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HISTOPATHOLOGIC AND CYTOCHEMICAL CHARACTERISTICS OF INTERVAL BREAST CARCINOMAS FROM THE STOCKHOLM MAMMOGRAPHY SCREENING PROJECT

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Combined morphological and cytochemical malignancy grading in addition to tumor stage was applied to assess the malignant potential of so-called interval carcinomas from the Stockholm randomized mammography screening study. Only interval carcinomas surfacing within two years from screening were included. Fifty-four percent of the tumors were in stage I and 46% of the carcinomas eligible for DNA analysis were diploid, i.e. low-malignant. An overrepresentation of prognostically unfavorable tumor characteristics was found only within the subgroup 'true' and 'early' interval cancer.

So-called interval carcinomas, i.e. tumors surfacing in the interval between two rounds of mammographic screening, were initially thought to represent a subset of highly aggressive breast neoplasias (1). This concept has later been challenged by reports showing that the prognosis of patients with interval carcinomas is similar to that of other patients with clinically detected breast cancer (2, 3) which also agrees with the findings that the so-called interval cancers constitute a heterogenous group (4).

It has been suggested that the first round of mammographic screening detects predominantly slowly growing carcinomas (5), whereas tumors diagnosed clinically during the interval between screenings would be of higher malignancy potential (6).

The incidence of interval cancer in the Stockholm screening trial rose with the length of the interval in the whole age-group, 40–64 years. During the final six months of the two-year interval, the incidence of interval cancer was 80% of the cancers detected in the control group during the same period (7). A more rapid increase in interval cancers among women aged 40–49 than in those aged 50 and above was reported from another Swedish trial, the two-county (WE), indicating a more rapid tumor growth in the younger age group (8). The distribution of rapidly growing, highly aggressive tumors during the interval and their relation to the age of the patients would have an impact on the estimation of an adequate length of the interval with a possible differentiation with regard to the age of the screened women.

Material and Methods

The patient material comprised 125 women who participated in the Stockholm screening trial where women aged 40–64 were offered to be screened twice with a single view mammogram with an interval of two years. The outline and results of the trial have been described in detail by Frisell et al. (9). All carcinomas were detected clinically either during the two years between the first and the second screening round ($n = 58$) or within two years after the second screening ($n = 67$). One hundred and nineteen patients underwent either modified radical mastectomy or partial mastectomy, axillary dissection and postoperative irradiation as primary treatment of resectable breast cancer. Two patients had only a local resection and four patients were not operated on primarily due to locally advanced and/or metastatic disease.

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The mammographic examinations were undertaken with a CGR mammograph model Senograph 500 T. Kodak OM-A film was used together with Kodak mammography cassettes and Kodak Min-R intensifying screens. A single oblique view ad modum Lundgren was used for screening (10). If malignancy was suspected, the patient was recalled for a conventional three-view mammogram.

All mammograms were re-scrutinized and the tumors classified as 'true' interval cancer (A), 'observer error' (B), 'unrecognized' (C) or 'technical error' (D) according to previously described definitions (4, 11). When no sign of tumor was seen on the previous mammogram, the cancer was called 'true' interval cancer. The 'observer error' cases were cancers missed because of obvious oversight by the examinor. The cancer was classified as 'unrecognized' when subtle increase of density or a structural variation was seen on a previous mammogram but the disarrangement of parenchymal pattern was not indicative enough of malignancy for the radiologist to recommend a biopsy, even retrospectively, when the subsequent diagnosis was known to the examinor. 'Technical errors' represented tumors positioned outside the imaging field.

The original histopathologic slides were all reviewed by a senior pathologist (RN). The ductal carcinomas were classified as tubuloductal or ductal carcinoma of comedo type according to a modification of the WHO classification (12) proposed by Linell. This classification splits invasive ductal carcinomas into two biologically different groups which has been shown to have prognostic implications (13). Tumor stage was assessed according to the UICC criteria (14).

The DNA measurements were performed on 4 μm thick sections of archived, paraffin-embedded material by means of a modification of the image cytophotometric method described by Adams based on light transmission of Feulgen-stained tumor nuclei (15). Approximately 100 tumor cells were measured in each tumor. Fifty control cells were measured in order to identify the normal diploid (2c) values. The tumors were classified as 'euploid' or 'aneuploid' according to their histogram type ad modum Auer et al. (16): tumors with DNA values predominantly in the normal, diploid (2c) and/or tetraploid (4c) regions were categorized as euploid i.e. low malignant whereas tumors with highly increased and scattered DNA values were considered as aneuploid, i.e. highly malignant.

Results

The distribution of tumor stage (pTNM) is shown in Table 1. With the exception of six patients who had distant metastases and/or advanced local tumor growth at the time of diagnoses, all patients (119) were primarily treated with modified radical mastectomy or partial mastectomy and axillary dissection.

