Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures

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SUMMARY

Primary tumor removal, usually considered intrinsically beneficial, can perturb metastatic homeostasis, and for some patients results in the acceleration of metastatic cancer. The continuous-growth model is required to yield to an interrupted-growth model, the implications of which are episodes of tumor dormancy. This Review analyzes the recent evolution of two paradigms related to the development of breast cancer metastases. The evolution of the paradigms described herein is supported by a growing body of findings from experimental models, and is required to explain breast cancer recurrence dynamics for patients undergoing surgery with or without adjuvant chemotherapy.

KEYWORDS angiogenesis, breast cancer, growth model, metastasis development, tumor dormancy

REVIEW CRITERIA

This Review includes a summary of the authors' work over the past two decades as well as a series of specific reviews related to different topics involved in the research line. Data were obtained from the author's own work, from continuous reading of the oncology literature during the past 20 years, and by searching the PubMed database. There was no restriction as to publication date for the papers searched on PubMed. The search terms used included "angiogenesis", "dormancy", "hormone receptor", "growth model", "menopausal status", "metastasis" and "recurrence".

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INTRODUCTION

A fundamental lesson of scientific thinking is the concept that science develops mostly from failures. The conceptual tools (that is, models or 'paradigms') that are used to understand reality eventually demonstrate their inability to depict a reliable picture—in other words, they fail. We are then forced to implement new paradigms that can be used until they in turn fail, and so on. Such a process is tangible in oncology research, in which conceptual failures result in therapeutic failures, which ultimately result in disease recurrence and the death of patients.

In this Review, we analyze the evolution of two paradigms failing to explain the development of breast cancer metastases. As described herein, the assumption that metastases display continuous growth from inception is not reflected in clinical data. The observed and expected findings show a much better correlation when an interrupted tumor growth model is assumed, and this implies episodes of 'tumor dormancy'. Moreover, the traditional concept that primary tumor removal is intrinsically beneficial should be viewed with caution. Indeed, experimental and clinical findings indicate that excision of the tumor can perturb metastatic homeostasis and for some patients results in the acceleration of metastatic cancer. Taking into consideration the paradigms of tumor dormancy and the effects of surgery, a new model is developed that is not completely satisfactory and includes unresolved questions that will require further investigation. Within the scientific method, however, it is virtually impossible to prove a given model. Models can be disproved only when they result in substantial departure from observed findings. Until that time, we are justified in using them.

CONTINUOUS GROWTH VERSUS TUMOR DORMANCY

Growth models

The early exponential growth model proved to be adequate only for standard *in vitro* studies, while a satisfactory growth description *in vivo*

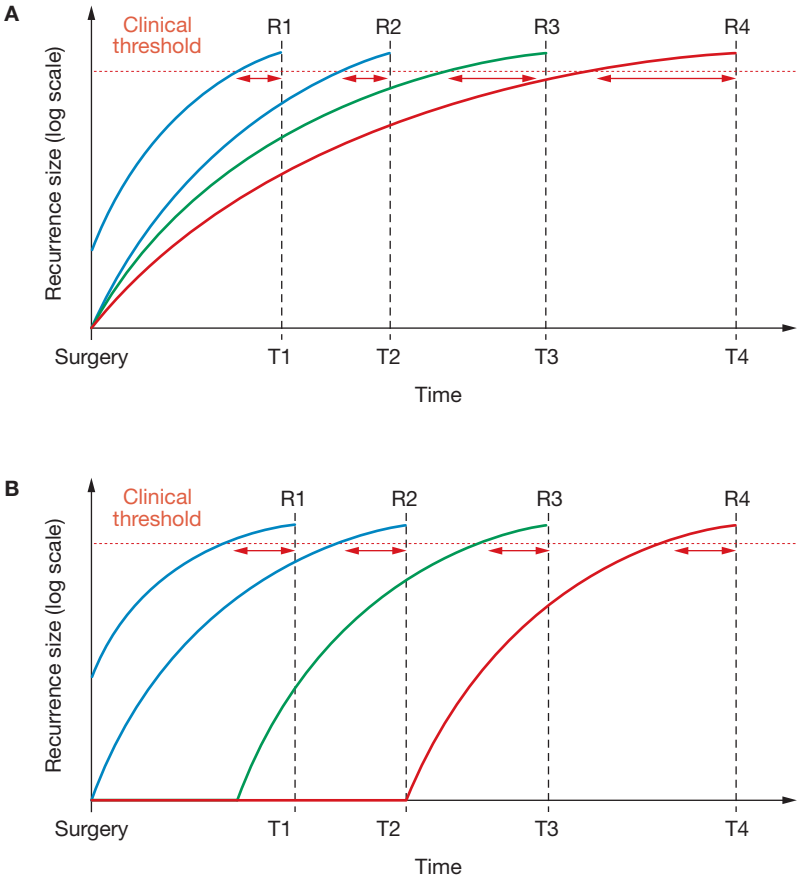

Figure 1 Size versus time chart of metastasis development. (**A**) Metastasis development during the subclinical phase according to a continuous-growth model. Recurrences with different disease-free survival (DFS) times can result from tumor foci of different sizes at the time of primary tumor removal with similar growth rates (R1 and R2) or from foci of the same initial size with different growth rates (R2, R3 and R4). The clinical diagnosis is performed some time after the metastasis size exceeds the clinical threshold (double-headed arrows) and, according to the principles of continuous growth, the longer the DFS, the longer this time period. (**B**) Metastasis development during the subclinical phase according to the tumor dormancy hypothesis. All recurrences have similar growth rates, and recurrences with different DFS times result from tumor foci of different sizes at the time of primary tumor removal (R1 and R2) or foci of the same initial size with different dormancy times (R2, R3 and R4).

