# Risk for Distant Recurrence of Breast Cancer Detected by Mammography Screening or Other Methods

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**Context** Selection of systemic adjuvant therapies for women diagnosed as having breast cancer is based on risk estimations for cancer recurrence. In such estimations, tumors detected by mammography screening are considered to be associated with a similar risk of recurrence as tumors of similar size found by other methods.

**Objective** To compare the risk of recurrence and survival among women with cancerous tumors detected by mammography screening compared with other methods (outside of screening).

**Design, Setting, and Patients** Retrospective study comparing clinical, histopathological, and biological features of cancerous tumors detected by mammography screening compared with tumors detected outside of screening. Women diagnosed as having breast cancer in 1991 or 1992 were identified from the Finnish Cancer Registry (n=2842). The median follow-up time was 9.5 years. Cancer biological variables were analyzed from tumor tissue microarrays using immunohistochemistry or in situ hybridization and included *ERBB2*, *TP53*, and *MK167* expression and *ERBB2* amplification data.

**Main Outcome Measures** Univariate and multivariate analyses of potential risk factors for distant recurrence of breast cancer and 10-year survival.

**Results** Of the 1983 women with unilateral invasive breast cancer, data on tumor diameter were available for 1918 women. Women with cancerous tumors detected by mammography screening had better estimated 10-year distant disease-free survival than women with tumors found outside of screening (tumor size of ≤10 mm [n=386] 92% vs 85% [$P$=.04]; 11-20 mm [n=808] 88% vs 76% [$P$<.001]; 21-30 mm [n=409] 86% vs 63% [$P$=.008]; >30 mm [n=315] 68% vs 50% [$P$=.12], respectively). In a Cox multivariate model that included cancer biological factors, the relative hazard ratio for distant recurrence among women with tumors detected outside of screening (HR, 1.90; 95% confidence interval, 1.15-3.11) was significantly higher than among women with tumors detected by mammography screening ($P$=.01). Breast cancer diagnosis by mammography screening was an independent prognostic variable reducing the relative HR for distant recurrence. This effect was equal to or greater than the effect of 1-cm decrease in tumor diameter (HR, 1.20; 95% confidence interval, 1.10-1.31).

**Conclusions** Cancerous tumors detected by mammography screening are associated with a better prognosis than tumors of similar size found outside of screening. The risk of distant metastases is overestimated for women diagnosed as having cancer by mammography screening unless the method of detection is taken into account in risk estimations.

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THE INCIDENCE OF CANCEROUS tumors detected by mammography screening is increasing due to its expanding use. In general, women with cancerous tumors detected by screening have more favorable prognoses than women whose tumors were found outside of screening or tumors that are detected between screening rounds.[1-7] However, the generally favorable prognoses of women with cancerous tumors detected by mammography screening may be attributable to several biases, such as selection bias (the population screened is not representative of the general population), the lead-time bias (women with tumors detected by screening are diagnosed earlier during their natural history than women with tumors found outside of screening), the length bias (women with indolent tumors spend a longer time in the asymptomatic phase

**For editorial comment see p 1062.**

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than women with fast-growing tumors, and are, therefore, more likely to have tumors detected by screening), and possibly overdiagnosis (some tumors detected by mammography screening might have never surfaced during the woman's life span outside of screening).[8]

In general, cancerous tumors detected by mammography screening are smaller than those found outside of screening.[6,9-12] In addition, a few studies have found that cancerous tumors detected by screening have histological and biological features that are suggestive of a relatively low malignant potential compared with tumors detected between mammography screening rounds or tumors found outside of screening. In these studies, tumor detection by mammography screening has been linked with the presence of fewer axillary nodal metastases and less tumor necrosis, higher histological grade of differentiation, smaller mitotic counts, higher content of estrogen and progesterone receptors, less frequent expression of *TP53* and *ERBB2*, and a lower cell proliferation rate.[1,3,6,9,10,13-15] Such features, together with the generally smaller size of cancerous tumors detected by mammography screening, might account for the generally favorable prognosis and the mode of tumor detection might not have an independent prognostic value. Most studies report that tumors detected between mammography screening rounds are approximately similar to tumors found outside of screening programs,[1,16-18] although a few studies find these tumors to be associated with better outcomes.[4,19]

Although these findings are suggestive of a less aggressive biological nature of cancerous tumors detected by mammography screening compared with tumors found outside of screening programs, it has not been shown that tumors detected by mammography screening have better outcomes than other tumors when their generally smaller size is taken into account (ie, when tumors of similar diameter are being compared). Two studies, both based on small numbers of patients, have suggested that cancerous tumors detected by mammography screening have better outcomes than tumors detected outside of screening—even when a comparison is made within the same tumor node metastasis T category.[6,13] However, the tumor node metastasis T categories may contain tumors with markedly different diameters (T1, ≤20 mm; T2, 21-50 mm; and T3, >50 mm). Because tumors detected by mammography screening are generally smaller than tumors detected outside of screening, more tumors detected during screening are expected to have a diameter at the lower end within each T category.

