

Skin test reactivity in patients suffering from lung and breast cancer

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Mast cells and histamine-mediated reactions may be altered in patients with cancer. In an attempt to characterize the possible skin defects in patients with cancer, we tested 22 patients suffering from lung cancers, 30 from breast cancers, and 30 age-matched normal individuals, using several compounds, in investigating the pathophysiology of the skin response. Histamine hydrochloride (10 and 100 mg/ml) and codeine phosphate (9%) were tested by prick test. Substance P (50 and 500 ng per injection site), phentolamine (20 µg per injection site), and carbachol (1 µg per injection site) were tested by intradermal skin tests. Skin mast cells were also microscopically examined in 10 patients with lung cancer, five with breast cancer, and 10 normal subjects. The mean wheal sizes induced by all the tested substances were similar in patients with cancer and chronic bronchitis and in normal individuals. The flare to histamine, codeine phosphate, and substance P was completely abolished in 7/22 patients with lung cancer, but the lack of flare was not related to the age of the patients, nor to the staging of cancer, nor to metastasis. The mean numbers of alcian blue-stained or toluidine blue-stained positive mast cells were similar in normal subjects and in subjects with cancer. This study does not confirm the skin hyporeactivity of patients with cancer. (J ALLERGY CLIN IMMUNOL 1991;87:1066-72.)

The inverse relationship between cancer and allergy is suggested by some epidemiologic studies,¹ but the reasons are not completely clear and may combine a difference in immune response between allergic individuals and patients with cancer, a mast cell abnormal reactivity in patients with cancer, and/or a decreased histamine skin reactivity in patients with cancer. The increase in mast cell numbers in tumor tissues has already been observed by Paul Ehrlich² and although this observation has been ignored for many decades, recent studies have demonstrated that some neoplastic tissues are infiltrated by mast cells.³⁻⁵ In the National Surgical Adjuvant Breast and

Abbreviations used

NSCLC: Nonsmall cell lung cancer
SCLC: Small cell lung cancer
TNM: Tumor, node, metastasis
WHO: World Health Organization

Bowel Project (United States), the number of mast cells was related to the survival rate of patients suffering from rectal cancer, a high number being associated with a poor prognosis.⁵ In small cell lung carcinoma, the tumor is highly infiltrated by mast cells (Bousquet J. Unpublished observation) and the cell line allowing the longer in vitro coculture of human mast cells is obtained from SCLC.⁶ Animal studies have confirmed a mast cell abnormality in cancer,⁷ and these cells might be involved in angiogenesis and metastasis.⁸ These studies appear to indicate that mast cells may be abnormal in numbers and function in patients suffering from cancer. In another study, Burtin et al.⁹ have found that histamine skin tests were depressed in patients suffering from various advanced cancers and that the skin reactivity returned to normal or subnormal levels in patients who underwent a carcinologic treatment.

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TABLE I. Characteristics of patients suffering from lung carcinoma

Patient No.	Age (yr)	Histology	TNM classification		WHO classification
			Anatomic classification	Stage	
1	71	SCLC<	T4N3M1	IV	3
2	69	SCLC	T3N3M1	IV	3
3	66	NSCLC	T4N2M0	IIIb	1
4	71	NSCLC	T2N2M0	IIIa	1
5	33	NSCLC	T4N2M0	IIIb	3
6	59	NSCLC	T4N3M0	IIIb	2
7	52	SCLC	T3N1M0	IIIa	Impossible to determine
8	73	SCLC	T3N3M0	IIIb	2
9	49	NSCLC	T3N1M0	IIIa	1
10	50	NSCLC	T3N1M0	II	2
11	67	NSCLC	T2N1M0	I	0
12	66	NSCLC	T2N0M0	IIIb	1
13	45	SCLC	T3N3M0	IV	2
14	51	NSCLC	T3N3M1	IV	1
15	67	NSCLC-SCLC	T3N2M1	IV	3
16	60	SCLC	T3N2M1	IV	2
17	60	NSCLC	T4N2M1	IV	Impossible to determine
18	66	NSCLC	T3N2M1	IV	2
19	72	NSCLC	T3N2M1	IV	3
20	71	NSCLC	T3N2M0	IIIa	Impossible to determine
21	60	NSCLC	T3N2M0	IIIa	1
22	63	NSCLC	T3N2M0	IIIa	2

