AN OVERVIEW OF BREAST CANCER

Adnan Ezzat, MB, BCh, FRCPC; Madras Raja, MD, MRCP(UK); Assem Rostom, FRCR; Ferdinand Zwaan, MD, PhD, MRCPath; Mohammed Akhtar, MD, FCAP, FRCPA; Shouki Bazarbashi, MB, BS; Stig Ingemansson, MD, PhD; Abdulmajeed Al-Abdulkareem, FRCSC

Breast cancer is a major health problem in many parts of the world. Its impact in Saudi Arabia will be more obvious when the national data is released from the National Cancer Registry (NCR) in the near future. It is the most common cancer referred to the King Faisal Specialist Hospital and Research Centre (KFSH&RC). This is a retrospective review of all female breast cancer cases treated at KFSH&RC over a 15-year period. Patients were divided into two groups at the time of their referral to KFSH&RC: metastatic and nonmetastatic. We describe the demographic data, cancer-related information and the treatments offered to all patients. Comparisons were made between Saudi and non-Saudi, and the Saudis were examined in relation to their region of referral and observed to see if any changes occurred during the study period. As well, we tried to compare our results with experience elsewhere. A total of 1584 female breast cancer patients were treated at KFSH&RC between 1975 and 1991. Early breast cancer (Stages I, II) represented 36%, while 64% presented with advanced or metastatic disease (Stages III, IV). The majority of patients were premenopausal (64%). For patients with Stages I-III (1005), mastectomy was performed in 85% and lymph node dissection in 93%. Only 30% had no pathologic lymph node involvement and in 49% of the patients, lymph node dissection was adequate (≥10 nodes removed). Estrogen and progesterone receptors were known in 30% of the patients. Sixty-two percent and 72% of patients referred from the central region and the northern region had Stages II and III, respectively. For the non-Saudis, we observed more premenopausal patients (76%) and fewer Stage III. At 15 years, the relapse-free survival in Stages I, II and III was 33%, 36% and 18%, and the overall survival was 80%, 64% and 45%, respectively. Breast cancer in this population affects younger patients (premenopausal) and a higher proportion present with metastatic or locally advanced disease. Management strategies should incorporate conservative surgery when appropriate, and adequate lymph node dissection. This should be coupled with increasing public awareness and education and institution of screening programs. Overall survival is clearly linked to the stage of the disease. *Ann Saudi Med 1997;17(1):10-15.*

Cancer of the breast is the most common cancer among women in many countries, and poses a major health problem. In several countries worldwide, there has been a steady increase in breast cancer. In the U.S., it accounts for 32% of cancer in women, with a 1% to 2% annual rate of increased incidence since the 1960s; an average of five new cases are diagnosed, and one death related to breast cancer occurs every 15 minutes in the U.S.[1] There is a wide variation in incidence between countries, and also within any country, for which several causes are cited. Saudi Arabia has recently set up a National Cancer Registry and the first data have been collected and published.

King Faisal Specialist Hospital and Research Centre (KFSH&RC) has been the foremost tertiary cancer referral center in Saudi Arabia since it opened in 1975. Hospital data on breast cancer are available from that date. We have reviewed our experience and compared it to that in other countries, where more comprehensive data are available, and suggest steps to improve breast cancer care.

Material and Methods

The Tumor Registry of KFSH&RC has identified a total of 1723 cases of breast cancer between 1975 and 1991. The latter year was chosen to allow adequate follow-up. This study period was arbitrarily divided into three five-year periods: 1975-80, 1981-85, and 1986-91. The medical records of these patients were reviewed retrospectively and the data were collected using two different forms. One form with limited database was developed for patients referred as Stage IV (Group A).

From the Departments of Oncology (Drs. Ezzat, Raja, Rostom, Zwaan, Bazarbashi), Pathology (Dr. Akhtar), and Surgery (Drs. Ingemansson, Al-Abdulkareem), King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Ezzat, Head, Section of Medical Oncology, Department of Oncology, MBC 64, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 29 September 1996. Received 13 July 1996.

