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Breast cancer and spider telangiectasias at diagnosis and its relation to histopathology and prognosis: a population based study.

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Abstract

Introduction: Angiogenesis in one of the hallmarks of breast cancer. The status of angiogenesis is important in therapy choice. Spider telangiectasias (telangiectasias) may reflect an increased ability to form vessels. Our first aim was to identify patients and tumor characteristics associated with the occurrence of telangiectasias at the time of breast cancer diagnosis. The second aim was to study the overall survival in relation to the occurrence of telangiectasias at the time of breast cancer diagnosis.

Methods: A standardized questionnaire was used to interview 1682 consecutive breast cancer patients about risk factors between 1980 and 2009. Occurrence of telangiectasias at the time of breast cancer diagnosis on the upper thorax, head and/or neck was recorded by one physician.

Results: In the cohort, 93 women (5.5%) had telangiectasias. Occurrence of telangiectasias was positively associated with weight, odds ratio (OR) 1.02(95% confidence interval (CI) 1.00-1.05) per kg, ever-use of oral contraceptives OR 2.67(CI 1.55-4.63) and hormone replacement therapy OR 2.68(CI 1.63-4.39), and negatively associated with parity OR 0.45(CI 0.25-0.79). Telangiectasias were not present in patients with comedo breast cancer. Patients with occurrences of telangiectasias diagnosed before the age of 50 had a statistically non-significant worse overall survival, whereas the patients with occurrences of telangiectasias diagnosed at age 50 or after had a statistically significant better overall survival (P interaction=0.016). The relationship between occurrence of telangiectasias and overall survival in the older patient-group was independent of ever-use of HRT.

Conclusion: Hormonal risk factors for breast cancer were associated with the occurrence of spider telangiectasias. The occurrence of telangiectasias may reflect the angiogenic status of the tumor. We hypothesize that telangiectasias could be used as selection criteria for anti-angiogenic therapy in younger breast cancer patients. Therefore, patients with comedo breast cancers may be a group that may benefit less from anti-angiogenic therapy.

Keywords

Angiogenesis

Breast cancer

Hormone influence

Hormone replacement therapy

Oral contraceptive pills

Spider telangiectasia

Introduction

Angiogenesis is one of the hallmarks [1] of breast cancer that is related to the malignancy of the tumor [2]. It has been shown that angiogenesis in breast tissue is regulated by hormones [3,4] through a response element in the gene coding for vascular endothelial growth factor (VEGF) [5]. However, the direction of angiogenic regulation by sex hormones is still disputed [6], indicating a complex relationship.

Spider telangiectasias (telangiectasias), also known as spider veins or spider angiomas, usually develop on the upper part of thorax, neck and face, and commonly develop in women during exposure to high amounts of estrogens [7], such as during pregnancy [8]. Patients who express telangiectasias in the skin have an increased ability to form vessels, due to hormonal influences. Telangiectasias in the skin can also be seen in patients with liver cirrhosis, and these patients have high serum levels of estrogens [9,10]. Due to high serum levels of sex hormones, estrogens among them, overweight postmenopausal women are at increased risk of developing breast cancer [11].

Angiogenesis in tumors often occurs via angiogenic sprouting. This process involves many different signaling pathways, such as secretion of basic fibroblast growth factor (bFGF) and VEGF by the tumor. Tumors recruit endothelial cells from normal healthy tissue in nearby vessels, inducing sprouting towards the site of secretion [2,12]. One study by Coradini *et al*. showed that VEGF is differentially expressed between ductal and lobular breast cancer: with higher concentrations in ductal breast cancer and lower concentrations in lobular breast cancer [13]. Dabrosin *et al*. has shown in several studies that estradiol induces angiogenesis in breast cancer via the VEGF pathway [14-21].

We hypothesize that the angiogenetic status of the tumor tissue resembles the normal tissue in the patient. If a patient has a higher propensity to form telangiectasias in the skin, the same could be true for the tumor, and telangiectasias may serve as a proxy marker for the angiogenic status of the tumor. In a recent publication by Jubb *et al.* the need for different kinds of markers indicating whether or not angiogenic therapy is appropriate for each patient was lifted [22].

The primary aim of the study was to investigate the relationship between the occurrence of telangiectasias and tumor histopathology, body weight, height, receptor status, and endogenous and exogenous hormonal factors in a cohort of breast cancer patients. The second aim was to study the occurrence of telangiectasias in relation to overall survival.

Material and methods

Patient material

The 1682 breast cancer patients included in this study were all seen by one physician between January 1 1980 and June 1 2009 at the Department of Oncology, Skåne University Hospital, Lund. A standardized questionnaire was filled-out by the physician. Information regarding previous family history of cancer, as well as reproductive and hormonal factors was obtained. Additional information concerning date of diagnosis, pure histopathologic subtype, estrogen receptor (ER) - and progesterone receptor (PR - status) was collected from pathological reports and patients' charts. Pathological slides were not reexamined. Follow-up was performed until 1st of June 2009. The Department of Oncology, Skåne University Hospital in Lund has a population-based catchment area of approximately 300'000 inhabitants, serving the Southern Health Care region in Sweden with adjuvant and metastatic treatment of breast cancer. Informed consent was obtained from all patients in the study, and the study was approved by an ethical board in Sweden.