At present, cancer detection based on mammography screening is not considered to be of significant importance when assessing the risk of breast cancer recurrence, or in decision making on the need of adjuvant therapies in the diagnosis of early breast cancer. The most commonly used scheme for assessment of the risk of recurrence is probably the one proposed by the International Consensus Panel that classifies node-negative tumors as minimal to low risk (≤10% at 10 years) when the primary tumor is smaller than 2 cm in diameter, the estrogen receptor and/or progesterone receptor status is positive, histological grade is 1 (well differentiated), and age at presentation is 35 years or older.[20] Neither these criteria nor those included in the Nottingham Prognostic index, which consists of tumor size, histological grade, and the axillary nodal status,[21] include the method of cancer detection in the outcome assessment. Thus, if cancerous tumors detected by mammography screening were associated with better outcomes than tumors of similar size detected outside of screening, women might be subjected to adjuvant therapies at a smaller risk level for cancer recurrence.

In the present study, we compared the survival outcomes of women with cancerous tumors detected by mammography screening with women whose tumors were detected outside of screening. To minimize the effect of the selection bias on the results, we chose the female population of Finland, which has an attendance rate in the mammography screening program approaching 90%.[22] We also compared the histological and biological features of tumors found in mammography screening and outside of screening to find out whether such factors could explain the effect of the mode of cancer detection on outcome.

## METHODS

### Patients

Five well-defined geographical regions comprising about 50% of the Finnish population were selected for the study.[23] We identified 2930 women diagnosed as having breast cancer within these regions in 1991 or 1992 from the Finnish Cancer Registry, which constitutes 53% of 5551 women diagnosed with breast cancer in Finland during this period. The study was approved by the ethical committee of surgery and the hospital district of Helsinki and Uusimaa. Permission was provided by the Ministry of Social Affairs and Health, Finland, to use paraffin-embedded tissue.

Clinical data were extracted from the hospital records using data collection forms. An effort was made to record clinical information about 50 characteristics. Relapse and survival data also were extracted from the files of the Finnish Cancer Registry and the hospital registries when available. For study inclusion, the following information was required for each patient: the date of diagnosis, age at diagnosis, information about other malignancies, postsurgical primary tumor size, axillary nodal status, follow-up data, and the vital status data at the end of follow-up. This information was available in 2656 (91%) of the 2930 eligible patients. The proportion of patients varied from 79% in southwestern Finland to 97% in eastern Finland. We also included 186 patients who fulfilled the inclusion criteria but who were not identified in the original computer search because the place of residence was outside the specified regions. Thus, the total number of patients entered into the database was

2842 (data available at http://www.finprog.org). We excluded patients for the following reasons (a single patient may have been excluded for more than one reason): having lobular (n=17) or ductal (n=186) carcinoma in situ; having distant metastases at diagnosis (n=136); having synchronous or metachronous bilateral breast cancer (n=261) or other malignancy (except for basal cell carcinoma or cervical carcinoma in situ, n=235); and not having underwent breast surgery (n=42). We excluded women (n=49) in which the method of cancer detection was not known from the remaining 2032 patients, which left a total of 1983 women with unilateral invasive breast carcinoma.

The method of cancerous tumor detection was based on the hospital case record data. According to this source, 443 (22%) of the 1983 women were diagnosed based on tumors detected by mammography screening; 3 (0.7%) among patients aged 39 years or younger; 48 (10.8%) among patients aged 40 to 49 years; 277 (62.5%) among patients aged 50 to 59 years; 102 (23.0%) among patients aged 60 to 69 years; and 13 (2.9%) among patients aged 70 years or older. Of the 1540 women who were diagnosed based on tumors detected outside of screening, 125 (8.1%) were among patients aged 39 years or younger; 381 (24.7%) were among patients aged 40 to 49 years; 247 (16.0%) among patients aged 50 to 59 years; 291 (18.9%) among patients aged 60 to 69 years; and 496 (32.2%) among patients aged 70 years or older. To verify the correctness of the method of detection, the hospital case record data were compared with the Finnish National Registry for Cancerous Tumors Detected by Mammography Screening, which is located at the Finnish Cancer Registry. This registry was not complete, but 70% of the women who were diagnosed as having cancerous tumors detected by mammography screening in the hospital case records were also identified in the Finnish registry as having cancerous tumors detected by mammography screening.

The nationwide mammography screening program has been active in Finland since 1987. Because of legislation, 460 municipalities in Finland had to screen women aged 50 to 59 years during 1991 and 1992. However, a few of the municipalities decided also to screen other age cohorts (40-49 years, 60-69 years, or ≥70 years). No other mass mammography screening took place concomitantly with these public screenings. Screening was based either on mammography alone or mammography combined with palpation and/or ultrasound examination. The most common screening interval was 2 years. Of the 443 women with cancerous tumors detected by mammography screening, 106 had tumors detected during the first screening round (ie, usually performed at approximately age 50 years); 194 women had tumors detected during the second or a later round; and data on the round of detection was not available in 143 women. Cancerous tumors also were detected in women (1) between mammography screenings; (2) prior to an invitation for mammography screening was received; (3) who were invited but did not participate in screening; and (4) who lived in a municipality that decided not to organize mammography screening.

