Klin Wochenschr (1981) 59:819–829

Klinische Wochenschrift

Übersichten

Pathobiology of Breast Cancer: Hypothesis of Biological Predetermination and Long-Term Survival

H. Vorherr

Departments of Obstetrics-Gynecology and of Pharmacology,
The University of New Mexico, School of Medicine, Albuquerque, New Mexico

Summary. The pathobiology of breast cancer is complex: clinically "early" breast cancer may be tumorbiologically "late" progressing rapidly toward death. Accordingly, it has been suggested that two different breast cancer populations (slow tumor growth and long survival – fast tumor growth and short survival) exist, which cannot be identified by pathohistological criteria. However, these "populations" are most likely either patients with localized disease and occult metastases (long survival) or with diagnosable regional and occult or overt systemic spread (short survival). Since even small tumors (0.1 to 0.3 cm in diameter) can spread systemically, in most patients breast cancer upon clinical diagnosis may be considered an inevitably lethal disease. Present treatment modalities can only improve the quality of life and delay death, even though the overall long-term survival rates of breast cancer are better or at least equal to those of other cancers. However, with other cancers (Table 2) it is decided within the first 5 years which patients are cured because the survival rates for 5, 10, 15, and 20 years are similar. In contrast, survival rates of patients with breast cancer steadily decline and there is no point in time when patients can feel really safe; this is indicative of a peculiar tumor pathobiology of this disease, the nature of which remains to be investigated. Progress in the fight against breast cancer is only possible by application of sensitive physical, reliable immunological, and specific biochemical methods for early diagnosis and development of efficient therapeutic modalities for inhibition of growth or complete eradication of metastasized cancer cells.

Key words: Breast cancer – Pathobiology – Survival

Pathobiologie des Mammakarzinoms: Hypothese der biologischen Prädetermination – Langzeit-Überleben

Zusammenfassung. Die Pathobiologie des Mammakarzinoms ist komplex. Brustkrebs diagnosed als klinisch im Frühstadium kann tumorbiologisch schon im Spätstadium sein und die Überlebenszeit ist kurz. Demzufolge wurde auf das Bestehen von zwei verschiedenen Brustkrebspopulationen hingewiesen: (1) langsames Tumorwachstum und lange Überlebenszeit, (2) rasches Tumorwachstum und kurze Überlebenszeit. Diese zwei Populationen sind nicht durch pathohistologische Kriterien identifizierbar. Sehr wahrscheinlich sind dies Patienten mit lokalisiertem Tumor und okulten Metastasen (lange Überlebenszeit) oder solche mit regionaler und systemisch okulter oder klinisch diagnostizierbarer Streuung (kurze Überlebenszeit). Da kleine Tumoren (0.1 bis 0.3 cm im Durchmesser) schon metastasieren können, so muß in den meisten Fällen Brustkrebs zur Zeit der klinischen Diagnose als unabwendbare tödliche Erkrankung angesehen werden. Da gegenwärtige Behandlungsmethoden nicht alle metastasierten Krebszellen vernichten können, so kann durch die Therapie nur die Qualität des Lebens verbessert und die Dauer verlängert werden. Trotzdem sind die Langzeit-Überlebensraten des Brustkrebses höher oder zumindest gleich denen anderer Karzinome. Allerdings ist bei anderen Malignomen (Tabelle 2) das Schicksal innerhalb von 5 Jahren entschieden und Patienten, die nach 5 Jahren noch leben, können als geheilt angesehen werden, da die Überlebensraten für 5, 10, 15 und 20 Jahre ähnlich sind. Im Gegensatz dazu nimmt die Überlebensrate für Brustkrebs ständig ab und zu keinem Zeitpunkt können sich die Patientinnen wirklich sicher fühlen; dies spricht für eine besondere Tumorpathobiologie dieser Erkrankung, deren Eigenheit noch zu erforschen ist. Fortschritt in der Bekämpfung des Brustkrebses ist nur möglich durch Anwendung von empfindlichen physikalischen, spezifischen biochemischen und verlässlichen immunologischen Methoden zur Diagnose sowie Entwicklung von therapeutischen Modalitäten zur Wachstumshemmung oder völliger Vernichtung metastasierter Karzinomzellen.

Schlüsselwörter: Brustkrebs – Pathobiologie – Überlebenszeit

The breast is the most common site of malignancy in women and the death rate from breast cancer (28 per 100,000 female population) has been constant for over 45 years (Shapiro et al. 1968; Feinleib and Garrison 1969; Black 1970; Miller 1976). The overall 5-year survival rate of all stages of breast cancer of 62% and 47% for white and black American females, respectively, has not changed over this period (Seidman et al. 1976). Breast cancer is the cause of death for 20% of U.S. women who die from malignant disease (Shapiro et al. 1968; Silverberg 1977). It has been estimated that during the year 1979, 106,000 new breast cancer cases will occur in the U.S. and 34,200 women are expected to die from breast cancer (Silverberg 1979).

Factors Influencing Survival of Breast Cancer Patients

Prognostic factors for survival of breast cancer are determined by various parameters. A good chance of survival of breast cancer patients appears to exist for patients with (a) a small tumor, (b) minor tumor blood vessel invasion, (c) well-differentiated tumors, (d) negative regional (axillary) lymph nodes, and (e) lymph node sinus histiocytosis (Friedell 1978).

Even though, in some patients the diagnosed primary tumor is very small, only 1 cm in diameter, the treating physician has to cope with 1 billion cancer cells in the patient's organism. Malignant cells may begin to escape into the lymphatic and systemic circulation, when the primary tumor is still less than 0.3 cm in diameter (Taylor 1978); even a primary tumor of only 1 mm in diameter contains already 1 million malignant cells and thus may metastasize (Baum 1976). In 1 to 5% of patients with in situ breast cancer systemic spread has occurred already (Ozzello and Sanpitak 1970; Ashikari et al. 1971; Millis and Thynne 1975; Westbrook and Gallager 1975).

