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Sleep Patterns, Sleep Disorders and Mammographic Density in Spanish Women: the DDM-Spain/Var-DDM study

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Highlights

- We explored sleep patterns and mammographic density, a marker of breast cancer risk.
- Sleep patterns or sleep disorders were not associated with mammographic density.
- These results do not support a relationship between breast cancer and sleep problems.

Abstract

We explored the relationship between sleep patterns and sleep disorders and mammographic density (MD), a marker of breast cancer risk. Participants in the DDM-Spain/var-DDM study, which included 2,878 middle-aged Spanish women, were interviewed via telephone and asked questions on sleep characteristics. Two radiologists assessed MD in their left crano-caudal mammogram, assisted by a validated semiautomatic-computer tool (DM-scan). We used log-transformed percentage MD as the dependent variable and fitted mixed linear regression models, including known confounding variables.

Our results showed that neither sleeping patterns nor sleep disorders were associated with MD. However, women with frequent changes in their bedtime due to anxiety or depression had higher MD (e^{β} :1.53;95%CI:1.04-2.26).

Abbreviations: BC, Breast Cancer; MD, Mammographic Density.

Keywords: Sleep patterns; Sleep disorders; Breast Cancer; Mammographic density.

1. Introduction

Hormonal changes around menopause affect sleep quality, and middle age women frequently experience sleep disorders [1]. Nightshift-work involving circadian disruption is a known risk factor for breast cancer(BC) [2]. Sleep deficit and sleep disorders can lead to circadian disruption and some authors have suggested that they might also modify BC risk.

Mammographic density, the most commonly used risk marker for BC, is the proportion of radiopaque area of the breast projection in the mammogram. Women with very dense breast have a 4 to 6-fold excess risk of BC compared to those women, with the same age and weight, which have low MD [3]. The association between sleep patterns, sleep disorders and mammographic density (MD) could provide additional data on their role on BC, but it has been barely investigated [3]. Our aim is to explore the relationship between sleeping patterns, sleep disorders and MD in Spanish women attending BC screening-programs, and its possible interaction with menopausal status.

2. Methods

This study was carried out in in 7 public population-based Spanish screening regional centers (Aragon; Balearic Islands; Castile-León; Catalonia; Galicia; Navarre; Valencia). These government-sponsored programs invite women aged 50-69 (45-69 in some regions) to biennial screening. In 2007-2008 we recruited 3,584 women (DDM-Spain) (participation rate:74.5%; range: 64.7–84.0% across centers), and collected basic epidemiological data; 3119 of these participants (age range: 47-71 years old), answered a telephone-administered questionnaire in 2010 (Var-DDM), which updated previous information and included several questions on sleeping habits and sleep disorders. In addition, they allowed access to their mammographic history; we could locate mammograms of 2,890 participants from this new screening round (average time between mammogram date and interview: 7.9 months). Postmenopausal status was defined as self-reported absence of

menstruation in the last 12 months. We excluded 12 women without weight data or night-shift work history information.

Two trained experienced radiologists estimated the percentage of MD in a continuous scale, assisted by DM-Scan, a free semi-automated computer tool (<http://dmscan.iti.upv.es>) that has demonstrated high reproducibility and validity. 44,9% of the mammograms were fully-digital mammograms, while analogical (11,7%) and digital images printed on film (43,4%) were digitalized (Totalook MammoAdvantage, max. optical-density:4.2; and Microtek Medi-700 max, max.optical-density:4.0). Both intra- and inter-rater intra-class correlation were >0.8 .

The possible association of MD with sleep pattern and sleep disorders was evaluated by multivariate mixed linear regression models with random screening-center-specific intercepts. We used log-transformed percentage of MD as the dependent variable and included as potential confounders: age at mammogram; menopausal status; body mass index (BMI); number of childbirths; family history of BC; hormonal replacement therapy use; tobacco use, alcohol consumption; calorie intake; physical activity; night-shift work history; radiologist and type of mammogram. The regression coefficients and standard errors of these models were exponentiated to calculate the relative increase of geometric means (GM) of MD comparing groups of participants across categories. Models were constructed separately for pre and postmenopausal women and a statistical interaction served to test heterogeneous effects according to menopausal status.