Allergens and nonspecific agents induce skin reactions characterized by a wheal and a flare. The wheal is due to leakage of capillaries leading to plasma extravasation, whereas the flare is related to a neurovascular response by an axon reflex in which substance P appears to be one of the neurotransmitters.^{10, 11} The wheal-and-flare reaction can be induced by codeine phosphate, a mast cell secretagogue investigating mast cell releasability,¹² histamine exploring the target organ,¹³ phentolamine, an α -adrenergic agonist, and acetylcholine or carbachol, vasodilating agents, by their parasympathomimetic activity.^{14, 15}

With all these compounds in the same study, it is possible to investigate many components of the wheal-and-flare reaction as well as skin mast cell reactivity.^{16, 17}

We attempted (1) to study the skin reactivity of patients with lung and breast cancers, (2) to test if patients with advanced cancer have a different skin reactivity from patients with early stages or if the histologic type of the cancer might influence skin tests, (3) to characterize the components of the wheal-and-flare reaction that might be abnormal, and (4) to characterize skin mast cells in patients with cancer. We studied the skin response induced by histamine, co-

deine phosphate, substance P, phentolamine, and carbachol in 22 patients suffering from lung cancer, 30 having a breast cancer, and 30 age-matched normal individuals. Since mast cells may be abnormal in patients suffering from cancer, we also examined skin mast cells in 15 patients with cancer and 10 normal individuals.

MATERIAL AND METHODS

Patients

Thirty normal individuals, ranging in age from 35 to 70 years (mean $\pm$ SD, 51.2 $\pm$ 9.5 years), were carefully selected and were found to be apparently free from pathologic conditions that are known to alter the skin response.¹⁰ Among these individuals, 12 were smokers.

Twenty-two patients suffering from lung cancer were only investigated when the disease was confirmed by histologic examination, the cancer staged according to the new TNM staging classification,^{18, 19} and performance index was quoted according to WHO²⁰ (Table I). Patients ranged in age from 33 to 73 years (mean $\pm$ SD, 62.2 $\pm$ 9.8 years).

Thirty patients suffering from breast cancer were only investigated when the disease was confirmed by histologic examination and the cancer staged according to the classification of Scarff and Hanley,²¹ Scarff and Toloni,²² and Bloom²³ (Table II). Patients ranged in age from 31 to 71 years (mean $\pm$ SD, 55.2 $\pm$ 11.2 years).

No patient with cancer who had received chemotherapy

TABLE II. Characteristics of patients suffering from breast carcinoma

Patient No.	Age (yr)	Histologic classification	Scarff ^{21, 22} and Bloom ²³ staging	Metastasis
1	68	Infiltrative carcinoma	II	0
2	64	Adenocarcinoma	II	0
3	64	Infiltrative carcinoma	—	0
4	56	Noninfiltrative carcinoma	—	0
5	51	Paget	—	0
6	43	Adenocarcinoma	I	0
7	74	Adenocarcinoma	II	0
8	70	Carcinoma	—	0
9	66	Infiltrative carcinoma	—	0
10	66	Adenocarcinoma	II	0
11	64	Adenocarcinoma	III	0
12	51	Infiltrative carcinoma	II	0
13	50	Adenocarcinoma	—	0
14	43	Adenocarcinoma	III	0
15	50	Adenocarcinoma	II	+
16	45	Infiltrative carcinoma	III	+
17	52	Invasive adenocarcinoma	II	+
18	30	Invasive adenocarcinoma	III	+
19	59	Invasive adenocarcinoma	III	+
20	68	Infiltrative carcinoma	—	+
21	49	Carcinoma	—	+
22	35	Adenocarcinoma	II	+
23	56	Adenocarcinoma	III	+
24	52	Invasive adenocarcinoma	III	+
25	62	Infiltrative carcinoma	III	+
26	42	Adenocarcinoma	II	+
27	62	Carcinoma	III	+
28	53	Invasive adenocarcinoma	III	+
29	39	Adenocarcinoma	—	+
30	42	Galactophoric adenocarcinoma	III	+