called for mathematical functions that reflect growth-retarding features. Among these, the Gompertzian function[1] was generally considered adequate to describe neoplastic growth in the range of measurable tumors. When extrapolated to a very early growth phase, however, the Gompertzian model does not have an initial exponential region of sufficient duration and usually has an implausibly short initial doubling time.[2] More-complex models were, therefore, proposed to partially overcome these drawbacks.[3] In spite of their partial inadequacy, early growth models rendered remarkable services to oncology. The development of adjuvant systemic treatments was based on the exponential model[4] and refined by models based on Gompertzian growth kinetics.[5] It should be emphasized that all these models assume the implicit hypothesis that tumors must always grow. They are 'continuous growth' models. According to a continuous-growth model, the metastasis development following primary tumor removal can be illustrated as shown in Figure 1A. Recurrences with different disease-free survival (DFS) times result either from tumor foci with different sizes and similar growth rates (R1 and R2) or from foci with the same initial size and different growth rates (R2, R3 and R4). The diagnosis of recurrence is usually recognized some time after the metastasis size has exceeded the clinical threshold and, according to the continuous-growth model, the longer the DFS, the longer this time period (Figure 1, double-headed arrows).

Local recurrences

In patients who are regularly followed up, the detection of local recurrences is preceded by a series of physical examinations during which no tumor is detected (i.e. the patient is clinically negative). This all-or-none phenomenon was chosen to test continuous-growth kinetics in a series of 120 breast cancer patients at the National Cancer Institute of Milan, who underwent mastectomy without postoperative irradiation and for whom the primary tumor site was also the site of first disease relapse (local recurrence).[6] According to the hypothesis of continuous growth, in each patient the diameter of the recurring tumor was measured, and the diameter that the tumor would have reached at the immediately preceding negative physical examination was also calculated. The study proved that the continuous-growth model yielded tumor sizes significantly too large to have been missed at the previous physical examination, and the growth rates were significantly lower than those consistent with clinical data, which were notably similar among themselves. Moreover, it was noticed that discrepancies between expected and observed results were resolved, at least in part, by assuming that growth interruption or 'tumor dormancy' had occurred.

On the basis of these findings, the concept of uninterrupted (constant or retarded) growth of locally recurring tumors was rejected and the concept of tumor dormancy was assumed as a

working hypothesis. According to this assumption, the picture of metastasis development during the subclinical phase is changed (Figure 1B): the same DFS times (R2, R3, R4) as in Figure 1A will result from different tumor dormancy times followed by similar growth times.

Treatment failures

A further investigation of the time distribution of treatment failures, which was studied utilizing the cause-specific hazard function for locoregional and/or distant recurrence as first event, was performed in 1,173 patients undergoing mastectomy as primary treatment for operable breast cancer.[7] The results of this study confirmed the inadequacy of the continuous-growth models. The recurrence pattern showed an early, fairly broad peak at about 18 months after surgery, followed by a second peak at about 60 months and then a tapered plateau-like tail extending up to 15 years (Figure 2A). Over half of all relapses occurred during the early peak. A more detailed analysis for recurrences of the first peak revealed a sharp two-peaked hazard function for premenopausal patients (Figure 2B), whereas the recurrence growth pattern in postmenopausal patients displayed a wide peak that was almost symmetrical in shape (Figure 2C).[8]

The second peak of the recurrence rate at about 60 months is not so well established as the first peak, and might be the result of a statistical fluctuation. The best argument against this interpretation comes from the fact that this peak has been confirmed in other databases[9–13] (even for mortality data and for patients receiving adjuvant chemotherapy) and might also be identifiable in other reports.[14–21] The comparative examination of different databases provides evidence that recurrence-risk peaks have rather similar timing for different patient subsets, thus suggesting that the disease course following surgical removal of the primary tumor basically follows a common pathway. Moreover, the finding that the risk level for the studied events at a certain time is influenced by tumor and host traits (e.g. the first peak is much less pronounced in series in which the prognosis is better) indicates that the pace of the common pathway is governed by pre-existing risk factors likely to result in converging hazards, which display a common resonance.

The multipeaked nature of the recurrence and mortality patterns strongly suggests that the process of overt clinical metastases has discontinuous features that could not easily be explained by uninterrupted tumor growth since tumor seeding. The tumor dormancy

