

Drug Use in Relation to Outcome of Mammography Screening

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Abstract

Background: We found previously that women with a false-positive result in mammography screening used significantly more anxiolytic- and antidepressant drugs in the two years prior to their screen than did women who later had a negative screen. When the European Agency for Evaluation of Medicinal Products in 2003 recommended restricted use of hormone therapy suggested alternatives for treatment of menopausal symptoms included antidepressants and other drugs for neurological disorders. Our hypothesis was that antidepressants use to some extent had replaced hormone use, and that this change in particular had affected women at risk of later becoming false-positive in mammography screening.

Methods and findings: We undertook a difference-in-differences study including women with a false-positive screen and matched controls of women with a negative screen from the Copenhagen screening program 1997-2006, and their prescribed drugs in 1995-2008. For each group of women defined by calendar period (1997-2003 or 2004-2006), screening result (false-positive /negative), and timing (2 years before/2 years after the screening event) we calculated the proportion of drug users. Risk ratios (RRs) were used for comparison of two proportions, and ratios of risk ratios (RRRs) for comparison of four proportions.

For all women, the use and doses of hormone therapy decreased from 1997-2003 to 2004-2006. While the proportion of women using antidepressant drugs remained fairly stable, the doses increased. No statistically significant difference was found in use of anxiolytic- and antidepressant drugs from before to after the screening event between women with false-positive and negative screens neither in 1997-2003 (RRR 1.04, 95% confidence interval (CI) 0.92-1.17) nor in 2004-2006 (RRR 0.97, 95% CI 0.78-1.21). However, before the screening event in 1997-2003 women with a later false-positive

screen had a statistically significantly higher use of these drugs than women with a later negative screen (RR 1.13, 95% CI 1.05-1.21). In 2004-2006 this difference was not statistically significant (RR 1.07, 95% CI 0.95-1.21), but the difference in doses reached RR 1.27 (95% CI 0.93-1.63).

Conclusion: We found no impact of a false-positive screen on use of anxiolytic- and antidepressant drugs either before or after the EMEA recommendations of restrictive use of hormone therapy.

Keywords: Mammography; Breast cancer; Screening; False-positive; Anxiolytic drugs; Antidepressant drugs; Hormone therapy

Introduction

The purpose of mammography screening is to reduce breast cancer mortality [1]. However, screening comes along with some controversial side effects. A major concern is false-positive results (i.e., positive screening results in women without breast cancer). In Denmark, the risk of a false-positive result over 10 screens has been estimated to be 7-16% [2], while this rate can be much higher in other countries such as the United States where it was estimated to be 63% [3,4].

False-positive screening results have been found to pose negative psychological effects [5,6]. A recent study from Denmark showed that women with a false-positive screening result were more likely to experience psychological distress for up to 3 years as compared to women with a negative screening result [7]. In Denmark, where access to the general practitioners (GPs) is free of charge, about one third of all contacts to GPs concerns psychological disorders [8], and the GPs are entitled to prescribe anxiolytic- and antidepressant drugs. It is therefore reasonable to expect an increase in the use of these drugs if a false-positive screening result causes anxiety. To test this hypothesis, we undertook a population-based register study in Denmark covering the period 1997-2006 [8]. We found that women with a false positive screening result had a higher consumption of anxiolytic- and

antidepressant drugs after this screen than they had before. But the same change over time was seen in women with negative screening results. Our study did therefore not support a causal association between a false-positive screening result and increased use of anxiolytic- and antidepressant drugs.

However, over the two years prior to the screen, there were significantly more users of anxiolytic- and antidepressant drugs among women with a later false-positive than among women with a later negative screening result. This could indicate selection. Hormone therapy has been widely prescribed to women with menopausal syndromes [9]. But data concerning negative side-effects such as increased risk of breast [10] and ovarian cancer [11], dementia and mild cognitive impairment [12] started to be published in the summer of 2002. Therefore, the European Agency for Evaluation of Medicinal Products (EMA) in December 2003 issued a recommendation on appropriate, restricted use of hormone therapy [13], and the use decreased [14]. Non-hormonal alternatives for treatment of menopausal hot flashes have been searched for, and suggested alternatives include antidepressants and drugs used for a variety of neurologic and psychiatric disorders [15].