or radiation therapy was accepted into the study because these treatments might interfere with the results of performance of skin tests. In none of the patients was the weight loss >5%.

All subjects volunteered to participate in the study and gave their informed consent. None of the subjects tested had taken any drugs that might modify skin tests according to a study previously published.^{16, 24}

Methods

Histamine. Two concentrations of histamine dihydrochloride (Stallergènes Laboratories, Fresnes, France) were tested, 100 and 10 mg/ml. The shelf life of the extract was tested, and we found no decay activity during a period of 2 months.

Codeine phosphate. One strength of codeine phosphate (Stallergènes Laboratories) was tested, 9%. We also tested the shelf life of the extract and found no decay activity after a 2-month period.

Substance P. Two strengths of substance P (Calbiochem Laboratories, Basel, Switzerland) were tested, 50 and 500 ng per injection site. Every day of the test, a new dilution was made in saline.

Phentolamine. One strength of phentolamine (Ciba-Geigy Laboratories, Basel, Switzerland) was tested, 20 µg per injection site. Every day of the test, a new phentolamine ampule was used.

Carbachol. Only one strength of carbachol (Calbiochem) was tested, 1 µg per injection site. The extract was freshly prepared each test day.

Diluents. The diluents used to dilute tested substances were also tested, a 50% glycerol solution and a normal saline.

Skin tests

Phentolamine, carbachol, substance P, and saline were tested by intradermal skin tests according to the classic method.²⁵ Histamine, codeine phosphate, and the 50% gly-

TABLE III. Results of skin tests in patients suffering from cancer and in control subjects

	Control subjects	Breast cancer	Lung cancer
No. of subjects	30	30	20
Age (m $\pm$ SD) (yr)	51.2 $\pm$ 9.5	55.2 $\pm$ 11.2	
Histamine (100 mg/ml)			
Wheal	9.2 $\pm$ 2.7	8.5 $\pm$ 2.6	8.7 $\pm$ 3.1
Erythema	28.2 $\pm$ 8.2	31.2 $\pm$ 5.1	26.5 $\pm$ 5.5
Histamine (10 mg/ml)			
Wheal	5.2 $\pm$ 1.4	4.7 $\pm$ 1.0	4.8 $\pm$ 1.5
Erythema	20.7 $\pm$ 7.6	19.5 $\pm$ 8.7	19.8 $\pm$ 5.5
Codeine phosphate (9%)			
Wheal	6.4 $\pm$ 1.2	5.7 $\pm$ 1.2	6.2 $\pm$ 2.1
Erythema	17.9 $\pm$ 8.3	16.5 $\pm$ 5.5	16.5 $\pm$ 7.8
Substance P (500 ng)			
Wheal	14.9 $\pm$ 2.7	15.3 $\pm$ 4.8	14.2 $\pm$ 4.6
Erythema	34.8 $\pm$ 11.6	30.5 $\pm$ 9.4	33.5 $\pm$ 5.9
Substance P (50 ng)			
Wheal	12.4 $\pm$ 2.9	12.2 $\pm$ 2.6	11.2 $\pm$ 2.3
Erythema	31.2 $\pm$ 13.2	27.4 $\pm$ 11.0	26.2 $\pm$ 5.1
Carbachol			
Wheal	14.5 $\pm$ 3.6	14.0 $\pm$ 2.7	13.7 $\pm$ 3.2
Erythema	29.2 $\pm$ 9.9	27.7 $\pm$ 3.6	26.0 $\pm$ 5.1
Phentolamine			
Wheal	12.8 $\pm$ 3.6	12.9 $\pm$ 3.7	12.9 $\pm$ 3.2
Erythema	22.0 $\pm$ 5.3	20.4 $\pm$ 8.9	20.4 $\pm$ 9.6

m, Mean.

