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by [Pesch B](#), [Harth V](#), [Rabstein S](#), [Baisch C](#), [Schiffermann M](#), [Pallapies D](#), [Bonberg N](#), [Heinze E](#), [Spickenheuer A](#), [Justenhoven C](#), [Brauch H](#), [Hamann U](#), [Ko Y](#), [Straif K](#), [Brüning T](#)

Affiliation: Research Institute of Occupational Medicine of the German Social Accident Insurance (BGFA), 44789 Bochum, Germany. pesch@bgfa.de

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Night work and breast cancer – results from the German GENICA study

by Beate Pesch, PhD,^{1,2} Volker Harth, MD, MPH,^{1,2} Sylvia Rabstein, MSc,² Christian Baisch, MA,³ Markus Schiffermann, MA,³ Dirk Pallapies, MD,² Nadine Bonberg,² Evelyn Heinze,² Anne Spickenheuer, MSc,² Christina Justenhoven, PhD,⁴ Hiltrud Brauch, PhD,⁴ Ute Hamann, PhD,⁵ Yon Ko, MD,³ Kurt Straif, MD,⁶ Thomas Brüning, MD²

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Objective Some epidemiological and animal data indicate that night work might increase the risk for breast cancer. We have investigated the risk in a German population-based case–control study known as GENICA (Gene ENvironment Interaction and breast CAncer).

Methods The GENICA study involved interviews to assess shift work information in 857 breast cancer cases and 892 controls. We estimated risks of employment status and night shift characteristics using conditional logistic regression models, adjusting for potential confounders. Resampling and bootstrapping were applied to adjust the risk estimates for a potential selection bias.

Results Among 1749 women, 56 cases and 57 controls worked in night shifts for ≥ 1 year, usually in the healthcare sector (63.0% of controls). Female night workers were more frequently nulliparous and low-educated than day workers (28.6% versus 17.8% and 12.3% versus 9.2%, respectively). Fewer women in night work had ever used post-menopausal hormone therapy (35.7% versus 51.9%). Having ever done shift or night work was not associated with an elevated breast cancer risk when compared to women employed in day work only [odds ratio (OR) 0.96, 95% confidence interval (95% CI) 0.67–1.38 and OR 0.91, 95% CI 0.55–1.49, respectively]. Women who reported >807 night shifts, the third quartile of the distribution among controls, experienced a breast cancer risk of 1.73 (95% CI 0.71–4.22). Night work for ≥ 20 years was associated with an OR of 2.48 (95% CI 0.62–9.99) based on 12 cases and 5 controls.

Conclusions Long-term night work was associated with a modestly, but not significantly, increased breast cancer risk, while having ever done night work was not. The precision of the results was limited by a low prevalence of night work in this study population.

Key terms case–control study; occupation; shift work.

Night work is inevitable for important tasks in the healthcare, service, and transport sectors. A variety of shift systems have been implemented, and it is predicted that in the near future that night shifts will become more common in many economic fields (1). Disturbances of the human day–night rhythm due to night work can cause desynchronization of internal biological clocks that govern most functions of the body (2). The neuro-

hormone melatonin plays a major role in linking light perception with chronobiology and its secretion can be influenced by exposure to light at night (LAN) (3, 4). It has been discussed that changes in melatonin levels caused by LAN might be related to the development of breast cancer (5, 6).

Recently, the International Agency for Research on Cancer (IARC) assessed the carcinogenicity of night

¹ Equal contribution.

² Research Institute of Occupational Medicine of the German Social Accident Insurance (BGFA), Ruhr University Bochum, Germany.

³ Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany.

⁴ Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University Tübingen, Germany.

⁵ Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany.

⁶ International Agency for Research on Cancer (IARC), Lyon, France.