3. Results

A total of 2,878 women provided information on sleep pattern characteristics. Most of the women reported regular sleep schedules (i.e. going to bed every day at the same time in the last 10 years), with average bedtime at 11:52 pm and average nighttime sleep duration of 6.8 hours/day. Prevalence of regular naps was 44% and almost half of those women took naps daily (657 women).

Sleep disorders lasting at least one year were reported by 45.5% of the women, usually difficulties falling or staying asleep at night. Less than 1% of the women reported obstructive sleep apnea (n:23) or restless legs syndrome (n:6). Nine percent of participants had history of night-shift work (n: 269).

The GM of the percentage of MD in all participants was 13.3% (95%CI:12.9-13.8), in premenopausal women 20.0% (95%CI:19.8-24.5) and in postmenopausal 12.6% (95%CI:12.2-13.1). As expected, MD was inversely associated with age (P:0.001) and BMI (P:0.001).

Overall, sleeping patterns were not associated with MD, and neither sleep duration ($e^{\beta}_{\text{trend/hour}}:1.01$; 95%CI:0.98-1.03) nor usual bedtime (P:0.534) were related to MD (Table 1). Regarding sleep disorders, no association was found with reporting sleep disorders ($e^{\beta}:1.04$; 95%CI:0.98-1.10), years with sleep disorders, age at sleep disorders onset, or type of sleep disorders. However, premenopausal women with more than 10 years of sleep disorders had lower MD ($e^{\beta}:0.64$; 95%CI:0.41-0.99), although this category included only 13 women.

Finally, frequent changes in bedtime for at least one year, overall, were not associated with MD. Nevertheless, women that attributed these bedtime time changes to anxiety or depression had higher MD than the rest of the women ($e^{\beta}:1.53$; 95%CI:1.04-2.26), especially postmenopausal women ($e^{\beta}:1.71$; 95%CI:1.11-2.64). Menopausal status didn't modify any of the reported results.

4. Discussion

We did not find any association between MD and sleep patterns, napping or sleep disorders. Sleep deprivation, which might be a surrogate for circadian disruption, has been hypothesized to be related to BC. The lack of association of sleep duration with MD, a risk marker for BC, is coherent with the results of a recent meta-analysis that don't support the association of sleep deficiency with BC [2].

Regarding MD and sleep disorders, the only published study on this issue found no association in premenopausal Chinese women [3], which is consistent with our results. As an isolated result, we

found higher MD in women reporting changes in their bedtime because of anxiety or depression; these problems imply other exposures unrelated to sleep disruption (i.e. prolactin changes due antidepressants [4].)

One limitation of this study is the use of self-reported sleep information; however, there is evidence that self-reported sleeping habits may be accurate at capturing sleep duration [5]. Also, we used different types of mammograms and had two readers; however, all models were adjusted for these possible sources of error. Among our strengths are the population-based nature of the study sample and the use of continuous measure of MD, as recommended by previous authors.

In conclusion, our results suggest that sleep patterns or sleep disorders are not associated with MD, and do not support the possible relationship between them and BC.

Contributors

All authors participated in the design of the study, the interpretation of the data and the writing of the manuscript, and all authors saw and approved the final version.

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Ethical approval

The DDM-Spain and Var-DDM study protocol was formally approved by the Bioethics and Animal Welfare Committee at the Carlos III Institute of Health and all participants signed a consent form, including permission to publish the results from the current research.

Provenance and peer review

This article has undergone peer review.

Conflict of interest

The authors declare that they have no conflict of interest.

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Other members of DDM-Spain/Var-DDM Spain: María Casals, Inmaculada Martínez, María Eterra and Jesús Vioque.