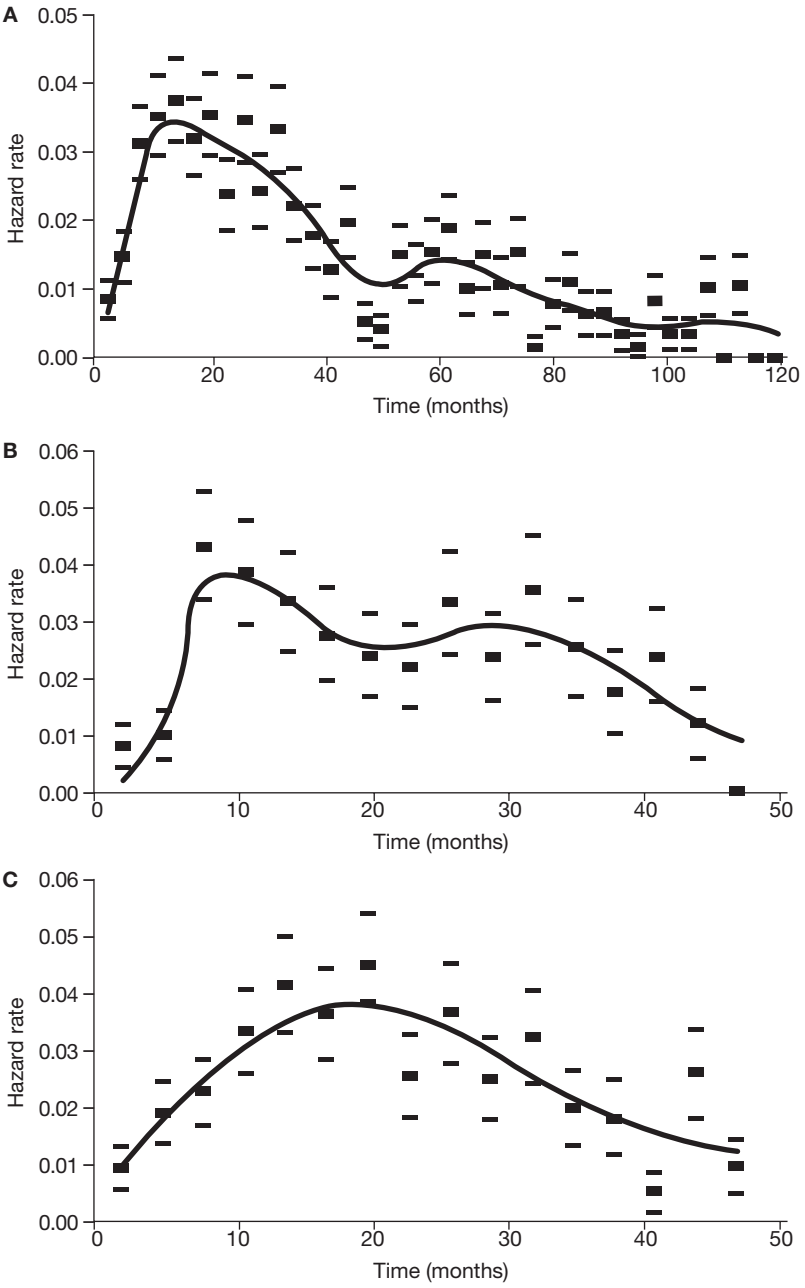

Figure 2 Hazard rate for recurrence of breast cancer in patients undergoing mastectomy (Milan series). (**A**) Hazard rate for tumor recurrence compiled from the data from 1,173 premenopausal and postmenopausal breast cancer patients undergoing mastectomy alone. The black squares relate to 3-month hazard rate values (with the corresponding standard deviations). The smoothed curve was obtained by a kernel-like smoothing procedure. (**B**,**C**) Detailed analysis of the first peak of recurrence risk (first 4 years following mastectomy) for premenopausal (B) and postmenopausal (C) patients. The black squares relate to 3-month hazard rate values (with the corresponding standard deviations). The smoothed curve was obtained by a kernel-like smoothing procedure.

concept explains these findings well. Indeed, it could be assumed that at the time of primary tumor removal micrometastatic foci might be in different biological steady states, most of which are dormancy states, which might switch to growth states after certain mean times and produce the discreteness of the hazard pattern that is observed. Moreover, differences in the recurrence-risk pattern that are related to menopausal status are in keeping with an abundance of findings about the age distribution of prognostic factors.[22,23]

TUMOR DORMANCY AND METASTASIS DEVELOPMENT

The occurrence of no growth of otherwise viable tumor foci is not a new concept.[24] Dormant tumor cells were observed in several experimental models involving animal tumors,[25–28] as well as in cell lines derived from human tumors.[29,30] Dormant, viable single cells have been identified in animal models,[31–33] and small dormant micrometastases and larger growing micrometastases have also been observed in human breast cancer.[34]

There have been reports of dormant avascular micrometastases for which, in animal models, the no-growth status is maintained by a balance between proliferation and apoptosis.[35] It has also been observed that angiogenic cells developed into early palpable tumors, whereas nonangiogenic cells developed into palpable tumors after much longer mean times (dependent on tumor type), during which they remained microscopic in size with absent or nonfunctional vasculature.[36] These results indicate that the onset and extent of angiogenesis are critical determinants of tumor progression and growth.

A molecular mechanism for tumor dormancy of single cells has been identified.[37] The tumorigenic cells express high levels of the urokinase-type plasminogen activator–urokinase-type plasminogen activator/receptor (uPA–uPAR) complex, which, by interacting with and activating fibronectin-bound $\alpha_5\beta_1$ integrin, initiates a signaling pathway through focal adhesion kinase (FAK), EGFR and extracellular signal-regulated kinase (ERK), leading to a high ERK-to-p38 ratio and rapid tumor growth *in vivo*. Inactivation of the uPAR–$\alpha_5\beta_1$ complex reverses the ERK-to-p38 ratio, favoring p38 activation and forcing these cells into growth arrest and dormancy *in vivo*.[37] This mechanism is particularly appealing as it proved to be modulated by extracellular signals *in vivo* and is consistent with a prominent role of the tumor cell and microenvironment interactions. It might reasonably be assumed that the repertoire of cancer-cell-surface proteins is crucial for the ability of tumor cells to receive, transmit and interpret clues from growth-permissive or growth-nonpermissive microenvironments, and to initiate signaling programs that respectively favor growth or dormancy.

