting in patients carrying *TP53*, *TP16* and *BRCA1* germline mutations would be optimally treated by chemotherapy both in an adjuvant and in a metastatic situation, while patients with breast cancer associated with *BRCAX*, *Pten* and *ATm* germline mutations should be managed by hormonal manipula-

tions. Patients with *BRCA2* germline mutations would fall somewhere in between with some patients being responsive to hormonal manipulations and others to chemotherapy. The high risk for bilaterality and multifocality in late occurring syndromes would argue for more extensive surgery and radiotherapy in the breast to prevent the appearance of new tumours ipsi- and contralaterally. Hormonal exposures may increase the risk for breast cancer in the later occurring syndromes. Organs outside the breast need to be screened for tumour disease in the early occurring syndromes. The presence of an *in situ* component in the later presenting syndromes would suggest that breast screening with mammography could be partially successful in contrast to such screening among patients with earlier presenting syndromes. The lymphocyte infiltration in *BRCA1* is probably not a tumour response but merely reflects a retained normal function of the breast epithelium and the neoplastic breast epithelium to attract IG-A-secreting lymphocytes that have been antigen-primed in the bowel. This represents a normal defence system in the mother–child contact mediated with Ig-A secreted into the breast milk to prevent infections in the newborn.

Risk prediction in later presenting syndromes could be cumbersome due to the relatively low disease penetrance and interaction with other genetic and hormonal factors.

5. Conclusion

The following postulates can be derived from the general hypothesis presented in this paper.

The age distribution at diagnosis of breast cancer in the different syndromes parallels the different age at tumour initiation for each syndrome. Early initiation of tumour disease leads to an early average age at diagnosis and the converse applies as well.

Syndromes occurring at a younger age often show new mutations and involve genes that affect many tumour types.

Syndromes developing at an early age are more frequently associated with mutations in general cell cycle regulating genes than those occurring at a later age, thus leading to a broad tumour spectrum in multiple organs. Syndromes developing in later life more often involve genes restricted to a function in the breast or in a few tissues. Individuals with mutations initiated early in life are less likely to have many overlapping protective genes, thus leading to a rather high disease penetrance, while individuals at risk of getting disease later in life may have overlapping gene systems leading to lower disease penetrance and later age of onset, perhaps through apoptosis and breast involution.

Founder mutations are mainly seen in syndromes diagnosed at a later age as the severe phenotype associated with the Li–Fraumeni syndrome leads to a reduction of fitness and hence a negative selection of mutation carriers.

Bilateral and multifocal disease are generally more common in syndromes with tumours presenting in the breast later in life.

Hormonal risk factors play little or no role in patients with breast tumours associated with *TP53* or *TP16* germline mutations. *BRCA1* and *BRCA2* tumours develop at epithelial sites that undergo substantial differentiation after pregnancy. Non-functioning BRCA1/BRCA2 protein will lead to an increased breast cancer risk following pregnancy with a failure in differentiation. A protective effect following pregnancy on the breast cancer risk is anticipated in patients with *BRCAX*, *Pten* and *ATm* mutations. Similarily, an adverse effect from hormone replacement therapy (HRT) is anticipated only in *BRCAX*, some *BRCA2*, *ATm* and *Pten* families with tumours expressing ER and PGR.

Chemoprevention using anti-oestrogens are probably only effective in syndromes occurring late in life (some cases of *BRCA2*, *BRCAX*, *ATm* and possibly *Pten*).

Tumour prognosis is poor for the early syndromes (*TP53*, *TP16* and *BRCA1* and some *BRCA2* patients), while rather good for *BRCAX*, *ATm* and *Pten* patients.

BRCA1 tumours possibly develop at the natural site for Ig-A lymphocyte interaction with the breast epithelium. Therefore it is conceivable that the presence of lymphocytes in *BRCA1* tumours do not represent a immune response against the tumour, but instead a natural homing of the gut lymphocytes to the breast to provide IG-A secretion into the breast milk at pregnancy.

New syndromes associated with breast cancer can easily be fitted into the hypothetical scheme presented. This could help clinicians and researchers to better design clinical and experimental research studies into the hereditary setting.

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