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Mammography Screening Initially Yields Large Tumors and Several Years Later an Increase in Small Tumors-Transient Medium Sized Tumors Appeared

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Abstract

Objective: To study tumor size and stage alteration at diagnosis during the first period of mammography screening and describe the sequence in the assumed size reduction and follow increase in small tumors

Study Design: Three randomized samples of breast cancers were sorted out from 1993, 1995, and 1997 and a control group from 1987 two years before screening was introduced in 1989. Among 2090 patients from the Stockholm Cancer Center database 1011 representing the screened age 50-60 years were analyzed in the two age groups 50-59 and 60-69 years. Tumor size was grouped as: <=10 mm, 10-20 mm, and >20 mm. The interrelations between these size groups was followed three times during 5 years.

Results: In the 1993 sample a significant reduction in tumor size > 20 mm was observed compared to the control group (P<0.001) and was accompanied by an increase in tumors for intermediate tumor size 10-20 mm in the screened age group 60-69 years (P<0.05). There was a significant increase of more favorable tumor stages (Stage I) (P<0.02) and reduction in Stage IIA (P<0.001). In 1995 a similar but reduced tendency was found and in 1997 the difference found so far was equilibrated but a significant increase in tumors ≤ 10mm appeared for the first time in the screened age group 60-69 years.

Conclusion: The reduced numbers of tumors > 20 mm found after start of screening explains that screening has yielded about 50% of such tumors compared to the controls of which most are tumor stage II-III. At the same time as screening continues there is first a transient increase in intermediate tumors size and finally an increasing numbers of small tumors ≤ 10 mm resulting in more favorable tumor stages.

Keywords: Mammography screening; Tumor size; Overdiagnosis; Tumor regression

Introduction

Mammography screening has resulted in both a reduced death rate from breast cancer [1,2] and an increase in the incidence of breast tumors [3-6]. Tumors are diagnosed at a smaller size and lower grade, resulting in more frequent implementation of breast-conserving surgery and reduced mortality [7]. Because ductal carcinomas *in situ* (DCIS) are reportedly being more frequently diagnosed since the introduction of mammography screening, there is controversy as to what proportion of these tumors would have reached a clinical stage during the affected women's lifetimes [8,9]. Consequently, the possibility of overdiagnosis of breast cancer is being debated [10,11].

Since mammography screening was introduced in 1989 in the Stockholm Gotland County of Sweden for women aged 50–69 years, the age group for screening has been extended; by 2005 it included women aged in their forties and, by 2012, older women up to 74 years of age. Participation in general mammography screening has remained at a level of 70% since its introduction. Including women attending private centers into the investigation, in total 85–90% underwent one mammography investigation in the previous 2 years during 1994 and 1995, a time period from which data in this study were derived [12]. We recently reported that larger breast tumors (>20 mm) were less frequently diagnosed after the first 2 years of screening (1991), whereas approximately 8 years thereafter a significantly increased number of small tumors (≤ 10 mm) were diagnosed [13]. Mean tumor size, cellular genomic instability, and proliferative activity of cancer cells we reported to be decreased in tumors diagnosed among women aged 60–69 years in comparison with unscreened patient populations (1) younger than 50 years and (2) 70 years and older. Furthermore, survival was improved [13]. The sequence of changes in size resulted in a transient redistribution in favor of tumors 10–20 mm in size and a reduction in the size interval of 20 mm or more. The Stockholm breast cancer 5-year screening trial in 1981 revealed a more favorable tumor stage (decrease in tumor stage II-IV abbreviated II+ tumors) in the study population compared with the control clinically detected breast tumor population investigated 2.5 years after the start of the study [14]. On subdivision according to age, this phenomenon was observed only in the age group 50–59 years old in the study group ranging in age from 40 to 64 years, suggesting that the more favorable tumor stages appeared in the second age decade of screened women. We found a similar effect in the age group 60–69 years old in a screened sample of

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women aged 50–69 years [13]. Furthermore, in the Stockholm breast cancer screening trial there was an increase the first 2 years in stage II+ tumors, with the peak within the first year, in the study group compared with the control group. This finding was interpreted as a hidden stage II+ tumor group within the control group, representing a spontaneous regression of these tumors. The aim of this study was to determine the time that elapsed before increased numbers of smaller tumors (≤ 10 mm) were diagnosed, the duration of the period during which more numerous intermediate-sized tumors were diagnosed and further analyze the problem with the "hidden stage II+ tumors in a none screened population.