Of the carcinomas detected during the two intervals 30/58 (51.7%) and 48/67 (71.6%) respectively were classified as 'true' interval cancer. The distribution of mammographic subgroups is shown in Table 2. There was no overrepresentation of 'true' interval cancer in women under 50 years of age (22/32 = 68.8%) compared to older women (56/93 = 60%).

Tumor material suitable for DNA measurements was obtained from 99 tumors. Histopathologic classification and results of DNA analyses are shown in Tables 3 and 4. As many as 33/37 (89%) of the ductal carcinomas of comedo type were aneuploid which is in concordance with the observation by Linell & Rank (13) that this histologic subgroup is associated with an increased risk of early death as compared to the tubuloductal type, where 15/40 (37, 5%) exhibited increased and scattered DNA values exceeding the normal range, indicative of DNA aneuploidy. Eight lobular carcinomas eligible for DNA analysis were euploid as were all tubular carcinomas which agrees with previous reports (17, 18).

Twenty out of 33 (61%) and 33/66 (50%) of the tumors analysed for DNA ploidy and detected during the first and second year respectively after screening were DNA aneuploid. Thus, aneuploid carcinomas constituted 54% of the

Table 1

Relationship between tumor stage (pTNM) and length of interval in 119 patients operated with modified radical mastectomy or partial mastectomy and axillary dissection (all M0)

Stage	Interval I		Interval II	
	≤ 1 yr	> 1 yr ≤ 2 yrs	≤ 1 yr	> 1 yr ≤ 2 yrs
Tis	4	2	1	3
T1N0	9	14	9	26
T1N1	1	8	2	10
T2N0	3	3	3	5
T2N1	1	7	4	2
T3N0	0	0	0	0
T3N1	0	1	1	0
Total	18	35	20	46

Table 2

Distribution of mammographic subgroups (n = 125)

	Interval I		Interval II	
	≤ 1 yr	> 1 yr ≤ 2 yrs	≤ 1 yr	> 1 yr ≤ 2 yrs
A	8	22	15	33
B	5	7	1	1
C	5	8	5	12
D	2	1	0	0
Total	20	38	21	46

Tumors classified as 'true' interval cancer (A), 'observer error' (B), 'unrecognized' (C) or 'technical error' (D).

Table 3

Histopathologic classification of 121 mammary carcinomas

Histopathological type	n	(%)
Tubular carcinoma	5	(4.1)
Tubuloductal carcinoma	53	(43.8)
Ductal carcinoma of comedo type	38	(31.4)
Ductal carcinoma in situ	8	(6.6)
Lobular carcinoma	10	(8.2)
Lobular carcinoma in situ	2	(1.7)
Mucinous carcinoma	2	(1.7)
Medullary carcinoma	1	(0.8)
Intracystic papillary carcinoma with invasive growth	2	(1.7)

Table 4

Distribution of DNA ploidy in 90 invasive mammary carcinomas (only main histological subgroups included)

	Euploid	Aneuploid
Tubular carcinoma	5	0
Tubuloductal carcinoma	25	15
Ductal carcinoma of comedo type	4	33
Lobular carcinoma	8	0
Total	42	48

whole material which equals the proportion found in an unselected population with clinically detected breast cancer (19, 20). An overrepresentation of aneuploid tumors was found exclusively among the early (i.e. surfacing within one year from screening) 'true' interval carcinomas (13/16 = 81%). Ductal carcinomas of comedo type were equally more frequent during the first than during the second year of each interval, 17/40 (42.5%) and 21/81 (25.9%) respectively.

Discussion

Screening mammography may primarily detect tumors which have a slow development (long sojourn time) but may also detect rapidly growing tumors (short sojourn time) with a higher sensitivity, provided the intervals between screening are shorter than the average sojourn time (21). Screening mammography is performed at arbitrary time intervals without taking biological characteristics, e.g. variations in tumor growth rate, into account. The generally applied two-year interval is probably not optimal which is indicated by the two-fold increase of clinically detected cancers during the second year. This seems, however, not to influence the distribution of prognostically unfavorable carcinomas.

The heterogeneity of interval carcinomas has been demonstrated in a previous study, where the highly aggressive tumors as judged from DNA ploidy, estrogen receptor content and axillary nodal involvement were found predominantly within the subgroup 'true' interval cancer (4). An overrepresentation of aneuploid, supposedly rapidly proliferating tumors was in the present report only demonstrated among the relatively few de novo carcinomas surfacing within one year from screening. A higher mortality could hypothetically be expected within this group of patients but is hardly likely to have an impact on the prognosis of the whole group of patients with interval carcinomas. Yet unpublished data from the Stockholm mammography screening trial rather indicate a higher overall survival in patients with interval cancer compared to patients with clinically detected cancers belonging to the control group. However, as has been shown in the recent report on mortality on the Stockholm trial (22), 17 (44%) of the 39 breast cancer deaths in the study (i.e. screened) population belonged to the interval group. Comparative studies of various tumor characteristics within the different subgroups from the trial are now in progress.

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