Fifty-nine percent of the cancerous tumors detected by screening and 71% of the tumors detected outside of screening were treated with mastectomy and axillary dissection; 39% and 25% with breast-conserving surgery and axillary dissection; 0% and 2% with mastectomy without axillary dissection; and 2% and 2% with lumpectomy without axillary dissection, respectively. A total of 266 women received postoperative radiotherapy for cancerous tumors detected by screening (60%) and 889 women received postoperative radiotherapy for cancerous tumors detected outside of screening (58%). In both cohorts, postoperative breast irradiation was performed in 93% of the women following breast-conserving surgery. Thirty-nine percent of the women with cancerous tumors detected by screening and 56% of women whose cancerous tumors were detected outside of screening received chest wall and axillary radiotherapy following mastectomy. A total of 96 (22%) women with cancerous tumors detected by screening received systemic adjuvant therapy and 628 (41%) women with cancerous tumors detected outside of screening received systemic adjuvant therapy. In the age group of 50 to 69 years, adjuvant systemic therapy was given to 79 (21%) of the 374 women with cancerous tumors detected by screening and to 208 (39%) of the 531 women with cancerous tumors detected outside of screening. Tamoxifen was given to 432 women, of whom 392 (91%) were older than 50 years and the combination of cyclophosphamide, methotrexate, and 5-fluorouracil was given to 275 women, of whom 237 (86%) were aged 50 years or younger. Eight women (0.4%) received both tamoxifen and the combination of cyclophosphamide, methotrexate, and 5-fluorouracil. The type of adjuvant therapy received was not known in 9 women. Only 107 (9%) of the patients with node-negative tumors were treated with adjuvant systemic therapy. Of these, 10 had tumors detected by screening and 97 had tumors detected outside of screening. Eighty-six (95%) of the women with node-positive tumors detected by screening and 512 (91%) of those with node-positive tumors detected outside of screening received adjuvant systemic therapy. The median follow-up survival time was 9.5 years (range, 0.2-10.8 years; range 8.2-10.8 years if 2 women who moved out of the country shortly after receiving a diagnosis are excluded).

### Histopathological Characteristics

Histological typing and evaluation of the grade components (mitotic count, nuclear pleomorphism, and tubule formation) was usually performed according to the World Health Organization classification system,[24] although the criteria used in tumor classification cannot be stated with certainty in retrospect. The main difference between these criteria and those published by Elston and Ellis[25] is that the latter use semiquantitative assessment of tubule formation and define more accurately how

to perform mitotic counting. The tumors were classified into 3 histological types: ductal carcinoma (not otherwise specified, includes apocrine, mixed mucinous, and atypical medullary types), lobular carcinoma (infiltrating lobular carcinoma with variants), and the special histological types (tubular, medullary, cribriform, papillary, and pure mucinous carcinomas). More than 50 pathologists performed histological typing and grading at the time of the diagnoses.

The longest primary tumor diameters were extracted from pathology reports (69%) or from surgery or mammography reports. In case of multiple invasive lesions (n=192, 10%), the diameter of the largest lesion was recorded. The status of estrogen and progesterone receptors was determined either by immunohistochemistry (60% and 62%, respectively) or the dextran-coated charcoal method, and was classified as positive or negative.

### Preparation of Tumor Microarrays

Formalin-fixed, paraffin-embedded tumor samples were used for tissue microarrays. Representative tumor regions were first defined from sections stained with hematoxylin-eosin and marked. Tumor tissue array blocks were made by punching a 0.6-mm tissue cylinder through a histologically representative area of each donor tumor block, which was then inserted into an empty recipient tissue array paraffin block using a specific instrument.[26] From the tumor samples available, 19 tissue array blocks were prepared. Each contained 50 to 144 tumor samples. Sections of 5 µm were cut and processed for immunohistochemistry and chromogen in situ hybridization. Evaluation of the tissue array slides was aided by the use of a computer-controlled and motorized specimen stage (EcoDrive, Märzhauser Inc, Wetzlar, Germany) installed on a BX50 microscope (Olympus, Tokyo, Japan).

### Immunohistochemistry

For ERBB2 staining, the sections were deparaffinized, followed by antigen retrieval (autoclave treatment at 121°C for 2 minutes in a 10-mM sodium citrate buffer with a pH of 6.0). The primary antibody (*CB11*, Novocastra Laboratories, Newcastle, England) was diluted 1:200 in an antimouse-peroxidase polymer blocking solution (Powervision, Immunovision Inc, Daly City, Calif) and incubated overnight at 4°C. The antimouse-peroxidase polymer (Immunovision Inc; 30 minutes at room temperature) and diaminobenzidine chromogen were used for visualization. The sections were counterstained with hematoxylin and embedded. A positive and a negative control sample (tumors with and without *ERBB2* amplification in fluorescent in situ hybridization) were included in every staining batch. Evaluation of immunohistochemistry was performed using an objective magnification of 20. Only strong intensity immunostaining (ie, 3+) present on the cell membrane of the majority of cancer cells was scored as positive for ERBB2. The TP53 protein was immunostained with the DO7 antibody (Novocastra Laboratories) at a dilution of 1:500 and the MK167 protein (Ki-67) using the MM-1 antibody (Novocastra Laboratories; dilution 1:1000). Staining for MK167 and TP53 proteins were considered positive when more than 20% of cancer cell nuclei showed staining.

