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A New Cancer Hypothesis

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Abstract — Despite intensive efforts to cure breast cancer, treatment generally fails, as evidenced by the age-adjusted mortality rate for breast cancer. For 60 years, breast cancer mortality remained virtually constant. As treatment failed to improve the life prospect of the average patient, it is based on false premises, e.g. Halsted's hypothesis, according to which the tumor is the only threat to the patient. Yet there is more to cancer than just the tumor. Two hallmarks of cancer, cachexia, and paraneoplasia, are usually ignored, since it is assumed that they are caused by the tumor. But what if it is the other way round, and cancer is first of all a cachexia accompanied by a tumor? At least this could explain why, in most cancers, treatment fails.

Cancer is a chronic systemic disease with local manifestations like arteriosclerosis, which is also systemic and manifested solely by its local manifestations, e.g. stroke and myocardial infarction. In the same way as treatment of an ailing heart does not cure the underlying arteriosclerosis, tumor removal does not cure cancer, as it is 'metabolically' systemic.

It is proposed here that carcinogens deplete a vital substance and induce a metabolic deficiency that ends in cachexia. In order to survive, the organism grows a protective organ – the tumor – that replenishes the missing substance. During the preclinical phase of cancer, deficiency is slight and compensated only by a minute tumor. With time, it gets worse and the tumor has to grow more and more in order to make up for the loss, causing pain and secondary damage to vital functions. The patient seeks help and the disease starts its clinical course. When deficiency worsens, the patient becomes cachectic and dies.

Such a metabolic relationship exists in pernicious anemia, which illustrates how a tumor might be protective. Cancer is viewed here as pernicious cachexia induced by the loss of a vital metabolite and compensated by the tumor. Until the discovery of the missing substance, treatment ought to preserve the tumor and alleviate its secondary manifestations.

An amazing statistic

Among the myriad statistical curves that describe the fate of cancer patients in the world, one stands out vividly, portraying a harsh reality (Fig. 1). Despite continuing efforts to eradicate breast cancer upon detection, from 1930 to 1990, age-adjusted mortality from breast cancer has remained virtually constant (1,2). Sixty years of continuous debate about the appropriate treatment of breast cancer did not improve

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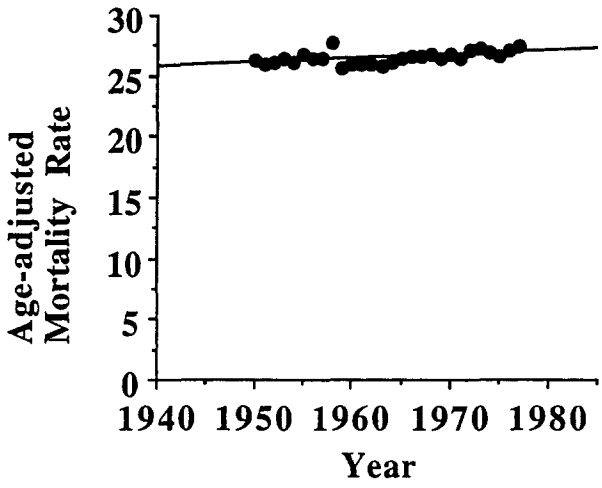

Fig. 1 Age-adjusted mortality rate. Breast cancer in US females.

Table Tumor progression

Biological (stages)		
Non-invasive:	In situ carcinoma	11.7%
Invasive:	1 Localized	42.5%
	2 Regional	33.6%
	3 Distant	9.0%*
Clinical (phases)		
1. Inception	Pre-clinical phase	
2. Detection	Clinical phase	

Stage classification was adapted from Ref. 3, p. I.21. Stages 3 and 4 are pooled.
*3.3% were unclassified (Ref. 3, p. IV.17)

the life prospect of the average patient. No other epidemiological phenomenon manifests such a constant behavior. All other statistics continually vary.

The curve highlights the failure of breast cancer treatment and its underlying theories, particularly that of W. S. Halsted (1852–1922). Accordingly, the tumor starts when a normal cell is transformed into a malignant one. It proliferates faster than its normal neighbors and forms a small nodule. Initially, it is localized, and when attaining a certain size, it spreads through lymphatic vessels into adjacent tissues. As tumor continues growing, some of its cells spread through blood vessels to remote organs where they settle as metastases. This hypothesis implies that tumor removal should cure the patient, yet 60 years of intensive effort to remove the tumor did not change the biological outcome of the disease (Fig. 1). Obviously, the hypothesis is wrong and should be modified.