Tumor growth and the development of the metastatic process can be represented schematically (Figure 3A). Tumor cells leave the primary site as single cells and seed at a distant site or tissue where they may lodge for some time in a quiescent state.[28,32,33,38,39] This first dormant state, denoted S1, lasts until tumor-cell or seeded-tissue changes induce cell proliferation. The transition from resting to growing tumor is likely to have prominent stochastic features.[40,41] The growing phase following S1 might lead to different fates depending on the ability to induce angiogenesis. Indeed, only a subset (4–10%) of primary tumor cells and presumably a subset of metastatic cells have the angiogenic phenotype.[35,42] Angiogenic micrometastases in the presence of antiangiogenic factors and nonangiogenic micrometastases, therefore, cannot expand to more than the size of avascular foci, containing a range of 2×10^3 to 1.5×10^5 cells.[31,42,43] Micrometastases can escape the second dormant state (S2) by at least two mechanisms. For instance, the removal of an angiogenesis inhibitor might release those cells already capable of inducing neovascularization, or a subset of tumor cells within the micrometastases might switch to an angiogenic phenotype.[35,36]

In the described model, proposed for breast cancer[44] as well as for other cancers,[45] metastatic tumors can either grow continuously or sojourn in the two dormant states S1 and S2. Orderly transitions between these two dormant states eventually result in progressive appearance of clinical metastases. In a computer simulation of this model, however, development of the early peak was detectable only by assuming some precipitating event at or near the time of surgery.[46] Even a simple examination of the recurrence-risk pattern (see Figure 2) suggests the occurrence of a triggering event that causes recurrence synchronization. After excluding some possible non-biology-based explanations of this finding,[8] we can hypothesize that surgical removal of the primary tumor may in itself have this triggering effect.

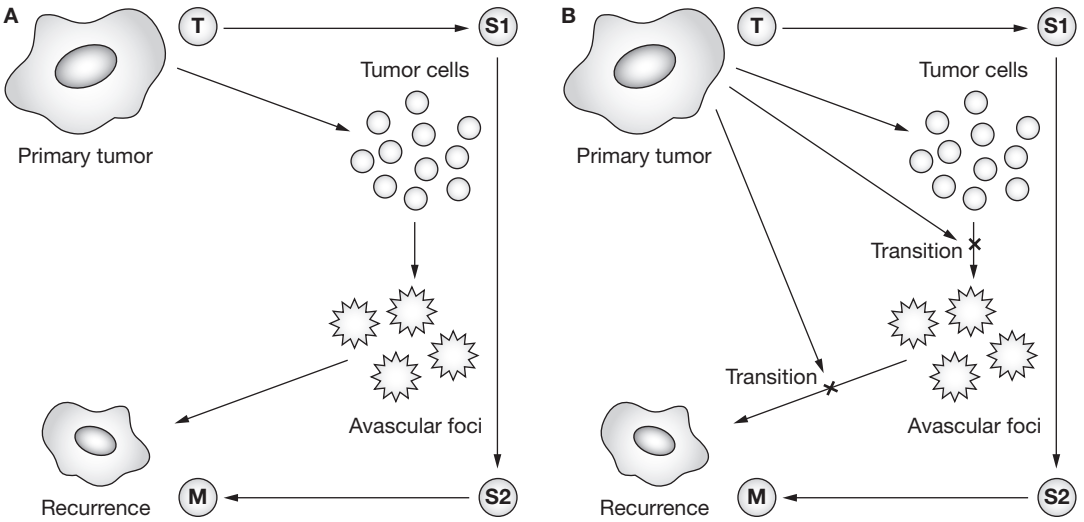

Figure 3 Outline of the metastatic process of breast cancer. (**A**) Tumor cells leave the primary tumor (T) as single cells and seed the distant tissue, where they may lodge for some time in a quiescent state (S1) or go on proliferating. Quiescent cells can be induced to proliferate by intrinsic or microenvironmental changes. Growth following S1: nonangiogenic micrometastases (and angiogenic micrometastases in the presence of antiangiogenic factors) cannot grow to more than the size of avascular foci (S2). A further growth phase implies the absence or removal of angiogenesis inhibitors in order to release those already capable of inducing neovascularization, or else the switch to an angiogenic phenotype of a subset of tumor cells within hitherto nonangiogenic micrometastases. Only after the start of the vascular phase may micrometastases grow until overt clinical recurrence ensues (M). (**B**) It may be hypothesized that the presence of the primary tumor exerts some kind of homeostatic effect upon distant metastases, resulting in inhibited proliferation and/or enhanced apoptosis. In the presurgical condition the primary tumor somewhat restrains S1→S2 and S2→M transitions, causing the dormancy of single cells and avascular micrometastases. Primary tumor removal might concur to enhance transitions and then to fuel the metastatic process.

PRIMARY TUMOR REMOVAL AND METASTASIS DEVELOPMENT

Primary tumor removal in animal models

The presence of 'outbursts' of metastatic growth following surgical excision of the primary tumor is a well-recognized phenomenon in both the experimental and the clinical setting.[47,48] A biphasic effect of surgery on lifespan was observed: very early surgery in the Lewis lung tumor model in mice resulted in a few long-term survivors, while delayed surgery had a detrimental effect on lifespan.[49] In rodents, partial or total tumor removal resulted in stimulation of cell proliferation in macrometastatic foci via a growth-stimulating factor.[49–53] Effective systemic treatment given before or immediately after surgery completely suppressed the proliferation increase and delayed metastasis growth in murine mammary tumor studies.[54]

Investigations have started to elucidate the mechanisms by which primary tumor removal might accelerate the metastatic process. Single cells might be induced to proliferate via the conversion of noncycling G0 cells,[53,55] and dormant avascular micrometastatic foci could be switched to active angiogenesis by shifting the balance between positive and negative angiogenic factors.[36,43,56] Alternatively, changes in the steady-state dynamics resulting from the switching of a subset of tumor cells to angiogenic phenotype might also occur.[35] Surgical wounding in itself might also be involved. In animal models, proliferation enhancement of metastatic foci following surgical trauma has been observed,[52,57] and in animals and humans, wound-derived factors stimulating angiogenesis and proliferation have been recovered.[58,59] All these findings support the concept that the presence of the primary tumor might exert some kind of homeostatic effect upon distant metastases by mechanisms, which are not yet well elucidated, that result in inhibited proliferation and/or enhanced apoptosis. A hypothesized presurgical condition is illustrated in Figure 3B.

