IJC
International Journal of Cancer

Exposure to road traffic and railway noise and postmenopausal breast cancer: A cohort study

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Exposure to traffic noise may result in stress and sleep disturbances. Studies on self-reported sleep duration and breast cancer risk have found inconsistent results. In a population-based Danish cohort of 29,875 women aged 50–64 years at enrolment in 1993–1997, we identified 1219 incident, postmenopausal breast cancer cases during follow-up through 2010. Mean follow-up time was 12.3 years. Road traffic and railway noise was calculated for all present and historical residential addresses from 1987 to 2010. We used Cox proportional hazard model for analyses and adjusted for hormone replacement therapy use, parity, alcohol consumption and other potential confounders. We found no overall association between residential road traffic or railway noise and breast cancer risk. Among women with estrogen receptor negative breast cancer, a 10-dB higher level of road traffic noise (continuous scale) during the previous 1, 5 and 10 years were associated with 28% (95% CI: 1.04–1.56), 23% (95% CI: 1.00–1.51) and 20% (95% CI: 0.97–1.48) higher risks of estrogen receptor negative breast cancer, respectively, in fully adjusted models. Similarly, a 10-dB increase in railway noise (1-year mean at diagnosis address) increased risk for estrogen receptor negative breast cancer by 38% (95% CI: 1.01–1.89). There was no association between road traffic or railway noise and estrogen receptor positive breast cancer. In conclusion, these results suggest that residential road traffic and railway noise may increase risk of estrogen receptor negative breast cancer. As the first study on traffic noise and breast cancer results should be treated with caution.

Increasing noise from traffic occurs in parallel with urbanization. Epidemiological studies have found road traffic noise to be associated with higher risk for cardiovascular disease and diabetes.[1–3] Night time exposure to noise at normal urban levels has been associated with sleep disturbances, including short sleep duration and reduced sleep quality.[4] Also, living at relatively high traffic noise exposure might often be associated with light exposure at night from street light. Short sleep duration is suspected of causing breast cancer, possibly through suppression of melatonin by longer light exposure, as melatonin possesses anticarcinogenic properties, including effects on estrogen synthesis and release, antioxidant defense, immune response and DNA repair.[5–10] Despite discrepancies, epidemiological studies have mainly indicated that night work increase risk for breast cancer,[11–13] whereas the few studies investigating effects of self-reported sleep duration on breast cancer risk are inconsistent, with findings of both hazardous and protective effects of short sleep duration.[14–20]

Traffic noise can also act as a stressor causing hyperactivity of the sympathetic autonomic nervous system and activation of the hypothalamus–pituitary–adrenal axis, resulting in increased levels of the glucocorticoid cortisol.[21,22] Glucocorticoids are involved in a variety of cellular and physical processes that might promote tumor progression including apoptosis, immune response and angiogenesis.[22] Though psychosocial stress has been suspected of affecting breast cancer risk and progression for many years, epidemiological studies have failed to find any clear relationship with risk for breast cancer,[23–25] whereas a number of studies have indicated that psychosocial stress and support may affect the course of breast cancer progression.[24,26]

Incidence rates and prognosis for breast cancer differ according to estrogen receptor (ER) status of the tumor, suggesting that ER positive (ER+) and ER negative (ER−) breast cancer have different etiology.[27,28] Similarly, classic risk factors including nulliparity, delayed childbearing and early menarche have been found stronger associated with ER+ breast cancer than for ER− breast cancer,[27,29] whereas

Key words: breast cancer, cohort, epidemiology, traffic noise
Abbreviations: BMI: body mass index; CI: confidence interval; ER: estrogen receptor; ER−: estrogen receptor negative; ER+: estrogen receptor positive; HRT: hormone replacement therapy; IRR: incidence rate ratio; MET: metabolic equivalent
Grant sponsor: Danish Environmental Protection Agency, the Danish Ministry of the Interior and Health and the European Research Council, EU 7th Research Framework Programme; **Grant number:** 281760
DOI: 10.1002/ijc.28592
History: Received 8 Oct 2013; Accepted 28 Oct 2013; Online 8 Nov 2013
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What's new?

Urbanization is linked to increased traffic noise, exposure to which is associated with stress and sleep disturbances. However, the impact of sleep duration and traffic noise exposure on breast cancer risk remains unclear. The present study suggests that residential exposure to road traffic and railway noise is associated with a dose-dependent increase in risk for estrogen receptor negative breast cancer. Exposure to road traffic and railway noise is considerable in many parts of the world, including the European Union, where more than 30% of the population is exposed to road traffic noise at levels exceeding WHO guideline values.

intake of vegetables seems protective mainly for ER− breast cancers.[30] Also, one study on long-term night work and breast cancer indicated an increased risk only among women with ER− breast cancer.[31] Therefore, studying overall breast cancer may mask a true association between a risk factor and ER subtypes of breast cancer.

We aimed to investigate the novel hypothesis that residential exposure to road traffic and railway noise increases the risk for breast cancer, potentially through sleep disturbance and stress, using a prospective cohort study of 29,875 women. We investigated effects of road traffic and railway noise on overall breast cancer and by ER status and, for road traffic noise, we investigated whether there was effect modification by baseline characteristics.