On this basis, we re-analyzed our previous study, dividing the observations into the years prior to and after the new EMA recommendation [13]. Our hypothesis was that antidepressant use to some extent had replaced hormone use, and that this change in particular had affected women at risk of later becoming false-positive in mammography screening.

Methods

The study followed the difference-in-differences methodology. The data included: Women recorded in the Copenhagen screening mammography register 1997-2006, and their prescribed drugs recorded in the Danish National Prescription Registry (DNPR) 1995-2008.

In the Copenhagen mammography screening program women aged 50-69 years are personally invited on a biennial basis. Information on screening date and outcome is recorded in the mammography screening register, with each woman identified by her unique personal number. All women who experienced a false-positive result during the study period were included in the false-positive group at their first false-positive screening result in the study period. For each false-positive woman, five women with the same age, the same screening date, and with a negative screening result were selected at random, using a computerized system, from the mammography register to form a comparison group. Once a

woman had experienced a false-positive screening result, she would not be included in the comparison group. The study period for each woman started two years before the screen, ranging from 1995 to 2006, and ended two years after the screen, ranging from 1997 to 2008. Women not present in Denmark during their entire four years of observation were excluded, leaving 11,436 women in the study.

In the DNPR, prescribed drugs are registered by the unique personal number. Consumption is measured in Defined Daily Doses (DDDs) defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [16] (WHO, 2009). We investigated the drug consumption in two major categories: genitourinary system and sex hormones drugs (G) including G03C estrogens, G03D progestogens, and G03F a combination of estrogens and progestogens (in the following referred to as hormone therapy), and nervous system drugs (N) including N02 analgesics, N05 psycholeptics, N06 psychoanaleptics, and N07 other nervous system drugs (in the following referred to as anxiolytic- and antidepressant).

We calculated the proportion of drug users and mean DDDs per user in the false-positive group and in the negative comparison group in the two years before and in the two years after the screening event. The analysis was made for screening events in 1997-2006; 1997-2003 (prior to EMA recommendation); and 2004-2006 (following EMA recommendation). Risk ratios (RRs) including 95% confidence intervals (CIs) were used for comparison between two proportions, e.g., proportion of drug users in 2004-2006 with that in 1997-2003 in the false-positive group after the screening event. Ratios of risk ratios (RRRs) including 95% CIs were used for comparison between four proportions, e.g., proportion of drug users in 1997-2006 in the false-positive group after the screening event compared with that before the screening event and divided by the same ratio for the negative group. Ratios of means, and ratios of ratios of means were used for comparison and mean DDDs per user. Statistical analyses were carried out with SAS 9.1. and Vassar Stats© Richard Lowry 1998-2015. Ratios of means with 95% CI were calculated in GraphPad, ©2016 GraphPad Software, Inc.

Results

Among the 11,436 women included in the study, 1906 were in the false-positive group and 9530 in the negative group. The data for the entire study population distributed by before and after screening event, drug use and screening result are reported in **Figure 1**. These data are later divided into the time periods before and after the EMA recommendations.