Occurrence of telangiectasias were assessed on the upper thorax, head and neck [23, 24] by the physician and recorded as yes/no. Weight, height, ever-use of oral contraceptive pills (OCP) and ever-use of hormone replacement therapy (HRT) were self-reported.

Life-time number of menstrual cycles was calculated as follows: number of cycles per year with the menstrual cycle lengths estimated as 28 days, starting from the age at menarche and ending at the age of menopause. We deducted nine months per full-term pregnancy, and actual reported breast-feeding time.

Information regarding ER and PR status was missing in 581 and 619 cases, respectively, due to the fact that it was not performed in the clinic at the time of diagnosis for these patients.

None of the patients in our study had a diagnosis of cirrhosis or a past history of treatment for alcohol-related liver disease.

Statistics

All statistical analyses were performed using IBM SPSS© 19.0. To stratify between pre- and postmenopausal breast cancer patients, the median age at menopause in the material was retrieved; 50 years old, which was then used as a cut-off between pre- and postmenopausal breast cancer patients in following analysis.

Only pure histopathologic types of breast cancer were used. Mixed, rare subtypes and those cases where it was only known to be an adenocarcinoma were grouped as others and used as a reference group. Comedo cancers were excluded from the multivariate model as none of the patients had telangiectasias.

The occurrence of telangiectasias at time of breast cancer diagnosis was studied in a logistic regression in relation to the different histopathologic subtypes (y/n), ever-use of oral contraceptives (OCP) (y/n), ever-use of hormone replacement treatment (HRT) (y/n), height (m) and weight (kg) and life-time number of menstrual cycles of the patients (linear). Odds Ratios (OR) were estimated with 95% confidence intervals (CI).

The overall survival for patients with occurrences of telangiectasias at time of breast cancer diagnosis was studied using Kaplan-Meier compared to those patients without.

The hazard for patients with occurrence of telangiectasias (y/n) at time of breast cancer diagnosis was studied using a cox regression model including age at diagnosis (linear), tumor size status (T1, T2, T3 or T4) and positive node status (N0, N1, N2 or N3). Hazard rations (HR) were estimated with 95% CI.

Two-tailed P-values were used for all analyses. A P-value of less than 0.05 was regarded as significant.

Results

Patient characteristics

The present study included 1682 women diagnosed with breast cancer. The most common histopathologic subtype was ductal breast cancer (42%), followed by comedo (9%), lobular (8%), tubular (3%), and mucinous breast cancer (1%). Rare subtypes and/or mixed diagnoses constituted the last 37%, and were grouped as "Others". "Others" included 14% *in situ* tumors Median age at diagnosis was 56 years, (range 23-90 years). Patients with comedo carcinoma were younger than patients with the other subtypes of breast cancer; median age at diagnosis was 50 years, (range 27-80 years). Patients with mucinous breast cancers were older: median age at diagnosis was 62 years, (range 37-79 years). Tumor grade was evenly distributed among the histopathologic subtypes, with the exception of tubular and mucinous breast cancers that were more often grade 1. Tumor size status (T) was evenly distributed among the histopathologic subtypes, with the exception of tubular cancer that were more often T1 (91%), compared to the other subtypes. A similar pattern was seen in node status, were tubular and mucinous breast cancers were differently distributed compared to the other subtypes (Table 1). Tumors from patients with occurrences of telangiectasias were more often T1 (70% vs 49%), whereas node status was evenly distributed in both groups (Table 2).

Ever-use of hormones and hormone receptor status

Compared to the group of breast cancer patients without occurrences of telangiectasias at time of diagnosis, ever-use of OCP was more common in the patient group with occurrence of telangiectasias. The same was true for ever-use of HRT. Parity had a similar pattern in both groups (Table 2). Ever-use of OCP was higher in patients with comedo carcinoma and lower in patients with mucinous carcinoma. Ever-use of OCP was evenly distributed among the remaining histopathologic subtypes. Ever-use of HRT was less common in patients with comedo and mucinous breast cancer (12%), and more common among patients with tubular and lobular breast cancers (28% and 27%) respectively. Parity was evenly distributed throughout the different histopathologic subtypes, with the exception of patients with mucinous breast cancer who were more often nulliparous. In the cohort, 68% were ER-positive and 58% were PR-positive were this information was available (Table 1). Tumors from patients with occurrence of telangiectasias were often ER-and PR-positive (Table 2).

