The Biology and Natural History of Breast Cancer from the Screening Perspective

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A review of the tumor biology of breast cancer from the screening perspective reveals important research issues. It is not known if the induction phase includes any detectable preneoplastic lesions. Evidence for the existence of preneoplasias is conflicting. The effect of removal of such lesions on the incidence of breast cancer has not yet been studied. The mechanisms that govern progression of in situ lesions—or even small preclinical invasive cancers—are not fully understood. It is not clear to what extent progression into cancers with metastatic behavior occurs. Current predictors for progression are weak.

One major benefit of the scientific evaluation of the screening programs is that we can learn more about the natural history of the disease. Mammographic screening detects tumors that are smaller in size than those detected by clinical examination only. There is an inverse relationship between tumor size and the probability that the patient has acquired axillary metastases. These facts, taken together, indicate that the mortality reduction seen in screening is a result of a real impact on the natural history. Calculations of the lead time gained in randomized screening projects give empirical proof that a third of the cancers progress from a localized stage to a disseminated disease relatively late in the preclinical phase of the tumor. Analyses of interval cancers in screening have pointed to the conclusion that the net growth rate of the primary tumor does not directly parallel metastatic ability, and that the tumors grow faster in younger women.

Mass screening for breast cancer is a large-scale intervention which significantly alters the steady state situation of incidence rate, stage distribution, and survival time which prevailed when the disease is detected and treated in the ordinary clinical setting. This disturbance gives an opportunity to gain deeper insight into the natural history of breast cancer. To obtain maximum information from screening studies, the preferable method would be to conduct randomized experiments with an unscreened control group over a very long period. This is, however, no longer ethically possible and screening techniques have already been introduced into daily clinical practice. Nevertheless, data from prospectively monitored screening programs can still shed new light on the natural course of mammary carcinoma. The field is open for many investigations, ranging from biological studies of certain tumor types to epidemiological analyses of changes in the incidence and prevalence of and the mortality from the disease.

In this article, aspects of the tumor biology of breast cancer that are important from the screening perspective will be reviewed, and results from screening investigations that can provide information about the natural history of the disease will then be discussed.

Tumor Biology

Background

Cancer is a somatic genetic disease. Its constituent cells have suffered irreversible alterations of their genomes. These changes are largely random and part of a multistep process [1, 2]. Basically, therefore, the natural history of any single cancer may be the consequence of processes that are partly determined by stochastic "chaotic" events. The integrated result is dynamic individuality at several levels, which probably serves to make each cancer unique.

This individuality makes it difficult to forecast the prognosis of the individual cancer. It follows that the effect of external interference will also be hard to determine in the individual case. It is customary to divide the carcinogenetic process into 2 phases: induction and progression.

Induction

During this phase, transition from normal growth control to malignant transformation takes place, presumably only in 1 cell, which will be the founder of the original monoclonal clinical cancer. Malignantly transformed cells are defined by their permanent "plus growth," i.e., they will—potentially forever—multiply even if there is no physiologic need for more tissue. The definition does not require that each cell of a cancer population has the property of infinite and uncontrolled multiplication. The abnormality is a phenomenon that characterizes a population of cells.

During the induction phase, the normal genome will undergo a series of permanent mutation-like events which, at one point, will lead to malignant transformation. The number of mutations may be in the range of thousands per genome [3]; however, the details of the genetic events are unknown. Activation of oncogenes may be driving forces of the transformation [4], but it is also clear that loss of controlling "cancer suppressor" genes plays a significant role in certain forms of neoplasia [5].

The point of interest with respect to screening is whether the induction phase includes any form of "preneoplastic lesion"
Progression may be looked on in 2 different ways. According to
one view, it is a phase characterized mainly by an increase in
the number of tumor cells. This, in turn, will increase the
probability that any one cell in the population will metastasize.

In Situ to Invasive Cancer Sequence

It would be of great value to have the answers to the following
questions:

1. Is carcinoma in situ an obligate preliminary step in invasive
cancer? Do all in situ cancers acquire a capacity for inva-
sion?
2. Is the progression from in situ to invasive growth a somatic
genetic event, and if so, what factors determine the likeli-
hood of its occurrence?
3. Can acquisition of an invasive capacity be monitored by any
method other than by microscopic examination (expression
of oncogenes has been suggested)? Is it a one- or a multihit
phenomenon?
4. Is potential for local invasion synonymous with vascular
invasion, or does the latter represent a further step in tumor
progression? What is the relation between invasion of lymph
and blood vessels, respectively?

