

Review

Endocrine and paracrine hormones in the promotion, progression and recurrence of breast cancer

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Both normal and neoplastic breast tissues are stimulated by endocrine and paracrine hormones. Epidemiological studies have demonstrated the significant role that hormones, growth factors and cytokines have in the promotion, progression and recurrence of breast cancer. Significant variations in the hormonal environment occur based on age, the cyclical changes occurring during the

menstrual cycle and (mammographically determined) variations in breast composition. These variations have a significant influence on rates of local recurrence of breast cancer and survival. This review analyses data relevant to these issues and suggests means by which operative results may be improved.

The past decade has seen changing concepts in the surgical control and cure of breast cancer, and in the molecular biology of cancer initiation and tumour-host interaction. This review demonstrates that the endocrine and paracrine hormone profile of the breast at the time of cancer resection modulates the subsequent course of the disease, and provides some understanding of the biological plausibility of this phenomenon. It brings together concepts of breast proliferation and ties them in a common theme: that the same factors which cause normal breast tissue to proliferate during pubescent development and during the cyclical changes of the menstrual cycle are involved in the promotion, progression and recurrence of breast cancer. This interplay is intimately related to the age of the patient, the cellular composition of the breast and the hormonal milieu as governed by the menstrual cycle or by the exogenous administration of sex hormones. An understanding of the mechanisms involved in the proliferation and maturation of normal breast tissue yields some insight into the hormonal influences that govern many facets of early breast cancer.

Mechanisms involved in the proliferation of normal breast tissue

Normal female breast development

The capacity of normal breast tissue to develop depends on three major interrelated factors: age, composition of breast tissue and hormonal environment (both past and present). The teenage period after puberty is the most proliferative stage in which the lobules are developing. The lobules become almost fully developed by the age of 25, although some lobular proliferation persists until about 35 years of age¹. Additionally, during each monthly cycle between menarche and menopause the ductal epithelium is renewed continuously by the cyclical menstrual hormones, although there is some decline in the epithelial turnover in later reproductive years². The breast goes through many changes during the menstrual

cycle: breast volume, fat to water ratio, lymph flow and temperature all vary as a result of hormonal changes. Childbirth with its postlactational involution tends to change the lobular structure to a more differentiated structure³. This results ultimately in a decrease in lobules without any significant changes in the ducts and connective tissue stroma. The major involution is associated with menopause. It includes a preclimacteric phase beginning at approximately 35 years of age, and a postmenopausal phase starting at menopause⁴. During this latter phase, the ductal and lobular epithelium, as well as the adjacent fibrous connective tissue stroma, regress and are each gradually replaced by adipose tissue. These involutinal changes take place over 15-20 years and depend on the interaction between the breast epithelium and the fibroconnective stroma¹. Clinically these changes produce the shrunken, pendulous breasts of the elderly, and result in very good mammographic visualization of the atrophied breast.

In the young premenopausal breast, approximately 15 per cent of volume consists of epithelial cells, whereas in the 60-year-old woman less than 5 per cent of the breast consists of epithelial cells⁵. In detailed analyses of mastectomy specimens, Anastassiades *et al.*⁶ evaluated breast composition at different ages. In the 31-40-year age group, 54 per cent of breasts have a large amount of solid tissue (mammary parenchyma and fibrous stroma) while none are extremely fatty. In contrast, over 70 years of age fatty breasts comprise 46 per cent of the specimens and only 8 per cent have solid tissue (Table 1). Similar changes in composition with age have been confirmed by others⁷; these changes are explained at least partially by changing hormonal influences over time.

Hormonal influences in breast development and involution

In physiological amounts, oestrogen and, to a lesser extent, progesterone, are mitogenic to breast tissue. Changes in the levels of these steroid sex hormones during the menstrual cycle profoundly influence both the stroma and the epithelium⁸. In premenopausal women, the proliferative activity of breast tissue is maximal during the luteal phase of the menstrual cycle, when increased progesterone levels synergistically enhance the effects of

Table 1 Relationship between age and breast composition

Age of patient (years)	Solid tissue* (%)	Fatty tissue (%)
31-40	54	0
41-50	17	8
51-60	10	7
61-70	4	11
>70	8	46

*Mammary parenchyma and fibrous stroma. Modified from Anastassiades *et al.*⁶

oestrogen⁹. The average epithelial proliferation during the luteal phase is reported to be 3-3.9 times greater than that during the follicular phase¹⁰. The peak in proliferative activity occurs in the mid-luteal phase^{9,11}, occurring on day 21 in the nulliparous and on day 25 in the parous woman¹². The nadir of proliferative activity occurs during the second week of the follicular phase. Proliferative rates also correlate with age^{9,13}. Younger individuals closer to menarche have a 2.5-fold higher proliferative activity compared with older women nearing menopause. Surprisingly, this does not correlate with oestrogen levels, which are higher among older (aged 28-40 years) than among younger (aged 18-23 years) women¹⁴. In postmenopausal women, epithelial proliferation rates are very low¹⁰.