Patients with occurrence of telangiectasias

Telangiectasias were evenly distributed among all histopathologic subtypes with the exception of comedo carcinoma, where no patients displayed telangiectasias. Patients with telangiectasias had a slightly higher median age at diagnosis compared to patients without telangiectasias. Patients with and without telangiectasias were similar with respect to height, but did differ in weight: 70.8 kg in patients with telangiectasias compared to 66.6 kg in patients without telangiectasias (Table 2). The mean height of all patients was 1.64 m, with very little difference between the different subtypes. The mean weight was 66.4 kg (Table 1).

Logistic regression

In the first model we adjusted for all variables simultaneously: histopathologic subtypes, age at diagnosis, parity, ever-use of OCP and HRT, height, weight and life-time number of cycles. Age at diagnosis OR 1.03 (CI 1.00-1.06), weight OR 1.02 (CI 1.00-1.05), ever-use of OCP OR 2.67 (CI 1.55-4.63) and HRT OR 2.68 (CI 1.63-4.39) were all positively associated with the occurrence of telangiectasias. Parity was not significant in this model (Table 3a).

Stratification according to age at diagnosis

We performed a second analysis, this time stratifying with a cut-off at 50 years old at time of diagnosis; pre- and postmenopause. There were no occurrences of telangiectasias in women diagnosed with lobular, tubular or mucinous cancer before age 50. In the younger patient-group the occurrence of telangiectasias were, with borderline significance, associated with increasing weight, OR 1.05 (CI 0.99-1.11), and, statistically significant, with decreasing number of children (parity), OR 0.49 (CI 0.27-0.89). In women diagnosed with breast cancer at age 50 or above, ever-use of OCP and HRT were both associated with increased occurrence of telangiectasias, OR 2.45 (CI 1.36-4.41) and OR 2.74 (CI 1.62-4.64), respectively (Table 3).

Stratification according to hormone receptor status

We then stratified the data according to ER- and PR-status, in the subgroup of patients where this information was available. In patients with ER-negative breast cancers, occurrence of telangiectasias was associated with increased ever-use of OCP and ever-use of HRT, OR 2.97 (CI 1.49 – 5.92) and OR 2.78 (1.45 – 5.32), respectively. In patients with ER-negative breast cancer, occurrence of telangiectasias was associated with higher

age at diagnosis, OR 1.10 (CI 1.03-1.18), increasing weight, OR 1.05 (CI 1.00 – 1.10) per kg, and increased ever-use of OCP, OR 9.57 (CI 2.11-43.28) and HRT, (OR 6.81 (CI 1.90-24.34). In patients with PR-positive tumors, occurrence of telangiectasias showed a similar pattern compared to patients with ER-positive tumors. The same was true for patients with PR-negative tumors, where occurrence of telangiectasias showed a pattern similar to that observed in patients with ER-negative tumors. The exceptions were weight and HRT, which lost their statistical significance, while ever-use of HRT was of borderline significance (Table 4).

Survival analysis

We performed survival analyses to investigate possible differences in overall survival between women with occurrences of telangiectasias and those without. The patient material was subdivided according to widely used age-groupings criteria according to age at diagnosis; diagnosed before age 50, diagnosed at age 50 to age 65, and diagnosed after age 65. Breast cancer patients with occurrence of telangiectasias diagnosed before age 50 had a non-significant, worse overall survival compared to those without. Patients with occurrence of telangiectasias diagnosed with breast cancer equal to or after age 50 and equal to or less than 65 years old had a better overall survival, (log rank P=0.03). Patients with occurrence of telangiectasias diagnosed after the age of 65 also had a better overall survival, log rank P=0.018. Since the outcome for overall survival for patients diagnosed at age 50-65 and later than 65 was similar, these two age-groups were merged in following analyses. In order to determine whether it was the HRT-intake that was responsible for the improved overall survival in the older patient group with telangiectasias, we performed a Kaplan-Meier analysis stratified according to ever-use of HRT. Regardless of HRT status, women with occurrence of telangiectasias had a better overall survival; however, the model did not reach statistical significance (Figure 1). An effect modification of age at diagnosis on the occurrence of telangiectasias was seen (beta value 3.03, P=0.016) (data not shown).

Cox regression

The second step was to use cox regression. In the first analysis, age at diagnosis was associated with longer survival in patients diagnosed before the age of 50, HR 0.97 (CI 0.95 – 1.00) per year. In patients diagnosed at age 50 years or older, age at diagnosis was associated with shorter survival, HR 1.07 (CI 1.06-1.08) per year, whereas the occurrences of telangiectasias were associated with longer survival, HR 0.50 (CI 0.30 – 0.82) (Table 5a). We added known prognostic factors such as tumor size (T-status; 1, 2, 3, 4) and positive nodal status (N-status; 0, 1, 2, 3) to the model, this had little impact on the previous results except for loss of statistical

significance in the association between to age at diagnosis and survival in patients diagnosed before age 50. As expected, increasing T-status and N-status were associated with shorter survival in women diagnosed with breast cancer before and after age 50 (Table 5b). In an analysis stratified according to ER-status, the occurrence of telangiectasias was associated with longer survival in patients with ER-negative tumors, HR 0.34 (CI 0.09 – 0.96), in women 50 years or older at breast cancer diagnosis. This risk reduction was not seen in patients with ER-positive tumors (data not shown).