Correspondence to: Professor T Brüning, Research Institute of Occupational Medicine of the German Social Accident Insurance (BGFA), Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany. [E-mail: bruening@bgfa.de]

work (7). On the basis of “limited evidence in humans for the carcinogenicity of shift work that involves night work” and “sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)”, an IARC working group concluded that “shift work that involves circadian disruption is probably carcinogenic to humans” (group 2A). The assessment of human data was based on results from eight epidemiological studies (8–15). Among these, two recently published studies reported no increased breast cancer risk (14, 15). Two large cohort studies, the nurses’ health studies I and II, observed that the risk increased with increasing numbers of night shifts (9, 10). Shortcomings in study design and control of potential confounders were limitations of some of the aforementioned studies, as well as a crude assessment of shift characteristics and night work (16). Here we present the risk estimates of night work for breast cancer in German women from the GENICA (Gene ENvironment Interaction and breast CAncer) study.

Methods

Study population and breast cancer risk factors

GENICA was a population-based case–control study conducted among women from the Greater Region of Bonn, Germany, as previously described (17). In brief, 1143 incident breast cancer cases and 1155 population controls were enrolled between 2000 and 2004 with response rates of 88% and 67%, respectively. Cases were enrolled from the major hospitals of the region. Controls were ascertained as a random sample from the population registries of the study region and frequency-matched to cases by age in 5-year classes. Inclusion criteria comprised age ≤ 80 years and Caucasian ethnicity. Incident cases were women with histopathologically confirmed breast cancer diagnosed within six months before enrolment. Data on known and suspected risk factors, including a detailed occupational history, were obtained by in-person interviews (hereafter referred to as the “core interview”). All participants gave written informed consent. The ethics committee of the University of Bonn approved the GENICA study.

In order to assess more detailed information on hormone therapy (18–20), subsequent telephone interviews were performed for 857 GENICA cases and 892 controls concerning their use of hormone prescriptions between 2004 and 2007. In addition, information on shiftwork status was sought (hereafter referred to as the “shift-status interview”). Of the 247 women reporting shift work, 223 (104 cases and 119 controls) could be reached for another telephone interview to collect detailed information on

shift work for each occupational period (hereafter referred to as the “shift interview”). Comprehensive plausibility checks were applied to assess night work and lifetime exposure to night shifts. Night work was defined as working the fulltime period between 24.00–05.00 hours according to the International Labor Organization (ILO) convention on night work (21). An almost equal number of 56 cases and 57 controls had *ever* worked in night shift for ≥ 1 year. Shift work and other information were truncated at the date of the core interview.

Statistical analysis

The GENICA study investigated the association of night work with breast cancer using logistic regression models conditional on age (20–44, 45–49, 50–54, 55–59, 60–64, 65–69, ≥ 70 years) among 857 breast cancer cases and 892 controls with shift-status information. We calculated risk estimates as odds ratios (OR) with 95% confidence intervals (95% CI) using PHREG procedure in SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

For model building, night work was forced into the statistical model. The set of potential confounders comprised menopausal status (pre- or postmenopausal), education, breast cancer in mother or sister, parity (nulliparous, 1–2, ≥ 3 children), age at first birth (nulliparous, < 25 , 25–29, ≥ 30 years), duration of oral contraceptive and hormone therapy use (never, > 0 –9, ≥ 10 years), body-mass index (< 22.5 , 22.5– < 25 , 25– < 30 , and ≥ 30 kg/m²), smoking (current, former, never), number of mammograms until two years before interview, and lifetime breastfeeding in months. Women were considered pre-menopausal if they reported bleedings in the year of interview and no bilateral oophorectomy. They were categorized as “low educated” if they had no occupational qualification and ≤ 8 years at school and “highly educated” if they had a university degree; otherwise education level was classified as “medium”. Each variable was added one at a time in order to assess whether it would modify the association between night work and breast cancer. None of the potential confounders changed the risk estimate of night or shift work by more than 10%. In the final model, a variable was considered a potential confounder if the respective risk estimate reached a significance level of 15%. The final models included family history of breast cancer, hormone therapy use, and number of mammograms.

The reference group was defined as women employed in day work only. Never-employed women were classified as a separate group. We categorized the self-assessed employment status as “employees” (white-collar occupations), “workers” (usually blue-collar occupations), and “others” (comprising self-employed women, family workers, and employed women not classified elsewhere). We estimated risks for: (i) having *ever* done night work, (ii) the duration of night work, (iii) the cumulative

number of night shifts with and without the condition of >3 night shifts per month using the corresponding third quartile among controls as a cut-off point (807 and 1056, respectively), (iv) age at first incidence of night work, and (v) time since last night work. Tests for linear trends were performed for quantitative exposure variables.