TABLE 1. *Distribution of patients (metastatic and nonmetastatic) during the study periods.*

	1975-1980	1981-1985	1986-1991
Number of metastatic (stage IV)	141 (62%)	232 (42%)	206 (26%)
Number of nonmetastatic (stage I-III)	88 (38%)	322 (58%)	595 (74%)
Total	229	554	801

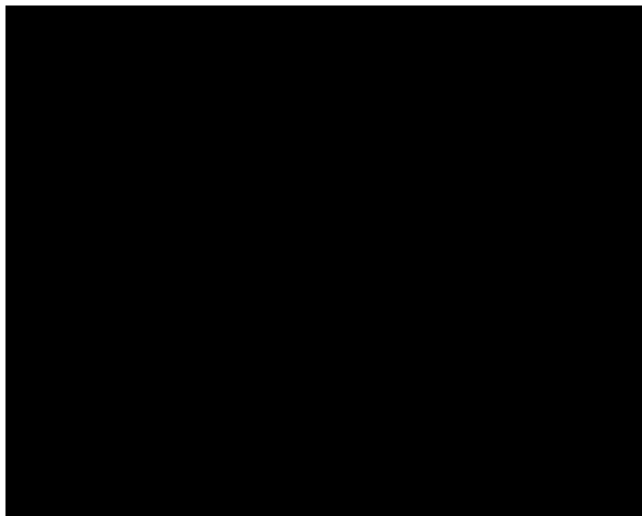

FIGURE 1. The overall survival for metastatic patients.

They comprised patients who presented or were referred to KFSH&RC with metastatic disease as their first diagnosis or patients who had previously been treated elsewhere and were then referred to KFSH&RC at the time of relapse with metastasis. We will briefly present the patients' characteristics in Group A over the study period without emphasis on specific management.

For patients who underwent curative treatments (Stages I-III), a more detailed database form was developed to incorporate more information about disease and outcome. They will be referred to as Group B. The pattern of referrals, cancer-related information and treatments offered will be presented and compared in relation to the three study periods between Saudi and non-Saudi, and among the Saudis themselves in relation to regional referrals.

For the purpose of the study, Saudi Arabia is divided into five regions: Central, Eastern, Western, Northern and Southern. The American Joint Committee on Cancer (AJCC)/TNM staging system was used for staging patients.

Statistical Methods

The proportion of patients with a given characteristic was compared by the χ^2 test or Fisher's exact test. Correlation between two continuous variables was determined with Spearman's nonparametric test. The survival in the metastatic group was measured from the date of diagnosis (metastatic at diagnosis) or the date of relapse (referred with relapse), respectively, to death sensored by the end of follow-up. For the nonmetastatic patients, survival was measured from diagnosis to death, sensored by the end of follow-up, relapse-free survival was measured from diagnosis to relapse or death sensored by the end of follow-up. The distributions of survival duration were estimated by the method of Kaplan and Meier.[2]

Ninety-five percent confidence limits (95% CL) for these probabilities and the median survival times were obtained using the method of Simon and Lee.[3] Levels of statistical significance for differences between these curves were obtained by the log-rank test.[4] Median follow-up time was estimated by reversing the codes for the sensoring indicator in a Kaplan-Meier analysis. All reported *P*-values are nominal two-sided values.

Results

During the study period, a total of 22,088 cancer cases were registered at KFSH&RC's Tumor Registry, of which 1723 (8%) were breast cancer. They represent 17% of the 9743 female cases registered. Thirty-four (2%) male breast cancers and 105 (6%) nonanalytic cases (seen for consultation only or refused therapy) will not be considered in this report. The remaining 1584 cases were divided into Group A = 579 (37%) and Group B = 1005 (63%), as described earlier. The distribution of these cases over the study period is shown in Table 1.

For patients in Group A, the median age was 46 years (17-84) and 73% were of Saudi nationality. The most common sites of metastases (in order of frequency) were bone (41%), skin and lymph nodes (25%), lung (19%), liver (19%), and brain (3%). About 50% had one metastatic site, 21% had two sites, 8% had three sites and 21% more than three sites. For the 304 patients (53%) who were referred to KFSH&RC with metastatic disease at presentation, the median survival was 22 months (95% CL: 18-25), with a median follow-up of 21 months (95% CL: 16-25). However, patients who were referred with metastatic disease at relapse (275 or 47%) had a median time to relapse of 11 months (95% CL: 9-13), while the median survival from time of relapse was 51 months (95% CL: 43-58), median follow-up of 27 months (95% CL: 23-32). There is a statistically significant difference (P=0.0001) between the two groups, as shown in Figure 1.