Discussion

The main findings were the positive associations between the occurrence of telangiectasias and age at diagnosis, weight, ever-use of OCP and HRT in women with breast cancer, and the negative association between the occurrence of telangiectasias and parity in women diagnosed with breast cancer before age 50. Occurrence of telangiectasias at time of breast cancer diagnosis was also associated with a better overall survival when diagnosed at age 50 and above.

To our knowledge, no studies have been performed investigating the occurrence of telangiectasias in breast cancer, and it's relation to survival. There are little empirical data published on the occurrence of telangiectasias in relation to hormones. Similar to the study by Li *et al.* [10], we found a positive association between age at diagnosis and the occurrence of telangiectasias, which suggests that age is a risk factor for the occurrence of telangiectasias. However, this positive association was only seen in patients diagnosed at age 50 or above. It is difficult to know whether age in itself is the risk factor or if age functions as a proxy marker for something else. Since the models we used were corrected for many hormonal factors, age is unlikely to be a proxy marker for these hormonal factors.

There was a significant interaction between age at diagnosis and the occurrence of telangiectasias on overall survival. In younger patients the occurrence of telangiectasias was non-significantly associated with a shorter overall survival, and in this age group, most deaths are breast cancer related. In older patients the occurrence of telangiectasias at time of breast cancer diagnosis was associated with an overall longer survival.

The association between the occurrence of telangiectasias and weight was not surprising considering the increased level of hormones in serum in overweight postmenopausal women, [23] and the hormone sensitivity of telangiectasias.

Considering the hormone sensitivity in the occurrence of telangiectasias, we strived towards including different kind hormone measures to investigate if the occurrence of telangiectasias could be linked to a specific hormonal factor or a specific time during life. Using weight, parity, and number of menstrual cycles allowed us to measure a large part of the exposure to endogenous hormones of a woman's reproductive years [24,25], and ever-use of OCP's and HRT make up most of the exogenous hormones used by women. We have previously reported that HRT was associated with longer overall survival regardless of ER-status, from a subset of 984 patients of this cohort [26]. Ever-use of both OCP and HRT seemed to be important regardless of stratification since the effect size was similar in all models. The exception was in ER-negative tumors where ever-use of OCP had a larger effect size than HRT. However, this difference should be viewed with caution since the subgroup analysis was done on a smaller sample size.

Perhaps a distinction should be made between patients that are ever-users of OCP's diagnosed with comedo breast cancer and those diagnosed with other histopathologic subtypes of breast cancer. The histopathologic subtype with most ever-users of OCP was comedo breast cancer. Yet, patients with comedo breast cancer showed no occurrences of telangiectasias in our cohort. It could be so that the etiology of comedo breast cancer is different than other subtypes of breast cancer [27]. Comedo breast cancer is often ER-negative [28] and might therefore depend on different proliferation pathways compared to those tumors commonly induced by HRT use for instance. This needs to be further elucidated.

Increasing parity was associated with fewer telangiectasias in patients with ER-negative tumors. With increasing number of children the risk of developing telangiectasias decreased, in the models which were not adjusted for breast-feeding duration. However, it made no difference to adjust for breastfeeding duration of first child in our models, the same results were seen and there was no association between breastfeeding duration of first child and the occurrence of telangiectasias. We find this interesting since pregnancy in itself is a previously known risk factor for developing telangiectasias in the skin [8]. This finding indicates that the protective mechanism in parity might be different from the pregnancy itself. This needs to be further studied.

Menopausal status and ER- and PR-status seems to have limited impact on the different hormonal factors' association to the occurrence of telangiectasias, seeing that a difference in the variables was only noted in parity. However, they seem to be of greater importance regarding overall survival since both menopausal status and ER-status influenced the association between survival and the occurrence of telangiectasias at breast cancer diagnosis. Since women diagnosed with breast cancer at age 50 or above are more probable to be postmenopausal, and thereby are more expected to have ER-positive tumors, they are more likely to have received anti-hormonal therapy. The anti-hormonal therapy could be one explanation for the improved survival for the patients with occurrences of telangiectasias, considering the hormonal association in telangiectasias. Another, highly speculative, explanation could be that since patients with occurrences of telangiectasias are more prone to form vessels, the quality of their intra-tumor vessels are better which could serve as help for transportation of the therapeutics into the site of the tumor.