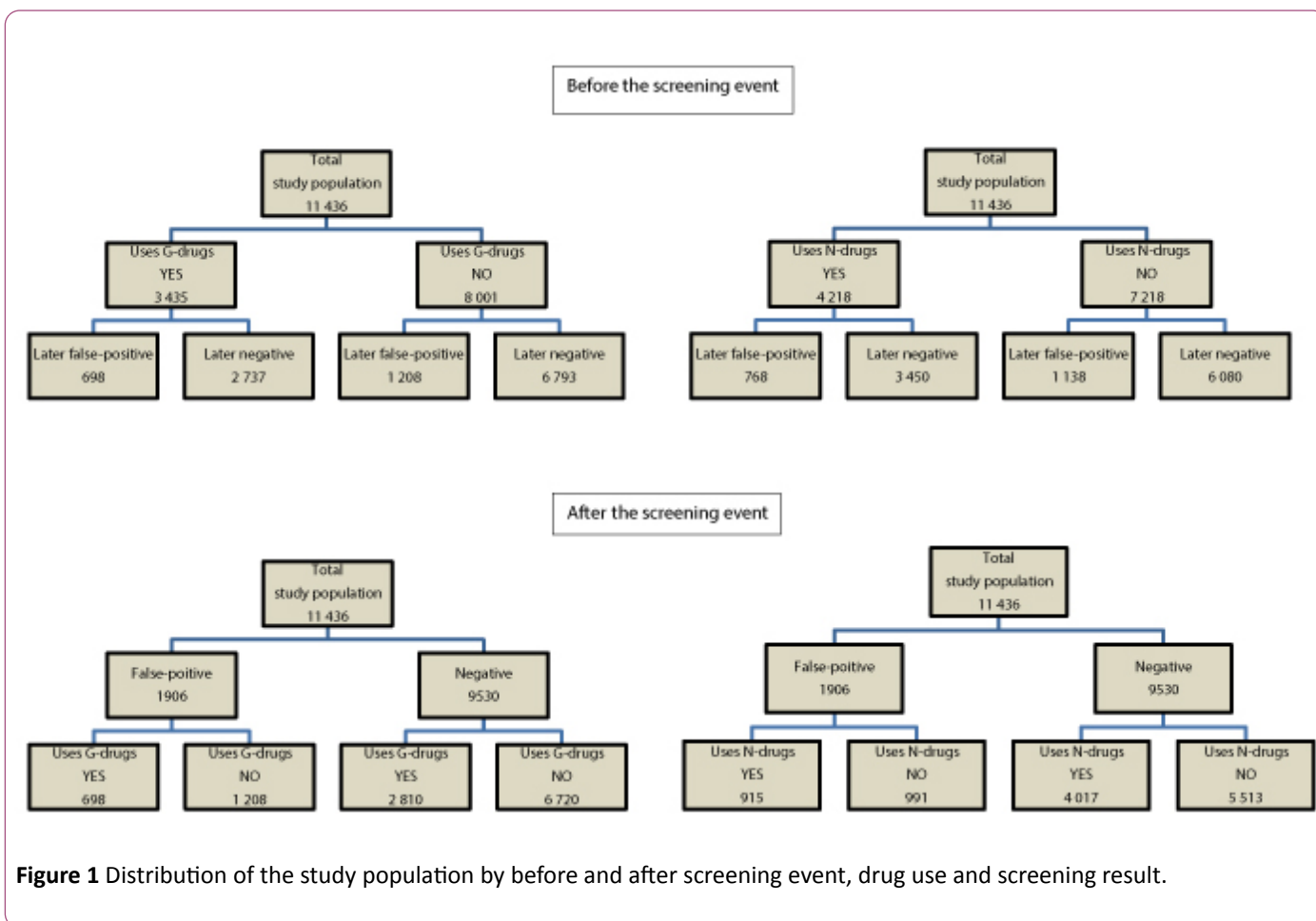


Figure 1 Distribution of the study population by before and after screening event, drug use and screening result.

Hormone therapy, summary results

In the entire period 1997-2006, the RRR (for false-positives in relation to negatives and after versus before screening event) for hormone therapy was 0.97 (95% CI 0.87-1.10), with similar patterns for 1997-2003 (RRR 0.99, 95% CI 0.93-1.06) and for 2004-2006 (RRR 0.93, 95% CI 0.71-1.22). For the mean

DDD of hormone therapy, these RRRs were 0.92 (95% CI 0.78-1.09), 0.92 (95% CI 0.78-1.13), and 0.90 (95% CI 0.75-1.13), respectively. In the case of progesterone, the figures concerning the mean DDD were RRR 0.80 (95% CI, 0.66-0.97), 0.18 (95% CI, 0.14-0.24) and 0.70 (95% CI, 0.58-0.85), **Table 1**.

Table 1 Ratio of risk ratios for after versus before, 95% confidence intervals and p-values*. * Ratio of risk ratios for after versus before, 95% confidence intervals, and p-values in number of women using drugs and in mean dose (DDD/woman) by mammography outcome, time period in relation to the screening event, and time period in relation to recommendation for prescription of hormone therapy. G-Drug=Hormone therapy; N-Drug=anxiolytic-and antidepressant drugs; DDD=Daily Defined Doses.