To account for a possible selection bias during the subsequent interviews, we applied a resampling procedure with 200 runs for both controls and cases according to the distribution of education in the core interview using Proc Surveyselect in SAS (SAS Institute, Cary, NC, USA). By means of bootstrapping, we calculated adjusted estimates of OR and 95% CI for night work risk estimates.

Results

Of the original 2298 GENICA participants, 1749 women were interviewed on their use of hormone prescriptions; among these women, in a subsequent interview, shift-status information was documented in 857 (74.2%) cases and 892 (78.0%) controls. We observed a lower proportion of low-educated controls in the shift-status assessment compared to the core interview (12.1% versus 14.7%, data not shown). Table 1 presents the distribution of breast cancer risk factors in cases and controls and age-adjusted OR. The GENICA study population is characterized by low parity and common use of hormone therapy. Long-term use of hormone therapy and familial breast cancer were confirmed as risk factors for breast cancer.

About 13% of all women had ever been employed in shift work. Almost an equal amount of 56 cases (6.5%) and 57 controls (6.4%) performed night work for ≥ 1 year. Among controls working in night shifts, 63.0% worked in healthcare. Table 2 depicts the distribution of potential risk factors for breast cancer by employment and shift status among controls. Female night workers were younger [median age 54 years, interquartile range (IQR) 42–62 years] especially when compared to women who had never been employed (median age 68 years, IQR 63–74 years). In comparison to the reference group of daytime workers, night-shift workers were more frequently nulliparous (28.6% versus 17.8%), low educated (12.3% versus 9.2%), and fewer had ever used hormone therapy (35.7% versus 51.9%). The group of women who had never been employed differed in the distribution of reproductive and lifestyle factors. Only 36.7% had ever used oral contraceptives and 6.7% were nulliparous.

Table 3 presents OR estimates for employment and shift work status with and without adjustments for potential confounders and for a potential selection bias due to losses in response. Compared to women

Table 1. Potential breast cancer risk factors in GENICA women. [Numbers may differ due to missing values; OR = odds ratio, 95% CI = 95% confidence interval]

Factor	Cases (N=857)		Controls (N=892)		OR ^a	95% CI
	N	%	N	%		
Age (years)						
≤49	199	23.2	195	21.9	.	..
50–59	268	31.3	276	30.9	.	..
60–69	288	33.6	304	34.1	.	..
70–80	102	11.9	117	13.1	.	..
Menopausal status						
Pre	218	25.8	207	23.5	1	..
Post	627	74.2	673	76.5	0.90	0.64–1.25
Education ^b						
High	116	13.5	142	15.9	1	..
Medium	634	74.0	642	72.0	1.23	0.94–1.61
Low	107	12.5	108	12.1	1.28	0.88–1.86
Parity						
Nulliparous	147	17.2	157	17.6	1	..
1–2 children	527	61.5	538	60.4	1.05	0.81–1.35
≥3 children	183	21.4	196	22.0	1.02	0.75–1.38
Age at first birth (years)						
Nulliparous	147	17.2	157	17.6	1	..
<25	341	39.8	360	40.4	1.01	0.77–1.33
25–29	241	28.2	253	28.4	1.03	0.77–1.37
≥30	127	14.8	121	13.6	1.14	0.81–1.59
Oral contraceptives (years)						
Never	274	32.1	291	32.7	1	..
>0–9	283	33.1	280	31.5	1.02	0.79–1.32
≥10	298	34.9	319	35.8	0.94	0.73–1.22
Hormone therapy (years)						
Never	415	48.7	445	50.0	1	..
>0–9	203	23.8	260	29.2	0.86	0.67–1.10
≥10	235	27.6	185	20.8	1.53	1.16–2.00
Cigarette smoking (pack-years)						
0	483	60.4	487	58.6	1	..
>0<15	155	19.4	171	20.6	0.89	0.69–1.16
≥15	162	20.3	173	20.8	0.92	0.72–1.19
Body-mass index (kg/m ²)						
<22.5	266	31.0	274	30.8	0.95	0.74–1.23
22.5–<25	218	25.4	216	24.2	1	..
25–<30	246	28.7	269	30.2	0.91	0.71–1.18
≥30	127	14.8	132	14.8	0.96	0.71–1.31
Breast cancer in mother or sisters						
No	747	87.2	830	93.1	1	..
Yes	110	12.8	62	7.0	1.98	1.43–2.75
Number of mammograms ^c						
0	120	14.0	134	15.0	1	..
1–9	551	64.4	599	67.2	1.04	0.78–1.39
≥10	184	21.5	158	17.7	1.36	0.96–1.92