Our theory is that the tendency to form vessels is similar in normal tissue and in tumor tissue, which could explain the necrotic core in comedo carcinoma. Comedo carcinomas have been noted to have high microvessel density [29], indicating ability to form vessels. However, comedo carcinoma also has a necrotic core, indicating that even though the microvessel density is high, the angiogenetic process is defect. It has been hypothesized that the necrotic core is due to the high growth rate of the tumor or increased intra-tumor pressure [30], but it might also be due to a decreased ability to form lasting vessels. One reason could be down-regulation, decrease or loss of VEGF via, for example an estrogen-dependent pathway [12]. This needs to be further studied.

The Department of Oncology of Skåne University hospital in Lund is the responsible university hospital for radio- and chemotherapy patients that are referred to for these types of treatment. Patients are not referred to other hospitals and this is therefore a population-based cohort from the Southern Health Care Region. The reason for the slightly younger median age at diagnosis compared to the general median age at diagnosis in Sweden (63 years old in 2008) could be due to the fact that older patients and patients that were only treated with surgery and not with adjuvant therapy (stage I) may not be referred to the Department of Oncology at Skåne University hospital in Lund. Overall the hospital receives around 60% of all breast cancer cases for therapy. Therefore our results may not fully be applicable to patients with stage I breast cancers or with a high age at diagnosis. Except for the slightly younger population, other recruitment biases seem unlikely. The material was collected for

research purposes, through a structured interview by the physician reducing the possibilities for different types of biases.

Conclusions

The occurrence of telangiectasias was associated with hormonal risk factors such as weight, ever-use of OCP and HRT and parity. It was also associated with better overall survival in older breast cancer patients. We propose that patients with occurrences of telangiectasias at time of breast cancer diagnosis in women diagnosed especially before age 50 may be beneficiary of anti-angiogenic therapy, and that patients with comedo breast cancer are a group of patients that may benefit less from anti-angiogenic therapy. This need to be tested within the scope of randomized clinical trials using anti-angiogenic therapy.

Competing interests

The authors declare that they have no competing interests'.

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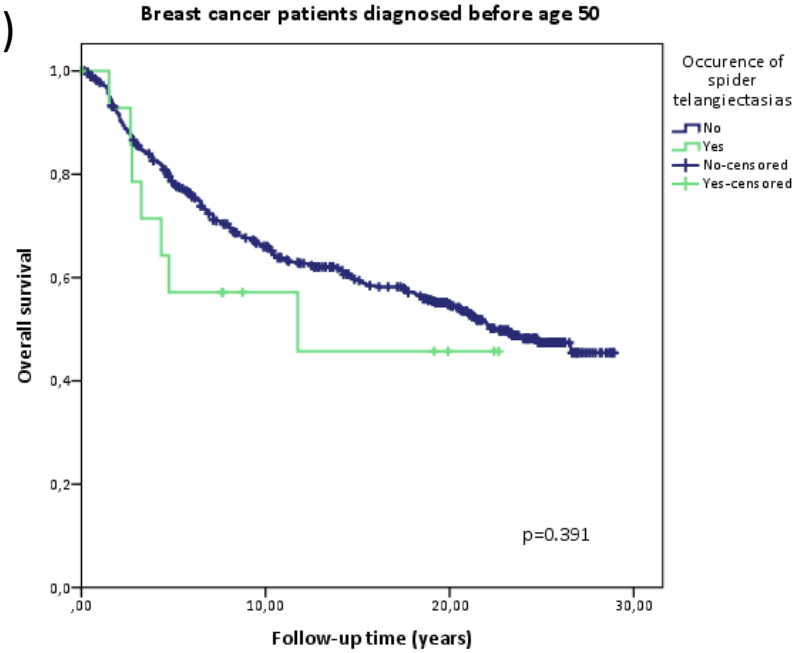
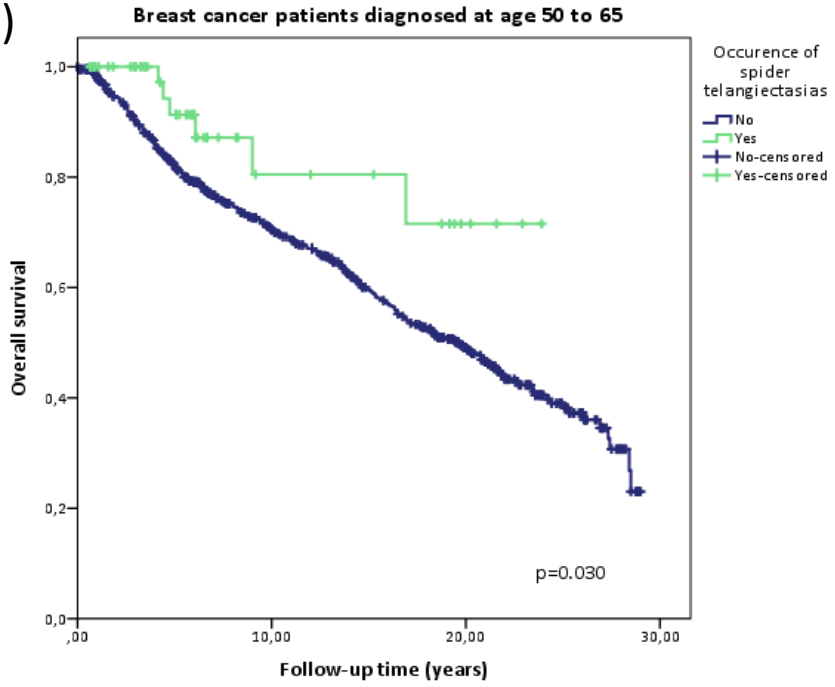
Figure 1 Overall survival of patients with occurrence of spider telangiectasias, stratified according to age at diagnosis. Kaplan-Meier of the occurrence of telangiectasias at time of diagnosis stratified based upon age at time of diagnosis; a) before 50 years of age (N=554), b) 50 to 65 years of age (N=718), and c) after 65 years of age (N=410). Log-rank tests were performed individually for each Kaplan-Meier analysis and are presented in each diagram respectively. The log-rank for all three models simultaneously was P=0.008. The overall survival for patients with occurrence of spider telangiectasias at time of diagnosis was worse for patients diagnosed before age 50 (a), and better for all patients diagnosed age 50 or after (b-c).