Type of mammography screen/ Drug type	Ratio after/before for number of women, by time of screening event, using drugs			Ratio after/before for mean dose (DDD/woman), by time of screening event		
	1997-03	2004-06	1997-06	1997-03	2004-06	1997-06
G - drugs	0.99 0.93-1.06 p=0.777	0.93 0.71-1.22 p=0.603	0.97 0.87-1.10 p=0.920	0.92 0.78-1.13 p=0.345	0.90 0.75-1.07 p=0.240	0.92 0.78-1.09 p=0.354
Estrogen (G03C)	0.93 0.75-1.15 p=0.507	0.93 0.79-1.17 p=0.689	0.95 0.81-1.10 p=0.480	0.93 0.77-1.13 p=0.493	0.83 0.67-1.03 p=0.097	0.91 0.75-1.11 p=0.377

Progesterone (G03D)	1.03 0.63-1.68 p=0.920	0.94 0.28-3.12 p=0.920	0.98 0.70-1.38 p=0.920	0.80 0.66-0.97 p=0.021	0.18 0.14-0.24 p<.0001	0.70 0.58-0.85 p=0.000
Combination of Estrogen and Progesterone (G03F)	1.01 0.85-1.20 p=0.920	0.96 0.62-1.48 p=0.841	1.01 0.86-1.18 p=0.920	0.91 0.78-1.06 p=0.215	1.01 0.87-1.17 p=0.887	0.92 0.79-1.07 p=0.265
N – drugs	1.04 0.92-1.17 p=0.543	0.97 0.78-1.21 p=0.806	1.02 0.92-1.14 p=0.671	1.05 0.88-1.26 p=0.572	0.97 0.84-1.13 p=0.689	1.02 0.86-1.21 p=0.806
Analgetics (N02)	1.04 0.82-1.32 p=0.764	0.91 0.58-1.43 p=0.689	1.03 0.91-1.18 p=0.639	0.91 0.67-1.26 p=0.584	1.11 0.80-1.53 p=0.549	0.94 0.69-1.30 p=0.718
Psycholeptics (N05)	1.08 0.90-1.30 p=0.390	0.91 0.64-1.28 p=0.578	1.03 0.91-1.17 p=0.663	0.98 0.79-1.22 p=0.887	0.97 0.79-1.19 p=0.764	0.97 0.79-1.21 p=0.806
Psychoanaleptics (N06)	0.93 0.72-1.20 p=0.578	1.09 0.74-1.61 p=0.645	0.97 0.80-1.18 p=0.777	1.19 1.05-1.35 p=0.007	0.84 0.76-0.94 p=0.003	1.03 0.94-1.20 p=0.351
Other (N07)	1.21 0.71-2.06 p=0.475	1.10 0.46-2.61 p=0.823	1.17 0.75-1.83 p=0.493	0.96 0.86-1.07 p=0.435	1.03 0.94-1.13 p=0.502	0.98 0.88-1.08 p=0.655

Anxiolytic- and antidepressant drugs, summary results

A similar pattern was seen for use of anxiolytic-and antidepressant drugs. In 1997-2006, the RRR for these drugs was 1.02 (95% CI 0.92-1.14), with no change between 1997-2003 and 2004-2006, RRR 1.04 (0.92-1.17) and 0.97 (95% CI 0.78-1.21), respectively. Also, here a similar pattern was seen for mean DDD of anxiolytic-and antidepressant drugs, the RRRs were 1.02 (95% CI 0.86-1.21), 1.05 (95% CI 0.88-1.26) and 0.97 (95% CI 0.84-1.13), respectively, **Table 1**.

Hormone therapy use, before the screening event versus after screening event

In the period before the screening event, women who later experienced a false-positive screening result had a higher consumption of hormone therapy than women who later experienced a negative screening result. The RRs for the

proportions were 1.28 (95% CI 1.19-1.36) for the entire period 1997-2006; 1.32 (95% CI 1.23-1.42) for 1997-2003, and 1.10 (95% CI 0.93-1.29) for 2004-2006. Smaller differences were seen between the two groups when it came to the mean DDD, where no difference was seen in 2004-2006, **Figure 2**.