^a Logistic regression conditional on age in 5-year groups.

^b Low education = no occupational qualification and ≤ 8 years at school; high education = university degree; medium = other than low or high.

^c Lifetime number of mammograms until two years before interview.

Table 2. Distribution of potential confounders in controls by shift work status. [Numbers may differ due to missing values.]

Factors	Ever employed, never shift work (N=740) ^a		Ever shift work (N=121) ^b		Ever night shift work (N=57) ^c		Never employed (N=30) ^d	
	N	%	N	%	N	%	N	%
Menopausal status								
Pre	168	23.0	38	32.5	20	36.4	0	0
Post	564	77.1	79	67.5	35	63.6	30	100
Parity								
Nulliparous	132	17.8	23	19.2	16	28.6	2	6.7
1–2 children	450	60.8	73	60.8	28	50.0	14	46.7
≥3 children	158	21.4	24	20.0	12	21.4	14	46.7
Education^e								
High	130	17.6	8	6.6	6	10.5	4	13.3
Medium	542	73.2	89	73.6	44	77.2	11	36.7
Low	68	9.2	24	19.8	7	12.3	15	50.0
Age at first birth								
Nulliparous	132	17.8	23	19.7	16	26.6	2	6.7
<25 years	285	38.5	57	47.5	19	33.9	17	56.7
25–29	217	29.3	28	23.3	13	23.2	8	26.7
≥30 years	106	14.3	12	10.0	8	14.3	3	10.0
Breast cancer in mother or sisters								
No	688	93.0	114	94.2	53	93.0	27	90.0
Yes	52	7.0	7	5.8	4	7.0	3	10.0
Oral contraceptive use								
Never	238	32.2	34	28.3	17	30.4	19	63.3
>0–9 years	228	30.9	47	39.2	19	33.9	5	16.7
≥10 years	273	36.9	39	32.5	20	35.7	6	20.0
Hormone therapy								
Never	356	48.1	71	59.7	36	64.3	17	56.7
>0–9 years	226	30.5	26	21.9	12	21.4	8	26.7
≥10 years	158	21.4	22	18.5	8	14.3	5	16.7
Smoking								
Never	405	54.7	59	48.8	29	50.9	23	76.7
Former	166	22.4	29	24.0	16	28.1	4	13.3
Current	169	22.8	33	27.3	12	21.1	3	10.0
Body-mass index (kg/m²)								
<22.5	237	32.0	28	23.3	15	26.8	9	30.0
22.5–<25	181	24.5	27	22.5	17	30.4	7	23.3
25–<30	219	29.6	41	34.2	16	28.6	9	30.0
≥30	103	13.9	24	20.0	8	14.3	5	16.7
Employment status								
Worker	50	6.8	22	18.2	5	8.8	–	–
Employee	609	82.3	91	75.2	47	86.0	–	–
Others ^f	81	11.0	8	6.6	2	5.3	–	–
Number of mammograms^g								
None	100	13.5	30	24.8	15	26.8	4	13.3
1–9	502	67.8	72	59.5	31	55.4	24	80.0
≥10	138	18.7	18	14.9	10	17.9	2	6.7