Normal homeostatic functioning of breast tissue during the menstrual cycle ensures epithelial cell turnover, alternating between cellular proliferation and programmed cell death (apoptosis). The balance between cell proliferation and cell death in the earlier reproductive years favours proliferation, as there is a progression of the cell population over each ovulatory cycle¹⁵. There is a common regulatory mechanism between mitosis and apoptosis, wherein apoptosis is regulated in a reciprocal relationship to mitosis by growth factors and trophic hormones¹⁶⁻¹⁸. The final outcome of a given cell cycle is dependent upon whether or not that cycle is supported by growth factors¹⁹. To maintain viability of a particular cell, at least one growth factor critical for this cell type must be available, otherwise the cell undergoes apoptosis²⁰. The rate of apoptosis is maximal in the late luteal phase, approximately 3 days after the peak of proliferative activity. The least apoptosis occurs just before ovulation, when the oestrogen levels are highest¹¹.

Growth factor potential of breast stroma

In addition to patient age and hormonal environment, a third factor is the ability of breast stromal cells to accrue and secrete growth factors for any given hormone level. Oestrogen has the most important endocrine influence on the breast and appears to act by triggering production of locally acting hormones (i.e. growth factors)²¹. Growth factors are a group of specialized polypeptides secreted by platelets, inflammatory cells, endothelial cells, fibroblasts and epithelial cells. Growth factors represent a system of signals that organize and coordinate cellular proliferation; they may function either as growth stimulators or growth inhibitors. At basal levels they provide a homeostatic environment, but at raised levels they are responsible for the rapid cell divisions that characterize foetal development, wound healing and neoplastic proliferation²². For a growth factor to act on a cell, that cell must express the

appropriate growth factor receptor. Growth factor activity is the local tissue mechanism of action of oestrogen and progesterone. While this activity has been studied in human mammary tissue only in the context of malignant epithelial cells, it is almost certainly crucial also to the regulation of the normal mammary epithelium²³.

In hormone-responsive breast cancer cells, oestrogen controls mammary proliferation through upregulation of stimulatory growth factors (transforming growth factor (TGF) α , insulin-like growth factor (IGF)2 and amphiregulin) and growth factor receptors (epidermal growth factor (EGF) and IGF-1 receptors), and downregulation of inhibitory growth factors (TGF- β)²³. Analogous effects have been observed with progestins²³. The most important mitogenic factors for mammary cells are members of the EGF family (EGF, TGF- α and amphiregulin)²⁴, each of which interacts with the same growth factor receptor (EGF receptor). Oestrogen and progesterone act on mammary epithelial cells to induce synthesis and secretion of additional growth factors. These growth factors may interact with receptors on nearby cells, enter the general circulation and exert distant effects, or adhere to extracellular matrix molecules²⁴. Cells deprived of these growth-promoting agents have a reduced proliferative rate, enter a G0 quiescent phase of the cell cycle or undergo apoptosis.

In the breast, the stroma and epithelium inter-communicate with each other through these growth factors in so-called paracrine loops. This communication is critical for breast development and proliferation²⁵. Stromal growth factors (EGF, TGF, IGF-1 and IGF-2) can modulate epithelial cell proliferation, and epithelial growth factors in turn can modulate stromal (i.e. fibroblastic and angiogenic) proliferation²⁵. In *in vitro* studies, oestrogen-induced proliferation of mammary epithelial cells is seen only when they are co-cultured with mammary stromal cells²⁶. In the absence of such stromal cells, no epithelial cell proliferation occurs; conversely, in the absence of epithelial cells stromal cells do not respond to oestrogen. These bidirectional fibroblast-epithelial cell interactions are required for growth responses to oestrogen²⁵. Similarly, an *in vivo* study in humans has demonstrated that production of the mitogenic growth factor for stromal cells, platelet-derived growth factor (PDGF), is restricted to benign and malignant breast epithelial cells, while the receptors for PDGF reside only on stromal cells²⁷. Other human studies have also confirmed the tendency for certain growth factors to be localized in stromal tissue²⁸. These findings suggest that PDGF increases breast epithelial proliferation by stimulating stromal cells that display their cognate receptors to produce another growth factor (IGF) which, in turn, is mitogenic for breast epithelial cells²⁵.