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Table 1. Association between sleeping characteristics, sleep disorders and mammographic density in Var-DDM Spain study (2010)

	Total (n: 2878)				Premenopausal (n: 348)				Postmenopausal (n: 2530)			
	n	e ^β	95% CI	P	n	e ^β	95% CI	P	n	e ^β	95% CI	P
Nighttime sleep patterns												
Regular sleep schedule^a												
Yes	2328	1.00			225	1.00			2103	1.00		
No	548	0.95	0.88 - 1.03	0.197	50	0.79	0.62 - 1.00	0.055	498	0.97	0.89 - 1.05	0.410
Average nighttime sleep duration^b												
< 7 hours/day	1144	0.97	0.91 - 1.04	0.384	98	0.88	0.72 - 1.06	0.183	1046	0.98	0.92 - 1.05	0.537
7-8 hours/day	1475	1.00			158	1.00			1317	1.00		
> 8 hours/day	241	0.98	0.88 - 1.10	0.744	19	1.10	0.77 - 1.59	0.598	222	0.97	0.86 - 1.09	0.627
<i>trend per hour/day</i>	2860	1.01	0.98 - 1.03	0.603	275	1.05	0.97 - 1.14	0.247	2603	1.00	0.98 - 1.03	0.791
Usual bedtime^c												
10 pm or before	339	0.93	0.85 - 1.03	0.155	22	1.08	0.77 - 1.53	0.650	317	0.93	0.84 - 1.02	0.124
after 10 pm and before 1 am	2102	1.00			214	1.00			1888	1.00		
1 am or later	431	1.05	0.96 - 1.14	0.255	39	1.04	0.79 - 1.36	0.779	392	1.05	0.96 - 1.15	0.309
<i>trend per category</i>	2872	1.01	0.97 - 1.06	0.534	275	1.02	0.90 - 1.17	0.712	2597	1.01	0.97 - 1.05	0.638
Naps during daytime												
Naps frequency												
No naps/week	1616	1.00			137	1.00			1479	1.00		
1-3 days/week	391	1.05	0.96 - 1.15	0.321	55	1.01	0.79 - 1.29	0.941	336	1.05	0.95 - 1.16	0.369
4-5 days/week	171	1.01	0.88 - 1.14	0.934	20	0.98	0.68 - 1.41	0.923	151	1.00	0.87 - 1.15	0.968
6-7 days/week	700	1.02	0.95 - 1.10	0.605	63	0.99	0.79 - 1.25	0.929	637	1.02	0.95 - 1.11	0.548
<i>trend per day</i>	2878	1.00	0.99 - 1.01	0.561	275	1.00	0.97 - 1.03	0.881	2603	1.00	0.99 - 1.01	0.516
Average nap duration												
No naps	1616	1.00			137	1.00			1479	1.00		
< 30 min	605	0.99	0.92 - 1.07	0.828	57	1.09	0.85 - 1.38	0.500	548	0.98	0.90 - 1.06	0.614
30-60 min	588	1.06	0.98 - 1.15	0.118	74	0.92	0.74 - 1.15	0.454	514	1.09	1.00 - 1.18	0.053
> 60 min	69	1.03	0.84 - 1.25	0.806	7	1.11	0.62 - 1.99	0.734	62	1.01	0.82 - 1.25	0.910
<i>trend per 30 min</i>	2878	1.02	0.99 - 1.06	0.200	275	0.98	0.89 - 1.08	0.679	2603	1.03	0.99 - 1.07	0.149
Cumulative nap time												
No naps	1616	1.00			137	1.00			1479	1.00		
< 120 min/week	631	0.99	0.92 - 1.07	0.863	63	1.06	0.83 - 1.33	0.653	568	0.98	0.91 - 1.07	0.700
120-240 min/week	400	1.12	1.03 - 1.23	0.011	49	0.99	0.77 - 1.28	0.952	351	1.14	1.04 - 1.26	0.008
> 240 min/week	231	0.96	0.85 - 1.07	0.446	26	0.88	0.63 - 1.22	0.439	205	0.97	0.86 - 1.10	0.621
<i>trend per 120 min/week</i>	2878	1.01	0.98 - 1.04	0.419	275	0.97	0.89 - 1.07	0.579	2603	1.02	0.98 - 1.05	0.307
Sleep disorders												