a)


Breast cancer patients diagnosed before age 50
Occurence of spider telangiectasias
No
Yes
No-censored
Yes-censored
Overall survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
10,00
20,00
30,00
Follow-up time (years)
p=0.391

b)


Breast cancer patients diagnosed at age 50 to 65
Occurence of spider telangiectasias
No
Yes
No-censored
Yes-censored
Overall survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
10,00
20,00
30,00
Follow-up time (years)
p=0.030

c)

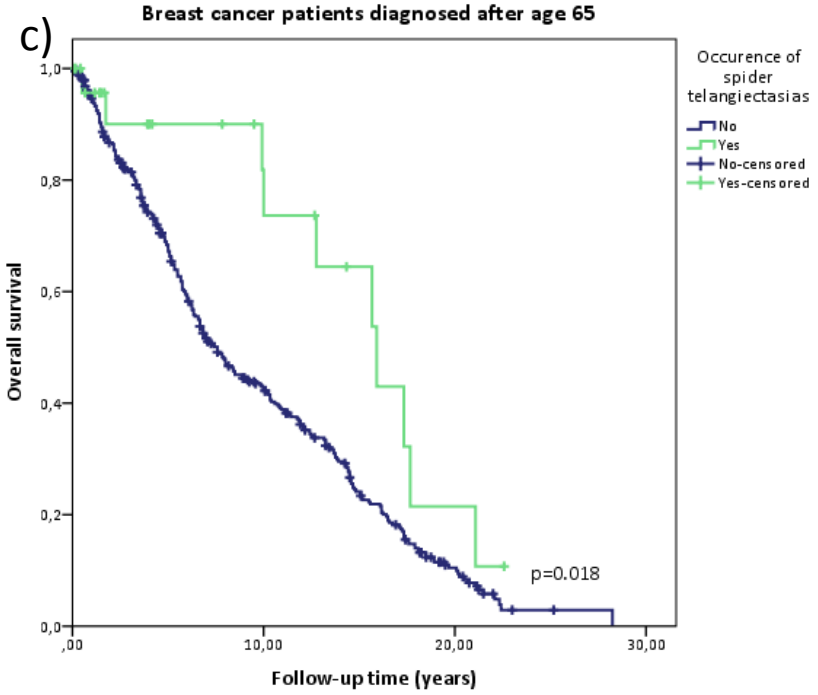

Breast cancer patients diagnosed after age 65
Occurence of spider telangiectasias
No
Yes
No-censored
Yes-censored
Overall survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
10,00
20,00
30,00
Follow-up time (years)
p=0.018