In addition, stromal tissue also acts as a reservoir of growth factors. The extracellular matrix binds many growth factors, as well as proteases and protease inhibitors^{29,30}. These proteases and protease inhibitors facilitate the activation of latent growth factors and the release of bound factors²⁹. Thus, the extracellular matrix sequesters a variety of growth factors that can be readily activated, and plays a major role in the growth of the mammary epithelium. The stroma not only regulates the growth and differentiation of normal mammary epithelium; it also has a regulatory role in the infiltrative growth of cancer. For epithelial malignancies (carcinomas), the mesenchyme or stroma is the regulatory environment for neoplastic development and progression. In hormone-dependent

cancers, this regulatory environment is modified by past and present exposure to hormones, which controls the stromal reservoir of growth factors. Breast cancers are unusual in that they are typically very desmoplastic, the stroma accounting for the majority of the tumour volume. This stromal microenvironment influences the behaviour of the neoplastic epithelium³¹. For example, DeCosse *et al.*³², using a murine mammary tumour, demonstrated different rates of tumour growth with different stromas. Furthermore, the stromal cells surrounding cancer cells are phenotypically different from those within non-cancerous breast tissue^{25,33}, and the former have raised levels of growth factors and proteases^{28,30}. The changing composition of the surrounding stroma with age probably accounts for part of the large difference in local recurrence rates between the very young and the elderly.

Effect of age on growth factor activity

As mentioned previously, during ageing there is a profound change in the relative proportion of stromal, epithelial and adipose tissue components, which in turn affects the growth factor content of the breast. Many reports demonstrate that levels of growth factors and growth factor receptors decrease with age³⁴⁻³⁸. There is an age-dependent decrease in growth hormone and serum IGF-1 levels, beginning after 30 years of age^{34,35}. Decrease in the levels of these factors induces the atrophy of muscle, bone and skin and contributes to the frailty of the elderly.

In the young breast, normal growth during the lobular stage of development is associated with the highest levels of IGF-1³⁹. Involution, beginning at the preclimacteric phase, is related to a decline in growth factors⁴⁰. In the postmenopausal group (aged above 55 years), where involution is nearly complete, levels of oestrogen and growth factors are quite low²⁷.

Oestrogen and growth factors as tumour promoters

Clinical data have linked a woman's lifetime exposure to oestrogen and progesterone with the development of breast cancer. This observation is based on the increased cancer risk associated with early menarche, late menopause, late first full-term pregnancy and nulliparity. Oophorectomy markedly decreases the proliferation of mammary tissue and rapidly involutes the breast. There is a direct relationship between the degree of protection against breast cancer development and age at oophorectomy^{41,42}. Bilateral oophorectomy performed before 35 years of age is associated with a 64 per cent reduction in the risk of breast cancer, compared with a reduction of only 32 per cent when performed in women aged 35-39 years⁴². Women who have never had hormonally functioning ovaries demonstrate a near total absence of breast cancer; they have an incidence of breast cancer similar to that observed in men⁴³. These hormonal influences on breast cancer rates result from effects on epithelial cell replication; such cell division is essential to the genesis of human cancer⁴⁴.

Breast cancer risk tends to correlate directly with the age at which involution occurs. However, if the process of involution becomes interrupted after its commencement, but before its completion, by a late first pregnancy, the mammary epithelial cells are again stimulated into proliferation. The resulting delay in involution might lead

to the persistence of epithelial and stromal elements in older breasts which could, conceivably, increase the risk of breast cancer⁴⁵.