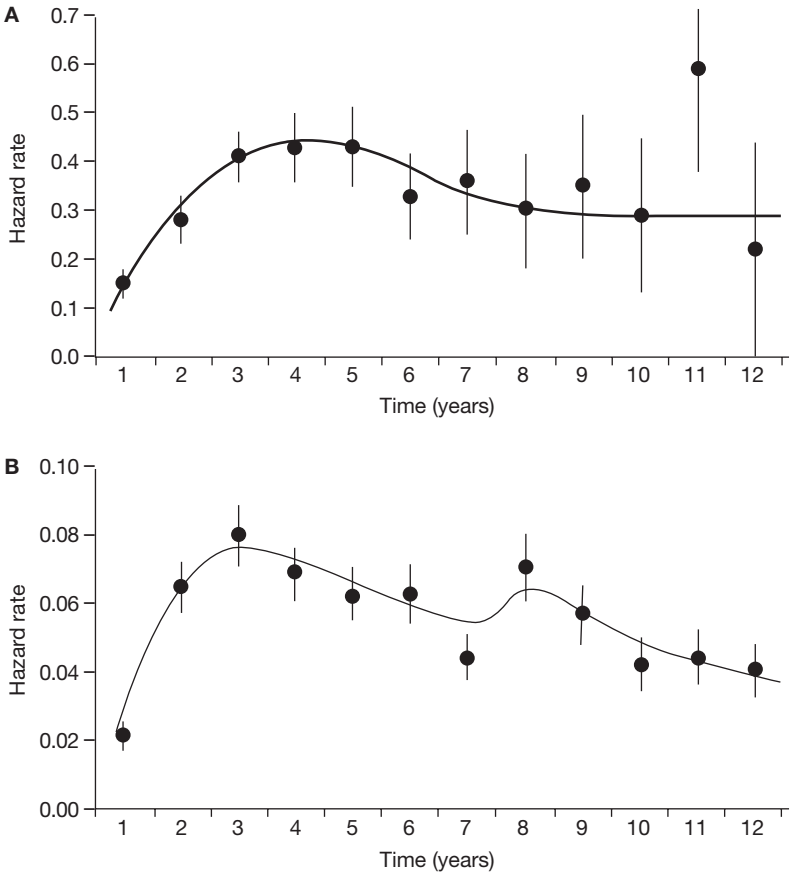

Figure 4 Hazard rate for death of breast cancer patients: comparison between untreated patients and patients undergoing mastectomy. (**A**) Death-specific hazard rate for 250 patients from the historical database of Bloom *et al.*, who did not receive any form of surgery, radiation therapy or hormone therapy. The circles represent yearly hazard rate values (with the corresponding standard deviations). The smoothed curve shows a single death risk surge followed by a near-constant plateau. (**B**) Death-specific hazard rate for 1,173 patients undergoing mastectomy alone ('Milan Series'). The circles represent yearly hazard rate values (with the corresponding standard deviations). The smoothed curve shows a double-peaked pattern with hazard rate values clearly lower than the corresponding values of the Bloom series (note the different units on the hazard rate axis). Permission obtained from Nature Publishing Group © Demicheli R *et al*. (2001) *Br J Cancer* **85:** 490–492.

Primary tumor removal and disease outcome in patients with breast cancer

Clues as to how primary tumor removal can affect breast cancer outcome have been reported.[60] The hazard rates for death of patients who did not receive any form of effective treatment were calculated from the database reported by Bloom and coauthors[61] and were compared with the above-mentioned series ('Milan series')[6] of patients undergoing mastectomy alone (Figure 4). The hazard curves showed an increase in the risk of death followed by a near-constant plateau for the untreated patients and a double-peaked pattern (with hazard rate values clearly lower) for patients undergoing mastectomy. The different patterns of death risk can be attributed to the multiple consequence of mastectomy: the 'cure' of a considerable fraction of patients (shown by the lowering of hazard rates), and the change in the natural timings of recurrence and death for other patient subsets (shown by the different hazard rate curves).

Further persuasive arguments for an effect of primary tumor removal on outcome are provided by the congruence between the recurrence-risk pattern (Figure 2A) and the putative surgery-related changes in the metastatic process. Indeed, removal of the primary tumor will result in sudden release of its restraints on the metastatic process (Figure 3B), with a marked increase in the transition rate between S1 and S2 by stimulated proliferation of a number of single cells (the 'Fisher effect'),[53] and between the S2 and M phases by induced angiogenesis in some micrometastases (the 'Folkman effect').[35]

It can be assumed that the early sharp peak in hazard rate observed for premenopausal patients (Figure 5) can be ascribed to development of angiogenic activity in a considerable number of previously avascular micrometastases. The sharpness of this peak supports the supposition that a triggering event occurs. The position of the peak, implying rapid activation and tumor growth within 8–10 months, is in quite good agreement with estimates of tumor growth following dormancy release (30 ± 8 weeks or less) obtained by very different methodology.[62] The subsequent broader peak at 28–30 months could result from the Fisher effect, resulting in the development of successive avascular micrometastases, followed by 'spontaneous' switching to the angiogenic phenotype after a certain period in the S2 phase. For postmenopausal patients, for whom the first sharp peak is absent and the single broad peak is at 18–20 months, it should be assumed that surgery-driven accelerating effects are much more modest (Figure 6). Furthermore, the model's assumptions suggest that the rather poor prognosis after the diagnosis of local recurrence might be related to the surgery undertaken for tumor control rather than having to postulate 'tertiary' spread of the disease.