Sleep disorders (>1 year)												
No	1568	1.00			181	1.00			1387	1.00		
Yes	1310	1.04	0.98 - 1.10	0.228	94	0.90	0.75 - 1.09	0.296	1216	1.05	0.98 - 1.12	0.144
Current sleep disorders	1005	1.02	0.96 - 1.09	0.509	71	0.90	0.73 - 1.11	0.314	934	1.03	0.96 - 1.10	0.381
Past sleep disorders	305	1.09	0.99 - 1.21	0.090	23	0.92	0.66 - 1.29	0.629	282	1.11	1.00 - 1.23	0.056
Years with sleep disorders^d												
No sleep disorders	1568	1.00			181	1.00			1387	1.00		
< 5 years	528	1.07	0.99 - 1.16	0.092	52	0.95	0.75 - 1.20	0.664	476	1.08	1.00 - 1.18	0.064
5-10 years	368	1.00	0.91 - 1.09	0.933	26	0.91	0.67 - 1.24	0.552	342	1.00	0.91 - 1.11	0.948
>10 years	372	1.03	0.94 - 1.13	0.562	13	0.64	0.41 - 0.99	0.046	359	1.05	0.95 - 1.15	0.351
<i>trend per 5 years</i>	2836	1.00	0.98 - 1.02	0.881	272	0.92	0.84 - 1.01	0.068	2564	1.00	0.98 - 1.02	0.933
Age at sleep disorders onset^e												
No sleep disorders	1568	1.00			181	1.00			1387	1.00		
<46 years old	383	1.02	0.94 - 1.12	0.600	51	0.87	0.68 - 1.11	0.262	332	1.04	0.94 - 1.15	0.414
46-55 years old	642	1.05	0.97 - 1.13	0.235	40	0.91	0.70 - 1.19	0.511	602	1.06	0.98 - 1.15	0.161
>55 years old	251	1.04	0.93 - 1.16	0.534	0	-	-	-	251	1.04	0.93 - 1.17	0.470
Type of sleep disorder^f												
No sleep disorders	1568	1.00			181	1.00			1387	1.00		
Difficulty falling asleep	993	1.03	0.95 - 1.11	0.544	71	1.02	0.78 - 1.33	0.897	922	1.03	0.94 - 1.12	0.540
Difficulty staying asleep (awakenings)	1066	1.01	0.93 - 1.09	0.829	73	0.87	0.67 - 1.12	0.282	993	1.02	0.94 - 1.11	0.666
Others ^g	129	1.10	0.95 - 1.28	0.184	10	1.07	0.66 - 1.76	0.778	119	1.11	0.95 - 1.29	0.191
Frequent changes in bedtime for > 1 year												
No	2620	1.00			243	1.00			2377	1.00		
Yes	258	1.07	0.96 - 1.20	0.208	32	1.00	0.73 - 1.37	0.986	226	1.07	0.96 - 1.21	0.231
Have you ever needed medications to sleep?												
No	2118	1.00			222	1.00			1896	1.00		
Yes	760	0.99	0.92 - 1.06	0.746	53	0.91	0.72 - 1.14	0.411	707	0.99	0.92 - 1.06	0.791

All models are adjusted for age, body mass index, number of childbirths, hormonal replacement therapy use, family history of breast cancer, physical activity, tobacco consumption, alcohol and calorie intake, type of mammogram, radiologist, night-shift work history, menopausal status (only for all women) and including screening center as a random effect term.

Interaction with menopausal status was not significant $P > 0.05$.

^a2 women didn't report regularity in sleep schedule.

^b18 women didn't report their nighttime sleep duration

^c6 women didn't report their bedtime.

^d42 women didn't report the number of years with sleep disorders.

^e34 women didn't report the age at sleep disorders onset.

^fCategories not exclusive

^gIncludes obstructive sleep apnea and restless legs syndrome