### Chromogen In Situ Hybridization

In brief, the microarray slides were deparaffinized and incubated in 0.1-M Tris hydrochloride (pH, 7.3) at 92°C for 10 minutes, followed by cooling for 20 minutes at room temperature. Enzymatic digestion was performed by applying 100 µL of digestion enzyme onto the slides (Digest-All III solution, Zymed Inc, San Francisco, Calif). Following dehydration, a ready-to-use digoxigenin-labeled *ERBB2* DNA probe (Zymed Inc) was applied on the slides. The sections were denatured on a thermal plate and hybridization was performed overnight at 37°C. The ready-to-use digoxigenin-labeled *ERBB2* probe was detected by means of sequential incubations with mouse antidigoxigenin (diluted 1:300; Roche Biochemicals, Mannheim, Germany), antimouse-peroxidase polymer (Immunovision Inc), and diaminobenzidine chromogen. The tissue sections were lightly counterstained with hematoxylin and embedded. A positive and a negative control sample (tumors with and without *ERBB2* amplification in fluorescent in situ hybridization) were included in every hybridization batch. The sections were evaluated using a 40 magnification dry objective. Amplification was defined as 6 or more signals per nucleus in more than 50% of cancer cells or when large gene copy clusters were seen.

### Statistical Analysis

Frequency tables were analyzed using the $\chi^2$ test. Life-tables were calculated according to the Kaplan-Meier method. Distant disease-free survival was computed from the date of the diagnosis to occurrence of metastases outside the regional area or to death from breast cancer. The log-rank test was used to compare time-to-event distributions, which were expected to be random over time.[27] Multivariate survival analyses were performed using method of tumor detection (mammography screening, 0; outside of screening, 1); grade (well differentiated, 0; moderately or poorly differentiated, 1); the status of estrogen and progesterone receptors (positive or borderline, 0; negative, 1); ERBB2 protein immunostaining (negative, 0; positive, 1); *ERBB2* amplification status (no amplification, 0; amplification, 1); histological type (lobular or special, 0; ductal, 1); and age at detection grouped to account for the nonlinear risk associated with age. The tumor size in centimeters and the number of metastatic axillary lymph nodes were entered as continuous variables into the multivariate model. The final multivariate model was constructed using backward Cox stepwise proportional hazards regression,[28] and a *P* value of .05 was adopted as the limit for inclusion of a covariate. All *P* values are 2-sided. We used Statview statistical software (version 5.0, SAS Institute Inc, Cary, NC).

**Table 1.** Association of Tumor and Therapy Factors With the Method of Detection in 1983 Women With Breast Cancer*

| Factor | All Age Groups | | | Ages 50-69 Years, No. (%) | | |
|---|---|---|---|---|---|---|
| | Screening, No. (%) (n = 443) | Outside of Screening, No. (%) (n = 1540) | *P* Value | Screening, No. (%) (n = 379) | Outside of Screening, No. (%) (n = 538) | *P* Value |
| Primary tumor diameter, mm | | | | | | |
| ≤5 | 32 (7) | 22 (1) | <.001 | 30 (8) | 10 (2) | <.001 |
| 6-10 | 138 (31) | 194 (13) | | 124 (33) | 80 (15) | |
| 11-20 | 195 (44) | 613 (40) | | 163 (43) | 219 (41) | |
| 21-30 | 38 (9) | 371 (24) | | 29 (8) | 130 (24) | |
| >30 | 25 (6) | 290 (19) | | 18 (5) | 85 (16) | |
| Not available | 15 (3) | 50 (3) | | 15 (4) | 14 (3) | |
| No. of positive axillary nodes | | | | | | |
| 0 | 346 (78) | 908 (59) | <.001 | 299 (79) | 346 (64) | <.001 |
| 1-3 | 74 (17) | 369 (24) | | 62 (16) | 127 (24) | |
| 4-9 | 14 (3) | 134 (9) | | 12 (3) | 38 (7) | |
| ≥10 | 2 (1) | 34 (2) | | 1 (<1) | 14 (3) | |
| Not available | 7 (1) | 95 (6) | | 5 (1) | 13 (2) | |
| Histological type | | | | | | |
| Ductal | 312 (70) | 1154 (75) | .04 | 266 (70) | 392 (73) | .03 |
| Lobular | 72 (16) | 244 (16) | | 61 (16) | 101 (19) | |
| Special type | 59 (13) | 142 (9) | | 52 (14) | 45 (8) | |
| Not available | 0 | 0 | | 0 | 0 | |
| Histological grade | | | | | | |
| 1 | 137 (31) | 252 (16) | <.001 | 118 (31) | 92 (17) | <.001 |
| 2 | 159 (36) | 541 (35) | | 134 (35) | 182 (34) | |
| 3 | 57 (13) | 337 (22) | | 45 (12) | 121 (22) | |
| Not available | 90 (20) | 410 (27) | | 82 (22) | 143 (27) | |
| Estrogen-receptor content | | | | | | |
| Negative | 96 (22) | 362 (24) | .36 | 77 (20) | 144 (27) | .72 |
| Positive | 202 (46) | 864 (56) | | 174 (46) | 306 (57) | |
| Not available | 145 (33) | 314 (20) | | 128 (34) | 88 (16) | |
| Progesterone-receptor content | | | | | | |
| Negative | 115 (26) | 483 (31) | .68 | 95 (25) | 215 (40) | .008 |
| Positive | 186 (42) | 740 (48) | | 158 (42) | 234 (43) | |
| Not available | 142 (32) | 317 (21) | | 126 (33) | 89 (17) | |
| *ERBB2* | | | | | | |
| *CB11* expression | | | | | | |
| Negative | 238 (54) | 920 (60) | .21 | 197 (52) | 317 (59) | .24 |
| Positive | 42 (9) | 205 (13) | | 36 (9) | 75 (14) | |
| Not available | 163 (37) | 415 (27) | | 146 (39) | 146 (27) | |
| Amplification | | | | | | |
| Absent | 237 (53) | 881 (57) | .06 | 194 (51) | 312 (58) | .13 |
| Present | 40 (9) | 211 (14) | | 35 (9) | 79 (15) | |
| Not available | 166 (37) | 448 (29) | | 150 (40) | 147 (27) | |
| *TP53* expression | | | | | | |
| Negative | 189 (43) | 819 (53) | .44 | 161 (42) | 274 (51) | .12 |
| Positive | 39 (9) | 196 (13) | | 32 (8) | 78 (14) | |
| Not available | 215 (49) | 525 (34) | | 186 (49) | 186 (35) | |
| *MK167* expression | | | | | | |
| Negative | 168 (38) | 636 (41) | .04 | 144 (38) | 222 (41) | .03 |
| Positive | 75 (17) | 391 (25) | | 56 (15) | 130 (24) | |
| Not available | 200 (45) | 513 (33) | | 179 (47) | 186 (35) | |
| Adjuvant systemic therapy | | | | | | |
| Not given | 341 (77) | 876 (57) | <.001 | 295 (78) | 323 (60) | <.001 |
| Given | 96 (22) | 628 (41) | | 79 (21) | 208 (39) | |
| Not available | 6 (1) | 36 (2) | | 5 (1) | 7 (1) | |