According to the tumor dormancy model, factors related to menopausal status control the effects of surgical treatment. There is strong evidence to support the idea that recurrence of

metastatic disease following resection depends to some extent upon the sex-hormone milieu at the time of breast cancer resection. It has been reported that the risk of postresection cancer spread is two to four times greater among women in the follicular phase of their menstrual cycle at the time of resection than among women undergoing surgery in the early luteal phase of their menstrual cycle.[63] Furthermore, this post-resection cancer spread is mediated by estrogen-induced control of tumor cell VEGF content and capillary permeability.[64]

Outcome following adjuvant chemotherapy

Confirmation of the main features of the metastasis development model outlined above came from analysis of the recurrence risk for patients receiving adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF).[13,65] The analysis demonstrated that nearly all benefit of CMF treatment occurs during the first 4 years following resection and chemotherapy, and that the reductions in recurrence occur in specific, temporally separate recurrence clusters in the first and third years, for both menopausal statuses (Figure 7A,B). These findings suggest that the recurrence pattern following mastectomy might result from the superimposition of three metastatic clusters peaking at about 7–10 months, 17–20 months and 27–33 months, respectively (Figure 7C,D). The first and the third clusters are chemosensitive and are nearly obliterated by adjuvant CMF, while the intermediate cluster is relatively refractory to the administered treatment. The cluster sizes in premenopausal and in postmenopausal patients are quite different. Young premenopausal women display prominent peaks of chemosensitive recurrences in the first and third years, which mask the second peak; by contrast, these two peaks are obscured by the dominance of the intermediate one in older patients.

These results are expected if the model assumptions are that following surgical removal of the primary tumor, two highly proliferative, surgery-driven processes are under way. In response to effective cytotoxic chemotherapy that targets proliferating cells, reductions in recurrence rates would be expected to occur at different times, as in fact occurs. The model assumes, moreover, that during treatment administration other metastases, such as those not engaged into transition processes between dormant states, display minor proliferative activity and there might be metastases that are nonresponsive (for single cells)[66,67] or mildly responsive (for avascular micrometastases) to cytotoxic drugs, thus escaping important treatment effects. The second-year recurrences that are poorly affected by adjuvant therapy could arise by this mechanism.

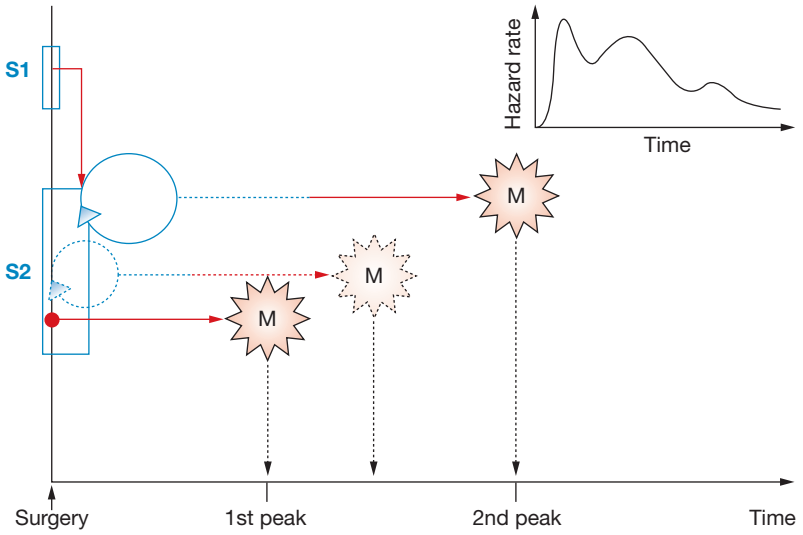

Figure 5 Outline of the hypothesized dynamics of metastasis development in premenopausal patients with breast cancer. Removal of the primary tumor (time = 0) results in a sudden increase in the rate of transition from S1 to S2 (by stimulated proliferation of a number of single cells) and from S2 to M (by the induction of angiogenesis in avascular micrometastases). In a considerable fraction of premenopausal patients, a number of S2 micrometastases are capable of giving rise to neovascularization, but are restrained by the primary tumor; therefore, they switch to angiogenic activity after the tumor is removed, and will reach clinical size (M) in about 8–10 months (1st peak). Single cells from S1 start proliferating and quickly generate micrometastases that are mostly avascular and not growing, since apoptotic activity balances proliferative activity (solid circular arrow). These micrometastases may resume growing after spontaneous switching to the angiogenic phenotype, a process with a more protracted mean time. They will reach clinical size only after 28–30 months (2nd peak). The surgery-driven acceleration of the metastatic process, resulting in the two hazard rate peaks, exceeds the 'regular' transition from S2 to M, the contribution of which arises at an intermediate time (dashed circular arrow and arrow). Hazard rate versus time diagram: the two peaks are followed by the 60-month peak.