Hypothesis of Two Breast Cancer Populations

The pathobiology of breast cancer is complex, the disease may, more than other forms of cancer, remain dormant for many years; also stage of the malignancy upon clinical diagnosis and course of breast cancer vary greatly from patient to patient. Already in 1954, McKinnon suggested two types of breast cancer, a metastasizing incurable and a nonmetastasizing curable variety. Also, Slack et al. (1969) in view of the tumor pathobiology, hypothesized that two populations of breast cancer patients exist, one with a fast growing tumor (~20% of patients) and one with a slow growing tumor (~80% of patients). In patients with fast growing breast cancer, the tumor doubling time was 2-fold increased and the "risks of nodal involvement and of occult metastases were several times greater" than in the slow growing tumor population (Slack et al. 1969). Recently, again Fox (1979) suggested that two populations of breast cancer patients exist, one with a short (3 to 4 years) and one with a long (5 to 10 or more years) time of survival. In the one group (~60%), by histological criteria the tumor is malignant but the "cancer" is biologically benign and these patients survive. The cancer in the other group (~40%) is malignant both by histological and tumor-biological criteria and despite treatment fatal within a short time. As McKinnon (1954) pointed out, the histopathology of the primary tumor cannot discriminate between metastasizing and nonmetastasizing cancers, or between lethal and nonlethal types. Because the two different breast cancer populations cannot be identified and separated by histological criteria, in no instance is prediction of the length of survival possible (Fox 1979). Also, in some patients the diagnosis "mammary carcinoma" is subject to an individual decision by the pathologist. "The dividing lines between epithelial hyperplasia, intraduct carcinoma, and early invasive ductal carcinoma are not clear-cut" (Baum 1976); however, these ambiguous cases represent only a small number of the total breast cancer population.

Challenge of the Concept of Two Breast Cancer Populations: Breast Cancer Survival in Relation to the Stage of Disease

The concept of two different breast cancer populations, which supposedly cannot be identified by pathohistological criteria (Fox 1979), ignores the commonly agreed prognostic factors for survival of breast cancer as mentioned before. Thus, clinicians know by experience that many patients who present with axillary lymph node metastases and disseminated carcinoma at the time of mastectomy, will die within a few years from the disease (Mueller et al. 1978) (Table 1), because at the time of primary treatment, considerable local and distant cancer spread exists. Metastases to axillary nodes are an expression of a poor prognosis. "If the lymph node – surely the most hostile environment for a cancer cell – becomes the focus of an established metastasis then the biological war between tumour and host is already lost" (Baum 1976). More so, since axillary (parasternal) lymph node metastasis does not necessarily precede systemic spread, regional lymph node involvement may serve as evidence of the aggressiveness of the disease (Devitt 1965). In many patients (~85%), subclinical metastasis has already occurred before mastectomy (Slack et al. 1969). Accordingly, patients who present with

Table 1. Survival rates in percentages of breast cancer patients after therapy

Subject	Years of survival			
	5	10	15	20
Breast Cancer				
All stages	(40–50) [6][a]	(29–41) [6]	24 [5]	20 [10]
	46 [5]	30 [5]	(24–31) [6]	21 [5]
	57 [3]	38 [7]	30 [10]	(24) [6]
	60 [4]	40 [10]	35 [6]	30 [3]
	60 [10]	42 [3]	36 [3]	38–44 [6]
	60–65 [6]	47–52 [6]	41–45 [6]	40 [4]
		48 [6]		47 [9]
		50 [4]		
		50 [9]		
Stage I (localized disease)	(76–79) [6]	51 [7]	51 [5]	30 [7]
	81 [3]	(61–77) [6]	(56–64) [6]	48 [5]
	83 [5]	63 [5]	61 [3]	55 [3]
	83–85 [6]	69 [3]	67–68 [6]	(57) [6]
	90 [2]	72–74 [6]	74 [2]	62 [6]
		75 [4]		
		79 [2]		
Stage II (regional spread)	(32–48) [6]	(21–34) [6]	(13–23) [6]	(11) [6]
	46 [3]	25 [11]	21 [2]	19 [5]
	49 [5]	29 [2]	22 [5]	21 [3]
	50 [2]	29 [5]	24 [3]	24 [6]
	50–56 [6]	30 [3]	28–31 [6]	
		34–39 [6]		
		38 [8]		
Stage III (systemic spread)	(6–12) [6]	0–12 [1]	0–8 [1]	7 [6]
	7–21 [6]	2–12 [6]	(1–5) [6]	(7) [6]
	9–27 [1]	(3–5) [6]	4–8 [6]	
Control Population	92 [5]	77 [12]	65 [12]	60 [5]
		85 [5]	75 [5]	

[a] References:

[1] Brinkley and Haybittle 1968
[2] Campos 1972
[3] Myers 1973
[4] Adair et al. 1974
[5] Brinkley and Haybittle 1975
[6] Asire and Shambaugh 1976
[7] Baum 1976
[8] Carbone 1977
[9] Moskowitz 1977
[10] Mueller et al. 1978
[11] Edelstyn 1979
[12] Key 1979

( ) = Survival rates for blacks

no detectable regional metastasis at the time of mastectomy and thus probably have only minimal systemic cancer spread, may survive up to 10 or 20 or more years. Consequently, time of survival depends on the stage of clinical disease at primary treatment (Table 1). Survival rates are expressed as the relative survival which is the ratio of the observed proportion of breast cancer patients surviving to the expected proportion for women of similar age in the general population (Myers 1973). Patients with stage 0 (tumor less than 1 cm in size; staging according to Leis, 1977) and stage I (breast tumor only) of breast cancer had a 97% and 70 to 75% 10-year survival, respectively, whereas the 10-year survival of patients with breast cancer stage II (axillary metastasis) was only 38%; survival of patients with breast cancer stages II and III (systemic spread) was reduced to 25% (Carbone 1977; Leis 1977). According to Edelstyn (1979), the 10-year survival for patients with axillary metastasis is only 25%. Moreover, the poorer survival of black breast cancer patients (Table 1) is probably related to the delay in diagnosis and treatment of the disease. Even though early diagnosis of breast cancer may improve the cure rate by 30 to 35% within the first 7 years after primary treatment (Baum 1976), many "early" breast cancers by tumor pathobiological criteria may be "late", i.e., metastatic spread already exists and the patient is incurable. Therefore, it is not surprising that only 15% of 6,775 patients with early breast cancer survived 25 years (Bond 1968).