*Percentages may not equal 100 due to rounding.

## RESULTS

### Clinicopathologic Features of Cancerous Tumors Detected by Screening

Cancerous tumors detected by mammography screening were most common in the age groups of 50 to 59 years and 60 to 69 years. In the age cohort of 50 to 69 years, 379 (41%) of the women were diagnosed as having breast cancer by mammography screening; 50 to 59 years, 53%; and 60 to 69 years, 26%. Thirty-eight percent of tumors detected by screening were 10 mm in diameter or smaller compared with only 14% of tumors found outside of screening ($P<.001$); tumors of these sizes were less commonly associated with axillary lymph nodes metastases (21% vs 35%; $P<.001$, TABLE 1). Tumors detected by mammography screening were often one of the special histological types (13% vs 9%; $P=.04$) and expressed the MK167 antigen less often (17% vs 25%; $P=.04$). Thirty-one percent of the tumors detected by mammography screening were histologically well differentiated (grade 1) compared with 16% of tumors found outside of screening ($P<.001$). In general, these differences were similar when the comparisons were limited to the age cohort of 50 to 69 years that contained the majority (86%) of the women with tumors detected by mammography screening (Table 1).

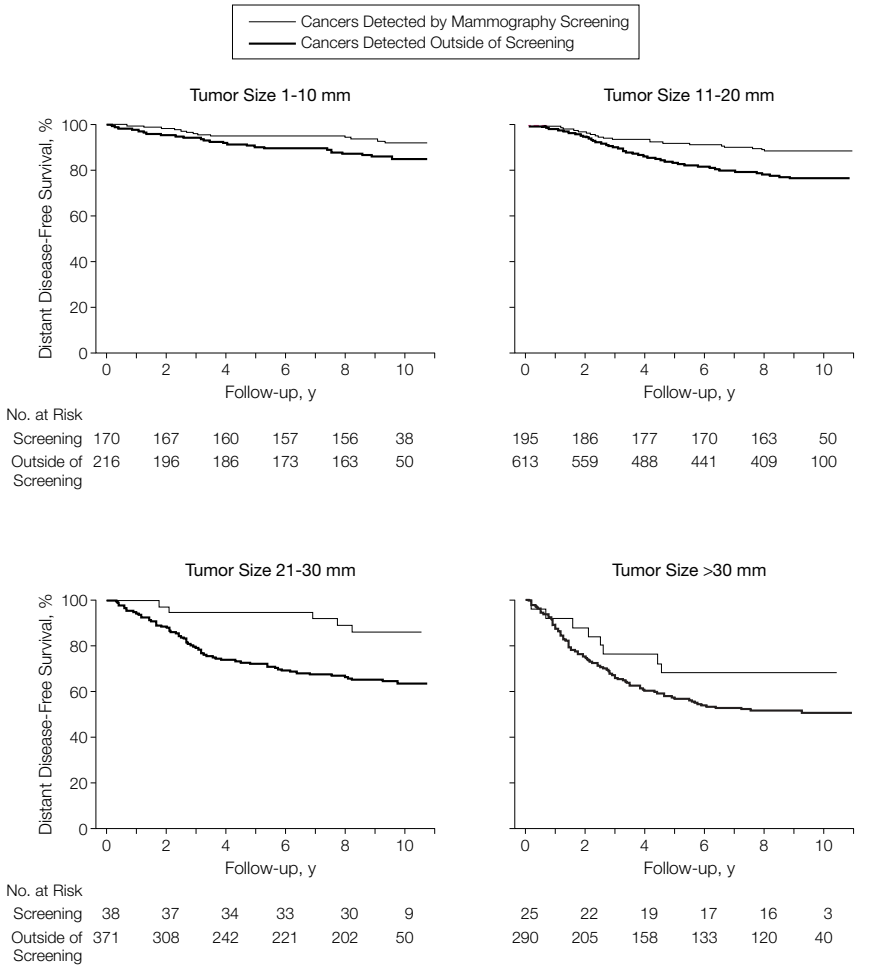
### Influence of the Primary Tumor Size on Outcome

