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Diagnosis and Prognosis of Breast and Ovarian Cancer

A Population-Based Study of 234 Women

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The diagnosis and prognosis for 135 women with breast cancer and 99 women with ovarian cancer in a well-defined geographical area, and a follow-up of 7–15 years are described, based on patients' records. Diagnosis was initiated in primary care for 53% of women with breast cancer, and for 57% of women with ovarian cancer. Median patient delay was 1 week for breast cancer, and 3.5 weeks for ovarian cancer patients, and median provider delay was 3 weeks for both groups. Crude, relative, and corrected 5-year survival was 73%, 91%, and 82% in breast cancer, and 40%, 49%, and 43% in ovarian cancer. Cox multiple regression analyses showed that stage IIIA and IV, and young age were associated with impaired disease-related survival in breast cancer. In patients with ovarian cancer, stages III and IV at diagnosis, old age, and systemic symptoms dominating at presentation were predictive of reduced disease-related survival while a family history of cancer was predictive of increased survival.

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Breast cancer is the most common cancer in women in the Western world, being 5–10 times more common than ovarian cancer (1, 2). In 5–10% of women with breast or ovarian cancer the family history is compatible with a dominant inheritance pattern with a higher disease penetrance for patients with breast cancer (3).

Ovarian cancer is usually diagnosed at an advanced stage with occult disease manifestations, and often has a poor prognosis. Breast cancer is often diagnosed at an early stage, with a more favorable prognosis. It has been shown that a long patient delay correlates with a shorter survival time in breast cancer patients (4), but this has not been described for ovarian cancer (5).

Whenever it is suspected that a patient might have cancer, the prime instinct of most physicians is to speed up the diagnostic procedure, and to establish a diagnosis as soon as possible. Differences in provider delay have shown no prognostic impact for either of the diseases (5, 6), but the psychological distress seems to increase with length of total delay (7). Therefore both patient and provider delay should be kept at a minimum.

Studies have been conducted from a GP perspective on symptom presentation and diagnostic work-up of breast cancer (8, 9), but we found no studies of this kind in relation to prognosis, and no studies of ovarian cancer from a GP perspective. The aim of our study was to investigate the diagnostic data in patients' records from primary and hospital care, and to relate these data to prognosis measured as survival.

MATERIAL AND METHODS

This study is based on all incident cases of invasive breast and ovarian cancer in a predominantly rural district with 18 health centers and one hospital. The female population of the district was 60 744 in 1988, and 63 260 in 1994. For breast cancer the two years 1988 and 1992, and for ovarian cancer the eight years from 1987 to 1994 were studied. The patients were identified by information from the Regional Tumor Registry, which also supplies dates of diagnosis and death. From the Tumor Registry records of 238 women (137 with breast cancer and 101 with ovarian cancer), 3 women were diagnosed at autopsy, and the records of one woman with breast cancer could not be found, leaving us with the records of 135 women with breast cancer and 99 women with ovarian cancer available for investigation.

The investigation was based on patients' records obtained from primary care and from the departments of gynecology and surgery, but also hospital records of other units

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involved in the diagnostic process. We defined the first diagnostic unit as the medical facility at which the woman was first seen with symptoms leading to the diagnosis of cancer. We separated the time between onset of symptoms and start of treatment (total delay) into patient delay, which we defined as the time between onset of symptoms and time of first consultation with a physician, and provider delay, which was the time between the first consultation and start of treatment.

We also extracted clinical data from the patients' records: the presence of symptoms and signs and those that dominated at presentation; number of general practice appointments in the 12 months before diagnosis; the diagnostic methods used; family history of cancer; previous malignancies; who discovered the cancer; treatment; and disease stage. Substaging according to the TNM classification was only established for patients with breast cancer.

The causes of death were verified by examining the records of all the women who died during the follow-up period.

A general screening mammography program offering all women between 50 and 69 years of age a mammogram every other year was introduced in the district in 1990 with a participation rate of 80%. The radiological department was responsible for the program in which there was no GP involvement, as is the case for such programs throughout Sweden.