In general the clinical stage of breast cancer at the time of treatment correlates well with the patient's prognosis. However, the possibility exists that in patients with equal extent of breast cancer, the assumption that two different populations (one with short survival and one with long survival) exist may be valid, but presently no characteristics and methods are available to define these patient populations. Of course, factors such as age of the patient, general health, hormonal status, reproductive history, familial breast cancer history, race, and environment may also play a prognostic role but these are difficult to be evaluated retrospectively. In addition, the immune status may also play a role. However, immunologic factors are not the only host factors that influence the outcome of cancer metastasis, nor is immunogenicity the only tumor cell property that contributes to the metastatic phenotype (Fidler and Kripke 1980).

Is Breast Cancer an Inevitably Fatal Disease?

Cancer cells in the breast may exist 8 to 10 years before the tumor is clinically detectable. The average duration of life for patients with untreated breast cancer from the time of clinical diagnosis is approximately 3 years (Taylor 1978). According to Baum (1976) and Mueller and Ames (1978), breast cancer must be considered a lethal systemic disease and neither initial stage and age at diagnosis, nor histopathologic and immunologic features or type of treatment appear to prevent the fatal outcome even though treatment may improve the quality of life and delay death. Thus, it appears that death from breast cancer occurs eventually because once one of the approximately 10^{20} body cells has been changed into a malignant cell (Burnet 1977), cancer cell multiplication and eventual spread follow.

"Biological Predetermination" and Long-Term Survival of Breast Cancer Patients

Thirty years ago, MacDonald (1951) developed the concept of "biological predeterminism" in view of the fact that "early" breast cancer may be "biologically late". Because ultraradical breast cancer surgery failed to improve the cure rate, this has been held as "evidence of biological predeterminism in cancer of the breast, in which the presence of disease beyond the limits of the conventional procedure ... is simply evidence of almost inevitable dissemination to more remote sites" (MacDonald 1951). In 1954 McKinnon elaborated on that concept, stating: "As the failure of early treatment is due to later development of remote metastases from earlier remote spread of cancer cells, it must be postulated that, in most (if not all) lethal breast cancer, remote spread takes place through the blood-stream before treatment can be instituted, and that consequently neither early nor extensive treatment of the primary lesion can effect any material reduction in mortality".

According to the concept of biological predetermination, the probability of dying from breast cancer is constant (Allan 1978), even though the time of survival varies with the stage of clinical disease and the host-tumor relationship. Thus, 5, 10, 15, and 20 years after primary therapy, approximately 40%, 60%, 70%, and 80% of breast cancer patients of the Syracuse metropolitan area have died of the disease (Mueller and Ames 1978; Mueller et al. 1978) (Fig. 1; Table 1). As reported by Brinkley and Haybittle (1975), 21 years after primary breast cancer treatment 82% of patients were dead and only 18% may be regarded as cured of their disease (Fig. 2). The New Mexico Tumor Registry shows that 10 and 15 years after primary therapy 52% and 65% of patients have died; the respective values for the average control population are 23% and 35% (Key 1979) (Table 1).

In contrast to the dim outlook on long-term survival of breast cancer, there are some rather optimistic reports. Thus, Moskowitz (1977) reported a 47% 20-year survival of breast cancer patients; "however the data for 20 years are not as firm as the data for 10 years", showing an overall 50% survival rate (Moskowitz 1979). Campos (1972) observed a high 15-year survival rate of 74% for patients with localized disease, but only 184 patients were studied. Adair et al. (1974) observed a 38% survival (cure) 30 years after primary breast cancer treatment. However, these authors studied 1,458 patients, whereas Myers (1973) followed up 63,000 breast cancer cases and the 20-year survival rate is only 30% (Table 1).

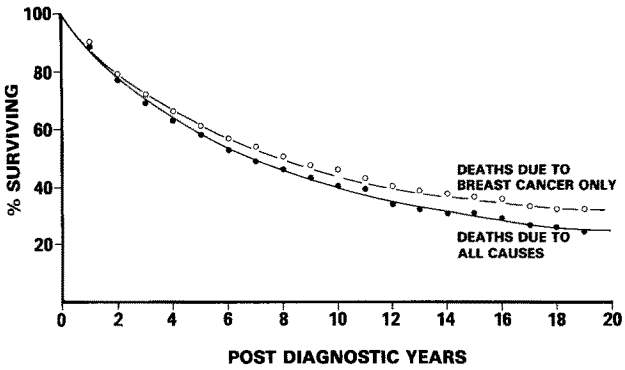

Fig. 1. Survival curves for 3,558 breast cancer patients. The survival curves constructed by the life-table method show that approximately 60% and 80% of all breast cancer patients are dead after 10 and 20 years, respectively (lower curve) and that almost 90% died from breast cancer (upper curve). From Mueller et al. (1978) with kind permission

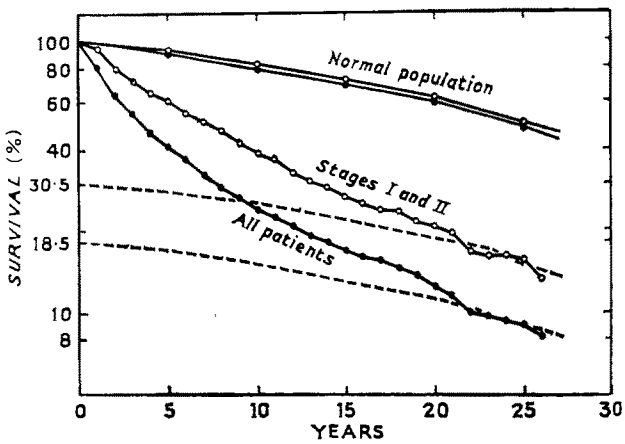

Fig. 2. Survival curves for breast cancer patients and normal population. After primary treatment, the chance of dying from breast cancer during a 20 year period is 2 to 3 times higher than that of an age-matched control population. Even though after 20 years the life expectancy of surviving patients approaches that of a normal population, the probability of dying from breast cancer is still greater. The interrupted lines are extrapolated backwards from the point at which they become parallel with the lines for the normal population. The intercepts on the vertical axis indicate that approximately 30% of breast cancer patients stage I and stage II and 20% of all patients in the group might be considered "cured". From Brinkley and Haybittle (1975) with kind permission