The erythema was only calculated in patients who presented a reaction.

The results are expressed in mean $\pm$ SD of the mean diameter of the reaction (millimeter).

erol solution were tested by modified prick tests according to a technique previously described in detail.²⁴ The wheal and the flare were recorded by the Scotch (3M, St. Paul, Minn.) tape technique 10 minutes after the performance of the test.

Skin mast cells

Skin mast cells were studied on biopsy specimens obtained on the ulnar surface of the arm by a 3 mm punch biopsy device. All mast cells of the surface of the punch biopsy specimen were enumerated after fixation by formalin or Carnoy's solution and staining by alcian blue/safranin or toluidine blue according to Marshall et al.²⁶ Results were listed as numbers of mast cells per biopsy specimen of 3 mm of diameter.

Study design

All subjects had the same skin test study with all substances described above. Moreover, 10 patients with lung cancer, five with breast cancer, and 10 normal subjects had a study of skin mast cells. The study was done within 2 months. Statistical analyses were performed with nonparametric tests (Mann-Whitney U test).

RESULTS

Wheal reaction

Diluents did not elicit any positive reaction. All patients and normal subjects had a positive wheal to all agents tested. The mean wheal sizes induced by all agents were similar and nonsignificantly different in normal individuals and patients suffering from lung or breast cancers (Table III). There was no difference in the wheal reaction when TNM or performance index according to WHO was considered for lung cancers or the Scarff and Hanley,²¹ Scarff and Toloni,²² or Bloom²³ classification or the TNM for the breast cancers.

Flare reaction

Diluents did not induce a noticeable flare. The most striking finding observed in this study is the complete absence of the flare reaction induced by histamine, codeine phosphate, and substance P in some individuals suffering from lung cancer, whereas it was present in most normal individuals and most subjects with breast cancer (Fig. 1). However, it was not possible

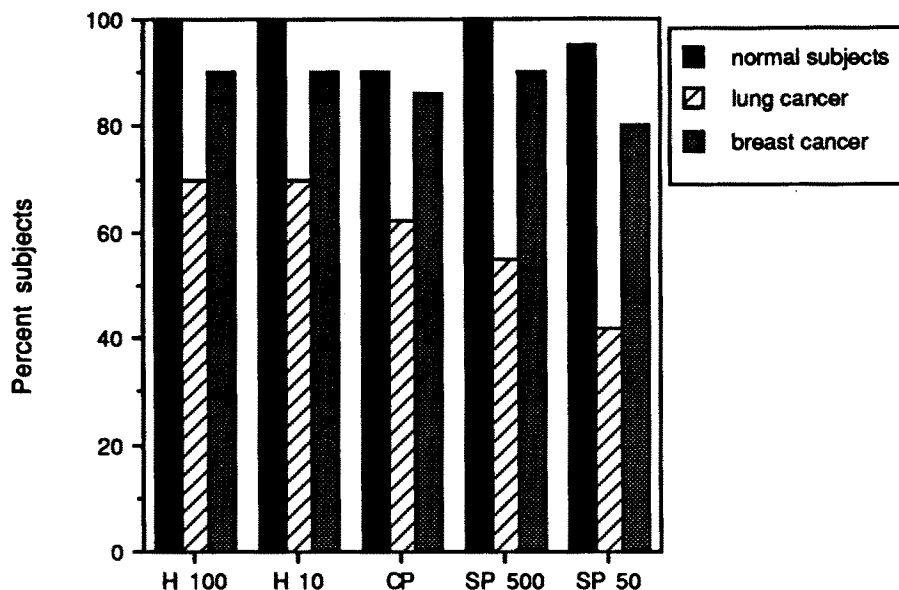


FIG. 1. Percentage of normal subjects and patients with cancer presenting a flare reaction with histamine dihydrochloride, 10 and 100 mg/ml (*H 10* and *H 100*), codeine phosphate (*CP*), and substance P (*SP*), 50 and 500 ng per injection site.