Anxiolytic- and antidepressant drugs use, before the screening event versus after screening event

Women who later experienced a false-positive screening result also had a higher consumption of anxiolytic-and antidepressant drugs than women who later experienced a negative screening result; the RRs being 1.11 (95% CI 1.05-1.18) for the entire period 1997-2006, and 1.13 (95% CI 1.05-1.21) and 1.07 (95% CI 0.95-1.21) for 1997-2003 and 2004-2006, respectively. A difference in mean DDD derived exclusively from the late period with a RR of 1.27 (p=0.0594 for difference between means), **Figure 2**.

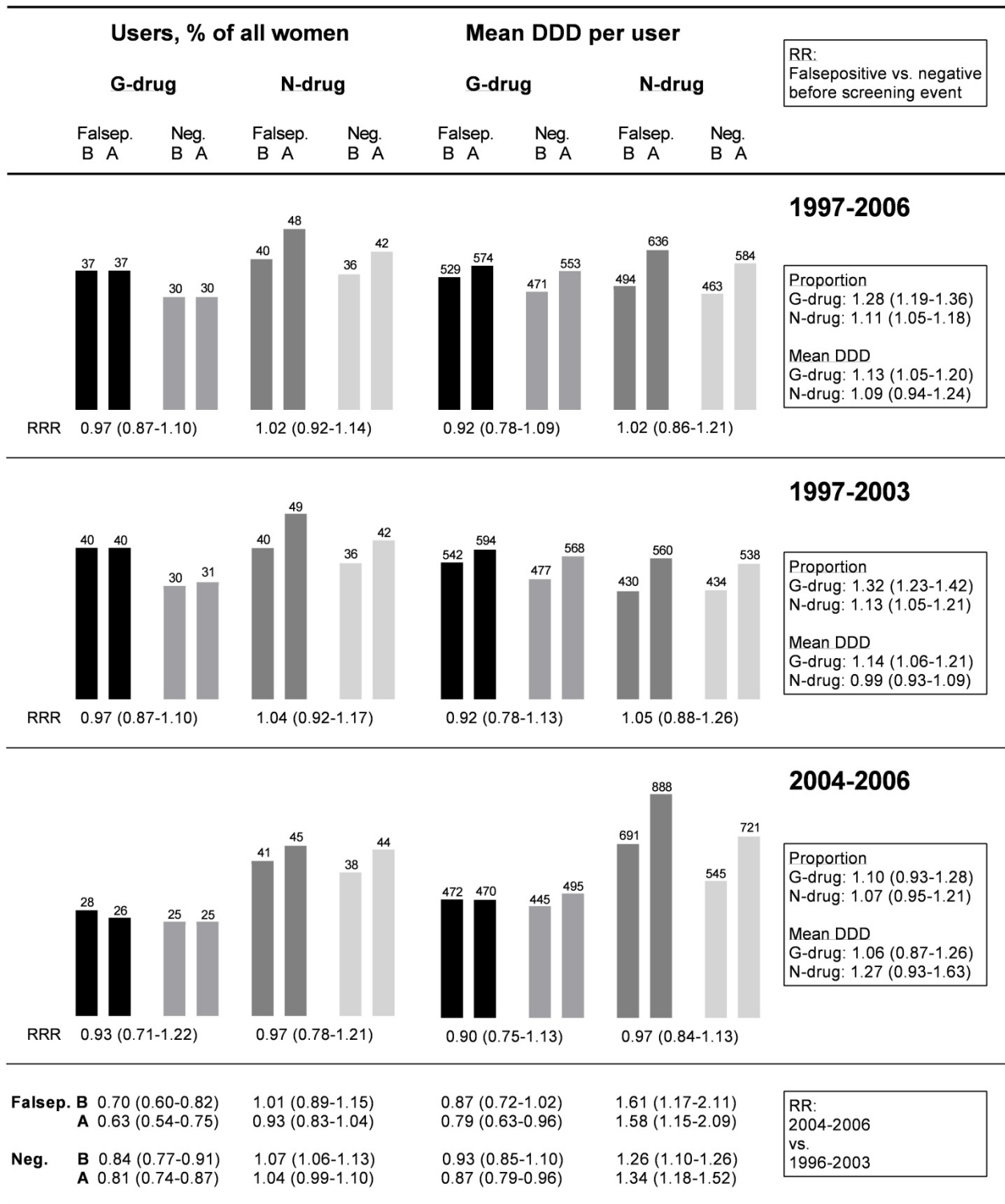


Figure 2 Ratios of risk ratios for proportion of users and ratios of ratios of mean DDD/user. Comparison of women with false-positive and negative screens in mammography screening. G-Drug=Hormone therapy; N-Drug=anxiolytic- and antidepressant drugs; DDD=Daily Defined Doses.

Hormone therapy use by time period

The proportion of users of hormone therapy changed statistically significantly from 1997-2003 to 2004-2006. For women in the false-positive group, the RR was 0.70 (95% CI

0.60-0.82) before their screening event and RR 0.63 (95% CI 0.54-0.75) after their screening event. This decline from 1997-2003 to 2004-2006 was significantly smaller for women in the negative group ($p < 0.001$); the “before screening event”

RR being 0.84 (95% CI 0.77-0.91), and the “after screening event” RR being 0.81 (95% CI 0.74-0.87), **Table 2**.

Table 2 Number of women using drugs by mammography outcome, screening event, and prescription recommendation*. *Number of women using drugs by mammography outcome, time period in relation to the screening event, and time period in relation to recommendation for prescription of hormone therapy; ratio of risk ratios, 95% confidence interval and p-value. G-Drug=Hormone therapy; N-Drug=anxiolytic-and antidepressant drugs; DDD=Daily Defined Doses.