Statistical methods

We analyzed the data using SPSS version 10.0 for Macintosh. Different Cox regression models were tried to determine the effects on survival of possible prognostic factors and we here present backward models. The survival curves were calculated using the Kaplan–Meier method. The relative survival rate was the ratio of the observed (or crude) survival rate to the expected age-adjusted survival rate for the total Swedish population (10). The corrected disease-specific survival rate was calculated by excluding patients who died from causes unrelated to breast or ovarian cancer. The cut-off date for the survival analysis was 1 January 2002. The median potential observation time (time from the date of diagnosis to the cut-off date) was 9.9 years (range 9.0–14.0) for breast cancer patients, and 11.6 years (range 7.0–15.0) for ovarian cancer patients.

Continuous variables such as age and delay were dichotomized at the first or third quartile in order to simplify comparisons between the variables by localizing subgroups with the highest hazard ratios in the Cox regression models.

The study was approved by the local ethics committee.

RESULTS

Breast cancer

Invasive breast cancer was diagnosed in 58 women two years before the start of screening mammography, and in 79 women two years after the start of screening. This gave a crude incidence of 95/100 000 in 1988 and 127/100 000 in 1992. Age-standardized incidence to the Swedish population was 114/100 000 in the studied county for the period 1988–1992. One woman was diagnosed at autopsy, and for one woman the medical records could not be found, which left 135 women with breast cancer in the study group.

The characteristics of the patients according to type of cancer are presented in Table 1. Most of the women (64%) were of rural origin (in accordance with the demographics of the studied area), and their mean age was 65.0 years (SD = 14.6). Almost one-fifth of the women with breast cancer had been treated for some type of cancer before, whereof 13 women (10%) were treated for breast cancer. Twelve women (9%) reported a first-degree relative with breast cancer.

The breast tumor was discovered by a relative or by a physician en passant in 18 women (13%). A GP was the physician of first contact for one half of the women (53%), and in most cases only one GP visit was required to

Table 1

Characteristics of women with breast and ovarian cancer. Values are numbers (percentages) of women unless stated otherwise. Substaging done for breast cancer only

	Breast cancer N = 135	Ovarian cancer N = 99
Mean (SD) age in years	65.0 (14.6)	63.1 (14.3)
Rural domicile	87 (64)	64 (64)
Previous cancer	24 (18)	9 (9)
Family history of cancer	23 (17)	26 (26)
GP as physician of first contact	72 (53)	56 (57)
Median (range) of GP visits	1 (0–8)	2 (0–10)
Stage at diagnosis		
I	50 (37)	29 (29)
IIA	46 (34)	
		}12 (12)
IIB	19 (14)	
IIIA	6 (4)	
		}38 (39)
IIIB	1 (.7)	
IV	13 (10)	20 (20)
Crude/relative/corrected survival, %		
5-year	73/92/82	40/49/43
6-year	67/88/79	37/47/39
7-year	64/88/77	31/41/34
8-year	58/84/75	31/40/33[2]
9-year	55/83/72	32/40/35[3]
10-year	46/84/60[1]	33/40/38[4]

[1]n = 57; [2]n = 88; [3]n = 76; [4]n = 69.

establish the diagnosis. GPs performed fine-needle aspiration biopsies in 10 out of 72 (14%) women.

The physician disclosed the diagnosis at a consultation with 81 women (60%). For the remaining 54 women (40%), the diagnosis was given by mail or by phone, or by another person.

A majority of the breast cancers (85%) were in stage I or II at diagnosis and the survival rates were high. The survival curves for women with breast and ovarian cancer are presented in Fig. 1.

Frequencies of initial signs and symptoms are presented in Table 2. For most of the women, the disease presented as a lump or swelling in the breast (73%), while visual signs of breast cancer such as a wound, or retraction of the nipples or skin were found in 32 women (24%).

In Table 3 we give time intervals from onset of symptoms to start of treatment divided into patient and provider delay. A majority of breast cancer patients presented with their symptoms within two weeks, although 25% delayed seeking medical care by 9 weeks or more. As for the provider delay, treatment started within one month after the first consultation in most women.

In Table 4, we present details of the diagnostic process for the 17 women (13%) with more than 8 weeks of provider delay. For 6 of those women all three diagnostic methods were primarily positive, and for 3 of these 6 women the delay was caused by the provider.