Oral contraceptives have been implicated in promoting breast cancer; their influence on breast epithelium is complex. Since they are administered during a time when the ovaries are functional and since they inhibit gonadotropin secretion, ovarian steroidogenesis is reduced. Furthermore, since the combined influence of oestrogen and progesterone during the luteal phase of the natural menstrual cycle maximizes mitotic activity, there is concern that oral contraceptives may further increase breast proliferation. One study¹³ showed that the rise in the proliferative index of mammary epithelial cells was related to the potency of the oestrogen but not the amount of progesterone used. However, clinical studies do not reveal any consistent association between breast cancer rates and different formulations of oral contraceptive⁴⁶⁻⁴⁸. The minimal dose of sex steroid necessary to provide acceptable contraception appears to produce total breast proliferation rates very close to those occurring during a natural cycle^{10,13,49}. After correcting for age and phase of the menstrual cycle, Anderson *et al.*¹³ reported increased breast epithelial proliferation with oral contraceptive use only in nulliparous women, whereas the parous breast was almost unaffected. Review of population-based epidemiological studies shows a modestly increased risk of breast cancer associated with long-term use of oral contraceptives in younger, but not older, women^{50,51}. This increased risk in younger women may be balanced by a subsequent long-term reduction in breast cancer risk in older women who have discontinued use for over 10 years⁵². However this paradoxical risk-protection effect might not apply to all subgroups (very young and/or nulliparous). Although many studies⁵³⁻⁵⁵ found duration of oral contraceptive use before a full-term pregnancy was associated with a greater cancer risk than use thereafter, such results have been questioned^{51,56}. Statistically, pregnancy tends to be followed for several years by an increased risk of breast cancer, until a long-term protective effect resulting from changes in the susceptibility of breast tissue (i.e. postlactational involution) predominates^{3,57}. Thus, studies focusing on very young patients with breast cancer associated with the contraceptive pill may find smaller risk differentials if the short-term effect of a full-term pregnancy is an increase in breast cancer risk⁵⁸. Longer follow-up of at least 10-20 years of young nulliparous women using the pill is necessary to confirm this hypothesis, suggested by some preliminary results with long-term use of oral contraceptives^{53,56}.

Perhaps the least appreciated hormone-related risk factor for breast cancer is the extent and pattern of mammographic density within the breast. Mammographic density reflects the amount of epithelial and stromal elements relative to the proportion of fat, which is radiologically translucent. Parenchymal densities noted on mammography are closely associated not only with age but also with hormone-related breast cancer risk factors⁵⁹⁻⁶⁴. Several controlled studies^{59,60,65,66} support an association between dense mammographic parenchymal patterns and an increased risk of breast cancer. These studies provide strong, although indirect, evidence for the hypothesized role played by involutional parenchymal changes in determining breast cancer risk. Individuals with greater than 50-75 per cent of the breast occupied by mammographic density have 3-5 times the risk of

developing breast cancer as compared to those of the same age with the least amount of mammographic density^{60,66}

Oza and Boyd⁶⁵ suggest that the percentage of mammographic density may reflect the potential growth factor activity of the breast stroma. This suggestion is consistent with the hypothesis that an excess of growth factors promotes breast cancer. Experiments in mice have demonstrated that overexpression of several growth factors and their receptors is a strong risk factor for mammary cancer⁶⁷. Younger age is associated with a very dense mammographic pattern and would be expected to be associated with high growth factor activity. Postmenopausal women have less mammographic density which would be associated with diminished growth factor content^{59,61,68}. For a given age and menopausal status, women with relatively greater mammographic density (and thus greater growth factor capacity) have the greater cancer risk. Oestrogen replacement therapy after menopause is associated with increased breast parenchymal density in 24 per cent of patients⁶⁹, while therapy with tamoxifen, oophorectomy, or administration of gonadotropin-releasing hormone agonist (GnRHA)⁷⁰ in premenopausal women results in a routine decrease in mammographic density. All of these mammographic density changes that occur with hormonal changes appear to reflect changes in proliferation of the epithelial and stromal elements. The greater the involutonal changes that the breast undergoes, the less the mitogenic response to stimulation by hormones³. Oestrogen is much less effective in stimulating the completely involuted atrophic breast, as that tissue is a poor source of oestrogen-induced growth factors²⁷. The controversial association between oestrogen replacement therapy and breast cancer risk in postmenopausal women⁷¹⁻⁷³ might suggest that once involution has progressed sufficiently, the effects of exogenous oestrogens on cancer risk are minimal⁴⁵. This is supported by the relative lack of mammographic density increase after initiation of oestrogen replacement therapy in postmenopausal woman⁶⁹; it is most evident in women who have probably completed breast involution (i.e. multiparous women over 56 years of age)⁷⁴. However, the type of hormone replacement may have a determinant role in cancer risk, as the addition of progestin to oestrogen appears to increase mammographic density more readily^{69,75-77}. It cannot be determined from clinical studies using a relatively short follow-up whether breast cancer incidence is affected by such combined hormonal therapy. However, older epidemiological studies on the age of both surgical and natural menopause illustrate that the effects on breast cancer incidence are not appreciated for 10-20 years, and that such hormonal effects last throughout the remainder of the individual's lifetime^{42,58,78}. In contrast, any effect that 5 years of combined hormone replacement therapy might have probably will not become evident until the latency period reaches 15 years. Any earlier effects on breast cancer rates are likely to reflect stimulation of pre-existing cancers, and not the proliferative effect that such hormones have on normal postmenopausal breast tissue which might contribute to new cancers.