In Group B, 74% were of Saudi nationality and the majority (64%) were premenopausal. Thirty-seven percent were <40 years of age, 54% were between 40 and 60 years and 9% were >60 years. The left breast was involved in 50%, the right 48% and 2% had bilateral disease. Only 17% of the patients were diagnosed and treated at

KFSH&RC. The type of surgery was either mastectomy (85%) or conservative (15%) (breast-retaining). Though 93% had axillary nodal dissection, only 49% had more than 10 nodes removed. The rate of nodal involvement was as follows: 0=30%, 1-3=41% and >4=29%. However, of the patients who had more than 10 nodes removed, 30% were negative, 28% had one to three nodes involved, and in 42%, at least four nodes were involved, which is in marked contrast to patients in whom fewer than 10 nodes were removed, where only 20% had at least four nodes positive (*P*=0.0001).

Clinical staging for patients in Group B revealed that 5% were Stage I, 54% Stage II, and 41% Stage III. Of 301 patients with estrogen receptor status, and 271 patients with progesterone receptor status, 33% and 28% were known to be positive, respectively. Neoadjuvant chemotherapy was given to 5%, while 48% had chemotherapy, 25% were given Tamoxifen, and 54% had radiation therapy as adjuvant treatments. The 10 years relapse-free survival for Stages I, II and III were significantly different (Table 2, Figures 2 and 3).

When the data were analyzed in relation to the three time periods, there was a steady increase in the total number of patients referred, with a simultaneous decline in the proportion of metastatic disease from 62% in period I to 26% in period III. There was also an increase in Stage II, with a corresponding drop in Stage III cases. However, there appeared to be little difference in whether radical or conservative surgery was performed on the breast. There was a significant increase in axillary lymph node dissection, though there is still a tendency to remove fewer than 10 nodes. There appeared to be a remarkable increase in the use of adjuvant chemotherapy and Tamoxifen, although the use of radiation therapy was not very much different. These data are summarized in Table 3. The survival curve shows a trend (*P*=0.07) of better survival in periods II and III (Figure 4).

A comparison of the referral pattern from the different regions of Saudi Arabia shows that while there is an increase in absolute numbers in all areas, the difference is most striking in the Eastern, Southern and Northern regions. The age distribution and menopausal status are similar in the different regions. A large proportion of patients from the Northern region had Stage III disease and were given more neoadjuvant chemotherapy. Also, a large proportion of patients from the Central region had Stage II disease. The regional data is shown in Table 4.

Comparison was also made between Saudi and non-Saudi patients. In the latter group, there were more premenopausal women, and a higher proportion of earlier stage clinical and pathological disease at presentation. Full details are shown in Table 5.

TABLE 2. *Patients' characteristics reflected as percentages observed during various periods of the study.*

	1975-1980 n=88	1981-1985 n=322	1986-1991 n=595	*P*
Menopausal				0.016
Premenopausal	59	58	67	
Postmenopausal	41	42	33	
Histology				.002
DCIS*	4	2	3	
IDC**	74	87	83	
Others	22	11	14	
Clinical stage				0.005
I	10	4	5	
II	40	51	59	
III	50	45	36	
Pathological stage				0.012
I	10	3	5	
II	51	52	60	
III	39	45	35	
Type of surgery				0.078
Mastectomy	82	89	83	
Conservative	18	11	17	
Nodes resected	79	93	96	0.0001
Number of involved nodes				0.004
0	25	26	33	
1-3	54	32	33	
4-10	21	29	25	
>10	0	13	09	
Adjuvant chemotherapy	17	54	50	0.0001
Adjuvant tamoxifen	15	14	32	0.0001
Adjuvant radiation	68	52	54	0.027

*DCIS=ductal carcinoma in situ; **IDC=infiltrating ductal carcinoma.