Breast cancer progression

Tumor progression is described within two frameworks: biological, and clinical. The first describes tumor behavior, and the second its clinical manifestations. Initially, the tumor is a non-invasive, in situ carcinoma. It then proceeds through three invasive stages: (1) localized, when the tumor is confined to the breast; (2) regional, when tumor cells enter regional lymph nodes, and (3) distant, when tumor cells spread into remote organs. Clinically, when a normal cell becomes malignant the transition is called disease inception. Initially, the tumor is small and cannot be detected by available diagnostic tools, and the disease proceeds through its preclinical phase. On tumor detection, the disease starts its clinical phase. The two frameworks do not overlap. A tumor may reach its invasive stage during the preclinical stage, long before diagnosis. In the year 1990, only 11.7% of breast tumors detected in the USA were non-invasive, 42.5% were localized, and 45.8% spread outside the breast (Table (Ref. 3, p.I.21)).

Mammography and adjuvant chemotherapy

Figure 1 indicates that, on detection, most tumors were already invasive, and their extraction did not cure the patient. Either treatment failed because the tumor was detected 'too late' or, the tumor spread metastases from its very beginning. It is hoped that, with mammography, tumors may be detected at an earlier stage. Yet mammography endangers the patient by various routes: (1) irradiation; (2) surgical intervention, e.g. open or closed biopsy and (3) false positive diagnosis that ends in unnecessary treatment. The smaller the tumor, the greater the hazard involved in its detection process (Fig. 2). Apparently, mammography will detect only some preinvasive tumors, leaving the biological outcome as it is (Fig. 1).

Many hope that adjuvant chemotherapy will sidestep these limitations. Yet even this treatment has serious limitations: (1) At this early stage, tumor cells are generally dormant and do not cycle, while chemotherapy destroys only cycling cells; (2) Initially, the tumor looks like normal tissue and is called minimal deviation tumor. The therapeutic margin of chemotherapy at this early stage is extremely narrow. Treatment destroys 'bad and good' cells, and the risk to the patient is high; (3) With time, tumors become resistant to chemotherapy (Fig. 2). The earlier the

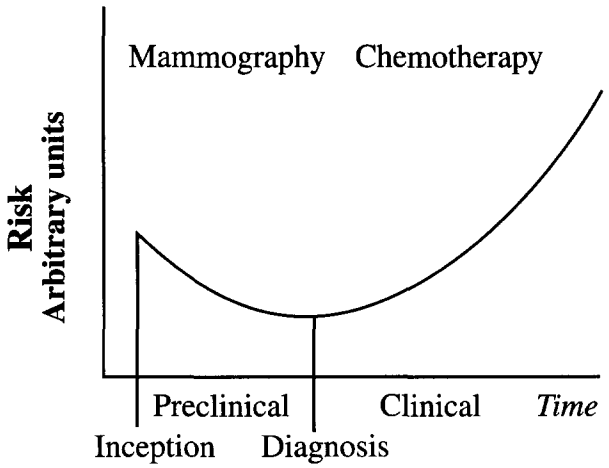

Fig. 2 Hypothetical risk due to mammography and chemotherapy.

treatment, the greater the risk. It seems, therefore, prudent to postpone chemotherapy until other means fail; (4) Micrometastases may not be so dangerous as generally assumed.

Long survival with micrometastasis

The cancer survival report No. 5 from the US National Institutes of Health describes survival of 3369 patients with regional breast cancer diagnosed during 1950–1954 (4). Treatment consisted of mastectomy with or without irradiation. Figure 3 illustrates two facts. While 76% patients succumbed to the disease, 24% survived 20 years. Most of the time they were in remission and healthy. Since they eventually died from their disease, we can conclude retrospectively that all carried undetected micrometastases. Some carried metastasis for at least 19 years. For example, in a woman who lived with micrometastasis that long, during this prolonged remission her organism apparently 'knew' how to live with, and adapt to micrometastasis. Let's examine the fate of 10% women that died in the period between 10–20 years. 34% survived 10 years, and 24% survived 20 years. Ten per cent thus died from breast cancer between Years 10 and 20. Since living at least 10 years, we may conclude that they carried hidden micrometastases for 10 years. For most of these years, they were healthy – otherwise they would have been treated. Micrometastasis itself may not be harmful.