^a Median age 58 years (interquartile range 51–65).^b Median age 56 years (interquartile range 45–62). For one woman, information on shift status was missing.^c Median age 54 years (interquartile range 42–62).^d Median age 68 years (interquartile range 63–74).^e Low education = no occupational qualification and ≤8 years at school; high education = university degree; medium = other than low or high.^f Other employment comprised self-employed women, women helping the partner in his business, and women in educational programs.^g Lifetime number of mammograms until two years before interview.

employed in day shifts only, the variables of having ever done shift or night work were not associated with breast cancer risk ($OR_{\text{bootstrap}} 0.96$, 95% CI 0.67–1.38 and $OR_{\text{bootstrap}} 0.91$, 95% CI 0.55–1.49, respectively). Never-employed women showed an elevated risk estimate for breast cancer compared to employed women, but this was, however, not statistically significant ($OR_{\text{bootstrap}} 1.61$, 95% CI 0.86–3.02).

We were able to assess detailed information on shift work in 90% of the validated shift workers. Results for night shift workers are presented in table 4. Cases had worked more night shifts during their lifetime than controls (median 791, IQR 360–1440 versus 318, IQR 180–807). Working ≥806 night shifts was associated with an increased risk of breast cancer, which however was not statistically significant ($OR_{\text{bootstrap}} 1.73$, 95% CI 0.71–4.22, based on 13 controls and 23 cases). Five controls and 12 cases reported having done night work for ≥20 years, which resulted in an $OR_{\text{bootstrap}}$ of 2.48 (95% CI 0.62–9.99). The risk estimate was 0.61 (95% CI 0.27–1.41) after ≥20 years since last night work. We found no significant trend for a cumulative number of night shifts ($P=0.14$), years in night shift ($P=0.16$), and time since last night shift ($P=0.09$).

Further analyses were performed and restricted to postmenopausal women and additionally adjusted for body mass index. In general, these risk estimates were similar to the results presented here and are given in two supplementary tables (see appendix).

Discussion

In our study, having ever done night shift work was not associated with an increased breast cancer risk. Cases experienced on average about 800 night shifts in comparison to 300 among controls. Long-term night work was found to be associated with a modestly increased breast cancer risk although this was statistically not significant. The risk estimates turned out to be robust with regard to adjustment for potential confounders and a potential selection bias. Similarly, modestly elevated breast cancer risks were observed only after long-term night work of ≥20 years in the nurses' health cohort studies (9, 10).

About 15–20% of the European and US workforce is engaged in a broad variety of shift systems (7). In Germany, approximately 10% of working women are currently employed in night work, mostly in the health and service sector, and the trend is increasing (22). In West Germany, women were prohibited from working at night in the industrial sector until the law was amended in 1992. Therefore, only 11% of female controls working the night shift were blue-collar workers; 7% of the controls had worked in night shifts for ≥1 year. The even lower

Table 3. Association between employment status and breast cancer in the GENICA study. [Numbers may differ because of missing values and refer to numbers of subjects in the adjusted model without bootstrapping. OR = odds ratio, 95% CI = 95% confidence interval]

Factor	Cases (N=857)		Controls (N=892)		OR ^a	95% CI	Adjusted OR ^b	95% CI	Bootstrap OR ^c	95% CI
	N	%	N	%						
Current or last occupation										
Employee	647	76.1	699	78.6	1.00		1.00		1.00	.
Worker	69	8.1	71	8.0	1.06	0.75–1.50	1.12	0.78–1.59	1.09	0.70–1.70
Others ^d	94	11.1	89	10.0	1.17	0.86–1.60	1.23	0.89–1.68	1.24	0.83–1.85
Never employed	40	4.7	30	3.4	1.55	0.94–2.55	1.60	0.97–2.66	1.68	0.89–3.17
Shift work										
Employed, but never in shift work	698	82.1	740	83.2	1.00	.	1.00	.	1.00	.
Ever in shift work	112	13.2	119	13.4	0.97	0.74–1.29	0.98	0.74–1.29	0.96	0.67–1.38
Never employed	40	4.7	30	3.4	1.51	0.92–2.47	1.54	0.93–2.54	1.61	0.86–3.02
Night shift work										
Employed, but never in shift work	698	92.7	740	92.7	1.00	.	1.00	.	1.00	.
Ever in night shift work	55	7.3	56	7.0	1.02	0.69–1.50	1.01	0.68–1.50	0.91	0.55–1.49