Our knowledge about these important issues, all of which
have a bearing on the natural history of breast cancer, is
meager. If a genetic step or several steps are, indeed, involved
in the in situ-invasive transition, which, in analogy with cervical
carcinoma [10], seems to be the most likely event, the process
may not primarily depend on elapsed time. The length of time
until the transition takes place may also be related in a complex
manner to basic characteristics of the in situ cell population
(e.g., growth rate, efficiency of DNA repair, rate of formation
of viable new genetic variants, exposure to external carcinogens).
This would imply that some in situ cancers would rapidly
progress to showing infiltrative behavior, whereas others may
never do so—a fact which would influence the benefit gained
from early removal of noninvasive tumors.

A high rate of histopathological multicentricity is seen in
specimens from women operated on for breast cancer. This
rate, ranging from 5% to 80%, is, in the majority of the studies,
higher than the incidence of synchronous cancers or the rate of
local recurrence after breast-conserving therapy [11-14]. In one
series comprising contralateral breast tissue removed from
women with breast cancer for cosmetic reasons, 42.5% con-
tained lesions morphologically interpreted as small, in situ or
invasive carcinomas [15]. One likely possibility is that these
small, morphologically cancer-like alterations may be preneo-
plastic lesions rather than frank carcinoma.

Thus, observations of preneoplastic lesions and in situ cancer
indicate the importance of finding markers that would predict
subsequent development to infiltrative behavior, notably in
cancer in situ lesions detected at screening. A search for
expression of genes coding for factors involved in cellular
motility and mutual recognition may be rewarding. The mere
finding of substantial heterogeneity may be unfavorable, if that
is a reflection of the inherent tendency to form new genetic
variants.

Development of Metastasizing Ability

Progression may be looked on in 2 different ways. According to
one view, it is a phase characterized mainly by an increase in
the number of tumor cells. This, in turn, will increase the
probability that any one cell in the population will metastasize.
The benefits of early detection should then have an inverse

Fig. 1. From the first transformed cancer cell, a clone of malignant
cells is formed by repeated divisions. Cancer cells are genetically
unstable and often have defects in their mitotic machinery. The result is
creation of a multitude of subclones (4 such subclones are illustrated).
These exist in an uneasy equilibrium with each other and the tumor
stroma where probably both cooperation and competition between cells
determine their proportion at any given time. There is also evidence of
"microheterogeneity" within each subclone with respect to expression
of surface markers, gene functions, etc., as illustrated in the "cuboid
cell clone."

(hyperplasia or benign neoplasia) which could be detected so
that its removal would interfere with the natural history. Reports on this point are conflicting. In experimental systems,
hyperplasia as a forerunner of malignancy has recently gained
some interest. There is evidence that one-gene-induced hyper-
plasia is a preneoplastic lesion but that malignant transforma-
tion requires additional (and largely unknown) events [6].

Another possible example of a preneoplastic lesion is a type
of fibroadenomatosis which is often referred to as "prolifer-
ative" and has been conjectured to have a high likelihood of
developing into carcinoma [7]. So-called radial scars have also
been suggested as forerunners of tubular carcinoma [8].

Thus, from the perspective of tumor induction, there are
several reasons to suggest that preneoplastic lesions may rep-
resent one pathway to invasive cancer. Intervention with
screening in these early stages would, however, require a better
understanding of the carcinogenic process, and identification of
reliable markers for lesions with a high risk of development into
cancer. A further requirement would be the development of
screening tools sensitive enough to detect small preneoplasias.

Progression

This phase begins once the malignant transformation of a cell
has been completed. The early subclinical part, in particular,
had been virtually impossible to investigate because of a lack of
methods for finding and following small cell populations in vivo.
Most investigators have concluded that tumors of a size at
which macroscopic detection becomes feasible, i.e., with a
cancer cell population of approximately $10^6$-$10^9$, are already
considerably heterogeneous [9]. This may, for example, be
evident as different contents of DNA, or expression of different
markers within the same tumor, as illustrated in Fig. 1.

In the context of the clinically significant part of the progres-
sion period, 2 interrelated problems are of special importance:
the relation between carcinoma in situ and invasive cancer, and
the development of a metastasizing capacity.