Table 1 Patient and tumor characteristics in relation to histopathology

	All	Ductal	Comedo	Lobular	Tubular	Mucinous	Others
Age at diagnosis: median(range)	56 (23-89)	58 (24-90)	50 (27-80)	60 (33-84)	55 (35-79)	62 (37-79)	55 (24-87)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of cases:	1682	701 (42)	150 (9)	141 (8)	43 (3)	25 (1)	622 (37)
Tumor grade*:							
1	468 (28)	206 (29)	29 (19)	35 (25)	26 (60)	10 (40)	162 (26)
2	679 (40)	308 (44)	69 (46)	53 (38)	14 (33)	10 (40)	225 (36)
3	368 (22)	165 (24)	44 (29)	45 (32)	2 (5)	3 (12)	109 (18)
4	28 (2)	9 (1)	3 (2)	5 (4)	0 (0)	l (4)	10 (2)
Height mean(m)	1.64	1.64	1.65	1.64	1.66	1.63	1.64
Weight mean(kg)	66.4	67.5	64.6	68.5	67.8	66.5	66.2
OCP ever-use:	702 (42)	296 (42)	76 (51)	59 (42)	18 (42)	4 (17)	249 (40)
HRT ever-use:	318 (19)	129 (19)	18 (12)	38 (27)	12 (28)	3 (12)	121 (20)
No. of children:							
0	277 (17)	118 (17)	23 (15)	22 (15)	8 (19)	9 (36)	105 (17)
1	313 (19)	129 (19)	26 (17)	26 (18)	7 (16)	5 (20)	119 (19)
2-3	954 (57)	411 (59)	85 (57)	81 (57)	24 (56)	11 (44)	342 (55)
≥4	127 (8)	36 (5)	16 (11)	13 (9)	4 (9)	0 (0)	58 (9)
T-size:							
0	84 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	84 (14)
1	838 (50)	366 (52)	63 (42)	66 (47)	39 (91)	13 (52)	291 (47)
2	595 (35)	281 (40)	69 (46)	54 (38)	4 (9)	7 (28)	180 (29)
3	120 (7)	49 (7)	15 (10)	16 (11)	0 (0)	4 (16)	36 (6)
4	7 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (4)	5 (1)
Unknown:	38 (2)	5 (1)	2 (1)	5 (4)	0 (0)	0 (0)	26 (4)
Node status:							
0	712 (42)	279 (40)	49 (33)	50 (35)	28 (65)	15 (60)	291 (47)
1	576 (34)	269 (38)	54 (36)	46 (33)	12 (28)	8 (32)	187 (30)
2	228 (14)	99 (14)	25 (17)	30 (21)	2 (5)	1 (4)	71 (11)
3	100 (6)	41 (6)	17 (11)	12 (9)	0 (0)	0 (0)	30 (5)
Unknown:	66 (4)	13 (2)	5 (3)	3 (2)	1 (2)	1 (4)	43 (7)

*Carcinoma *in situ* tumors are not included.

Table 2 Characteristics in relationship to the occurrence of spider telangiectasias at time of breast cancer diagnosis

	Spider Telangiectasia			
	Yes		No	
Age at diagnosis: median(range)	59 (32-79)		56 (24-90)	
Number of cases:	93	100%	1590	100%
Ductal	46	49%	655	41%
Comedo	0	0%	150	9%
Lobular	10	11%	131	8%
Tubular	3	3%	40	3%
Mucinous	1	1%	24	2%
Others:	33	35%	589	37%
Height mean(m)	1.65		1.64	
Weight mean(kg)	70.8		66.6	
OCP ever-use:	50	54%	652	41%
HRT ever-use:	39	42%	293	18%
Hormone receptor status:				
ER-positive	59	81%	690	67%
ER-negative	14	19%	338	33%
ER-missing	20		561	
PR-positive	50	69%	565	57%
PR-negative	22	31%	426	43%
PR-missing	21		598	
No. of children:	1,85			
0	19	20%	266	17%
1	11	12%	297	19%
2-3	58	62%	881	55%
≥4	3	3%	42	3%
T-size:				
0	3	3%	81	5%
1	65	70%	773	49%
2	21	23%	574	36%
3	3	3%	117	7%
4	0	0%	7	0%
unknown:	1	1%	45	3%
Positive node status:				
0	49	53%	663	42%
1	30	32%	546	34%
2	8	9%	220	14%
3	4	4%	96	6%
Unknown:	1	1%	38	2%

Table 3 Risk of occurrence of spider telangiectasias in relation to different hormonal factors and age

a) Including all, N=1469

	OR	95% CI for OR		P-value
		Lower	Upper	
Age at diagnosis	**1.04**	**1.01**	**1.06**	**0.007**
Weight	**1.02**	**1.00**	**1.05**	**0.018**
OCP (ever-use)	**2.69**	**1.57**	**4.57**	**0.0003**
HRT (ever-use)	**2.52**	**1.57**	**4.06**	**0.0001**
Parity	0.90	0.74	1.10	0.304

b) Stratified according to age at diagnosis, N= 481 and 907, respectively.

	Younger than 50 at diagnosis				Equal to, or older than 50 at diagnosis			
	OR	95% CI for OR		P-value	OR	95% CI for OR		P-value
		Lower	Upper			Lower	Upper	
Age at diagnosis	0.94	0.68	1.29	0.692	1.01	0.98	1.05	0.496
Weight	*1.05*	*0.99*	*1.11*	*0.077*	1.02	1.00	1.04	0.089
OCP (ever-use)	3.44	0.67	17.75	0.141	**2.45**	**1.36**	**4.41**	**0.003**
HRT (ever-use)					**2.74**	**1.62**	**4.64**	**0.0002**
Parity	**0.49**	**0.27**	**0.89**	**0.018**	1.03	0.82	1.29	0.804

a) Occurrence of spider telangiectasia at the time of breast cancer diagnosis in relation to age at diagnosis, weight, ever-use of both HRT and OCP and parity. b) Occurrence of spider telangiectasias at the time of breast cancer diagnosis stratified using age 50 as cut-off, which was the median age at menopause in the material. Both models were adjusted for histopathologic subtype; ductal, lobular, tubular, mucinous breast cancer, height and life time no of cycles simultaneously.