to correlate the absence of flare to the age of the patients or by WHO or TNM classifications. The histologic type of the cancer was also examined, and although the flare was present in 33.3% of SCLCs and 66.6% of NSCLCs, the difference was not significant. There was a concordance of the flare response induced by histamine, codeine phosphate, and substance P in 18/22 patients with lung cancer. The flare induced by carbachol or phentolamine was present in all subjects. When flare was present, the mean sizes of the flare responses were slightly decreased in patients with cancer by comparison to normal individuals (Table III).

Skin mast cells

The mean number of skin mast cells per 3 mm punch biopsy specimen was similar in patients with lung cancer (alcian blue-stained, 19.6 ± 6.8 cells; toluidine blue-stained, $22.1\% \pm 6.2\%$ cells), or breast cancer (alcian blue-stained, 20.5 ± 3.8 cells; toluidine blue-stained, 21.6 ± 6.5 cells) and normal individuals (alcian blue-stained, 21.8 ± 7.2 cells; toluidine blue-stained, 22.5 ± 9.2 cells) with both staining procedures.

DISCUSSION

This study demonstrated that patients suffering from lung or breast cancers have a normal wheal response but that some patients with lung cancer presented an abolition of the flare induced by histamine, codeine phosphate, and substance P. Results of the

flare response were independent from the stage of the cancer or age. Skin mast cells are in normal numbers in patients suffering from lung or breast cancers.

In this study, we examined several components of the skin reaction to assess whether there was a defect, since Burtin et al.⁹ had found a depressed skin reactivity to histamine, especially in patients with metastasis. We only studied patients suffering from lung or breast cancers for many reasons. We initially desired to use a rather homogeneous group of patients with cancer. Primary lung cancer is often related to a major cause, tobacco smoking,²⁷ that does not profoundly alter the skin reactivity,^{16, 28} and we had demonstrated previously that tobacco smoking did not affect skin reactivity, since patients with chronic bronchitis have a normal wheal-and-flare reaction to histamine or codeine phosphate (unpublished observation). We checked carefully that none of the patients had a weight loss >5%, since malnutrition might affect the skin reactivity. It was also possible to investigate fully patients with breast cancers, and although they are more heterogeneous in terms of histology, the results obtained are consistent with results of patients with lung cancer. We also carefully selected the normal individuals. Age represents an important factor to be considered since skin tests are modified by age.²⁹ Patients with lung cancer tended to be slightly older, but the results of this study were unlikely to be affected by age because (1) the ages in each group are distributed over four decades, (2) the flare response to carbachol and phentolamine is subnormal in patients

with lung cancer, and (3) the absence of flare was not age related. Finally, we carefully checked drugs administered to all subjects tested to avoid possible drug interference.^{10, 17}

It was found that patients with lung or breast cancer react with a normal or slightly decreased wheal with all compounds tested. The stage of the cancer, or metastasis, or its histologic classification do not alter the wheal reaction. These results may be surprising, since Burtin et al.⁹ observed that patients with cancer with metastasis had a decreased wheal to histamine. This discrepancy may be due to the techniques used or to the selection of patients. Both studies were carefully performed, but in the present study, we used prick testing for histamine and Burtin et al.⁹ used intradermal testing. The major differences in the results of both studies appeared to be the lack of wheal of patients of Burtin et al. for concentrations of histamine ranging from 0.1 to 2 µg/ml. According to the calculations of Dreborg et al.¹⁷ and Dreborg³⁰ between prick and intradermal tests, Burtin et al.⁹ used fivefold to tenfold lower concentrations of histamine, and we might have found differences with a lower concentration of histamine. Moreover, the selection of patients appears to be different. We tested non-malnourished adults having a lung or a breast cancer ranging in age from 31 to 71 years, whereas Burtin et al.⁹ tested patients as old as 97 years with various types of cancers being treated in a renutrition unit, half of these patients having malnutrition (weight loss >20% and/or prealbumin <0.15 gm/L). These two latter points may be of relevant importance in the discrepancies observed. Finally, all patients in the present study were tested before any carcinologic treatment was started.