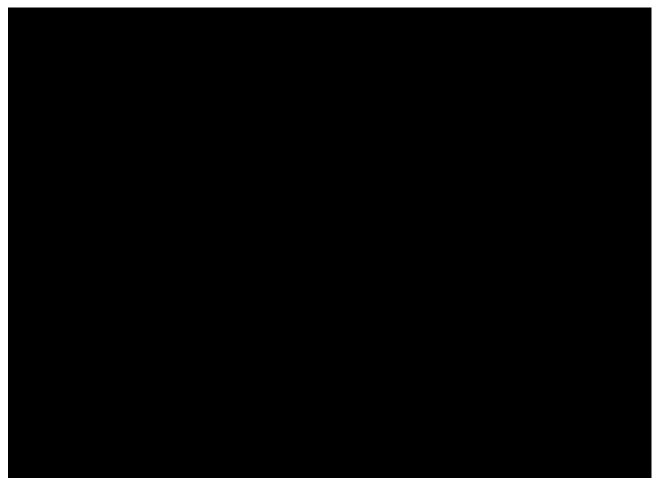

FIGURE 2. The relapse-free survival by stage.

TABLE 3. *Patients' characteristics reflected as percentages in relation to region of referral.*

	Central	East	West	South	North	Outside	*P*
Total number of patients							0.0001
Period I	14	5	6	5	2	14	
Period II	30	23	36	30	29	45	
Period III	56	72	58	65	69	41	
Menopausal							0.02
Premenopausal	66	71	57	57	66	68	
Postmenopausal	34	29	43	43	34	32	
Age class							0.03
<40	42	41	30	30	41	40	
41-60	50	50	58	59	55	54	
>60	8	9	12	11	4	6	
Clinical stage							0.00001
I	5	4	4	2	3	10	
II	62	57	54	51	25	54	
III	33	39	42	47	72	36	
Pathological stage							0.005
I	6	4	3	2	4	9	
II	61	58	58	52	33	55	
III	33	38	39	46	63	36	
Surgery at KFSH&RC	47	41	33	48	45	43	0.027
Nodes resected	93	95	96	91	89	95	0.17
Number of positive nodes							0.824
0	32	34	30	24	26	30	
1-3	35	31	36	41	27	34	
4-10	26	25	24	23	31	25	
>10	7	10	10	12	16	11	
Neoadjuvant chemotherapy	4	3	6	6	18	4	0.0002
Adjuvant radiotherapy	55	52	56	48	43	62	0.086

Discussion

Breast cancer is not only the most common malignancy in women, but the incidence is increasing in several countries. Early breast cancer is potentially curable, while palliation is the objective in advanced disease.

Some of the increased diagnosis is due to more widespread screening programs and alterations in registration procedures in certain countries, but it appears there is a genuine increased incidence not accounted for by these factors.[5] These two aspects of breast cancer emphasize the importance of early diagnosis and appropriate management. This review highlights several features of breast cancer in women seen in Saudi Arabia. Apart from it being the most common cancer in women referred to KFSH&RC, our experience indicates that the pattern of disease is different than that reported in the literature.

There is a distinct variation in incidence between different countries, with higher frequencies observed in the West. Unpublished data from the Saudi National Cancer Registry indicate breast cancer to be the most frequent malignancy in adult women, accounting for 18% of the total. Studies looking at the relationship of age to incidence of breast cancer in North America and Europe

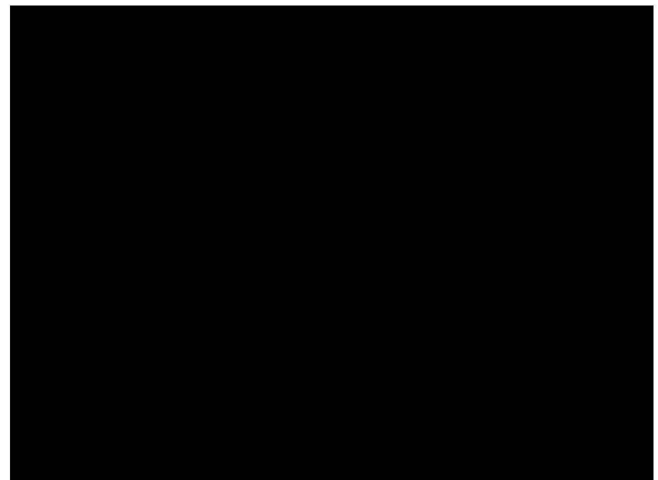

FIGURE 3. The overall survival by stage.

