Reproductive Events, Occurring in Adolescence at the Time of Development of Reproductive Organs and at the Time of Tumour Initiation, Have a Bearing on Growth Characteristics and Reproductive Hormone Regulation in Normal and Tumour Tissue Investigated Decades Later — A Hypothesis

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Abstract — Both animal and human data indicate that reproductive events taking place early in reproductive life may have an important influence on growth characteristics and reproductive hormone regulation in both normal tissue and neoplastic tissue investigated later in life.

Introduction

The measurement of estrogen and progesterone receptor contents (ER and PGR) in breast and uterine tumour tissue has become an important clinical instrument in predicting disease-free survival (1, 2, 3, 4, 5, 6) and for the selection of endocrine therapy (1, 7). As ER was the first receptor to be used clinically, most studies correlating clinical and epidemiological data with receptor levels have been made for ER. Still, our knowledge of what governs the ER content of a tumour is limited. It is known that the ER content of breast tumours varies greatly between patients (8), and is also age dependent with higher levels in older, postmenopausal patients (1, 2). Generally patients with more differentiated tumours (9) and with lower tumour proliferation rates (10, 11, 12, 13) have higher ER content. Estrogen also seems to stimulate its own receptor content both in tumour tissue (14, 15) and in normal tissue (16, 17). Progesterone reduces the concentration of both its own receptors and ER (14, 18, 19, 20).

From the available research data the author would like to forward the hypothesis that early reproductive events occurring at the time of tumour initiation and at the time of development of that specific reproductive organ, profoundly effect the proliferation and hormonal regulation in the normal tissue and in tumours from that
organ investigated decades later. Such reproductive events as a rapid increase in endogenous sex hormone levels, a pregnancy or the exogenous administration of sex hormones need to be taken into account for understanding the particular growth characteristics, hormonal levels or hormone receptor levels in normal or tumour tissue in a given woman.

Evidence for and discussion of the hypothesis

In animal models, the susceptibility of the mammary gland to chemical carcinogenesis correlates with the rate of cell proliferation of the glandular epithelium at the time of exposure to the carcinogen (21, 22). In the mammary gland cell proliferation is highly dependent on age, being higher in younger animals (23) and in younger women (23, 24, 25). Proliferation is also related to the topographic location in the gland being highest in terminal end buds (animals) or in the intralobular terminal ducts (humans) (23). The proliferation is modified by hormonal factors and parity (26). Different patterns of age sensitivity for induction of mammary tumours in mice have been noted after diethylstilbestrol exposure (27, 28) and after 3-methylcholanthrene or 7,2-dimethylbenzantracene exposure (29, 30, 31). In general young mice or mice close to their start of ovulation show a high degree of sensitivity. Cultured normal breast cells have been found to retain their growth characteristics in vitro corresponding to that woman's age at cell removal (32).

It is generally believed that the early reproductive years are very important for the human breast cancer carcinogenesis (33). As such, the susceptibility for radiation induced breast tumours has also been found to be very high in adolescent women (34). Henderson et al (35) have proposed a new hypothesis a new hypothesis of breast cancer development in relation to early established regular normal menstrual cycles, as risks associated with exogenously administered hormones in early adulthood and in pubertal years. A substantial number of human breast cancers therefore may be initiated in early reproductive life, that is between the ages of 10 to 25.

What evidence is there that breast tumour ER levels, tumour growth characteristics or plasma hormone levels determined at the time of tumour diagnosis f.i. at 45 years of age reflect reproductive events and the normal physiology at f.i. 18 years of age?

First, tumours in premenopausal breast cancer patients have been found to have a higher proliferation rate than tumours in postmenopausal patients measured either by thymidine labelling indices (25, 36, 37, 38) or by S-phase determination in a cell flow cytograph (39, 40). This indicates that a tumour possibly initiated at a younger age has a higher proliferation rate, thus reflecting the normal physiology of the glandular tissue at the time of initiation.

A higher cell proliferation also increases the number of clonal chromosome aberrations in a tumour (41) which is in accord with the finding that tumours in premenopausal breast cancer patients are more aneuploid than tumours in postmenopausal patients (42). Further, possibly reflecting the increased tumour proliferation rate, the hormone receptor level of the tumours is lower in premenopausal patients compared with postmenopausal patients (1). Endogenous estrogen occupying ER-sites (15, 43, 44), thus falsely reducing ER levels, or higher progesterone levels premenopausally reducing ER levels (14, 45, 46) have earlier been hypothesized as explanations for the lower ER content in young patients.

In animals, prenatal sex hormone treatment significantly effects later hormone receptor content of normal tissues and later risk of breast and genital neoplasia (47). Whether later hormonal exposure could permanently alter hormonal and hormone receptor levels in animals is not known. However, in ovariectomized rats (Fischer 344) a persistence of low hypothalamic activity after removal of long estrogen treatment has recently been found (48). Administration of combined oral contraceptives (COC) during adolescence to women permanently increases the ratio of plasma prolactin and breast tumour ER investigated at diagnosis in young premenopausal breast cancer patients (49), and permanently increases the ratio of plasma prolactin and ER levels in histopathological normal endometria in young women without tumours (50). The age at investigation, duration of COC-use, menstrual cycle phase or parity could not explain the increased ratio. The results indicate that both neoplastic and normal tissue corroborates the same changes years after the administration of the hormones.

Other studies on COC have found that ever users have lower ER contents of their tumours than never users (51, 52, 53, 54). These latter studies have not looked at starting age for COC-
use, which most probably is of importance for these findings.

Patients with an early first full term pregnancy (a normal physiological state with high endogenous levels of sex hormone levels) show a higher frequency of ER-poor breast tumours compared with other women with breast cancer (55). This is in accordance with the findings on ER in regard to the administration of COC at young ages. Use of COC could hormonally in some aspects be compared with an artificial pregnancy. Possibly an early pregnancy or the administration of COC downregulates ER levels permanently due to increasing plasma progesterone at the time of initiation.

Hormonal levels may also be permanently altered by reproductive events, as the findings of increased levels of plasma prolactin decades later after use of COC in adolescent girls (49, 50). A recent publication has also found that a normal pregnancy permanently alters plasma prolactin levels for at least 15–20 years after the pregnancy (56). This effect was postulated through similar findings by Yu et al (57).

Conclusions

Thus both experimental and human research data exist that indicate that tumour growth characteristics, hormone and hormone receptor levels both in tumours and normal tissue are permanently altered by reproductive events.

We are early in the beginning of unravelling the knowledge of how risk factors influence tumour biology. Further research is greatly needed to be able to understand more about the physiology of normal hormone and hormone receptor regulation at different ages and its interaction with organ and tumour development and reproductive events.

The evolving knowledge of differentiation genes and oncogenes also needs to be incorporated in order to better understand the normal and neoplastic growth of reproductive organs at the cellular level.

In breast cancer some of the more urgent research areas seem to be; how to better understand why receptor rich tumours occur, what the epidemiological characteristics of patients with tumours discrepant in ER and PGR levels are, how well the receptor content of various normal tissues in tumour patients correlates with receptor contents of their tumours, how well the tumour biology reflects the normal physiology at the time of initiation. Studies now undertaken in breast cancer patients obviously need to be done in patients with other reproductive tumours (such as ovarian, cervical and endometrial carcinoma).

The time has come to say that the characteristics of a tumour are not random events but reflects at least partly the physiology of that individual at the time of initiation.

References