	Before screening event				After screening event				1997-03	2004-08	1997-08
Type of mammography screen/ Drug type	1997-03	2004-06	(2004-06/1996-03 RR,CI,p)	1997-06	1997-03	2004-08	(2004-08/1996-03 RR,CI,p)	1997-06	(After/Before; RR,CI,p)	(After/Before RR,CI,p)	(After/Before RR,CI,p)
False positive											
G – drugs, current use (G03C estrogens, G03D progestogens, and G03F a combination of estrogens and progestogens).											
yes	570	128		698	580	118		698			
no	873	335		1208	863	345		1208			
% yes	39.5	27.6	0.70 (0.60-0.82))<0.0001	36.6	40.2	25.5	0.63 (0.54-0.75))<0.0001	36.6	1.02 (0.93-1.11)) 0.7038	0.94 (0.96-1.17)) 0.5842	1.0 (0.92-1.09)) 1.000
N – drugs, current use (N02 analgesics, N05 psycholeptics, N06 psychoanaleptics, and N07 other nervous system drugs).											
Yes	580	188		768	705	210		915			
No	863	275		1138	738	253		991			
% yes	40.2	40.6	1.01 (0.89-1.15)) , 0.875	40.3	48.9	45.4	0.93 (0.83-1.04)) 0.198	48.0	1.22 (1.12-1.32)) <0.0001	1.12 (0.96-1.30)) 0.145	1.19 (1.11-1.28)) <0.0001
Negative											
G – drugs, current use (G03C estrogens, G03D progestogens, and G03F a combination of estrogens and progestogens).											
yes	2155	582		2737	2233	577		2810			
no	5060	1733		6793	4982	1738		6720			
% yes	29.9	25.1	0.84 (0.77-0.91)) <0.0001	28.7	30.9	24.9	0.81 (0.74-0.87)) <0.0001	29.4	1.04 (0.99-1.09)) <0.0001	0.99 (0.90-1.10)) 0.8653	1.03 (0.98-1.07)) 0.2444
N-drugs, current use (N02 analgesics, N05 psycholeptics, N06 psychoanaleptics, and N07 other nervous system drugs).											
yes	2571	879		3450	3009	1008		4017			
no	4644	1436		6080	4206	1307		5513			
% yes	35.6	38.0	1.07 (1.00-1.13)) 0.040	36.2	41.7	43.5	1.04 (0.99-1.10)) 0.116	42.2	1.17 (1.12-1.22)) <0.0001	1.15 (1.07-1.23)) 0.0001	1.16 (1.12-1.21)) <0.0001