Oestrogen and growth factors affect tumour progression

The concept of ovarian influence on breast cancer was first recognized by Cooper in 1836⁷⁹. He noted that breast

tumours often fluctuated in size during the menstrual cycle, demonstrating 'shrinkage' at the beginning of each cycle, as well as at the onset of menopause. These observations led logically to surgical castration for advanced premenopausal breast cancer, as first reported by Beatson in 1896⁸⁰. This line of reasoning was quite remarkable since it was developed before the discovery of steroid sex hormones four decades later⁸¹. Subsequent clinical studies with hormone manipulation have noted a 30-35 per cent response rate in unselected patients with metastatic breast carcinoma, and up to an 81 per cent response rate in oestrogen receptor-positive/progesterone receptor-positive cancers^{82,83}. As two-thirds of breast cancers contain varying amounts of oestrogen receptor⁸⁴, hormone manipulation either alone or in combination with chemotherapy is a mainstay of clinical practice. The importance of growth factors in breast cancer progression has been reviewed recently⁸⁵.

Tumour recurrence: role of cancer cell stimulation at the time of surgical resection

The microenvironment of growth factors in the breast maintains a low (basal) level of growth factor activity if it is unstimulated by sex steroid hormones. However, growth factor activity is increased temporarily during tissue repair following breast surgery and is further enhanced by sex steroid stimulation⁸⁶. At surgical resection, the same growth factors expressed by cells that mediate inflammation and tissue repair (i.e. platelets, macrophages, lymphocytes, fibroblasts and endothelial cells) are also involved in cancer proliferation²². The growth factor/cytokine signals required for repair of damaged tissue can also be recognized by neoplastic cells. The chemo-attractant, mitogenic and angiogenic effects of such growth factors might support any stray cancer cells left behind at operation⁸⁷.

At the time of breast cancer resection, the microenvironment of the partial mastectomy wound is enriched with growth factors, not only from the invading inflammatory cells but also from the sex hormone-regulated epithelial-stromal cells in the breast tissue adjacent to the surgical site. This enriched growth factor microenvironment can modulate implantation, local invasion, survival and growth of otherwise fragile tumour cells shed at surgery which would otherwise not survive⁸⁷. The following considerations demonstrate how the hormonal environment and breast tissue composition (as reflected by the woman's age) at the time of tumour resection will affect cancer recurrence.

The hormonal environment at the time of breast cancer surgery affects survival

Recently, serious consideration has been given to the consequences of performing breast cancer surgery during different phases of the menstrual cycle. Clinical studies have determined that timing of breast surgery with respect to the menstrual cycle affects prognosis. The majority of studies find that the luteal phase is the optimal period for performing surgery⁸⁸, although McGuire and colleagues⁸⁹ questioned whether these findings might result from chance alone. By dividing the menstrual cycle arbitrarily into enough subgroups, there is a high probability of finding a statistically significant difference in one of the groups. A recent meta-analysis of 21 published studies

demonstrated a statistically significant ($P=0.02$) effect on prognosis⁹⁰; there was a 16 per cent reduction in the 5-year mortality rate for surgical treatment performed during the luteal phase. Three of the larger studies⁹¹⁻⁹³ allowed closer scrutiny of the data by displaying prognostic results for each day of the menstrual cycle. Their results are remarkably similar in terms of favourable and unfavourable days for performing cancer surgery (Table 2).

These studies indicate that the least favourable timing for breast cancer surgery is the second week of the menstrual cycle (the late follicular phase), when apoptosis is minimal. The increased growth factor activity that blocks apoptosis is attributed to the oestrogen that is rising and peaking unopposed during this period, and which can upregulate growth factor receptors (EGF receptors)⁹⁴ and stimulate stromal cells to secrete growth factors⁹². Furthermore, oestrogen protection from apoptosis may persist for 1-2 days after withdrawal of unopposed oestrogen¹⁸, allowing for an unfavourable result on the 14th day of the cycle when the oestrogen level is beginning to fall. This effect of increased growth factor activity blocking the apoptotic pathway in the late

follicular phase may allow any tumour cells shed at operation to gain a selective growth advantage. In contrast, optimal surgical results are obtained in the late luteal phase of the cycle and into the first 2 days of menstruation, during which there are decreasing or low levels of oestrogen. Maximal cellular apoptosis occurs during the late luteal phase when stromal growth factors are in an inactive state and unable to support the growth of stray cancer cells. Extension of the days of best prognosis into the first 2 days of the subsequent cycle⁹² may result from a preponderance of parous women, who tend to have a few days' delay in their peak point of proliferative activity (and thus in their peak day of apoptosis) compared with nulliparous women¹². In addition, women who have regular menstrual cycles lasting longer than the typical 28 days tend to have a longer follicular phase, but the luteal phase is relatively unaffected and lasts approximately 14 days after ovulation¹⁴.