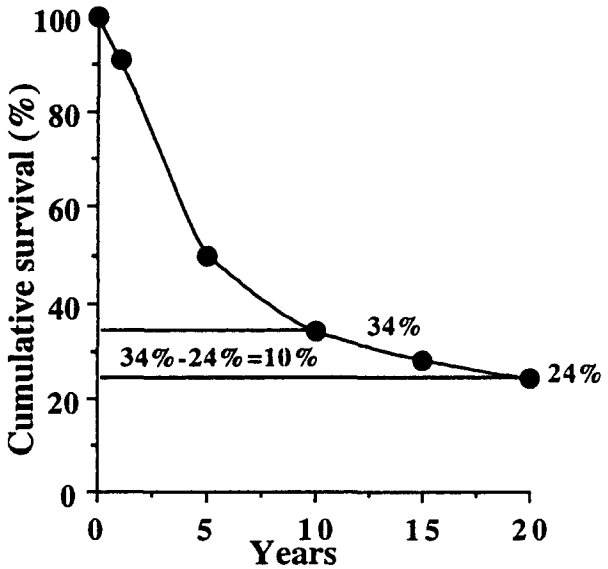

Fig. 3 Cumulative survival of US females with regional breast cancer.

In the USA, 33.6% of white females with breast cancer have (Ref. 4 p. IV.17). The age-adjusted incidence for all stages was 113.6/100 000 (Ref. 5, p. 117). A total of 38/100 000 females carried micrometastases for at least 10 years (= 0.336*113.6) which makes about 9500 patients per year in the entire country. This estimate is extremely conservative. Actually, thousands of apparently healthy females carry micrometastasis for at least 10 years. Should they be poisoned with adjuvant chemotherapy? The nature of this adaptation to micrometastasis is still unknown. Supposing that medicine could harness it for another 20 years, cancer would turn into a benign disease. We may thus conclude that, unless a metastasis impinges upon a vital organ, it is relatively harmless.

Iatrogenesis

Despite these arguments, Figure 1 still remains puzzling since contradicting clinical experience. Treatment helps many patients, it alleviates their suffering, and even prolongs their life. Should the curve therefore decline? Yet it does not, since for every patient who benefits from the treatment, another one is harmed by it and dies earlier, balancing out the biological outcome. Not all patients need chemotherapy. Some, e.g. the 24% long survivors, seem to do well without it. Others may even be resistant to the treatment. There is no justification for poisoning patients with resistant tumors as is done today. Figure 1 indicates that, for each patient who benefited from treatment, another one, with a resistant tumor, succumbed to it. Many breast cancer patients are hit by iatrogenesis.

Aggressive chemotherapy harms mainly non-responders and should be stopped. Patients should be tested first to establish how they respond to treatment,

as happens during digitalization, where the drug dose is gradually raised until the patient becomes slightly poisoned (bigeminy), whereupon it is slightly reduced. Why not test cancer patients in the same way and spare the non-responders unnecessary suffering?

When to treat?

Mastectomy seems to be justified only for localized tumors, since aiming at preventing metastasis. Thus, 45.8% of patients (Table) will not benefit from mastectomy. Those who still advocate mastectomy in these patients claim that it prevents local complications, e.g. a large tumor, skin ulceration, and local infection. Why not treat these complications when the time comes and refrain from mutilating the patient? Mastectomy may be postponed and augmented by plastic surgery techniques. Some patients are anxious to remove the tumor, which may be done in a gentler way than by mutilating mastectomy. Above all, they ought to be told the truth: that they carry a widespread disease – and allowed to be encouraged by statistics like those shown in Figure 3.

Most patients with apparent localized tumors carry widespread disease. This can be deduced retrospectively from another statistical publication describing the fate of patients with localized tumors (4). A total of 62% survived 20 years. Thus, in 38%, the disease had spread to distant organs killing the patients as time went by. What if the entire group with apparent localized tumors carried micrometastases? Those who 'knew' how to live with their disease, fared better, exactly as happens in patients with regional disease.

These doubts call for a thorough evaluation of breast cancer treatment. Since treatment does not cure, why not postpone treatment as much as possible? Why not treat the symptoms only when they bother the patient?