^a Logistic regression conditional on age in 5-year groups.^b Logistic regression conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms.^c Corrected for a potential selection bias using a resampling and bootstrapping procedure with logistic regression models conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms.^d Other employment included self-employed women, women helping the partner in business, and women in educational programs.**Table 4.** Quantitative assessment of night shift and its association with breast cancer in GENICA women with >1 year night shift work. [Numbers may differ because of missing values and refer to numbers of subjects in the adjusted model without bootstrapping. OR = odds ratio, 95% CI = 95% confidence interval]

Factor	Cases (N=746)		Controls (N=793)		OR ^a	95% CI	Adjusted OR ^b	95% CI	Bootstrap OR ^c	95% CI
	N	%	N	%						
Cumulative number of lifetime night shifts										
Employed, but never in shift work	698	93.6	740	93.3	1.00	.	1.00	.	1.00	.
<807 night shifts	25	3.4	40	5.0	0.66	0.40–1.10	0.66	0.40–1.11	0.65	0.34–1.26
≥807 night shift	23	3.1	13	1.6	1.81	0.91–3.60	1.78	0.89–3.58	1.73	0.71–4.22
Cumulative number of lifetime night shifts for shift systems with >3 nights per month										
Employed, but never in shift work	698	93.9	740	94.3	1.00	.	1.00	.	1.00	.
<1056 night shifts	25	3.4	33	4.2	0.79	0.47–1.34	0.80	0.47–1.36	0.79	0.40–1.57
≥1056 night shifts	20	2.7	12	1.5	1.69	0.82–3.48	1.66	0.80–3.46	1.61	0.63–4.10
Duration of night shift work										
Employed, but never in shift work	698	93.6	740	93.3	1.00	.	1.00	.	1.00	.
>0–4 years	15	2.0	25	3.2	0.68	0.36–1.29	0.64	0.34–1.24	0.65	0.28–1.48
5–9 years	11	1.5	12	1.5	0.85	0.38–1.90	0.93	0.41–2.15	0.93	0.31–2.82
10–19 years	10	1.3	11	1.4	0.94	0.39–2.23	0.91	0.38–2.18	0.83	0.27–2.60
≥20 years	12	1.6	5	0.6	2.47	0.87–7.05	2.49	0.87–7.18	2.48	0.62–9.99
Age at time of first night shift work										
Employed, but never in shift work	698	93.6	740	93.3	1.00	.	1.00	.	1.00	.
<20 years	14	1.9	28	3.5	0.56	0.30–1.06	0.53	0.28–1.03	0.52	0.23–1.20
20–29 years	25	3.4	17	2.1	1.52	0.81–2.84	1.51	0.80–2.83	1.50	0.67–3.40
30–39 years	6	0.8	5	0.6	1.03	0.33–3.22	1.25	0.38–4.15	1.26	0.23–6.04
≥40 years	3	0.4	3	0.4	1.04	0.21–5.18	0.98	0.19–5.09	1.02	0.11–9.09
Years since last night shift										
Employed, but never in shift work	698	93.6	740	93.3	1.00	.	1.00	.	1.00	.
Current night work	14	1.9	13	1.6	1.09	0.50–2.35	1.10	0.51–2.38	1.07	0.39–2.88
>1–9 years	6	0.8	5	0.6	1.22	0.37–4.00	1.04	0.31–3.53	1.20	0.20–5.63
10–19 years	13	1.7	8	1.0	1.48	0.63–3.50	1.69	0.69–4.14	1.67	0.52–5.38
≥20 years	15	2.0	27	3.4	0.64	0.34–1.20	0.62	0.33–1.19	0.61	0.27–1.41

^a Logistic regression conditional on age in 5-year groups.^b Logistic regression conditional on age, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms.^c Corrected for a potential selection bias using a resampling and bootstrapping procedure with logistic regression models conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms.

prevalence of long-term night work limited the precision of our results on the night work risk for breast cancer.