Materials and Methods

In this cross-sectional study diagnosed with breast cancer aged 50–69 years were analyzed according to data recorded from randomized samples in the years 1993 (n=455), 1995 (n=608), and 1997 (n=617), and a control sample from 1987 (n=410), 2 years before the start of screening. From this sample, 989 patients with breast cancer aged 50–69 years were investigated. The data were analyzed in two subgroups according to age at cancer diagnosis (50–59 and 60–69 years), in which the elder group had a greater possibility to reach a higher rate of mammography screening events and reveal a stronger effect. The frequencies of three tumor size ranges were investigated: ≤10 mm, 10–20 mm, and >20 mm. The numbers of tumors in each age group were counted and the distribution into the three size ranges is numerically presented in Tables 1-3, with percentage values calculated; thus, the sum for each age group is 100%. The data from the tables are illustrated in three histograms (Figures 1-3) showing the alteration in size frequency related to screening. Data for the screened subjects were compared with data for unscreened subjects from 1987 in the corresponding age groups (50–59 and 60–69 years), flanking the study groups in the figures and tables. In particular the diagnoses of DCIS were counted.

	Sample year						
	1987	*p*	1993	*P*	1993	*p*	1987
Age group, years	50-60		50–60		60–70		60-70
≤10 mm	*n*=10	n.s.	*n*=18	n.s.	*n*=22	n.s.	*n*=16
	13.6%		18.2%		20.7%		13.3%
10–20 mm	*n*=32	n.s.	*n*=43	0.08	*n*=59	<0.05	*n*=50
	43.2%		43.4%		55.7%		41.7%
>20 mm	*n*=32	n.s.	*n*=38	<0.05	*n*=25	<0.001	*n*=54
	43.2%		38.4%		23.6%		45%
Σ	*n*=74		*n*=99		*n*=106		*n*=120
	100%		100%		100%		100%

n.s., not significant

Table 1: Distribution of three tumor size intervals of two age groups in 1993.

	Sample year						
	1987	*p*	1995	*p*	1995	*p*	1987
Age group, years	50-60		50–60		60–70		60-70
≤10 mm	*n*=10	n.s.	*n*=34	n.s.	*n*=22	n.s.	*n*=16
	13.6%		19.0%		19.5%		13.3%
10–20 mm	*n*=32	n.s.	*n*=81	n.s.	*n*=60	0.08	*n*=50
	43.2%		45.3%		53.1%		41.7%
>20 mm	*n*=32	n.s.	*n*=64	n.s.	*n*=31	0.01	*n*=54
	43.2%		35.7%		27.4%		45.0%
Σ	*n*=74		*n*=179		*n*=113		*n*=120
	100%		100%		100%		100%

n.s., not significant

Table 2: Distribution of three tumor size intervals of two age groups in 1995.

	Sample year						
	1987	*p*	1997	*p*	1997	*p*	1987
Age group, years	50-60		50–60		60–70		60-70
≤10 mm	*n*=10	n.s.	*n*=33	n.s.	*n*=30	<0.05	*n*=16
	13.6%		18.6%		24.8%		13.3%
10–20 mm	*n*=32	n.s.	*n*=90	n.s.	*n*=61	n.s.	*n*=50
	43.2%		50.8%		50.4%		41.7%
>20 mm	*n*=32	0.06	*n*=54	n.s.	*n*=30	0.001	*n*=54
	43.2%		30.6%		24.8%		45.0%
Σ	*n*=74		*n*=177		*n*=121		*n*=120

n.s., not significant

Table 3: Distribution of three tumor size intervals of two age groups in 1997.