Survival of Breast Cancer in Relation to Age – Ultimate Cause of Death

In older breast cancer patients the disease seems to take a more rapid course (Fig. 3). Fifty percent of breast cancer patients of the age groups 21 to 50 and 51 to 70 years are dead within 11.5 and 7.2 years after primary therapy, respectively (Mueller et al. 1978); the corresponding values for the New Mexico breast cancer patients are 12.1 and 9.7 years (Key

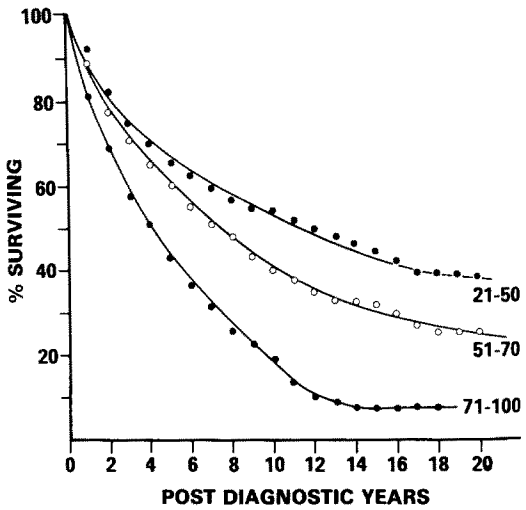

Fig. 3. Survival curves for breast cancer patients of three age groups. The survival curves for the three different age groups show that after treatment, younger breast cancer patients survive longer than older ones. Following diagnosis and treatment, 50% of the youngest, middle, and oldest group were dead after 13, 8, and 5 years, respectively. Age groups: 21 to 50 (1,223 patients); 51 to 70 (1,556 patients); 71 to 100 (779 patients). From Mueller et al. (1978) with kind permission

1979). In the group over 70 years of age, even in patients with stage I of breast cancer, 50% have died of their disease within 6 years and 90% by 12 years. However, literature data on the prognosis of breast cancer in relation to the age of the patient are inconsistent. Some authors report a better prognosis for premenopausal and other authors for postmenopausal breast cancer patients; some investigators find no age-related difference (Bässler 1978; Vorherr 1980). Ultimately almost all breast cancer patients (90 to 95%) die from their disease (Baum 1976; Mueller et al. 1978). This signifies that upon initial treatment in almost all patients there is some local and systemic spread which in many cases cannot be recognized by present methods. Depending on the amount of cancer spread, tumor pathobiology (histologic type and grade), and efficiency of the local and systemic host immune response, in some patients the metastases are held in a more or less dormant state whereas in others a more rapid progression occurs. However, sooner or later in most patients, the body defense breaks down and/or tumor cell aggressiveness becomes greatly enhanced, so that clinically advanced disease can be diagnosed. In 30 to 60% of these patients, short temporary control of tumor growth can be achieved by cytotoxic polychemotherapy or endocrine treatment. Nevertheless, even in patients responding with remission, death from the disease finally occurs. Myers stated in 1973: "Apparently reduction of the excess risk of dying of breast cancer even for localized disease awaits some new therapeutic methods". Helman summed it up in 1977: "For 80 years we have known about hormonal effects in breast cancer. The radiotherapists have had nearly 70 years of permutated use of irradiation for this disease. What has been the result? – still no cure and no increased survival. Worse still, doubt lingers whether we cure any of these patients, except possibly those with minute or occult disease".

Breast Cancer Survival in Comparison to Life Expectancy of Other Malignancies

Despite the definition of breast cancer as an inevitably fatal disease, which may evoke an unjustifiably negative attitude toward the proper treatment of the disease, breast cancer patients still have a much better life expectancy than women with carcinomas of ovary, stomach, and lung (Table 2). For cancers of endometrium, cervix, ovary, colon, stomach, and lung the patients' fate is decided within the first 5 years after primary treatment. Those patients who are alive after 5 years have a very high chance to be cured because their 10-, 15-, and 20-year survival rates are similar to those of 5 years. This is in contrast to the steadily declining survival rates of breast cancer indicating a difference in tumor pathobiology. The very low 5-year survival rates of stomach and lung cancer are indicative of the aggressiveness of these carcinomas. Whereas the pathobiology in regard to early spread may be similar for breast, stomach, and lung cancer, it apparently is dissimilar in regard to the behavior of disseminated tumor cells. Disseminated breast can-

Table 2. Survival rates for white females with cancers of breast, endometrium, cervix, ovary, colon, stomach, and lung for all ages and all stages of disease

Cancer site	Survival in percent			
	5 years	10 years	15 years	20 years
Breast	62	49	44	38
Endometrium	72	69	69	64
Cervix	58	53	50	50
Ovary	31	28	27	26
Colon	45	41	41	37
Stomach	13	12	9	8
Lung	12	9	7	–

Data from Surgical Rounds, 1978 and Cancer Patient Survival Report, 1976. From these reports it is not clear whether the deaths are due to the malignant disease alone, or to cancer and other noncancerous causes. For breast cancer, deaths are mainly the consequence of the disease and only 7 and 9% of deaths 10 and 20 years after primary treatment are due to other causes (Fig. 1)

cer cells may remain dormant for 10 to 20 years before they suddenly begin to rapidly proliferate causing clinically recurrent disease. Because 5 years after primary therapy almost all patients with stomach and colon cancer have died, it becomes obvious that disseminated tumor cells do not remain dormant but show rapid progression. At this time it is not possible to define environmental, immunological, hormonal, and biochemical factors which determine tumor cell dormancy or progression of breast cancer and other malignancies.

Future Goals: Prevention or Eradication of Breast Cancer

Prevention of Breast Cancer

Data of some recent reports indicate that breast cancer can be considered as an inevitably lethal disease and the question arises, what can be done to remedy this situation, i.e., to avert certain death due to breast cancer? Unfortunately, at present no knowledge exists how to prevent the development of breast cancer (Fig. 4). Reliable tests for chemical, hormonal, viral or other factors possibly contributing to the development of breast cancer, which might be of use for its prevention are not known; the exception being bilateral prophylactic mastectomy in some women with an extraordinarily high risk of breast cancer. For example, a 19-year old female had a bilateral subcutaneous mastectomy with simultaneous reconstruction because her mother, a maternal aunt, and her maternal grandmother had died from breast cancer, and her 2 sisters had already developed the disease at ages 22 and 29 (Lynch et al. 1976). Even though of great potential importance for the prevention of breast cancer, at present, however, most treatment centers do not recommend prophylactic mastectomy for patients at extremely high risk of breast cancer.