The multitude of shift systems raised the question of an appropriate assessment of shift characteristics. The IARC working group concluded that the collection of shift work information in several studies was rather crude (7). The ILO has defined a night shift as work which is performed for ≥ 7 hours between 12.00–05.00 hours. (21). As our study focused on the risk of occupational shift work and breast cancer, the few women who reported healthcare duties in their families were not classified as night workers. The 12.00–05.00 time period includes the physiological peak of melatonin biosynthesis around 01.00–02.00 hours. (23). Artificial light at night can modify the diurnal melatonin production. It has been proposed that suppressed melatonin production may lead to an increased cancer risk, but further research is needed to fully establish the mechanistic pathways leading to circadian disruption and cancer (24–28). However, cancer as a systemic disease or the treatment thereof can interfere with biomarker levels, making case–control studies less suitable for the determination of melatonin and other biomarkers.

The limitations of our study included a low prevalence of night work, especially long-term night work, and the retrospective assessment of shift work in subsequent interviews. Primarily, GENICA aimed to investigate gene–environment interactions (29–31) and contributes to the International Breast Cancer Association Consortium (32, 33). When the first epidemiological results for night work as a potential risk factor for breast cancer were emerging, we added questions on shift work to our study. At that time, women were not aware that night work might pose a risk. However, participants in the consecutive interviews tended to be better educated. Therefore, we applied resampling according to the distribution of education in the core interview and bootstrapping to adjust the risk estimates for night work. The risk estimates were relatively robust with respect to this potential selection bias.

Women in night work can differ with regard to reproductive and hormonal factors that are established risk factors for breast cancer and potential confounding was raised as a concern (16). In our study, women working in night shifts were more frequently nulliparous, and hormone therapy use was less common. However, our results were very similar when comparing statistical models including only age with models additionally adjusting for hormonal and other factors, or full models, and do not provide evidence for potential confounding. Depending on the underlying causal model, other variables (eg, LAN from non-occupational sources, sleep deprivation and ensuing immune suppression) may also be considered as potential confounders or intermediate variables. To explore this further, future epidemiological studies on

circadian disruption and cancer should try to capture these domains of exposure. Finally, the effect of shift work on breast cancer may be also modified by individual susceptibility to different working schedules, which can result from differential adaptability to night shifts (34).

The lifetime numbers of night shifts or the years employed in night work are crude surrogate measures and do not fully represent the various characteristics of complex shift systems. For example, the direction of the shift rotation and the timing of recovery days can influence phase shifts of melatonin concentrations (35). Furthermore, there is not yet a consensus on how best to assess circadian disruption and its potential mechanistic links to cancer (36).

In conclusion, our results are in line with the IARC classification that long-term night work in women is probably associated with breast cancer and warrants further research (37). A major challenge is the quantitative assessment of night work and qualitative assessment of various shift systems. Shift systems are an integral part of the organization of work and strategies are needed to minimize possible health hazards of night work.

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Appendix

Table A. Association between employment status and breast cancer in postmenopausal women. [Numbers may differ because of missing values and refer to numbers of subjects in footnote b model; OR=odds ratio; 95% CI=95% confidence interval.]

Factor	Cases (N=627)		Controls (N=673)		OR ^a	95% CI	Adjusted OR ^b	95% CI	Adjusted OR ^c	95% CI
	N	%	N	%						
Current or last occupation										
Employee	454	73.1	512	76.2	1.00	..	1.00	..	1.00	..
Worker	58	9.3	64	9.5	1.02	0.70–1.48	1.08	0.74–1.59	1.08	0.74–1.59
Others ^d	74	11.9	66	9.8	1.30	0.91–1.85	1.36	0.95–1.95	1.36	0.95–1.95
Never employed	35	5.6	30	4.5	1.37	0.82–2.29	1.43	0.85–2.42	1.43	0.86–2.41
Shift work										
Employed, but never in shift work	510	82.1	564	83.9	1.00	..	1.00	..	1.00	..
Ever in shift work	76	12.3	78	11.6	1.06	0.76–1.48	1.05	0.75–1.48	1.05	0.74–1.49
Never employed	35	5.6	30	4.5	1.33	0.80–2.21	1.37	0.81–2.30	1.36	0.81–2.29
Night shift work										
Employed, but never in shift work	510	93.8	564	94.2	1.00	..	1.00	..	1.00	..
Ever in night shift work	34	6.3	35	5.8	1.09	0.67–1.77	1.05	0.64–1.73	1.06	0.65–1.73

^a Logistic regression conditional on age in 5-year groups.