The mean DDD of hormone therapy decreased less and was statistically significant only for the “after” RRs being 0.79 (95% CI 0.63-0.96) for the false-positive group, and 0.87 (95% CI 0.79-0.96) for the negative group, **Table 3**.

Anxiolytic- and antidepressant drugs use by time period

The proportion of users of anxiolytic-and antidepressant drugs did not change from 1997-2003 to 2004-2006 for women in the false-positive group; the RR in the “before” period was 1.01 (95% CI 0.89-1.15), and it was 0.93 (95% CI

0.83-1.04) in the “after” period. The changes in women in the negative group were borderline statistically significant, RR 1.07 (95% CI 1.00-1.13) in the “before” period, and 1.04 (95% CI 0.99-1.10) in the “after” period, **Table 2**.

Table 3 Mean dose (DDD/woman) of drugs used by mammography outcome, screening event and prescription recommendation*. *Mean dose (DDD/woman) of drugs used by mammography outcome, time period in relation to the screening event, and time period in relation to recommendations for prescription of hormone therapy; ratio of risk ratios, 95% confidence interval and p-value. G-Drug=Hormone therapy; N-Drug=anxiolytic-and antidepressant drugs; DDD=Daily Defined Doses.

Type of mammography screen/ Drug type	Before screening event				After screening event				1997	2004	1997
	1997-03	2004-06	(Before RR,CI,p)	1997-06	1997-03	2004-06	(After RR,CI,p)	1997-06	(After/Before RR,CI,p)	(After/Before RR,CI,p)	(After/Before RR,CI,p)
False positive											
G - drugs	542.92	472.34	0.87 (0.72-1.02)	529.97	594.61	470.61	0.79 (0.63-0.96)	573.69	1.10 (1.01-1.19)	1.00 (0.76-1.28)	1.08 (1.00-1.17)
N-drugs	430.29	691.07	1.61 (1.17-2.11)	494.13	560.91	888.32	1.58 (1.15-2.09)	636.05	1.30 (1.06-1.60)	1.28 (0.89-1.85)	1.29 (1.07-1.55)
Negative											
G-drugs	477.64	445.60	0.93 (0.85-1.01)	470.82	568.02	495.50	0.87 (0.79-0.96)	553.13	1.19 (1.13-1.25)	1.11 (0.98-1.25)	1.17 (1.12-1.23)
N-drugs	434.34	545.52	1.26 (1.10-1.42)	462.67	538.36	721.73	1.34 (1.18-1.52)	584.37	1.24 (1.13-1.36)	1.32 (1.13-1.54)	1.26 (1.17-1.37)

However, the mean DDD of anxiolytic-and antidepressant drugs increased statistically significantly from 1997-2003 to 2004-2006 both in the false-positive group and in the negative group. In the false-positive group, the RR was 1.61 (95% CI 1.17-2.11) in the “before” period and 1.58 (95% CI 1.15-2.09) in the “after” period. In the negative group the RRs were 1.26 (95% CI 1.10-1.42) and 1.34 (95% CI 1.18-1.52), respectively, **Table 3**.

Discussion

We found no impact of a false-positive screening result on the use of hormone therapy and anxiolytic-and antidepressant drugs neither prior to nor after the EMEA recommendation on restrictive use of hormone therapy. Our previous results were therefore not confounded by changes in the drug prescription pattern over time.

We also found that women who later experienced a false-positive result constituted a selected group. Prior to the EMEA recommendation, use of hormone therapy was 32% more frequent and use of anxiolytic- and antidepressant drugs 13% more frequent in women who later experienced a false-positive result than in other women. While there was no difference between the users in the two groups of women in mean dose of anxiolytic- and antidepressant drugs prior to the EMEA recommendation, this difference came up to 27% afterwards.