Women with cancerous tumors found during the first screening round had similar outcomes as women with tumors found during the second or a later round ($P=.96$). Therefore, outcomes of all women with cancerous tumors detected by screening were compared with women whose tumors were found outside of screening in further analyses. Women with cancerous tumors detected by mammography screening had better distant disease-free survival than women whose tumors were found outside of screening in all tumor size categories examined (≤10 mm, 11-20 mm, 21-30 mm, >30 mm, FIGURE). In general, women with tumors detected by screening that were 11 to 30 mm in diameter were associated with similar outcomes as women with tumors found outside of screening that were 10 mm in diameter or smaller (TABLE 2). Similar differences in outcome were present when the largest single subgroups were compared (age cohort of 50-69 years and women with node-negative tumors). No significant difference in outcome was found between women with tumors detected by screening and women with tumors detected outside of screening in the size category of 30 mm or larger, but only a few patients with cancerous tumors detected by mammography screening were available for analysis in this subgroup (n=25). Only 19 (21%) of the 90 women with node-positive tumors detected by screening had distant recurrence.

### Influence of Age at Diagnosis on the Outcome of Women With Cancerous Tumors Detected by Screening and Outside of Screening

Because the proportion of cancerous tumors detected by mammography screening was higher in the age cohort of 50 to 59 years (53%) than in the other age groups (40-49 years, 11% of tumors; 60-69 years, 26%; and 70-79 years, 3%), age at detection needs to be taken into account as a confounding factor. Survival outcomes for women with cancerous tumors detected by mammography screening were better

**Figure.** Distant Disease-Free Survival by the Primary Tumor Size and Mode of Detection



than women with tumors detected outside of screening, irrespective of age at the time of the diagnosis. Variation in distant disease-free survival between the age cohorts was small compared with the large outcome differences between the women with tumors detected by screening compared with women with tumors detected outside of screening (TABLE 3). Of note, women aged 50 to 59 years whose tumors were found outside screening had roughly similar 10-year distant disease-free survival (73%) as women with similarly detected tumors in the other age cohorts (72% for ages 40-49 years; 69%, ages 60-69 years; and 67%, ages ≥70 years), despite a much larger proportion of women in the age cohort of 50 to 59 years who had tumors detected by mammography screening.

### Multivariate Survival Analyses

Because the age distribution of women with tumors detected by screening was different from that of the women with tumors detected outside of screening, and because tumors detected during screening were better differentiated, expressed the progesterone receptor more frequently, and had a lower cell proliferation rate as measured with staining for the MK167 protein, a multivariate analysis was performed to find out whether tumor detection in screening is an independent prognostic factor in the series. Tumor detection by screening turned out to be an independent prognostic factor (hazard rate [HR], 1.90; 95% confidence interval [CI], 1.15-3.11) together with the axillary lymph node status, the primary tumor size, the progesterone receptor content, *ERBB2* amplification, histological grade, and age at diagnosis (TABLE 4). In comparison, an increase of 1 cm in the tumor diameter was associated with an HR increase of 1.20 (95%, CI, 1.10-1.31) for distant metastases.

When breast cancer–specific survival (HR, 2.11; 95% CI, 1.16-3.85) or overall survival (HR, 1.63; 95% CI, 1.02-2.60) was chosen as the end point instead of distant disease-free survival, cancerous tumor detection outside of screening remained an independent adverse prognostic variable. Similarly, tumor detection mode was an adverse prognostic variable when the women, who had cancerous tumors detected by screening based on hospital case record data but whose tumors were not registered in the Finnish National Registry for Cancerous Tumors Detected by Mammography Screening, were deleted from the analysis (30% of cases detected by screening). Cancer detection by mammography screening was retained in the model with little change in the HR (2.09; 95% CI, 1.13-3.85). Within the subgroup of patients with node-negative tumors, who were aged 50 to 69 years at diagnosis and who did not receive adjuvant therapy (n=430), detection by mammography screening was also associated with a more favorable prognosis—independent of tumor size and the histological grade of cancer.

**Table 2.** Distant Disease-Free Survival According to the Primary Tumor Diameter

| | Screening | | Outside of Screening | | |
|---|---|---|---|---|---|
| Primary Tumor Diameter, mm | No. at Risk | 10-Year Survival, % | No. at Risk | 10-Year Survival, % | *P* Value |
| Node negative and positive | | | | | |
| All age groups | | | | | |
| ≤10 | 170 | 92 | 216 | 85 | .04 |
| 11-20 | 195 | 88 | 613 | 76 | <.001 |
| 21-30 | 38 | 86 | 371 | 63 | .008 |
| >30 | 25 | 68 | 290 | 50 | .12 |
| Ages 50-69 y | | | | | |
| ≤10 | 154 | 91 | 90 | 85 | .09 |
| 11-20 | 163 | 87 | 219 | 76 | .007 |
| 21-30 | 29 | 82 | 130 | 64 | .05 |
| >30 | 18 | 72 | 85 | 56 | .25 |
| Node negative at ages 50-69 y | | | | | |
| ≤10 | 143 | 93 | 79 | 87 | .09 |
| 11-20 | 114 | 91 | 149 | 79 | .009 |
| 21-30 | 22 | 86 | 78 | 72 | .20 |
| >30 | 7 | 86 | 29 | 74 | .50 |