^b Logistic regression conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms.

^c Logistic regression conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, number of mammograms, and body-mass index.

^d Other employment included self-employed women, women helping the partner in business, and women in educational programs.

Table B. Quantitative assessment of night shift and its association with breast cancer in postmenopausal GENICA women with >1 year night shift work. [Numbers may differ because of missing values and refer to numbers of subjects in footnote b model; OR=odds ratio; 95% CI=95% confidence interval.]

Factor	Cases (N=540)		Controls (N=597)		OR ^a	95% CI	Adjusted OR ^b	95% CI	Adjusted OR ^c	95% CI
	N	%	N	%						
Cumulative number of lifetime night shifts										
Employed, but never in shift work	510	94.4	564	94.5	1.00	..	1.00	..	1.00	..
<807 night shifts	16	3.0	26	4.4	0.70	0.37–1.31	0.65	0.34–1.23	0.65	0.34–1.24
≥807 night shifts	14	2.6	7	1.2	2.23	0.89–5.56	2.29	0.91–5.78	2.28	0.90–5.76
Cumulative number of lifetime night shifts for shift systems with >3 nights per month										
Employed, but never in shift work	510	95.0	564	95.0	1.00	..	1.00	..	1.00	..
<1056 night shifts	16	3.0	24	4.0	0.76	0.40–1.43	0.71	0.39–1.36	0.72	0.37–1.38
≥1056 night shifts	11	2.0	6	1.0	2.01	0.74–5.47	2.09	0.76–5.78	2.1	0.76–5.81
Duration of night shift work										
Employed, but never in shift work	510	88.4	564	88.7	1.00	..	1.00	..	1.00	..
>0–<5 years	9	1.6	20	3.1	0.52	0.24–1.14	0.46	0.21–1.03	0.47	0.21–1.04
5–9 years	7	1.2	5	0.8	1.55	0.49–4.92	1.54	0.48–4.97	1.55	0.48–5.02
10–19 years	5	0.9	4	0.7	1.43	0.38–5.34	1.45	0.38–5.57	1.48	0.39–5.66
≥20 years	9	1.7	4	0.7	2.47	0.76–8.06	2.60	0.89–8.57	2.65	0.78–8.48
Age at first night shift work										
Employed, but never in shift work	510	94.4	564	94.5	1.00	..	1.00	..	1.00	..
<20 years	13	2.4	15	2.5	1.05	0.50–2.19	0.99	0.47–2.11	1.00	0.49–2.14
20–29 years	12	2.2	11	1.8	1.14	0.49–2.62	1.12	0.48–2.59	1.24	0.48–2.61
30–39 years	2	0.4	4	0.7	0.55	0.10–3.02	0.54	0.10–3.02	0.52	0.90–2.94
≥40 years	3	0.6	3	0.5	1.07	0.22–5.34	1.03	1.11–2.50	1.05	0.20–5.47
Years since last night shift										
Employed, but never in shift work	510	94.4	564	97.5	1.00	..	1.00	..	1.00	..
Current night work	6	1.1	4	0.7	1.63	0.45–5.86	1.76	0.48–6.31	1.79	0.49–6.52
>1–9 years	3	0.6	3	0.5	1.03	0.21–5.10	0.84	0.16–4.39	0.82	0.16–4.35
10–19 years	7	1.3	4	0.7	1.95	0.56–6.74	1.91	0.55–6.67	1.90	0.55–6.64
≥20 years	14	2.6	22	3.7	0.74	0.38–1.45	0.71	0.36–1.40	0.71	0.36–1.41

^a Logistic regression conditional on age in 5-year groups.

^b Logistic regression conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms.

^c Logistic regression conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, number of mammograms, and body-mass index.