Mastectomy was performed in 76 women (56%); breast-preserving surgery in 41 women (30%), and 18 women (13%) did not undergo any surgery. Tamoxifen was prescribed to 65 women (48%), radiotherapy to 47 women (35%), and chemotherapy to 10 (7%) women.

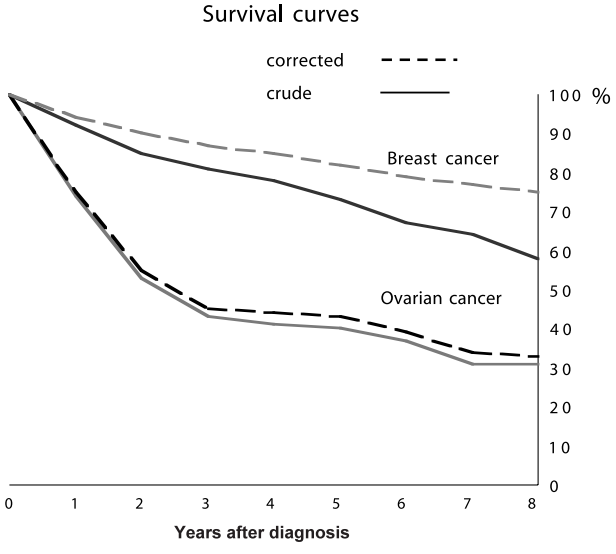

Fig. 1. Corrected and crude survival rates for a population-based sample of 135 women with breast cancer and 99 women with ovarian cancer.

The median age of the 18 women diagnosed by general screening mammography in 1992 was 60 years (range 50–69), and their 5-year crude survival rate was 100%. A palpable breast lump was found at diagnosis in 3 of these 18 women, and 7 were in stage II at diagnosis. By the last follow-up (median time 9 years), three of the screened women had died at 66, 73, and 76 years of age, none of them of breast cancer.

The variables that remained in the Cox multiple regression models, and thus with the most prognostic power, are presented in Tables 5 and 6.

Ovarian cancer

Between 1987 and 1994, 101 women were diagnosed with invasive ovarian cancer, which yielded a crude incidence of 21/100 000. Age standardized incidence to the Swedish population was 19/100 000 in the studied county for the years 1988–1992. Two women were diagnosed at autopsy, which left 99 women with ovarian cancer in the study group. Tumors of borderline malignancy (BOTs) were diagnosed in another 29 women. The crude 5-year survival rate for these women was 97%, but further data on BOTs will not be presented in this study.

As can be seen in Table 1, the majority of the women with ovarian cancer were of rural origin, and their mean age was 63.1 years (SD = 14.3). Half as many women with ovarian cancer as with breast cancer had a history of previous cancer (9%). More women with ovarian cancer reported a family history of cancer (26%), and 10 women (10%) reported of first-degree relatives with either breast or ovarian cancer, while others reported of 'gynecological' or 'stomach' or 'skeletal' cancers in the family. Mean age at first childbirth was 24.5 (SD = 6.6) years, and 23 women (23%) were nulliparous.

A GP was the physician of first contact for 57% of the women, and in most cases two GP visits were required to establish the diagnosis. GPs performed gynecological examinations in 29 out of 57 women (51%) first seen by a GP. More than half of the ovarian cancers (59%) were diagnosed in stage III or IV, and survival rates were considerably lower than those for women with breast cancer, as can be seen in Fig. 1.

Nine women had ovarian cancer of non-epithelial origin. The remaining 90 women with invasive epithelial ovarian cancer had a crude and corrected 5-year survival rate of 36% and 37%, respectively.