**Table 3.** Distant Disease-Free Survival by the Method of Cancer Detection and Age at Diagnosis

| | Screening | | | Outside of Screening | | |
|---|---|---|---|---|---|---|
| | | Survival, % | | | Survival, % | |
| | No. of Patients | 5 Years | 10 Years | No. of Patients | 5 Years | 10 Years |
| Age at diagnosis, y | | | | | | |
| ≤39 | 3 | NA | NA | 125 | 65 | 56 |
| 40-49 | 48 | 92 | 92 | 381 | 78 | 72 |
| 50-59 | 277 | 91 | 87 | 247 | 78 | 73 |
| 60-69 | 102 | 94 | 92 | 291 | 75 | 69 |
| ≥70 | 13 | NA | NA | 496 | 78 | 67 |

Abbreviation: NA, data not available because screening was rarely performed in women 39 years or younger and in women 70 years or older.

## COMMENT

The generally favorable outcomes of women with cancerous tumors detected by mammography screening compared with women whose tumors were found outside of screening might be explained by the smaller median tumor size detected by screening, or by their more favorable biological features. In line with some other series, tumors detected by mammography screening were smaller than the tumors detected outside of screening in the present

cohort.[6,9,10] Cancerous tumors detected by screening had also given rise to axillary lymph node metastases less often, were better differentiated, were more often of one of the special histological types, had a lower cell proliferation rate as assessed by immunostaining for the *MK167* antigen, and tended to be more often *ERBB2*-amplification negative and progesterone-receptor positive. However, these features did not fully explain the generally better outcomes of women with cancerous tumors detected by mammography screening because the mode of detection was an independent prognostic variable in multivariate analyses. Tumors detected by screening were much more common in the present series in the age cohorts of 50 to 59 years and 60 to 69 years because the municipalities seldom organized screening for women younger than 50 years or women older than 70 years. The different age distribution of the women with cancerous tumors detected by mammography screening is also unlikely to explain the favorable outcome because women with tumors detected by screening had superior survival compared with other women in all age cohorts examined. Tumor detection by mammography screening was an independent prognostic variable in a multivariate analysis that also included age. The generally favorable outcome is not explained by the treatments given because women with tumors detected by screening had received less systemic cancer therapies than women whose cancerous tumors were found outside of screening.

Women with cancerous tumors detected by mammography screening had better distant disease-free survival compared with women with a similar primary tumor size detected outside of screening. The relatively large size of the present series allowed evaluation of relatively narrow tumor diameter strata. This may be of importance because tumors detected by screening are generally considerably smaller in size than other cancerous tumors, which might bias comparisons within wider tumor size strata. We are not aware of any prior studies in which outcome of tumors of similar size detected by screening and outside of screening have been compared, but the present results are in accordance with 2 smaller studies that compared tumors detected by screening and other tumors within the tumor node metastasis group categories.[6,13] Both studies concluded that women with cancerous tumors detected by mammography screening may be associated with superior outcomes compared with other women when an adjustment is made for the tumor size. We found the influence of the method of detection on outcome to be substantial. For example, women with tumor diameters of 11 to 30 mm that were detected by mammography screening had approximately similar survival as women whose cancerous tumors were found outside of screening and were 10 mm or smaller in diameter.

Comparison of tumors of roughly similar size is likely to reduce the influence of the lead-time bias on outcome comparisons. Selection bias also is unlikely to play a major role in this nationwide series. Cancerous tumors detected by mammography screening may have biological properties different from other tumors, and, thus, the length bias (more indolent tumors are detected by screening) might be an important factor in explaining their generally favorable prognoses. However, apart from the histological grade, none of the tumor biological factors examined was strongly associated with the mode of cancer detection, and the method of detection was an independent prognostic variable in a multivariate survival analysis in which histological grade and a few cancer biological factors were included as covariates. Compared with tumors found outside of screening, tumors detected by screening are associated less often with symptoms or signs such as breast pain, pressure in the breast, or nipple discharge. Such symptoms, in turn, might be associated with some cancer invasiveness-related factors, such as neural or perineural microinvasion (causing pain), edema (feeling of pressure), vascular invasion, or duct obstruction or invasion (nipple discharge, pain, pressure). These parameters were not investigated in our study and might in part explain the poorer outcome of women with tumors detected outside of screening. Other factors related to tumor angiogenesis and metastasis formation might also be of importance and require further study.