As already observed by Burtin et al.,⁹ many patients suffering from lung cancer but only 3/30 patients suffering from breast cancer had a complete abolition of the flare response to histamine, codeine phosphate, and substance P, whereas the flare induced by phenolamine and carbachol was present in all patients. The defect appears to be linked to histamine receptors, since substance P is likely to mediate its flare response through the release of histamine by mast cells¹⁰ and both carbachol and phenolamine have different receptors. Therefore, this study highlights the links between histamine and substance P in the generation of the flare. The histologic type of cancer may be of relevant importance since only one third of patients with SCLC had a flare versus two thirds of patients with NSCLC. The difference between SCLC and NSCLC was not significant, but a low number of patients were tested. These data need further studies to be clarified, especially since SCLCs release neu-

ropeptides like bombesin that might alter the flare response.³¹ In contradistinction to Burtin et al.,⁹ we did not find differences according to TNM classification.

Skin mast cells are in normal numbers in patients with cancer and were found to have a normal reactivity, since the wheal induced by codeine phosphate, a mast cell secretagogue,¹⁶ is only slightly decreased in patients with cancer.

Skin tests of patients with lung or breast cancers demonstrate that the wheal is only slightly decreased whatever the histologic type or the TNM classification. This result differs from a previous study⁹ in which patients with metastasis had a decreased wheal response to histamine. The flare to histamine, codeine phosphate, and substance P is abolished in some patients with lung cancer, but this is not related to metastasis.

REFERENCES

1. Vena JE, Bona JR, Byers TE, Middleton E Jr, Swanson MK, Graham S. Allergy-related diseases and cancer: an inverse association. *Am J Epidemiol* 1985;122:66-74.
2. Ehrlich P. Contributions to theory and practice of histological staining. In: Himmelveit F, ed. *Collected papers of Paul Ehrlich*. London: Pergamon Press, 1916.
3. Fisher ER, Sass R, Watkins G, et al. Tissue mast cells in breast cancer. *Breast Cancer Res Treat* 1985;5:285-91.
4. Preslow TP, Keith EF, Cryar AK, et al. Heterogeneity and subcompartmentalization in the distribution of eosinophils in human colonic carcinoma. *Am J Pathol* 1984;116:207-13.
5. Fisher ER, Paik SM, Rockette H, et al. Prognostic significance of eosinophils and mast cells in rectal cancer: findings from the National Surgical Adjuvant Breast and Bowel project (protocol R-01). *Hum Pathol* 1989;20:159-63.
6. Hartzell S, Schulman ES, Brodsky I, Post TJ, Scavichio K, Krueger LJ. In vitro survival of human mast cells cocultivated with the "MACO" cell line. *Am Rev Respir Dis* 1989;139:A119.
7. Burtin C. Mast cells and tumor growth. *Ann Inst Pasteur Immunol* 1986;137D:289-94.
8. Crowle PK, Starkey JR. Mast cells and tumor-associated angiogenesis. In: Galli SJ, Austen KF, eds. *Mast cell and basophil differentiation and function in health and disease*. New York: Raven Press, 1989:307-15.
9. Burtin C, Noirot C, Giroux C, Scheimann P. Decreased response to intradermal histamine in cancer patients. *J ALLERGY CLIN IMMUNOL* 1986;78:83-9.
10. Foreman JC. Neuropeptides and the pathogenesis of allergy. *Allergy* 1987;42:1-11.
11. Lundblad L, Lundberg JM, Anggard A, Zetterstrom O. Capsaicin-sensitive nerves and the cutaneous allergy in man: possible involvement of sensory neuropeptides in the flare response. *Allergy* 1987;42:12-9.
12. Bousquet J, Djoukhar F, Hewitt B, Guérin B, Michel FB. Comparison of the stability of a mite and a pollen extract stored in normal conditions of use. *Clin Allergy* 1985;15:29-36.
13. Swain HH, Becker EL. Quantitative studies in skin testing. V. The whealing reactions of histamine and ragweed-pollen extract. *J ALLERGY* 1952;23:441-53.