Eradication of Breast Cancer

The relative ineffectiveness of present treatment modalities of breast cancer and the poor long-term results of survival seem to be contrasted by the misconception that when at the time of mastectomy no regional lymph node or systemic metastasis can be diagnosed, it is generally assumed that a large number of these patients will be "cured". Obviously this is not so, because for almost all patients there is no cure of breast cancer, but only extension of life. Although the therapy of breast cancer should combine local and systemic treatment, presently, no treatment modality allows us to eradicate spread of cancer cells completely beyond the reach of the knife at the time of mastectomy. Recently, postoperative, adjuvant cytotoxic chemotherapy alone or in combination with immunotherapy (BCG) has been used in an attempt to kill cancer cells which had spread regionally and systemically, or may have spread during mastectomy. Death in breast cancer usually results from micrometastatic dissemination to bone, lung, liver, and brain which has settled the outcome before primary treatment is given (Edelstyn and MacRae 1979). Therefore, postoperative chemotherapy has been recommended for patients with axillary metastasis because in these patients also systemic spread exists. Preliminary data show modest short-term results in reducing

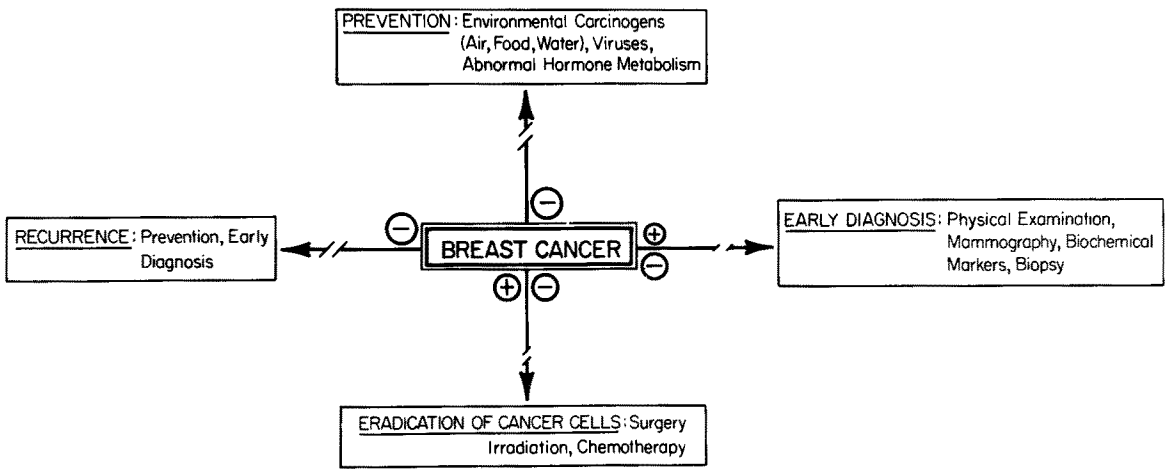

Fig. 4. The problem of prevention, early diagnosis, and eradication of breast cancer. No means for prevention of breast cancer is known at this time. Even if diagnosed at a relatively early stage, metastasis may already exist and eradication of cancer is impossible. Early breast cancer spread cannot be recognized, and in such patients the disease is ultimately fatal because recurrence cannot be prevented by present treatment modalities. When relapse of breast cancer can be clinically diagnosed, the disease is relatively far advanced and despite therapy death is always impending. ⊖Not possible; ⊕Possible. From Vorherr (1980)

the incidence of recurrent disease in premenopausal (Ahmann et al. 1978; Bonadonna 1978; Stoll 1978) but not in postmenopausal patients which are the majority in need of adjuvant chemotherapy. In contrast, other investigators (Table 3) observed that menopausal status had no bearing on the outcome of treatment; one investigator (Bonadonna, Table 3) changed his opinion as to menopausal status and effectiveness of chemotherapy. In one report (Jungi and Senn, 1978) postoperative chemotherapy was only beneficial in patients without axillary metastasis. On the other hand, adjuvant chemotherapy fails more often when it is needed most, namely in patients with extensive axillary metastasis (Wendt 1979; Table 3). In view of the value of postoperative chemotherapy, a much longer follow-up is needed to see if these early encouraging results are sustained (Edelstyn and MacRae 1979); long-term observations may show no benefit at all. Despite a decrease in the relapse rate by adjuvant chemotherapy, the overall survival remained unaffected (Dent 1977); also Velanta and Levý (1977) and Carter (1978) observed no difference in survival of patients with and without adjuvant chemotherapy. "Chemoprophylaxis has not proved itself useful or safe" (del Regato 1977). Sauer et al. (1979) stated: "There is no well defined group of patients with primary breast cancer which benefits from combination chemotherapy as an adjuvant treatment, since, at present, the effect of this therapy in respect to the duration of disease-free interval, survival, and possible long-term side effects remain unknown". Powles et al. (1980) reported that chemotherapy failed to prolong survival in patients with metastatic breast cancer; in some patients survival may even have been shortened. "We are far from convinced that adjuvant therapy has anything to offer" (Blamey 1979). Therefore, the danger exists that long-term results may show that chemotherapy actually decreases survival rates due to its weakening effect on the immune response. Moreover, the danger exists that chemotherapy induces cancer of other organs; especially the development of acute leukemia has been associated with adjuvant chemotherapy (Chabner 1977; Crowther 1979). Accordingly, it is not only necessary to obtain means of detection of micrometastasis but also to apply treatment with effective agents. Although progress in the systemic therapy of advanced breast cancer, involving a greatly increased complexity of treatment modalities has resulted in an extension of life, the overall benefits are modest and death is almost always impending. Even though, treatment of metastatic breast cancer with cytotoxic polychemotherapy achieves remission rates of 60 to 70% with an average duration of 15 months and a median survival of 20 months (average survival of nonresponders: 7 months) (Brennan and McMahan 1976;

Table 3. Adjuvant chemotherapy of breast cancer in patients with axillary metastasis