The conclusions from this analysis of clinical findings yield evidence that the metastatic process is similar for both menopausal statuses, although both Fisher and Folkman effects might be larger in younger women. Therefore, the model provides biological reasons for why adjuvant chemotherapy is especially effective in premenopausal patients.[68]

Menopause-related sensitivity to surgery

The proposed model suggests that premenopausal and postmenopausal patients might have

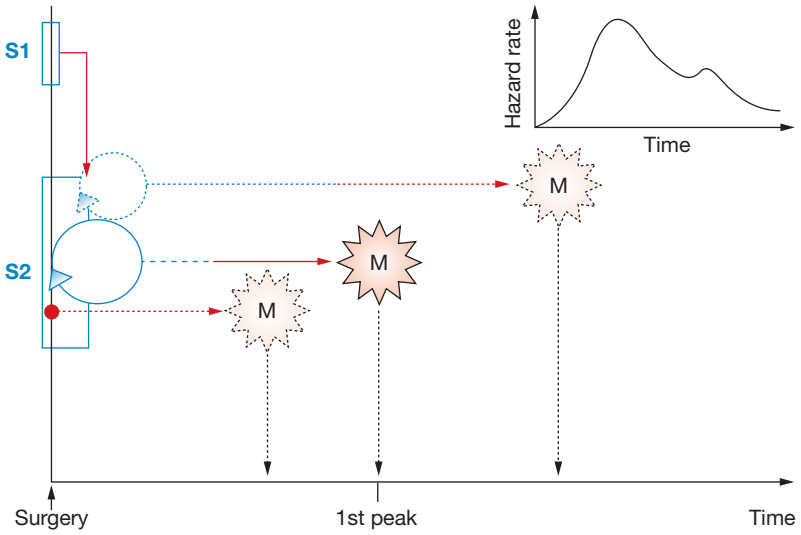

Figure 6 Outline of the hypothesized dynamics of metastasis development in postmenopausal patients with breast cancer. The processes described are similar to those for premenopausal women. For postmenopausal patients the surgery-driven acceleration of the metastatic process is moderate, the 'regular' transition from S2 to M predominates, and its contribution to the hazard rate curve hides both the early and the late peak. Hazard rate versus time diagram: the single peak is followed by the 60-month peak.

differing sensitivities to the accelerating effect of surgery. This hypothesis is quite reasonable. Although there is strong evidence that cumulative exposure to estrogens and progesterone has significant influence on the risk of breast cancer,[69] some reproductive events (puberty, pregnancy, lactation, weaning and menopause) affect the level of risk in different ways according to the age at diagnosis of breast cancer.[70] For example, histological grade and hormone receptor levels proved to have different age distributions and age-specific incidence rate patterns, with typical changes seen at menopause.[71] Even short-term changes of the host physiological conditions, such as those of the hormone milieu during the menstrual cycle, can result in measurable differences in some biological variables of breast cancer.[72,73] Indeed, levels of sex hormones that modulate angiogenesis in the normal female reproductive system, mainly via effects on endothelial cells,[74] also participate in the regulation of angiogenesis in breast tissue.

VEGF levels in normal breast tissue vary within each menstrual cycle.[75] Estrogens have been shown to regulate the bioactive fraction of VEGF in normal human breast tissue *in vivo*,[76] and to drive proangiogenic effects in animal models,[77] while tamoxifen caused anti-angiogenic effects.[78] Plasma levels of endostatin, a negative regulator of angiogenesis, are significantly higher in postmenopausal patients than in premenopausal ones[79] Furthermore, differences relating to angiogenesis have been observed between tumors of premenopausal patients and those of postmenopausal patients.[80,81]

Other findings also support the fact that tumor cells have subtle and rapid sensitivity to environmental factors. The circadian clock within cancer cells apparently coordinates the cancer growth rate.[82] The mechanisms of intermittent cancer growth include circadian clock coordination of VEGF-induced capillary permeability and blood flow.[83] As with the circadian cycle, cancer growth rate and postresection metastatic potential are each regulated by the mammalian reproductive cycle. The estrogen: progesterone ratio apparently regulates cancer-cell VEGF and basic fibroblast growth factor, and cancer growth rate and metastatic potential.[64,84] To conclude, it is reasonable to assume that some conditions related to menopausal status may favor neoplastic cell populations with peculiar traits relative to angiogenesis.

CONCLUSIONS AND FUTURE DEVELOPMENTS

Several issues remain to be addressed, as the interrupted-growth model clarifies some clinical observations whilst at the same time posing new questions. Regarding new treatment options, the model suggests both the usefulness of therapy with angiogenesis inhibitors[85] and of metronomic therapy (i.e. the steady schedule of comparatively low doses of certain cytotoxic agents targeting tumor-associated endothelial cells),[86] and the need to be watchful for possible interference with standard chemotherapy.

Starting from CMF, adjuvant chemotherapy has expanded into more-effective combinations with the introduction of anthracyclines, taxanes and trastuzumab. Adjuvant hormone therapy, such as with tamoxifen or aromatase inhibitors, is currently adopted in many clinical settings. It is not known how the recurrence dynamics change following application of these new adjuvant treatments. Mastectomy has been replaced by conservative surgery in most clinical conditions. The effect of the new surgical approach should be investigated, as the extent of damage induced by surgery may modulate the intensity of the proliferative stimulus.[59]