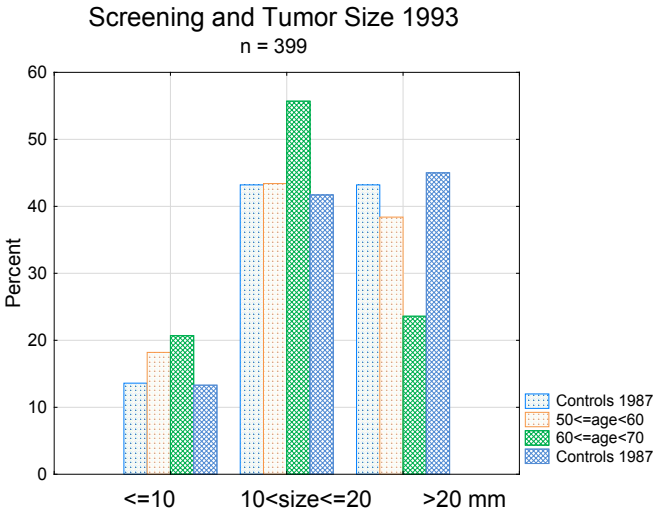

Figure 1: Tumor size data from 1993, 4 years after the introduction of screening, representing a maximum of three screening events. Compared with prescreening control data, in the 60–70 year age group there is a significant reduction in tumors >20 mm (p<0.001) and a significant increase in intermediate-sized tumors (10–20 mm) (p<0.05). The control data are shown for the age group 50–59 years to the left and the age group 60–69 years to the right.

Tumor stage

To investigate how change in tumor size distribution interfered with tumor stage, five stages related to the tumor size interval used in the figures were selected as follows, in line with the classification practiced during the early 1990s: (1) Stage I_{a-b} with tumor size ≤ 10 mm, no axillary lymph node metastasis (ALNM=0), and no distant metastasis (DM) (I_a 0 <5 mm and I_b 5-10 mm); (2) Stage I_c with tumor size 10-20 mm, ALNM=0, and DM=0; (3) Stage IIA with tumor size 10-20 mm, and ALNM 1–3 positive nodes with DM=0; (4) Stage IIB with tumor size 20–50 mm, and ALNM >3 positive nodes and DM=0; and (5) Stage IIIA with tumor size >50 mm and ALNM <9 positive nodes.

Statistical analysis

Statistical calculations were performed using the STATISTICA software package (StatSoft Inc., Tulsa, OK, USA). Statistical significance for categorical variables was calculated using the chi-squared test. The percentage values represented in the figures are compared with the control values for 1987 in each size interval; a value of p<0.05 was regarded as statistically significant.