Author	Agent	Incidence of recurrent disease: %						Time of observation (months)	Comment
		Treatment group			Control group				
		All Patients	Premenopausal	Postmenopausal	All Patients	Premenopausal	Postmenopausal		
Ahmann et al. 1978	L-Pam	31 (40[b])	42	25	–	–	–	20	No controls; CFP is more effective than L-Pam only in premenopausal patients
	CFP	21 (32[b])	15	24	–	–	–		
Bonadonna 1978	CMF	34.4	25	43.8	52.7	59.2	47.6	48	"Most of the improvement is in the premenopausal group"
Bonadonna et al. 1976	CMF	5.3 (3.6[a]) (8.8[b])	–	–	24 (17[a]) (40.7[b])	–	–	27	"There is no difference in the incidence of relapse between premenopausal and postmenopausal patients"
Bonadonna et al. 1977	CMF	26.3 (19.1[a]) (41.5[b])	12.7 (4[a]) (37[b])	35.2 (33[a]) (44[b])	45.7 (37.9[a]) (64.9[b])	46.1 (33[a]) (90[b])	42 (41[a]) (46[b])	36	Significant improvement only in premenopausal patients: no difference in survival

Table 3 (continued)

Author	Agent	Incidence of recurrent disease: %						Time of observation (months)	Comment
		Treatment group			Control group				
		All Patients	Pre-menopausal	Post-menopausal	All Patients	Pre-menopausal	Post-menopausal		
Buzdar et al. 1979	FDC + BCG	22	29 (35[b])	17 (21[b])	45	54 (63[b])	42 (52[b])	36	Prolongation of disease-free interval irrespective of menopausal status
Caprini et al. 1980	L-Pam CFP CFP + BCG	31.4 13.4 13.2	25 14.3 13.6	33.3 13 13	– – –	– – –	– – –	24 21 19	No controls; ... "statistically significant differences in favor of Polychemotherapy in the postmenopausal group ($P \leqq .017$)"
Carey et al. 1979	CMFVP	(60[b])	(48[b])	(59[b])	(67[b])	–	–	34	No own controls (control value from Bonadonna); significant improvement in premenopausal patients only
Cooper et al. 1979	CMFVP	(32[b])	—	—	—	—	—	96	No controls; no difference in treatment response between premenopausal and postmenopausal patients
Crowther 1979	Me CMF CMFV	50 7 31.4	– – –	– – –	30 30 48.5	– – –	– – –	36 36 30	With CMF or CMFV significant improvement; "menopausal status had little bearing on the outcome of [CMFV] treatment"
Fisher et al. 1975	L-Pam	9.7	3 (0[a]) (8[b])	11 (3[a]) (18[b])	22	30 (17[a]) (42[b])	21 (0[a]) (36[b])	8–9	"The findings were [only] statistically significant for premenopausal women"
Jungi and Senn, 1978	LMF + BCG	12 (15[a]) (27.8[b])	25	13.3	23.3 (22.9[a]) (50[b])	31	33.3	20	No statistical data evaluation; postmenopausal patients respond better
Nissen-Meyer 1979	C	41.5 (44[a]) (60[b])	38	43	49.2 (67[a]) (72[b])	47	53	120	"There seems to be no difference" in the treatment response between premenopausal and postmenopausal patients
Rivkin et al. 1979	Me CMFVP	28.1 10.2	– –	– –	– –	– –	– –	24	No controls; CMFVP is superior to Me; "Disease-free survival with CMFVP has been equal in pre- and postmenopausal women"

[a] 1–3 axillary lymph nodes affected
[b] ≥4 axillary lymph nodes affected

BCG = BCG vaccine; C = Cyclophosphamide; CFP = Cyclophosphamide-fluorouracil-phenylalanine mustard; CMF = Cyclophosphamide-methotrexate-fluorouracil; CMFV = Cyclophosphamide-methotrexate-fluorouracil-vincristine; CMFVP = Cyclophosphamide-methotrexate-fluorouracil-vincristine-prednisone; FDC = Fluorouracil-doxorubicin-cyclophosphamide; LMF = Leukeran-methotrexate-fluorouracil; L-Pam = L phenylalanine mustard; Me = Melphalan. Note: L-Pam is chemically identical to Me

Haskell 1977; Young 1977; Aisner 1978; Rainey et al. 1979), the quality of life changes often for the worse and no patient can be cured. Successful anticancer therapy requires development of agents with selective toxicity against cancer cells and without damage to normal cells. Perhaps in the future, combination of immunologic with endocrine and chemical approaches may be utilized more effectively for the cure of breast cancer. Effective treatment for systemic breast cancer is urgently needed.

Early Diagnosis of Breast Cancer and Prolongation of Survival

Since no therapeutic means are available to destroy all cancer cells which have spread from the primary tumor into regional lymph nodes and in the circulation, the only alternative seems to lie in the very early diagnosis of breast cancer (Fig. 4). At the present time, intensive clinical, x-ray, and laboratory screening efforts are being made to detect breast cancer very early. In some patients, breast cancer can be detected by mammography 2 to 3 years before a mass becomes palpable. Thus, mammography has been accredited with the reduction of breast cancer mortality by 10 to 30% (Helman 1977; Letton et al. 1977). However, it remains to be shown that mammography improves long-term survival of breast cancer (Stark 1976). Even though 20 to 30% of patients with early breast cancer seem to have a normal life expectancy (Baum 1976), for the vast majority of patients, breast cancer treatment can only prolong the time of survival to a more or less extent.

Conclusion

The pathobiology of breast cancer is different among patients and therefore the course of the disease varies greatly. An even more striking difference is observed when comparing the pathobiology of breast cancer with that of other malignancies. Even though the stage of breast cancer at the time of clinical diagnosis and therapy allows prognostic conclusions, in some patients with small tumors and undiagnosable systemic spread, death from progressive disease occurs within a relatively short time after mastectomy. In these patients, ageing, changes in immune status, and endocrine milieu may play a role. On the other hand, a clinically disease-free interval of 5 or more years after primary therapy does not allow the use of the term "cure".