TABLE 4. *Patients' characteristics reflected as percentages in relation to nationality.*

	Saudi n=743	Non-Saudi n=260	*P*
Menopausal			0.0001
Premenopausal	60	76	
Postmenopausal	40	24	
Age			0.0005
<40	35	42	
40-60	54	55	
>60	11	3	
Clinical stage			0.004
I	4	9	
II	54	56	
III	42	35	
Pathological stage			0.0008
I	3	9	
II	56	57	
III	11	34	
Surgery at KFSH&RC	44	37	0.037
Nodes resected	92	96	0.033
Number of involved nodes			0.905
0	30	30	
1-3	34	36	
4-10	26	25	
>10	10	9	
Adjuvant chemotherapy	46	54	0.028
Adjuvant tamoxifen	26	22	0.177
Adjuvant radiatherapy	53	59	0.125

show that the incidence in women younger than 40 ranges from 8% to 15%, compared to 35% in our experience.[6]

It could be argued that our figures, being hospital data, reflect a referral bias, but the National Cancer Registry figures for 1994 show that 30% of breast cancer is in those younger than 40 years. Some studies indicate different ages at menarche, weight at menopause, and varying estrogen levels as contributory factors to the difference in incidence between countries.[7,8] In the U.S., localized breast cancer accounts for 58% of the cases.[9]

The low frequency of early stage disease in this review reflects delayed presentation and referral, both matters of grave concern. This may be due to low awareness of the disease, lack of education and/or difficulty in access to specialized medical care. In keeping with experience at other centers, there is a significant difference in both overall and relapse-free survival between early and more advanced stages. One encouraging trend is the stage migration noted over the 15 years, though referral is still delayed.

The frequency of conservative surgery, adequate lymph node dissection and information on hormonal receptor status are unacceptably low. Management is tailored according to stage, menopausal and hormone receptor status of the individual patient. It has also been recognized that conservative breast surgery is a viable option in a significant proportion of women, without compromising the eventual outcome, while simultaneously offering less morbidity and a psychological advantage.[10,11] This becomes difficult when inadequate or improper initial treatment is offered to patients prior to referral, and necessary information is not made available.

TABLE 5. *Age-adjusted incidence/mortality of breast cancer per 100,000 women aged 35-74.*

	1970		1985	
Country	Incidence	Mortality	Incidence	Mortality
USA	173.6	53.5	211.9	53.4
England/Wales	129.5	64.2	152.7	68.4
Norway	108.2	40.6	131.8	41.6
Spain	73.3	23.8	99.0	36.2
Colombia	64.4	11.9	82.9	18.2
Singapore	48.2	19.7	78.0	32.1
Japan	31.9	11.1	69.7	14.7
India	47.6		60.7	
China	47.9		52.4	11.4

The vast majority of our patients had their primary diagnosis, as well as initial surgery, at other centers. This has led to inappropriate radical surgery, lack of information on axillary node status, which is the single most important prognostic factor, and on hormone receptor levels.

Our experience highlights the need for adequate staging and information on node status, which in many countries is defined as 10 lymph nodes dissected from level I and II. Our experience has shown that the probability of identifying more positive nodes is related to the total number of nodes removed (Figure 5). Recent evidence suggests that this is an important prognostic factor, since patients with more than 10 positive lymph nodes may benefit from high-dose chemotherapy with peripheral stem support. In common with practice elsewhere, there is increasing usage of adjuvant systemic therapy. Patterns of referral from the different regions will serve as a useful basis for appropriate deployment of resources.

In summary, it is clear that experience with breast cancer in Saudi Arabia is not identical to that in Western countries. The establishment of the National Cancer Registry is a timely measure, and this, combined with population statistics, will indicate the true magnitude of the problem. It is imperative that public awareness of the

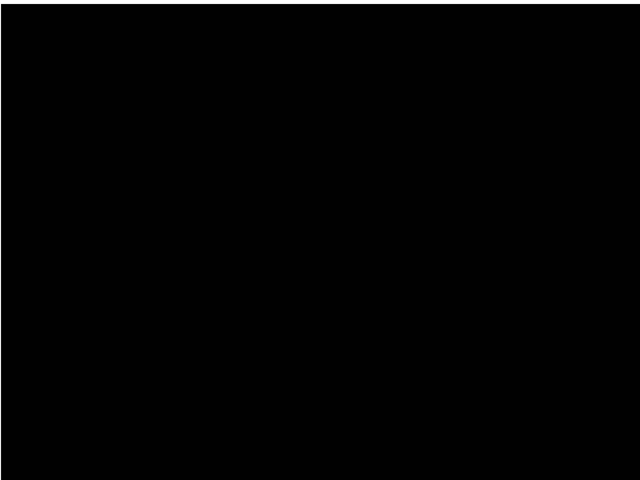

FIGURE 4. The overall survival by study period for Stages I to II (n=1005).