In Table 2 we present the total number of symptoms and signs present in the records. Many women presented with more than one symptom and only 21% had gynecological symptoms or signs. We also assessed which were the predominant symptoms and signs at presentation. Compression on the bladder or bowel was the main symptom in 25 women (25%), pain in 24 (24%), systemic symptoms and signs such as weight loss or fatigue in 16 (16%), abdominal

Table 2

Frequencies of initial symptoms and signs for women with breast cancer or ovarian cancer

Breast cancer (N = 135) Symptoms & signs	%	Ovarian cancer (N = 99) Symptoms & signs	%
Lump or swelling	73	Urinary + GI (compression)	38
Tenderness	14	Abdominal pain	38
Retracted nipple	13	Abdominal swelling	33
Retracted skin	12	Systemic (fatigue, weight loss)	26
Consistency change	10	Gynecological	21
Systemic (fatigue, weight loss)	6	Palpable tumor	7
Visible wound	4	Respiratory	5
Nipple secretion	3		
Eczema	3		

Table 3

Time intervals in weeks of the diagnostic process for women with breast cancer and ovarian cancer

	Median (inter-quartile range)	
	Breast cancer[1]	Ovarian cancer[2]
I. Patient delay	1 (0–9)	3.5 (0–9)
II. Provider delay	3 (2–6)	3 (1–6)
I+II Total delay[3]	6 (3–15)	7.5 (4–16.5)

[1]Information missing for 7 (patient delay), 3 (provider delay), and 9 (total delay) of the 135 women, respectively.
[2]Information missing for 19 (patient delay), 13 (provider delay), and 25 (total delay) of the 99 women, respectively.
[3]Geometrical means cannot be summed as can arithmetical means, which explains the seemingly discrepancy in values.

swelling in 10 (10%), and gynecological symptoms and signs in 9 women (9%).

Almost half of the women with ovarian cancer delayed one month or more before seeking medical care for their symptoms, and 25% of them delayed 9 weeks or more. Provider delay was less than a month for most women.

Radical surgery was performed in 44 women (44%), reductive surgery in 35 (35%), diagnostic surgery only in 12 (12%), and 8 (8%) did not undergo any surgery. Chemotherapy was prescribed for 76 women (77%), and radiotherapy for 8 (8%). Seventy-one women (72%) were treated in a tertiary care hospital.

The variables that remained in the Cox multiple regression models, and thus had the most prognostic power, are presented in Tables 5 and 6.

DISCUSSION

In this study we investigated the diagnosis of breast and ovarian cancer in relation to survival by reviewing both primary care and patients' hospital records of all incidental cancers in a well-defined population.

Negative prognostic predictors for crude, but not disease-specific survival for a woman with breast cancer included any previous type of cancer, and if the woman did not undergo surgery. These predictors disappeared in disease-specific survival, and were thus probably due to comorbidity. The shorter disease-specific survival for younger women with breast cancer has been shown in studies elsewhere (11, 12), and probably reflects an increased biological aggressiveness. Stages IV and IIIA disease were the only stage variables predicting breast-cancer-specific mortality. The small number of breast cancer deaths in this study probably explains the lack of association between other stages and mortality.

Disease stages III and IV and advanced age at diagnosis were the most important factors related to short survival for ovarian cancer patients, followed by systemic symptoms dominating at presentation, while a family history of cancer was related to a longer survival. Thus, when systemic symptoms dominated at presentation in ovarian cancer, this was an unfavorable prognostic sign independent of stage and age, a finding previously reported and labeled 'symptom-stage' (13). A family history of cancer mentioned in the patient records was a good prognostic sign for women with ovarian cancer. This seems to contradict previous findings that hereditary cancers are biologically more aggressive (14). In a subgroup analysis, we saw that patients with a family history of cancer generally were in a higher disease stage, but within stages III and IV a family history of cancer was a favorable prognostic sign. Perhaps this unexpected finding can be explained by a better treatment response to chemotherapy for aggressive tumors?

No relationship was found between patient or provider delay and survival for either breast or ovarian cancer. This is in contrast to several studies on breast cancer where long patient delay was related to shorter survival (4, 15). One probable explanation for this lack of correlation between patient delay and survival is the limited size of our study group, which implies a type II error. Another possible explanation is that a long patient delay is associated with slow-growing tumors that are biologically less aggressive, as has been suggested elsewhere (16).