The importance of the hormonal environment at the time of surgery can also be appreciated by analysing breast cancers diagnosed in postmenopausal women concurrently taking oestrogen replacement therapy. An

Table 2 Prognosis related to days elapsed from the onset of menstruation (day 1) until cancer surgery

Reference	Year	Endpoint	No. of patients	Days of the cycle	
				Best prognosis	Worst prognosis
Senie <i>et al.</i> ⁹³	1991	Recurrence	283	20-30* (especially last 5 days)	7-14
Veronesi <i>et al.</i> ⁹¹	1994	Recurrence	1175	20-33*	10-14
Badwe <i>et al.</i> ⁹²	1991	Death	249	18-2†	3-14 (especially 6-11)

*Menstrual cycles lasting longer than the typical 28-day cycle; †extension into the first 2 days of the subsequent cycle

Table 3 Relationship between age and local recurrence

Reference	Year	Operation	Follow-up	Age (years)	No. at risk	Local recurrence (%)
Donegan <i>et al.</i> ¹⁰⁴	1966	RM	5 years	<40	41	47
				40-59	249	22
				≥60	414	12.5
Kurtz ¹⁰⁵	1992	L + RT	11 years	<35	109	18.4
				35-50	702	12.7
				51-65	618	9.2
				>65	254	7.5
Haffty <i>et al.</i> ⁹⁹	1994	L + RT	6.4 years	<35	46	11
				35-50	152	7
				>50	350	4
Fowble <i>et al.</i> ¹⁰¹	1994	L + RT	8 years	<35	64	19
				35-50	363	9
				>50	553	6.5
Veronesi <i>et al.</i> ¹⁰⁶	1993	Quad; no RT	39 months	<45	63	17.5
				45-55	104	8.7
				>55	106	3.8
Veronesi <i>et al.</i> ¹⁰⁷	1995	Quad + RT	8.5 years	≤35	168	13
				36-45	690	11
				46-55	723	4.4
				56-65	454	2.9
				>65	198	4
Harris and Recht ¹⁰⁸	1991	L + RT	8.5 years	<35	62	24
				35-50	335	14
				51-65	256	10
				>65	130	3

Local recurrence is defined as tumour arising in the remaining treated breast tissue or the chest wall. RM, radical mastectomy; L, lumpectomy; Quad, quadrantectomy; RT, radiotherapy

improved prognosis has been found consistently in such individuals⁹⁵⁻⁹⁷, although this association should be interpreted cautiously. The improved survival has been attributed partially to more careful breast screening, resulting in an earlier diagnosis, as well as reflecting tumours with more favourable prognostic factors⁹⁵⁻⁹⁷. Alternatively, the improved survival might be attributed to a precipitous downregulation of the hormonal milieu, since these women presumably had their replacement therapy withdrawn more than 1-2 days before operation. These results are consistent with the importance of a hormonal environment that minimizes growth factor activity and maximizes apoptosis at the time of surgery.

Patient age as a prognostic predictor of local recurrence

The age of the patient with breast cancer at the time of breast-sparing surgery is an independent prognostic factor for local recurrence⁹⁸⁻¹⁰³; this may even apply after mastectomy^{104,105}. Table 3 summarizes seven major series addressing this issue. Age less than 35-40 years is consistently associated with a higher local recurrence rate than age over 55-65 years^{99-101,104,106-108}. The youngest age group has nearly double the average local recurrence rate of all age groups¹⁰⁹ and four to six times the rate of the oldest group alone^{99,100,103,104,106-108}.

The reasons for this continuously decreasing risk of local recurrence with age are elusive¹¹⁰. Several theories have been advanced to explain why younger age has such an adverse effect on local recurrence.

Proliferation rate. There is evidence that age is inversely related to the proliferation rate of both normal as well as cancerous breast tissue¹¹¹⁻¹¹³. Olsson *et al.*¹¹⁴ have suggested that, in young women, breast tumours proliferate at higher rates characteristic of normal breast tissue at that age. A more rapid proliferative rate in younger hosts could also explain their higher rate of early relapse and rapid evolution of disease^{115,116}. Cancers in the elderly, on the other hand, have a lower proliferative rate similar to that of their non-neoplastic epithelial cells. Furthermore, even tumours that occasionally show high proliferative rates in older women tend to be more indolent, suggesting additional protective effects on local recurrence related to increased age¹¹⁶.