Table 4 Occurrence of spider telangiectasias related to different hormonal factors, stratification according to ER- and PR-status.

Occurrence of spider telangiectasias	ER+				ER-			
	OR	95% C.I. for OR		P-value	OR	95% C.I. for OR		P-value
		Lower	Upper			Lower	Upper	
Age at diagnosis	1.03	0.99	1.07	0.126	**1.10**	**1.03**	**1.18**	**0.006**
Weight	1.02	0.99	1.04	0.257	***1.05***	***1.00***	***1.10***	***0.057***
OCP (ever-use)	**2.97**	**1.49**	**5.92**	**0.002**	**9.57**	**2.11**	**43.28**	**0.003**
HRT (ever-use)	**2.78**	**1.45**	**5.32**	**0.002**	**6.81**	**1.90**	**24.34**	**0.003**
Parity	1.02	0.77	1.34	0.916	0.96	0.57	1.60	0.863

Occurrence of spider telangiectasias	PR+				PR-			
	OR	95% C.I. for OR		P-value	OR	95% C.I. for OR		P-value
		Lower	Upper			Lower	Upper	
Age at diagnosis	1.02	0.98	1.06	0.284	**1.10**	**1.04**	**1.16**	**0.001**
Weight	1.02	0.99	1.05	0.133	1.02	0.98	1.07	0.278
OCP (ever-use)	**2.74**	**1.30**	**5.77**	**0.008**	**8.18**	**2.45**	**27.28**	**0.001**
HRT (ever-use)	**3.62**	**1.79**	**7.36**	**0.0004**	2.49	0.89	6.97	0.083
Parity	0.97	0.72	1.32	0.869	1.25	0.82	1.91	0.302

Occurrence of spider telangiectasia at time of breast cancer diagnosis was used as dependent variable, and was stratified according to ER- and PR-status. The models were adjusted for height and life-time number of menstrual cycles simultaneously. Included in the analyses: ER-positive N=590, ER-negative N=298, PR-positive N=489 and PR-negative N=368, respectively.

Table 5 Survival analysis for occurrence of spider telangiectasias related to age at diagnosis, T-status, and N-status.

a) Number of patients included in the analysis N= 552, and N=1128 respectively.

	Younger than 50 years at diagnosis				50 years and older at diagnosis			
	HR	95% CI for HR		P-value	HR	95% CI for HR		P-value
		Lower	Upper			Lower	Upper	
Age at diagnosis	**0.97**	**0.95**	**1.00**	**0.033**	**1.07**	**1.06**	**1.08**	**<0.0001**
Spider telangiectasias	1.42	0.67	3.01	0.362	**0.50**	**0.30**	**0.82**	**0.006**

b) Number of patients included in the analysis N=534, and N=1077 respectively.

	Younger than 50 years and older				50 years and older at diagnosis			
	HR	95% CI for HR		P-value	HR	95% CI for HR		P-value
		Lower	Upper			Lower	Upper	
Age at diagnosis	*0.98*	*0.96*	*1.00*	*0.077*	**1.07**	**1.05**	**1.08**	**<0.0001**
Spider telangiectasias	1.60	0.76	3.41	0.224	**0.52**	**0.31**	**0.87**	**0.013**
T1	1.00	ref.	ref.		1.00	ref.	ref.	
T2	**1.51**	**1.13**	**2.01**	**0.005**	**1.58**	**1.32**	**1.90**	**<0.0001**
T3	**4.18**	**2.80**	**6.24**	**<0.0001**	**2.28**	**1.69**	**3.07**	**<0.0001**
T4	**101.86**	**11.13**	**931.99**	**<0.0001**	**3.32**	**1.23**	**8.95**	**0.018**
N1	1.00	ref.	ref.		1.00	ref.	ref.	
N2	**2.45**	**1.75**	**3.43**	**<0.0001**	**1.46**	**1.18**	**1.82**	**0.001**
N3	**3.07**	**1.85**	**5.09**	**<0.0001**	**2.23**	**1.68**	**2.96**	**<0.0001**

a) Model includes age at diagnosis and occurrence of spider telangiectasias stratified based on age at time of breast cancer diagnosis; cut-off used was 50 years old, which was the median for menopause age in the cohort.

b) Model includes age at diagnosis, occurrence of spider telangiectasias and T-and N-status for the tumors.