Table 4

Description of the 17 women with a more than 8-week delay from presentation to treatment (provider delay) of breast cancer

Results of initial palpation–mammogram–cytology	Patient/provider delay (weeks)	Possible reasons for delay	Age group	Discovery mode	Stage at diagnosis	Died of breast cancer?
POS-POS-POS	30/11	Earlier contralateral fibroadenomatosis, summer holidays	–49	Self	IIB	Yes
POS-POS-POS	26/9	Christmas holidays	70–	Self	I	No
POS-POS-POS	104/11	Hospital delay	70–	Self	IIIA	No
POS-POS-POS	–/9	Patient depressed	70–	Self	I	No
POS-POS-POS	0/13	Hospital delay	70–	En passant	IIA	No
POS-POS-POS	–/54	Patient first refused investigation	70–	Self	IIA	No
POS-POS-INC	39/10	Summer holidays	50–69	Self	I	Yes
POS-POS-INC	3/10	Summer holidays	70–	Self	I	No
POS-INC-INC	26/10	–	70–	Self	IIA	No
POS-NEG-POS	1/45	First cytology delayed	50–69	Self	I	No
POS-NEG-INC	6/54	Fibroadenomatosis	50–69	Self	I	No
POS-NEG-NEG	26/22	Fibroadenomatosis	–49	Self	I	No
POS-NEG-NEG	–/9	–	70–	Self	IIA	No
NEG-POS-INC	–/22	Contraleteral fibroadenomatosis	50–69	En passant	I	No
NEG-INC-POS	0/22	Patient depressed	70–	En passant	IIB	No
NEG-INC-NEG	0/9	–	50–69	Control mammogram	I	No
NEG-INC-NEG	3/9	Patient first refused investigation	70–	Self	IIA	No

Abbreviations: POS = positive; NEG = negative; INC = inconclusive results of the different assessments, respectively.

Table 5

Prognostic predictors with any cause of death as dependent variable in Cox multiple regression analyses. Hazard ratios (HR) with 95% confidence intervals (CI)

Variable	HR (95% CI)	p-value
Breast cancer patients		
Stage IV	8.2 (2.9–23.1)	< 0.001
Stage I	1.0	–
Previous cancer	2.2 (1.2–3.9)	0.011
No surgery	3.4 (1.6–7.3)	0.002
Ovarian cancer patients		
Stage IV	20.9 (4.9–89.5)	< 0.001
Stage III	8.4 (2.4–29.4)	< 0.001
Stage I	1.0	–
Systemic symptoms dominating	6.2 (2.4–16.0)	0.001
Age > 76 years	4.7 (2.4–9.4)	< 0.001
Family history of cancer	0.4 (0.2–0.7)	0.005

Other non-significant variables included in the regression models:
For breast cancer patients: physician of first contact; discovery en passant; age < 53 years; family history of cancer; previous cancer; patient delay > 9 weeks; provider delay > 6 weeks; urban or rural patient; stage IIA; stage IIB; stage IIIA; mastectomy; breast-preserving surgery; radiotherapy; all the signs and symptoms listed in Table 2.
For ovarian cancer patients: all the signs and symptoms listed in Table 2 other than compression symptoms and predominant symptoms at presentation other than systemic symptoms; hormonal contraception; physician of first contact; previous cancer; previous benign gynecological disease; patient delay > 9 weeks; provider delay > 6 weeks; urban or rural patient; low tumor differentiation; chemotherapy; radiotherapy.

Table 6

Prognostic predictors with cancer-specific cause of death as the dependent variable in Cox multiple regression analyses. Hazard ratios (HR) with 95% confidence intervals (CI)

Variable	HR (95% CI)	p-value
Breast cancer patients		
Stage IV	70.4 (16.5–136.7)	< 0.001
Stage IIIA	8.0 (1.3–48.8)	0.02
Stage I	1.0	–
Age < 53 years	3.3 (1.4–7.9)	0.007
Ovarian cancer patients		
Stage IV	16.3 (3.8–69.2)	< 0.001
Stage III	6.8 (2.0–23.6)	0.002
Stage I	1.0	–
Systemic symptoms dominating	6.5 (2.3–18.7)	< 0.001
Age > 76 years	4.9 (1.9–12.6)	0.001
Family history of cancer	0.4 (0.2–0.8)	0.009