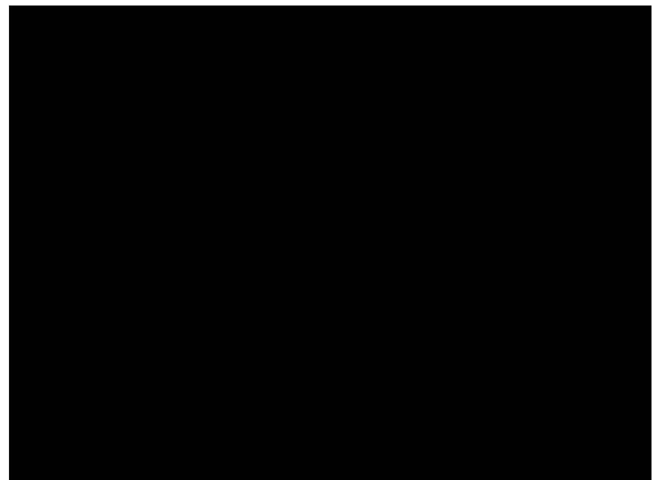

FIGURE 5. Scatter diagram between the number of nodes removed.

problem is increased through proper channels. Two areas to concentrate on are teaching breast self-examination and evaluating the place of mammographic screening in our population.

In many countries, screening programs are essentially for women over 50 years of age. This is due to the higher incidence of breast cancer in older women there, considerations of cost-benefit ratio, and past fears about radiation risks in younger women.[12,13] A recent review discounts the last factor, showing that even in women as young as 25, the benefits of mammographic screening far outweigh any risks.[14] Given the fact that breast cancer in Saudi Arabia occurs at an earlier age, the right population for screening needs to be defined. Access to specialized medical services must be ensured. The approach to diagnosis and initial management needs to be standardized. Early diagnosis cannot be overemphasized. Fine needle aspiration may often be sufficient to establish an initial diagnosis. Needless radical and mutilating surgery should be avoided. This may be possible even in locally advanced disease, utilizing neoadjuvant chemotherapy in the setting of properly conducted trials. Proper procedures to establish axillary node status and hormone receptor levels must be carried out. Where such services are not available, the patients should be referred early to the specialized centers. The aim is to render the best possible care for breast cancer patients on a par with the highest standards available.

Acknowledgments

I am grateful for the continued efforts and support of all members of the Oncology Data Unit, the health care workers who participate in the care of these patients, and to Lizzie Brock for her secretarial support.

References

1. Partrek JA, Holleb AI. The foremost cancer - revisited. CA Cancer J Clin 1995;45:197-8.
2. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
3. Simon R, Lee YK. Nonparametric confidence limits for survival probabilities and median survival time. Treat Rep 1982;66:37-41.
4. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-70.
5. Ursin G, Bernstein L, Pike MC. Breast cancer in trends in cancer incidence and mortality. Doll R, Fraumeni Jr., JF, Muir CS, eds. Cold Spring Harbor Laboratory Press 1994:241-64.
6. Kessler LG. The relationship between age and incidence of breast cancer. Cancer 1992;69:1896-903.
7. Pike MC, Krailo MD, Henderson BE, et al. Hormonal risk factors, breast tissue age and the age-incidence of breast cancer. Nature 1983;303:767-70.
8. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiologic Reviews 1993;15:48-65.
9. Parker SL, Tong T, Bolden S, Wingo PA. Cancer Statistics 1996;46:5-27.
10. Early Breast Cancer Trialists; Collaborative Group: effects of radiotherapy and surgery in early breast cancer. N Engl J Med 1995;333:1444-55.
11. Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995;333:1456-61.
12. Fox SA, Klos DS, Tsou CV. Underuse of screening mammography by family physicians. Radiology 1988;166:431-3.
13. American Cancer Society. 1989 survey of physicians attitudes and practices in early cancer detection. CA Cancer J Clin 1990;40:77-101.
14. Mettler FA, Upton AC, Kelsey CA, et al. Benefits versus risks from mammography. Cancer 1996;77:903-9.