We found that the EMEA recommendation was associated with a decreased use of hormone therapy but with an increased use of anxiolytic-and antidepressant drugs. In women who later experienced a false-positive result, use of hormone therapy decreased by 30% and by 16% in other women. While the EMEA recommendation was not associated with change in use of anxiolytic- and antidepressant drugs in women who later experienced a false-positive result, it was associated with a 7% increase in other women, and the mean dose in users increased with 61% in the false-positive group and with 26% in other women.

Since this population study was register-based, recall bias was not a problem. It was a strength of the study that the drug prescription data in the DNPR are comprehensive and valid [17]. The longitudinal record keeping enabled us to track drug consumption for each woman throughout the specified time frame, two years before and two year after the screening event. Certainly, drug prescription is not equivalent to actual consumption, but it is a reasonably good indicator, and this limitation applied equally to women in the false-positive and in the negative groups.

Between 38% and 45% of women were recorded with at least one prescription of anxiolytic-and antidepressant drugs during the latest two-year period in the years 2004 to 2006. This proportion might seem high. However, according to national statistics in a one-year period 2011 about 15% of

women in our studied age-group used antidepressant drugs, and an additional 2% of new users were recorded in a year [18]. In Denmark, the antidepressant drugs constitute about half of the total consumption of anxiolytic-and antidepressant drugs [18]. On this basis the recorded use in the present study is well in line with national statistics.

Use of hormone therapy increases breast density, and breast density increases the risk of a false-positive screening result [19]. The excess use of hormone therapy seen in the present study in the false-positive group before their screening event was therefore an expected finding.

The excess use of anxiolytic- and antidepressant drugs in the false-positive group before their screening event is more difficult to explain. However, a study from the population-based Saskatchewan Health records from 1981-1998, thus from before published side-effects of hormone therapy, revealed that in healthy women aged 45 years and above, users of hormone therapy were more likely also to use central nervous system drugs than were non-users [20]. The increased use of anxiolytic-and antidepressant drugs, especially in terms of increased doses, after the EMEA recommendation on restrictive use of hormone therapy, was supported by data from Sweden. According to the Swedish Prescribed Drug Register, women who discontinued use of hormone therapy between July 2005 and June 2009 were more likely to take up use of antidepressant treatment than were women who continued use of hormone therapy, incidence rate ratio 1.24 (95% CI 1.11-1.38) [21].

Estradiol therapy has been suggested for treatment of depression among peri-and early postmenopausal women [22], indicating that hormone therapy and anxiolytic-and antidepressant drugs may to a certain extent replace each other in the treatment of menopausal symptoms. It is noteworthy in our data, however, that the observed increase in doses of anxiolytic-and antidepressant drugs from the pre-EMEA recommendation period to the post-period were considerably larger than the observed decreases in doses of hormone therapy. For the false-positive group, it was a 61% increase versus a 13% decrease, and for the negative group a 26% increase versus a 7% decrease. In the post-EMEA recommendation period, users of anxiolytic-and antidepressant drugs in the false-positive group used on average almost one DDD per day for the entire two years prior to their false-positive screening result; increasing to more than one DDD per day during the two years after their screening event.

While elevated mental distress has commonly been perceived as a major side-effect of false-positive screening results, our findings indicated that the observed anxiety could probably to some extent be explained by pre-screening selective differences. Two years before the screening, the women who later experienced a false-positive result probably already had more psychological distress than women who later received a negative result. Before 2004, hormone therapy was to a certain extent used to alleviate these symptoms, while from 2004 onwards this role was in part taken over by the anxiolytic-and antidepressant drugs.

Conclusion

We found no impact of a false-positive screening result on use of anxiolytic- and antidepressant drugs, but we found that women who later experienced a false-positive screening result to some extent constituted a selected group with more users of these drugs even before their false-positive screening event, and the doses they used increased after the new restrictive EMEA recommendation for use of hormone therapy.

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Conflict of Interest Statement

All authors declare no conflict of interest.

Ethics

Use of screening data and medical information was approved by the Danish Data Inspection Agency (2001-41-6191).

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