Other non-significant variables included in the regression models:
For breast cancer patients: all the signs and symptoms listed in Table 2; family history of cancer; patient delay > 9 weeks; discovery en passant; physician of first contact; previous cancer; provider delay > 6 weeks; urban or rural patient; stage IIA; stage IIB; no surgery; mastectomy; breast-preserving surgery; radiotherapy; hormonal therapy; discovery en passant.
For ovarian cancer patients: all the signs and symptoms listed in Table 2 and predominant symptoms at presentation other than systemic symptoms; hormonal contraception; physician of first contact; previous cancer; previous benign gynecological disease; patient delay > 9 weeks; provider delay > 6 weeks; urban or rural patient; low tumor differentiation; chemotherapy; radiotherapy.

The GP involvement with a little more than half of the women first seen by a GP in the diagnostic work-up was similar for the two diseases. Why no more than half of the women were first seen by a GP can be explained by the fact that Swedish GPs lack a gatekeeper function; in Sweden people can see a specialist without a referral.

For the women with breast cancer and a provider delay of >8 weeks, triple assessment with palpation, mammography and fine-needle aspiration biopsy was often inconclusive or negative and thus a false-negative situation explained some of this delay. Furthermore, more women were diagnosed en passant in this group of women. In only three women (2%) a provider delay of >8 weeks seemed to be caused by the healthcare providers themselves.

Most women with breast cancer first noticed their cancer as a lump, while women with ovarian cancer had a more heterogenic distribution of signs and symptoms. However, a number of women with breast cancer presented with tenderness or consistency changes, and most women with screening-detected cancers were asymptomatic.

In the present study 80% of the screening-detected cancers were only detectable through mammography, and thus not palpable. In our study the impact of screening mammography was seen as an increase in breast cancer incidence with the magnitude of the increase corresponding to the number of cancers detected by screening. This is a previously described finding in the first years after the start of a screening program (17). The breast-cancer-specific survival for the 18 women screened was 100% after 9 years of follow-up.

Patient delay was shorter for women with breast cancer than for ovarian cancer patients. This reflects the differences in localization of the tumors with the breast tumors being readily palpable at a small size, and non-palpable tumors eventually detectable through mammography. Ovarian cancers can contrariwise grow large within the pelvic cavity before causing discomfort, and when they do, the symptoms are often obscure, and mistaken for urinary tract infections or irritable bowel symptoms (18, 19).

The stage distribution between breast cancer and ovarian cancer differed greatly, which explains most of the difference in mortality between the two diseases since stage I and stage IV ovarian cancer had the same prognosis as stage I and stage IV breast cancer.

Our study has limitations: first, regarding the small number of patients. This was compensated for by studying 2 535 patient-years for all incident cases of breast and ovarian cancer within a geographically well-defined area with only 1 of 234 patients lost to follow-up. Secondly, the accuracy of studying data such as patient delay and family history from patients' records may be questionable. Thus, to increase data reliability we reviewed patients' records from both hospital and primary care using the same criteria as those used in a previous study of cancer in children (20).

The incidence data in this study are comparable with those in other international studies (21) and in line with the Swedish national data (2, 22), and we hence suggest that our study is representative for all Swedish women.

Breast and ovarian cancer are diagnosed from totally different perspectives. Breast cancer is fairly common and readily detectable in the early stages by screening mammography. Ovarian cancer is less common, and screening has so far not been successful (23) apart from one pilot study (24). However, new blood tests identifying specific proteomic patterns using spectroscopy analysis seem promising for future screening of both breast and ovarian cancer (25, 26). For many years to come, there will nevertheless be room for improvement in detecting and discovering both breast and ovarian cancer by clinical methods.

CONCLUSION

In this population-based, long-term, follow-up study we compared the diagnostic work-up and patterns of signs and symptoms of women with breast and ovarian cancer. Advanced stage and age were the strongest predictors of impaired survival for ovarian cancer patients, while for breast cancer patients, advanced stage and low age were negative prognostic predictors. We found no correlation between patient delay and survival in women with breast cancer. Whereas systemic symptoms dominating at presentation were correlated with reduced survival, a family history of cancer correlated with increased survival in women with ovarian cancer.

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