**Table 4.** Cox Multivariate Survival Analysis

| Variable | β Coefficient | *P* Value | $\chi^2$ | RH (95% CI) |
|---|---|---|---|---|
| **All Patients** | | | | |
| No. of positive lymph nodes per metastatic node | 0.13 | <.001 | 58.1 | 1.14 (1.10-1.18) |
| Tumor size, per cm | 0.18 | <.001 | 16.3 | 1.20 (1.10-1.31) |
| Progesterone receptor (negative vs positive) | 0.53 | <.001 | 13.3 | 1.70 (1.28-2.25) |
| Detection outside screening | 0.64 | .01 | 6.4 | 1.90 (1.15-3.11) |
| Histological grade (grade 2 or 3 vs 1) | 0.65 | .01 | 6.1 | 1.92 (1.15-3.21) |
| *ERBB2* amplification (positive vs negative) | 0.32 | .04 | 4.1 | 1.38 (1.01-1.89) |
| Age at diagnosis, y | | | | |
| ≤39* | | | | 1.00 |
| 40-49 | –0.75 | .002 | 9.4 | 0.47 (0.29-0.76) |
| 50-59 | –0.49 | .049 | 3.9 | 0.61 (0.38-0.99) |
| 60-69 | –0.55 | .03 | 5.0 | 0.58 (0.36-0.93) |
| ≥70 | –0.48 | .047 | 4.0 | 0.62 (0.39-0.99) |
| **Node Negative, Age 50-69 Years, No Adjuvant Therapy** | | | | |
| Tumor size, per cm | 0.31 | .01 | 6.6 | 1.36 (1.08-1.72) |
| Detection outside screening | 0.62 | .03 | 4.7 | 1.86 (1.06-3.25) |
| Histological grade (grade 2 or 3 vs 1) | 1.37 | <.001 | 12.8 | 3.94 (1.86-8.35) |

Abbreviations: CI, confidence interval; RH, relative hazard.
*Reference category.

Some tumors detected by mammography screening might grow slowly; and indolent tumors might not ever surface during the life-span of the woman.[8] In a few autopsy studies, occult breast tumors have been detected in a substantial proportion of women representing the general population. In these studies, occult in situ carcinoma was found in 4.3% to 18% of women, and invasive breast cancer in 1.8% of women in one series consisting of forensic autopsies.[29-32] The biological behavior of untreated breast cancer has been investigated in a historical series consisting of patients who have refused surgery for early breast cancer. Many women survived longer than expected with untreated breast cancer (mean survival, 30-40.5 months from the onset of symptoms to death),[33] and several women with stage I, II, or III breast cancer who refused treatment survived for 5 years.[34] However, it is clear that the majority of self-detected tumors are aggressive and usually manifest with distant metastases during the first 10 years of follow-up and only rarely after the 15th year of follow-up.[35]

The mode of tumor detection was based on the data available in the hospital case records. We also examined the mode of tumor detection from the Finnish national mammography registry. Seventy percent of the women with tumors detected by screening (based on hospital case record data) were identified also in the screening registry files. Many of the remaining 30% of women who were not identified in the registry were also likely to have cancerous tumors detected by screening. However, this assertion could not be confirmed because the registry was incomplete. Removal of women from the cohort who had cancerous tumors detected by mammography screening, based on hospital records only, had little influence on the HR of distant recurrence associated with screening in a multivariate model.

Cancerous tumors detected during the first or a later screening round were combined in further analyses because the round of cancer detection had no significant effect on outcome ($P = .96$), and data on the screening round was missing in a proportion of the women. The detection outside of screening group consisted of self-detected cancerous tumors, tumors detected in women who did not participate in screening, and tumors detected between mammography screening rounds. Interestingly, survival of such women with cancer was roughly similar in the age cohort of 50 to 59 years as in the other cohorts, although the relative proportion of self-detected cancerous tumors was lower in the age group of 50 to 59 years than in the other age cohorts due to the more extensive screening performed in the 50- to 59-year age group. This finding is in line with a few other studies that have found cancerous tumors detected between mammography screening rounds are associated with approximately similar outcomes as other women with tumors detected outside of screening.[1,16-18] Tumor detection between mammography screening rounds appears to be more common among premenopausal women and women who use hormone replacement therapy, probably due to their denser breast parenchyma,[36] but the technical quality of the mammograms and the skill of the radiologist also are likely to be of importance. Tumors detected between mammography screening rounds are false-negatives 10% to 30% of the time,[16,18,37-39] but retrospective classification of tumors that were detected between mammography screening rounds into true interval tumors and missed tumors is demanding, and is seldom performed in the routine clinical praxis. For these reasons and the considerable logistic problems involved in a nationwide series, we made no attempt to subclassify tumors detected outside of mammography screening.

Any cohort of women with tumors detected by mammography screening may contain a few women with symptomatic cancer because some women might wait for the screening visit instead of making an appointment with a physician. Thus, the survival difference in favor of the screened cohort might be greater than the one we observed due to inclusion of some women with symptomatic cancer in the screened cohort. On the other hand, women who refused screening and who may have had an inferior outcome compared with women who participated in screening[40] were included in the subgroup of women whose cancerous tumors were detected outside screening. However, the proportion of women who refuse mammography screening is small in Finland.[22] In the age groups of 40 to 49 years, 60 to 69 years, and 70 years or older, the rate of participation in screening was largely dictated by the decision made by the municipality of residence to offer mammography screening.

We conclude that women with cancerous tumors detected by mammography screening have better survival outcomes than other women with tumors of roughly similar primary diameter. Cancerous tumor detection in mammography screening was a favorable prognostic variable independent of the number of axillary lymph nodes, the primary tumor size, age at cancer detection, and the histological grade. None of the histopathological or cancer biological factors explained the effect of cancerous tumor detection in screening on the risk for distant recurrence. Further research on factors related to cancer invasiveness and metastasis formation needs to be performed. For women with cancerous tumors detected by mammography screening, the risk of distant metastases may be overestimated unless the method of detection is taken into account in risk estimations.

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