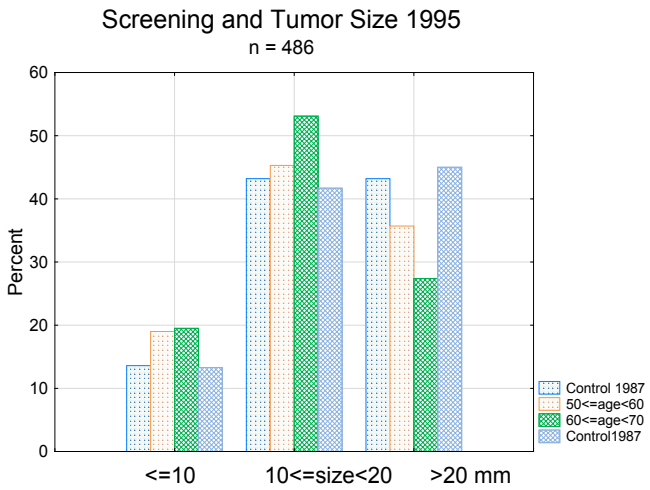

Figure 2: Tumor size data from 1995, 6 years after the introduction of screening, representing a maximum of four screening events. Compared with the 1987 controls, there is a significantly smaller proportion of tumors >20 mm in the 60–70 year age group (p<0.01); this difference is not significant in the 50–60 year age group. In the age group 60–69 years, the tumor size interval 10–20 mm is still increased but not to a significant extent (p=0.08). The control data are shown for the age group 50–59 years to the left and the age group 60–69 years to the right.

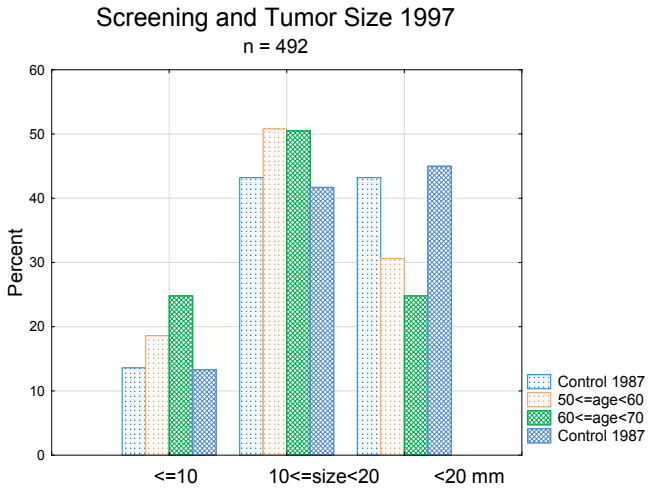

Figure 3: Tumor size data from 1997, 8 years after the introduction of screening, representing a maximum of five screening events. Tumors >20 mm are still significantly less frequent in the study age group 60–69 years than in the 1987 controls (p<0.001). In the 50–60 year age group it approaches significance (p=0.06). The frequency of small tumors (≤ 10 mm) is significantly greater in the 60–69 year age group than in the controls (p<0.05). The control data are shown for the age group 50–59 years to the left and the age group 60–69 years to the right.

Permission to analyze the patients' data was obtained from the Ethical Committee Nord, Karolinska Institute (2013/707-31/3).

Results

Patients in the age group 50-69 years (n=1011) were distributed to the control and study groups as: 1987 (n=197), 1993 (n=211), 1995 (n=293), and 1997 (n=313). The mean ages in 1993, 1995, 1997 and the control group 1987 for patients aged 50-59 years were 53,8, 53,9, 54 and 53,5 years and for the groups aged 60-69 years 63,6, 64, 63,6, and 64,5 years. Tumor size was missing in 6 patients 1993, in 2 patients 1995, in 15 patients 1997 and 10 patients in 1987.

Compared with control data from 1987, in 1993, 4 years after the introduction of screening, there was a significant reduction in numbers of tumors >20 mm among patients aged 60–69 years, accompanied by a simultaneous and significant increase in tumors 10–20 mm in size (Table 1). There was no significant difference in the frequency of tumors ≤10 mm in size in comparison with the controls. Tumor sizes >20 mm in subjects aged 50–60 years in 1993 were slightly reduced, but did not differ significantly relative to control data (Figure 1).

In the subjects from 1995, tumors of 10-20 mm still revealed a higher percentage than the 1987 controls for the age group 60–69 years; however, this difference was no longer significant. A slight increase in small tumors (≤10 mm) was found, but was not significant. The percentage of tumors >20 mm in the 50–60 year age group was apparently starting to decrease, but this change was not yet significant (Table 2 and Figure 2).

In 1997, 8 years after the introduction of mammography screening, the percentage of tumors >20 mm was significantly smaller in 60–69 year age groups and close to become significant in the 50-59 year age group. In patients aged 60–69 years, for the first time since the introduction of screening there was a significant increase in tumors ≤10 mm in size (Table 3 and Figure 3). The percentage of DCIS diagnosed during these years was 4.4% in 1993, 4.3% in 1995, and 3.9% in 1997.