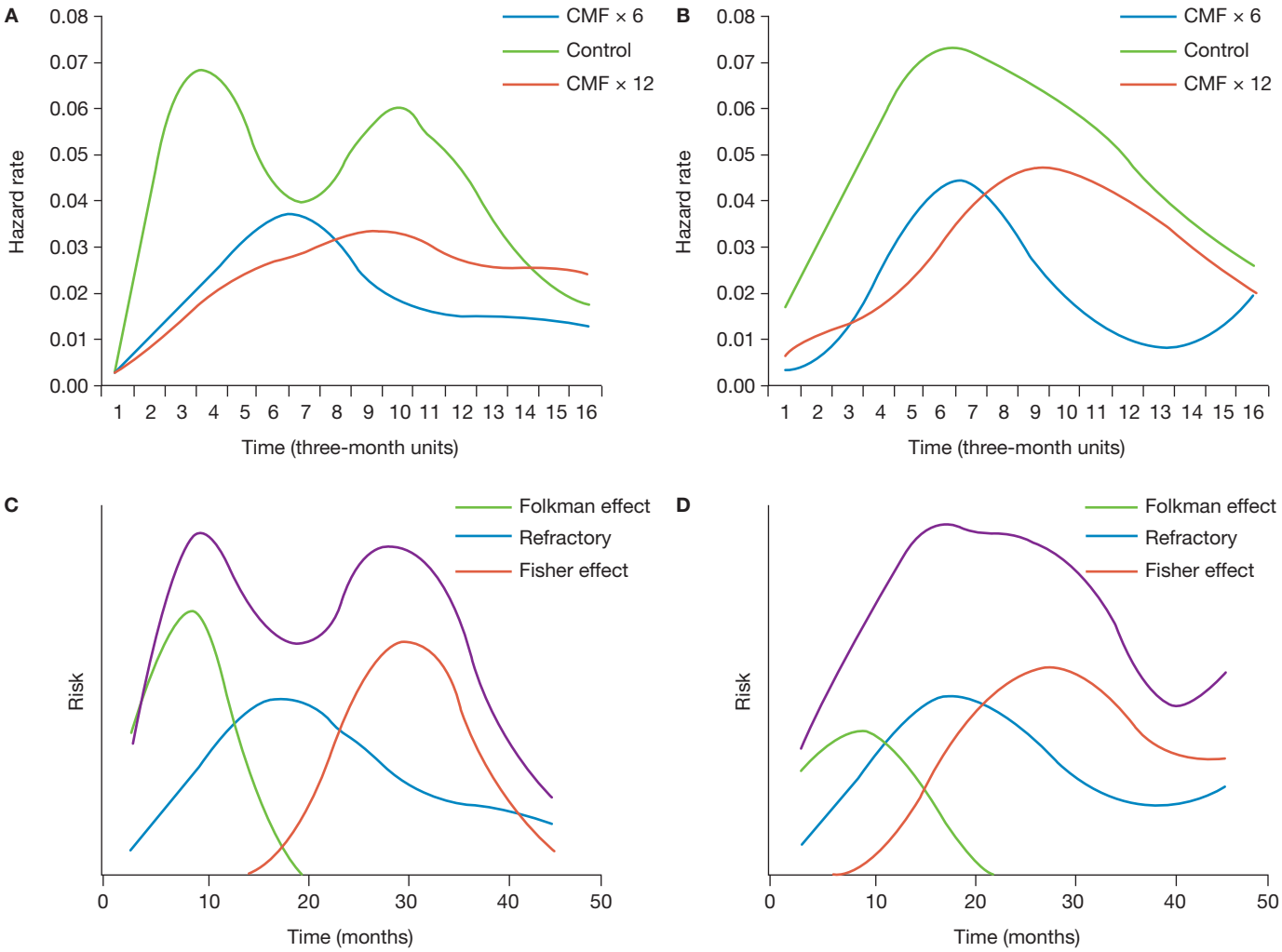

Figure 7 Pattern of CMF-sensitive and CMF-refractory recurrences occurring in the first 4 years following mastectomy. (**A**,**B**) Hazard rate for recurrence during the first 4 years following mastectomy for premenopausal patients (A) and postmenopausal patients (B): 6 cycles of CMF versus 12 cycles of CMF versus no adjuvant treatment. For both menopausal statuses, the recurrence reduction occurs at specific, temporally separate recurrence clusters at the first and third years. (**C**,**D**) The total recurrence pattern of untreated patients (purple) may be broken up into three metastatic clusters peaking at about 7–10 months, 17–20 months and 27–33 months. The first and third clusters are chemosensitive and are nearly obliterated by adjuvant CMF, while the intermediate cluster is relatively refractory to the administered treatment. At the first and third years, young (premenopausal) women (C) display prominent peaks of chemosensitive recurrences which hide the second (intermediate) peak, whereas for older patients (D) these two peaks are obscured by the dominance of the intermediate one. Abbreviation: CMF, cyclophosphamide, methotrexate and fluorouracil. Permission obtained from Oxford University Press © Demicheli R *et al.* (2005) Breast cancer recurrence dynamics following adjuvant CMF is consistent with tumour dormancy and mastectomy-driven acceleration of the metastatic process. *Ann Oncol* **16:** 1449–1457.

Primary preoperative chemotherapy has a varying and assessable effect on the primary tumor before surgery, and presumably it influences even micrometastases. It is likely that the recurrence dynamics will be affected, and careful analysis of these dynamics will provide new elements that will help to further clarify the process of metastasis development. Finally, as a primary tumor seems to be able to control the fate of its own metastases, what specific information is carried that keeps them in this quiescent state? What factors govern the initiation of metastasis in the early multipeak phases, when tumor traits probably dominate, and during the late plateau, when host factors might be more prominent? Answers to these questions are crucial as most, if not all, breast cancer patients are likely to harbor dormant neoplastic cells for the rest of their lives.[87]

KEY POINTS

- Established tumor growth models that assume continuous growth of a tumor fail to explain clinical findings from breast cancer patients with local or distant recurrence; such discrepancies may be explained by tumor dormancy
- The hazard rate for tumor recurrence soon after surgery displays a pattern that is related to menopausal status: a two-peaked hazard function for premenopausal patients and a single wider peak for postmenopausal patients
- It has been confirmed that in patients receiving adjuvant chemotherapy, recurrence risk is reduced at the first and third years for both menopausal statuses
- Subclinical metastases might be induced to grow by the conversion of single noncycling G0 cells or by the switching of avascular micrometastatic foci to active angiogenesis
- Assuming a triggering effect of surgical removal of the primary tumor, the early sharp recurrence peak seen in premenopausal patients can be ascribed to the switching of micrometastatic foci to the angiogenic phenotype, while the following broader peak might result from interruption of dormancy of a number of single cells
- For postmenopausal patients, the accelerating effects of surgery are much more modest

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