Tumour histopathology. Younger patients tend to have prognostically worse histological types of breast carcinoma, including inflammatory carcinoma, than patients over 50 years of age¹¹³. Older women more commonly have tubular and colloid carcinoma, oestrogen receptor-positive/progesterone receptor-positive status and low S phase tumours than do younger patients¹¹⁷. On multivariate analysis using other histopathological variables, young age remains a statistically significant risk factor for local recurrence^{109,115,118}. Fisher *et al.*¹¹⁸ evaluated 32 histopathological factors in a regression analysis of predictive factors for in-breast recurrence after lumpectomy and radiation therapy; they concluded that age less than 35 years is statistically the most important prognostic variable.

Pathology of residual breast tissue. Patients with breast cancer under the age of 40 have a worse prognosis regardless of surgical treatment modality (lumpectomy, quadrantectomy or mastectomy), indicating that multifocal disease, as the cause of increased local recurrence in

the young, plays only a minor role. Furthermore, most pathological studies on mastectomy specimens fail to show any relationship between age and multicentricity¹¹⁹. There are scattered reports, however, indicating a greater amount of residual microscopic carcinoma in completion mastectomy specimens from younger women. This might be predicted, as tumours with an extensive intraductal carcinoma component are commoner in younger individuals. One study¹²⁰ investigated the incidence of multicentricity at a distance from the index tumour after simulated breast-conserving surgery. A total of 183 cases of ductal carcinoma treated by mastectomy and examined pathologically using 0.5-cm whole breast sections were investigated. At distances over 2.5 cm from the index tumour, there was a direct correlation between age less than 40 years and residual microscopic cancer. Using 4.5-cm margins from the index tumour (margins which would approximate to a quadrantectomy), however, a converse correlation was evident (Table 4). As the breast-sparing trials that employ quadrantectomy^{106,107} also demonstrate a higher local recurrence rate in younger patients, residual cancer foci in the immediate vicinity of the index tumour are unlikely to account for the age effect.

Young age as a resistance factor to radiation therapy. This is suggested by the multivariate analysis of the National Surgical Adjuvant Breast Project B-06 Trial, wherein young age was a significant risk factor for local recurrence in the group treated with lumpectomy and radiotherapy, but was no longer significant in the group of patients treated by lumpectomy without radiation therapy¹¹⁸. However, three other randomized trials evaluating breast-conserving surgery^{106,121,122} found young age to be the most important risk factor, even in the non-irradiated group.

Young age as a resistance factor to adjuvant chemotherapy. Adjuvant chemotherapy exerts its greatest benefit in premenopausal patients. However, this benefit is not as evident in those below 35 years of age. In this age group a relative lack of treatment response may be explained partially by the reduced rate of chemotherapy-induced menopause¹²³. However, this worse prognosis with young age is also evident in the node-negative groups that did not receive any adjuvant treatment¹²³.

Young age is associated with a richer endocrine hormonal environment. Kurtz¹¹⁰ has suggested that the increased rate of local recurrence in young women is due to their higher oestrogen levels. The importance of modulating the hormonal environment in the young patient with breast cancer before operation was first recognized by

Table 4 Relationship between age and multicentricity using 2.5- and 4.5-cm surgical margins around the index cancer

Age (years)	Multicentricity	
	2.5-cm margin	4.5-cm margin
< 40	9/23 (39)	2/23 (9)
40-59	41/124 (33)	15/124 (12)
≥ 60	9/36(25)	5/36 (14)

Values in parentheses are percentages. Of 183 cases, six were non-invasive ductal carcinomas and 177 invasive ductal carcinomas. Modified from Morimoto *et al.*¹²⁰

Table 5 Age and site of in-breast recurrence and contralateral cancer

Age (years)	No. of patients	Development of breast tumours		
		Ipsilateral breast		Contralateral breast
		Same quadrant as primary (surgical site)	Elsewhere (other quadrant)	
Harris and Recht ^{108*}				
< 35	62	13 (21)	2 (3)	7 (11)
35-50	335	33 (9.9)	12 (3.6)	25 (7.5)
51-65	256	24 (9.4)	3 (1.2)	12 (4.7)
≥ 65	130	3 (2.3)	1 (0.8)	8 (6.1)
Veronesi <i>et al.</i> ^{107†}				
< 35	168	18 (10.7)	4 (2.4)	10 (6.0)
36-45	690	56 (8.1)	20 (2.9)	35 (5.1)
46-55	723	28 (3.9)	4 (0.6)	33 (4.6)
56-65	454	12 (2.6)	1 (0.2)	26 (5.7)
≥ 65	198	5 (2.5)	3 (1.5)	6 (3.0)