Tumor stage	ALNM	1993	*p*	1993
		50-59 y		60-69 y
Stage I_{a-b}	0	14	n.s.	19
≤10 mm		21%		24%
Stage I_c	0	25	<0.02	47
10–20 mm		38%		59%
Stage IIA	1–3	18	0.001	7
10–20 mm		27%		9%
Stage IIB	>3	8	n.s.	5
20–50 mm		12%		6%
Stage III	<9	1	n.s.	2
>50 mm		2%		2%
Σ		66		80

ALNM, axillary lymph node metastasis

Table 4: Distribution of tumor stages of the two study groups in 1993.

Tumor stage	ALNM	1997	*p*	1997
		50-59 y		60-69 y
Stage I_{a-b}	0	29	n.s.	23
≤10 mm		24%		26%
Stage I_c	0	54	n.s.	38
10–20 mm		45%		43%
Stage IIA	1–3	26	n.s.	15
10–20 mm		21%		17%
Stage IIB	>3	8	n.s.	9
20–50 mm		7%		9%
Stage III	<9	4	n.s.	5
>50 mm		3%		4%
Σ		121		89

ALNM, axillary lymph node metastasis

Table 5: Distribution of tumor stages of the two study groups in 1997.

Tumor stage alterations

The samples from 1993 and 1997 were compared according to the five tumor stages presented in Materials and Methods (Tables 4 and 5). In 1993 a significant increase in tumor stage I_c was found in the age group 60–69 years in the tumor size interval between 10 and 20 mm, along with a significant reduction in tumor stage IIA for patients aged 60–69 years, in line with the frequency change seen in Figure 1. This finding indicates a significant trend toward a more favorable tumor stage. However, in 1997 this difference cannot be seen, signifying a periodic change.

Discussion

The study shows that the effect of mammography screening begins during the first years to yield mainly large tumors > 20 mm in the second screened age group 60-69 years (Fig. 1, Table 1), the group invited most times to screening. As a side effect of this the intermediate sized group (10-20 mm) increased significantly. This phenomenon is transient and lasted in this study up to 4 years after introduction of screening. It disappeared completely when small tumors ≤ 10 mm started to increase in 1997 (Fig. 3, Table 3). According to the time course of screening, a reduction of tumors >20 mm was seen 1993 in the age group 50–60 years old (Figure 3 and Table 3) and approaches significance in 1997.

In the 10–20 mm tumor size interval (1993) there is a significant increase in stage Ic in the age group 60–69 years compared with the age group 50–59 years ($p<0.02$) (Table 4) and a reduction in stage IIA tumors ($p=0.001$). In tumors >20 mm there was a reduction in the stage II+ tumors, from 14% to 8% (Table 4). The samples were too small to show significance. A stronger effect of screening was also found in our study regarding parameters reflecting tumor biology and survival [13] in addition to redistribution of tumor size and change in tumor stage.

A limitation in this study is that we have no detailed information of the number of mammography screening events attended from each invited patient. However, the follow-up during 1994 and 1995 in the Stockholm area showed that when the numbers of women invited to the general screening program every second year and those visiting private radiology centers for screening were combined, they together reached a high level of 85–90% for those who had undergone one mammography screening in the previous 2 years [12]. This high and balanced result justified the conclusion that women in the elder age decade for screening (60–69 years) had been invited for and had undergone screening more often than their younger counterparts (50–60 years old) that should be the case if participation in screening was high.

Why it takes up to 8 years before an increase in small tumors is seen at diagnosis in the study group might be explained by the fact that it is easier to detect slight changes on X-rays when there are some previous radiographs available for comparison. The mean tumor size has been gradually reducing the longer screening has been in practice, progressively focusing more on smaller tumors; however, the numbers of DCIS have not increased during the study period.