At present, no methodology exists which can effectively cope with the problem of breast cancer, and it appears that progress in the diagnosis and treatment of breast cancer can be achieved only by development of novel approaches such as diagnosis before systemic spread has occurred or by availability of efficient chemotherapy to kill all disseminated cancer cells. At this time the only alternative for prolongation of life is the early diagnosis of breast cancer by mammography, xerography, aspiration biopsy and thermography, even though carcinoma in situ and more so small invasive tumors of less than 0.1 to 0.3 cm in diameter may cause systemic spread. Present tests of biochemical markers, antigens, and antibodies cannot define patients at risk or those with early breast cancer. Already in 1951, MacDonald wrote: "«Early diagnosis» and «prompt treatment» are stock phrases which epitomize current efforts toward the clinical control of cancer"; thirty years later the "control" of breast cancer has not yet come through.

References

Adair F, Berg J, Joubert L, Robbins GF (1974) Long-term follow-up of breast cancer patients: The 30-year report. Cancer 33:1145–1150

Ahmann DL, Scanlon PW, Bisel HF, Edmonson JH, Frytak S, Payne WS, O'Fallon JR, Hahn RG, Ingle JN, O'Connell MJ, Rubin J (1978) Repeated adjuvant chemotherapy with phenylalanine mustard or 5-fluorouracil, cyclophosphamide, and prednisone with or without radiation, after mastectomy for breast cancer. Lancet 1:893–896

Aisner J (1978) Specialty rounds. Management of disseminated carcinoma of the breast. Am J Med Sci 275:4–16

Allan E (1978) Breast cancer: The error of the exponential. Eur J Cancer 14:1389–1393

Ashikari R, Hajdu SI, Robbins GF (1971) Intraductal carcinoma of the breast (1960–1969). Cancer 28:1182–1187

Asire AJ, Shambaugh EM (1976) Cancer of the breast. In: Axtell LM, Asire AJ, Myers MH (eds) Cancer patient survival report. Number 5. DHEW Publication No. (NIH) 77-992. US Dept. of Health, Education, and Welfare, National Cancer Institute, Bethesda, Maryland, p 157

Bässler R (1978) Pathologie der Brustdrüse. Springer, Berlin Heidelberg New York

Baum M (1976) The curability of breast cancer. Br Med J 1:439–442

Black MM (1970) Human breast carcinoma. Part I. Clinical considerations. NY State J Med 70:863–868

Blamey RW (1979) Adjuvant chemotherapy for breast cancer. Lancet 2:305

Bonadonna G (1978) Bonadonna's results at four years. Still big improvement for CMF group. Cancer Lett 4 (No 47):4

Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, De Lena M, Tancini G, Bajetta E, Musumeci R, Veronesi U (1976) Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405–410

Bonadonna G, Rossi A, Valagussa P, Banfi A, Veronesi U (1977) The CMF program for operable breast cancer with positive axillary nodes. Cancer 39:2904–2915

Bond WH (1968) The influence of various treatments on survival rates in cancer of the breast. In: Jarrett AS (ed) The treatment of carcinoma of the breast. Syntex Pharmaceuticals Ltd., Maidenhead, p 24

Brennan MJ, McMahan CA (1976) Analysis of recent breast cancer treatment studies. In: Homburger F (ed) The physiopathology