Values in parentheses are percentages. Patients were followed up for 8.5 years after *lumpectomy and radiotherapy or †quadrantectomy and radiotherapy

Schinzinger in 1889¹²⁴. He noted that young patients had a very poor prognosis and recommended that oöphorectomy be performed in these women before, or along with, the mastectomy, in order to 'involute' the breast and to 'contain tumour cells'^{124,125}. Horsley in 1944¹²⁶ furthered this concept, believing that the small number of residual cancer cells left after radical mastectomy could be stimulated by oestrogenic substances. He further hypothesized that oöphorectomy would have its greatest benefit during the perioperative period. The acute withdrawal of oestrogen would create an unfavourable 'soil' which should be deleterious to the survival and implantation of any cancer cells remaining after mastectomy. In the light of today's knowledge, this acute involution of the breast with preoperative or perioperative oöphorectomy results from decreased growth factor activity, which maximizes apoptosis.

A further explanation for local recurrence rates decreasing with age considers not only the endocrine environment but also the level of growth factor activity at the surgical site. The importance of this latter factor is emphasized by the results of two large clinical studies^{107,108} (Table 5). Age less than 35 years strongly influences the development of recurrent cancer in the same quadrant as the surgical site, but plays only a minor role in the development of cancer either in other quadrants of the ipsilateral breast or in the contralateral breast. These data cannot be explained by the effects of oestrogen alone on any remaining cancer cell. Rather it is hypothesized that this predilection for in-breast recurrence at the surgical site is attributable to the growth factors that concentrate locally at the site of injury. These growth factors can stimulate any free floating residual cancer cells that have been shed at surgery or any focus of ductal carcinoma *in situ* that remains in the breast in close proximity to the surgical bed⁸⁷. Therefore the tendency for recurrence at the original site is not merely due to multifocal disease around the index tumour. This predilection for the site of surgery occurs even after quadrantectomy, when all microscopic disease within the index quadrant has been removed.

The lower rate of local recurrence in the older patient with breast cancer is accounted for by the inverse

correlation of growth factor activity with age. The very low incidence of local (in-breast) recurrence in the elderly suggests that breast involution protects against local recurrence by presenting a diminished growth factor milieu at the surgical site following partial mastectomy. This lower growth factor activity in the elderly after surgical wounding may result not only from decreased levels of growth factor secretion but also from reduced expression of growth factor receptors.

Irrespective of the patient's age and breast composition, manipulation of the endocrine hormonal environment can modulate growth factor activity⁸⁶. Optimal surgical management, therefore, needs to be timed to minimize the effects of an oestrogen-rich environment, which augments the inventory and concentration of growth factors in the mammary stroma and epithelium, and which upregulates growth factor receptors. Operations should be timed for when oestrogen protection against apoptosis is at a minimum¹⁷. Malignant cells shed during cancer surgery under conditions of unopposed rising or peaking oestrogen may be better able to survive, proliferate and develop into local recurrences or micrometastases. In contrast, cells shed during periods of maximal apoptosis, i.e. when mammogenic growth factor activity has just been withdrawn, should be least able to survive.

Conclusions

Appreciation of the interplay between endocrine and paracrine hormones in normal as well as in neoplastic breast proliferation has allowed a re-evaluation of our thoughts on the host-cancer relationship. It has given impetus to study the need for hormonal manipulation in chemopreventive trials in high-risk individuals. Additionally, recognition of this hormonal interplay invites consideration of preoperative or perioperative therapies to offset the endocrine/growth factor stimulatory effects which vary with age, menstrual cycle status and breast composition. Breast surgeons have the capability of performing surgery in a setting of diminished growth factor capacity. To achieve optimal results in terms of lowered local recurrence and increased overall survival, the influence of growth factors on cancer cells must be

minimized; this can be accomplished to some degree by operating when maximal apoptosis is present. Antioestrogens, somatostatin analogues and GnRHA should be evaluated in the perioperative setting in terms of manipulation of the endocrine and paracrine hormonal environment. Data generated from prospective trials will allow breast surgeons to determine the optimal hormonal strategy for maximizing the benefits of their operative effort.

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