Conclusion

The issue as to whether mammography screening diagnoses breast tumor that should have regressed spontaneously is based on the detection of an increase in tumors, with more tumor stages II+ in the study population than in women with clinically detected breast tumor at the first year after the start of screening [12]. However, as shown in this study, mammography screening has initially yielded tumors larger than 20 mm (Figure 1 and Table 1), most of which are II+ stage tumors mainly due to the size. A similar result was seen 1991 [13]. It means that the "hidden tumors" are those tumors we do not observe in the bar > 20 mm as compared to the control (Fig.1-3) and this occurred already 1991[13]. An observation of more favorable tumor stage was found in the second screened age decade (60–69 years) in our own as well as the referred study [14]. By 1997 the initial differences between the age groups had disappeared, confirming the transient behavior of this phenomenon. However, small tumors start to increase. The percentage of DCIS is not increased in this study, but that is not astonishing since the tumors ≤ 10 mm has just started to increase.

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Conflict of Interest

This study did not involve the use of any commercial products with connection to the authors. The authors have no conflicts of interest to disclose.

References

1. Tabár L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, et al. (1985) Reduction in mortality from breast cancer after mass screening with mammography. Randomized trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1: 829-823.
2. Autier P, Koechlin A, Smans M, Vatten L, Boniol M (2012) Mammography screening and breast cancer mortality in Sweden. J Natl Cancer Inst 104: 1080-1093.
3. Feuer EJ, Wun LM (1992) How much of the recent rise in breast cancer incidence can be explained by increases in mammography utilization? A dynamic population model approach. Am J Epidemiol 136: 1423-1436.
4. Zahl PH, Strand BH, Maehlen J (2004) Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. BMJ 328: 921-924.
5. Jonsson H, Johansson R, Lenner P (2005) Increased incidence of invasive breast cancer after the introduction of service screening with mammography in Sweden. Int J Cancer 117: 842-847.
6. Møller B, Weedon-Fekjaer H, Hakulinen T, Tryggvadóttir L, Storm HH, et al. (2005) The influence of mammographic screening on national trends in breast cancer incidence. Eur J Cancer Prev 14: 117-128.
7. Coburn NG, Cady B, Fulton JP, Law C, Chung MA (2012) Improving size, lymph node metastatic rate, breast conservation, and mortality of invasive breast cancer in Rhode Island women, a well-screened population. Breast Cancer Res Treat 135: 831-837.
8. Virnig BA, Wang SY, Shamilyan T, Kane RL, Tuttle TM (2010) Ductal carcinoma in situ: risk factors and impact of screening. J Natl Cancer Inst Monogr 2010:113-116.
9. Sørum R, Hofvind S, Skaane P, Haldorsen T (2010) Trends in incidence of ductal carcinoma in situ: the effect of a population-based screening programme. Breast 19: 499-505.
10. Jørgensen KJ, Gøtzsche PC (2009) Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. BMJ 339: b2587.
11. Allgood PC, Duffy SW, Kearins O, OÂ´Sullivan E, Tappenden N, et al. (2011) Explaining the difference in prognosis between screen-detected and symptomatic breast cancers. Br J Cancer 104:1680-1685.
12. TÃrnberg S, Ghassabei A (1997) Mapping the mammography department at Stockholm county hospital radiology clinics and the private radiology clinics in 1994 and 1995. Landstingsrapport Stocholm County.
13. Sennerstam RB (2013) During introduction of mammography screening analysis of three tumor size intervals in screened and post-screened periods clarified the short and long efficiency of screening. J Cancer Sci Ther doi: 10.4172/1948-5956.S7-006.
14. Frisell J, Eklund G, Hellström L, Glas U, Somell A (1989) The Stockholm breast cancer screening trial--5-year results and stage at discovery. Breast Cancer Res Treat 13: 79-87.