of cancer, Vol 2, 3rd edn. Karger, Basel München Paris London New York Sydney, p 182
Brinkley D, Haybittle JL (1968) A 15-year follow-up study of patients treated for carcinoma of the breast. Br J Radiol 41:215–221
Brinkley D, Haybittle JL (1975) The curability of breast cancer. Lancet 2:95–97
Burnet FM (1977) Morphogenesis and cancer. Med J Aust 1:5–9
Buzdar AU, Blumenschein GR, Gutterman JU, Tashima CK, Hortobagyi GN, Smith TL, Campos LT, Wheeler WL, Hersh EM, Freireich EJ, Gehan EA (1979) Postoperative adjuvant chemotherapy with fluorouracil, doxorubicin, cyclophosphamide, and BCG vaccine. A follow-up report. JAMA 242:1509–1513
Campos JL (1972) Observations on the mortality from carcinoma of the breast. Br J Radiol 45:31–38
Cancer Patient Survival Report (1976) Number 5. DHEW Publication No. (NIH) 77–992 Axtell LM, Asire AJ, Myers MH (eds). U.S. Dept. of Health, Education, and Welfare, National Cancer Institute, Bethesda, Maryland
Caprini JA, Oviedo MA, Cunningham MP, Cohen E, Trueheart RS, Khandekar JD, Scanlon EF (1980) Adjuvant chemotherapy for stage II and III breast carcinoma. JAMA 244:243–246
Carbone PP (1977) The estrogen receptor test as aid to breast cancer treatment. JAMA 237:157
Carey RW, Sohier WD, Kaufman S, Weitzman SA, Kelley RM, Lew RA, Halpern E (1979) 5-drug adjuvant chemotherapy for breast cancer. Cancer 44:35–41
Carter SK (1978) Adjuvant chemotherapy in breast cancer: Critique and perspectives. Cancer Chemother Pharmacol 1:187–195
Chabner BA (1977) Second neoplasm – A complication of cancer chemotherapy. N Engl J Med 297:213–214
Cooper RG, Holland JF, Glidewell O (1979) Adjuvant chemotherapy of breast cancer. Cancer 44:793–798
Crowther D (1979) Controlled adjuvant chemotherapy trials for breast cancer in the United Kingdom. In: Jones SE, Salmon SE (eds) Adjuvant therapy of cancer II. Grune & Stratton, New York, p 237
del Regato, JA (1977) Cancer of the breast. JAMA 238:2407–2410
Dent DM (1977) Adjuvant chemotherapy for breast cancer. S Afr Med J 52:714–716
Devitt JE (1965) The significance of regional lymph node metastases in breast carcinoma. Can Med Assoc J 93:289–293
Edelstyn GA (1979) Personal communication
Edelstyn GA, MacRae KD (1979) Trials of adjuvant chemotherapy in breast cancer. Lancet 1:324
Feinleib M, Garrison RJ (1969) Interpretation of the vital statistics of breast cancer. Cancer 24:1109–1116
Fidler IJ, Kripke ML (1980) Tumor cell antigenicity, host immunity, and cancer metastasis. Cancer Immunol Immunother 7:201–205
Fisher B, Carbone P, Economou SG, Frelick R, Glass A, Lerner H, Redmond C, Zelen M, Band P, Katrych DL, Wolmark N, Fisher ER (1975) l-Phenylalanine mustard (L-Pam) in the management of primary breast cancer. N Engl J Med 292:117–122
Fox MS (1979) On the diagnosis and treatment of breast cancer. JAMA 241:489–494
Friedell GH (Primary Therapy of Breast Cancer Study Group) (1978) Identification of breast cancer patients with high risk of early recurrence after radical mastectomy. Cancer 42:2809–2826
Haskell CM (1977) Management of metastatic breast cancer. Med Clin North Am 61:967–978
Helman P (1977) Whither breast cancer? Report on the inaugural meeting of the national breast cancer group. S Afr Med J 52:711–713
Jungi WF, Senn HJ (1978) Prognoseverbesserung durch adjuvante postoperative Chemotherapie des operierten Mammakarzinoms. In: Schmähl D (ed) Behandlung und Nachbehandlung des Mammakarzinoms, Vol 2. Thieme, Stuttgart, p 155
Key C (1979) Data New Mexico Tumor Registry. Personal communication
Leis HP Jr (1977) The diagnosis of breast cancer. CA-Ca J Clin 27:(No 4), 209–232
Letton AH, Wilson JP, Mason EM (1977) The value of breast screening in women less than fifty years of age. Cancer 40:1–3
Lynch HT, Guirgis H, Brodkey F, Maloney K, Lynch PM, Rankin L, Lynch J (1976) Early age of onset in familial breast cancer. Genetic and cancer control implications. Arch Surg 111:126–131
MacDonald I (1951) Biological predeterminism in human cancer. Surg Gynecol Obstet 92:443–452
McKinnon NE (1954) Control of cancer mortality, Lancet 1:251–254
Miller DG (1976) The early diagnosis of cancer. In: Homburger F (ed) The physiopathology of cancer, Vol 2, 3rd edn. Karger, Basel München Paris London New York Sydney, p 5
Millis RR, Thynne GSJ (1975) In situ intraduct carcinoma of the breast: A long term follow-up study. Br J Surg 62:957–962
Moskowitz M (1977) Screening for breast cancer. JAMA 238:213
Moskowitz M (1979) Personal communication
Mueller CB, Ames F (1978) Bilateral carcinoma of the breast: Frequency and mortality. Can J Surg 21:459–465
Mueller CB, Ames F, Anderson GD (1978) Breast cancer in 3,558 women: Age as a significant determinant in the rate of dying and causes of death. Surgery 83:123–132
Myers MH (1973) Breast cancer survival over three decades. Recent Res Cancer Res 42:87–91
Nissen-Meyer R (1979) One short chemotherapy course in primary breast cancer: 12-year follow-up in series 1 of the Scandinavian adjuvant chemotherapy study group. In: Jones SE, Salmon SE (eds) Adjuvant therapy of cancer II. Grune & Stratton, New York, p 207
Ozzello L, Sanpitak P (1970) Epithelial-stromal junction of intraductal carcinoma of the breast. Cancer 26:1186–1198
Powles TJ, Smith IE, Ford HT, Coombes RC, Jones JM, Gazet J-C (1980) Failure of chemotherapy to prolong survival in a group of patients with metastatic breast cancer. Lancet 1:580–582
Rainey JM, Jones SE, Salmon SE (1979) Combination chemotherapy for advanced breast cancer utilizing vincristine, adriamycin, and cyclophosphamide (VAC). Cancer 43:66–71
Rivkin S, Glucksberg H, Rasmussen S (1979) Adjuvant chemotherapy in stage II breast cancer. Proc Am Assoc Cancer Res 20:353
Sauer H, Jehn U, Wilmanns W (1979) Zum gegenwärtigen Stand der Internistischen Therapie des Mammacarcinoms. II. Adjuvante Chemotherapie, palliative Polychemotherapie, Chemoimmuntherapie – Stellenwert und Ergebnisse. Klin Wochenschr 57:921–926
Seidman H, Silverberg E, Holleb AI (1976) Cancer statistics, 1976. A comparison of white and black populations. CA-Ca J Clin 26:(No 1) 2–29
Shapiro S, Strax P, Venet L, Fink R (1968) The search for risk factors in breast cancer. Am J Public Health 58:820–835
Silverberg E (1977) Cancer statistics, 1977. CA-Ca J Clin 27:(No 1) 26–41
Silverberg E (1979) Cancer statistics, 1979. CA-Ca J Clin 29:(No 1) 6–21
Slack NH, Blumenson LE, Bross IDJ (1969) Therapeutic implica-

tions from a mathematical model characterizing the course of breast cancer. Cancer 24:960–971
Stark AM (1976) Critical appraisal of new early detection techniques. In: Heuson JC, Mattheiem WH, Rozencweig M (eds) Breast cancer: Trends in research and treatment. Raven Press, New York, p 279
Stoll BA (1978) Ovarian function and adjuvant chemotherapy for breast cancer. Lancet 1:1159
Surgical Rounds (1978) Cancer survival among women. Surgical Rounds 1:(No 3) 70–72
Taylor SG IV (1978) The systemic therapy of breast cancer. Ration Drug Ther 12:1–7
Valenta J, Levý J (1977) Combination of regional chemotherapy and mastectomy in the treatment of carcinoma of the breast. Five-year results. Neoplasma 24:415–420
Vorherr H (1980) Breast Cancer. Epidemiology, endocrinology, biochemistry and pathobiology. Urban & Schwarzenberg, Baltimore, Maryland
Wendt AG, Mill RC, Heusinkveld RS, Giordano GF, Jackson RA, Salmon SE, Jones SE (1979) Adjuvant treatment of breast cancer with adriamycin-cyclophosphamide +/− radiotherapy. Program and abstracts of the 2nd International Conference on the Adjuvant Therapy of Cancer, March 28–31, 1979. Tucson AZ University of Arizona Cancer Center (Tucson AZ), p 56
Westbrook KC, Gallager HS (1975) Intraductal carcinoma of the breast. A comparative study. Am J Surg 130:667–670
Young RC (1977) Perspectives in the treatment of breast cancer: 1976. Ann Intern Med 86:784–798

Received August 25, 1980
Accepted October 27, 1980

Prof. H. Vorherr, M.D.
The University of New Mexico
School of Medicine
Depts. of Obstetrics-Gynecology
and of Pharmacology
915 Stanford Drive N.E.
Albuquerque, New Mexico 87131
USA