Wisdom of the body

Figure 3 highlights a basic flaw in the theory of cancer. It emphasizes the tumor and ignores the patient. Halsted's hypothesis considers only tumors. The possibility that the organism 'knows how to live' with its tumor is not considered. Patient prognosis depends entirely on tumor stage which is only partially related to patient's prognosis. A patient with a localized tumor may die within five years, while 24% of patients with regional disease survived 20 years. There is no doubt that tumor stage and prognosis are correlated, but only partially. The knowledge in the organism of how to live with cancer is called 'Wisdom of the Body' (6), a powerful concept that was applied by W. E. B. Cannon to describe complex physiological processes like homeostasis (7).

Wisdom of the Body is an attribute of live organisms. It directs growing plants toward sunshine, guides amebas away from noxious agents, and determines the behavior of higher animals, which is studied by ethology. Wisdom of the Body is also wisdom of the species. It is inherited and ought to be distinguished from wisdom gained by experience and knowledge, which is not inherited. It is essential for individual survival and was molded by natural selection. According to Darwin's theory of natural selection, each live being on earth is best qualified to live on this planet, otherwise it would have been replaced by one better qualified. In other words, the wisdom of today's life-forms is most adequate for their survival under the present circumstances. From the medical point of view, since agents causing disease are part of the environment that 'selects the best fitted organisms', during evolution, Wisdom of the Body encountered all diseases and knows how to heal itself. It anticipates all diseases, and endows the long survivors with the knowledge of how to live with cancer.

This important asset, which is ignored by medicine, has to be considered in order to explain the fate of cancer patients. Halsted's cancer hypothesis has to be augmented to account for such hidden processes in our organism.

Cancer is a systemic disease

There is more to cancer than just the tumor. Two hallmarks of cancer – cachexia and paraneoplasia – are usually ignored, since it is assumed that they are caused by the tumor. In some cases, it appears as if cachexia and paraneoplasia accompany the tumor, yet usually weight-loss does not correlate with the type of cancer and its duration, nor with the site or number of metastases (8). Weight-loss is one of the earliest manifestations of malignancy (9), and cachexia can appear in patients with tumors that are less than 0.01% of the total body-weight (10). Also, paraneoplasia is unrelated to tumor size, location, or the degree of metastasis, and may antedate the discovery of the tumor by weeks, months, or even years (11). In spite of this, oncology maintains that tumor is the primary factor in cancer, and systemic effects are secondary. But, what if it is the other way around, and cancer is first of all a cachexia accompanied by the tumor? At least this would explain why in most cancers treatment fails.

Take for instance arteriosclerosis that is manifested by local phenomena, e.g. stroke and myocardial

infarction, and yet is essentially systemic. The same could apply to cancer which, like arteriosclerosis, is 'metabolically' systemic, and presents itself also by local phenomena, e.g. tumor. In the same way as treatment of an ailing heart does not cure the underlying arteriosclerosis, tumor removal does not cure cancer.

Tumor as protective mechanism

It is proposed here that carcinogens deplete a vital substance, inducing a metabolic deficiency that ends in cachexia. In order to survive, the organism mobilizes a protective organ, the tumor, that replenishes the missing substance. During the preclinical phase of cancer, deficiency is slight and compensated by a minute tumor. With time it gets worse and the tumor has to grow more and more in order to make up for the loss, causing pain and secondary damage to vital functions. The patient seeks help and the disease starts its clinical course. When deficiency becomes pronounced, the patient dies in a state of decompensation, known as crisis or relapse.

There is a disease called pernicious anemia that illustrates how a tumor might be protective. It is triggered by a 'carcinogen' preventing the entry of vitamin B_{12} into the body. During its pre-clinical phase, that lasts about two years, the patient is healthy. The clinical phase starts with anemia and 'paraneoplasia', known as combined degeneration of the spinal cord and brain. The bone marrow displays 'neoplastic' features, e.g. hyperplasia, maturation arrest, and ineffective erythropoiesis, that were regarded in the past as 'pseudoleukemia' (12). These are protective measures by the bone marrow that keep the patient alive. With time, the deficiency deepens more and more until reaching the state of decompensation, whereupon the patient dies.

Cancer is viewed here as pernicious cachexia, induced by the loss of a vital metabolite and compensated by the tumor. Until the discovery of the missing substance, treatment ought to preserve the tumor and alleviate its secondary manifestations (13–16).

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