14. Buckley CE, Lee KL, Burdick DS. Metacholine-induced cutaneous flare response: bivariate analysis of responsiveness and sensitivity. *J ALLERGY CLIN IMMUNOL* 1982;69:25-34.
15. Linbgrén BR, Brundin A, Andersson RGG. Inhibitory effects of clonidine on the allergen-induced wheal and flare reactions in patients with extrinsic asthma. *J ALLERGY CLIN IMMUNOL* 1987;79:941-6.
16. Bousquet J. In vivo methods for study of allergy: skin tests, techniques, and interpretation. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. *Allergy: principles and practice*. 3rd. ed. St. Louis: CV Mosby, 1988:419-36.
17. Dreborg S, Backman U, Basomba A, Bousquet J, Dieges P, Malling HJ. Skin tests used in type I allergy testing. Position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 1989;44(suppl 10):1-58.
18. Sobin LH, Hermanek P, Hutter RVP. *TNM classification of malignant tumors*. 4th ed. Geneva: UICC 1987.
19. Nelems B. Staging of lung cancer. *B C Med J* 1987;29:591-3.
20. World Health Organization. *The World Health Organization histological typing of the lung tumors*. 2nd ed. *Am J Clin Pathol* 1982;77:123-36.
21. Scarf RW, Hanley RS. Prognosis in carcinoma of the breast. *Lancet* 1938;2:582-3.
22. Scarf RW, Toloni H. *Histological typing of breast tumors*. Geneva: World Health Organization, 1986.
23. Bloom HJG. Value of histology in prognosis and treatment policy in breast cancer. *Front Radiat Ther Oncol* 1974;9:112-36.
24. Bousquet J, Calvayrac P, Guérin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of immunotherapy. *J ALLERGY CLIN IMMUNOL* 1985;76:734-44.
25. Norman PS. In vivo methods of study of allergy: skin and mucosal tests, techniques, and interpretation. In: Middleton E Jr, Reed CE, Ellis EF, eds. *Allergy: principles and practice*. 2nd. ed. St. Louis: CV Mosby, 1983:295-302.
26. Marshall JS, Ford GP, Bell EB. Formalin sensitivity and differential staining of mast cells in human dermis. *Br J Dermatol* 1987;117:29-36.
27. Stanley KE. Lung cancer and tobacco—a global problem. *Cancer Detect Prev* 1986;9:83-9.
28. Halonen M, Barbee RA, Lebowitz MD, Burrows B. An epidemiologic study of the interrelationships of total serum immunoglobulin E, allergy skin-test reactivity, and eosinophilia. *J ALLERGY CLIN IMMUNOL* 1982;69:221-8.
29. Skassa-Brociek W, Manderscheid J-C, Michel F-B, Bousquet J. Skin test reactivity to histamine from infancy to old age. *J ALLERGY CLIN IMMUNOL* 1987;80:711-6.
30. Dreborg S. The skin prick test, methodological studies, and clinical applications [Dissertation No. 239]. Linköping, Sweden: University of Linköping, 1987.
31. Carney DN, Cuttitta F, Moody DW, Minna JD. Selective stimulation of SCLC clonal growth by bombesin and gastrin-releasing peptide. *Cancer Res* 1987;47:821-5.