Materials and Methods

Study population

The study was based on the Danish Diet, Cancer and Health cohort, into which 29,875 female residents of Copenhagen or Aarhus aged 50–64 years without a history of cancer were enrolled between 1993 and 1997.[32] Participants had to be born in Denmark. At enrolment, each participant completed self-administered, interviewer-checked, questionnaires covering menopausal status, parity, age at menarche, use of hormone replacement therapy (HRT), education and lifestyle habits such as smoking habits, intake of vegetables and physical activity. Height and weight were measured by trained staff members according to standardized protocols. Women who were premenopausal at enrolment were excluded. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethical committees (Copenhagen and Frederiksberg), and all participants provided written informed consent.

Identification of outcome

Breast cancer cases diagnosed between baseline and death, emigration or the end of follow-up (December 31, 2010) were identified by linking the unique personal identification number of each cohort member to the nationwide Danish Cancer Registry.[33] Information on ER status was obtained from the Danish Breast Cancer Co-operative Group.[34]

Exposure

Residential address history for all female cohort members between July 1, 1987 and censoring was collected using the Danish civil registration system.[35] Road traffic noise exposure was calculated for the years 1990, 1995, 2000, 2005 and 2010 for all present and historical addresses using SoundPLAN (http://www.soundplan.dk/), a software implementing the joint Nordic prediction method for road traffic noise.[36] Using this method, the equivalent noise level can been calculated for each address in a position on the most exposed facade of the actual building and in each of the time periods: day (07–19), evening (19–22) and night (22–07), when a series of traffic parameters and topographical parameters are known. These input variables were: point for noise estimation, corresponding to geographical coordinate and height (floor) for each residential address, road links with information on annual average daily traffic, vehicle distribution (light, heavy), travel speed and road type; and building polygons for all Danish buildings provided by the Danish Geodata Agency (www.gst.dk). We obtained traffic counts for all Danish roads with more than 1000 vehicles per day from a national road and traffic database.[37] This database is based on a number of different traffic data sources ranked as follows: 1) Collection of traffic data from the 140 Danish municipalities with most residents, covering 97.5% of the addresses included in the present study. Included roads typically have more than 1000 vehicles per day and are based on traffic counts as well as estimated/modeled numbers. Traffic data represents the period from 1995 to 1998; 2) Traffic data from a central database covering all the major state and county roads; 3) Traffic data for 1995–2000 for all major roads in the Greater Copenhagen Area; 4) Smoothed traffic data for 1995 for all roads based on a simple method where estimated figures for distribution of traffic by road type and by urban/rural zone are applied to the road network and subsequently calibrated against known traffic data at county level (traffic performance).

We assumed that the terrain was flat, which is a reasonable assumption in Denmark, and that urban areas, roads and areas with water were hard surfaces, whereas all other areas were acoustically porous. No information was available on noise barriers or road surfaces. Road traffic noise was calculated as the equivalent continuous A-weighted sound pressure level (L_{Aeq}) at the most exposed facade of the dwelling at each address for the day (L_d; 07:00–19:00 h), evening (L_e; 19:00–22:00 h) and night (L_n; 22:00–07:00 h), and was expressed as L_{den} (den = day, evening, night). All values below 42 dB were set to 42 dB as this was considered a lower limit of ambient noise.

Table 1. Baseline characteristics of postmenopausal women in the Diet, Cancer and Health cohort by breast cancer status

Characteristic at enrollment	Total cohort[1] (n = 22,453)	Breast cancer cases[1] (n = 1,219)	L_{den} road < 58 dB[1] (n = 12,128)	L_{den} road ≥ 58 dB[1] (n = 10,325)
Age (years)	57.5 (51.1–64.4)	57.3 (51.1–64.4)	57.4 (51.1–64.4)	57.6 (51.1–64.5)
Number of births (%)				
0	12.3	15.6	10.7	14.3
1	15.2	17.2	13.9	16.8
2	44.6	44.0	46.0	42.9
>2	27.8	23.3	29.4	26.1
Age at first birth[2] (years)	23 (18–31)	24 (18–32)	23 (18–31)	23 (18–31)
Use of hormone replacement therapy (HRT) (%)				
Never	49.9	38.2	51.3	48.3
Former	15.9	13.3	15.5	16.3
Present	34.2	48.5	33.2	35.4
Duration of HRT use[3] (years)	4.0 (0.25–18.0)	5.0 (0.25–20.0)	4 (0.25–18)	4 (0.25–19)
Age at menarche (years)	14 (11–17)	14 (11–16)	14 (11–16)	14 (11–17)
Years of school attendance (%)				
≤7	33.8	30.2	32.4	35.5
8–10	49.5	50.0	49.5	49.4
>10	16.7	19.8	18.1	15.1
BMI (kg/m^2)	24.9 (19.9–33.8)	24.8 (20.4–33.9)	24.8 (20.0–33.7)	25.0 (19.8–34.1)
Drink alcohol (%)	97.0	97.6	97.5	96.6
Alcohol intake among active drinkers (g/day)	9.5 (0.71–42.0)	10.9 (0.91–43.8)	9.7 (0.71–41.0)	8.8 (0.71–43.4)
Smoking status (%)				
Never	42.2	43.6	45.0	39.0
Former	23.6	23.4	23.4	23.2
Current	34.2	32.9	31.1	37.8
Vegetable intake (g/day)	168 (49.5–385)	169 (52.8–382)	172 (52.4–382)	164 (45.5–387)
Physical activity (MET score)	59.0 (19.5–150)	58.0 (19.5–153)	59.5 (20.0–147)	58.5 (19.0–154)

[1]Values are medians (5–95 percentiles) unless otherwise stated.
[2]Among women with ≥ 1 birth.
[3]Among former and present users.

Railway traffic noise exposure was calculated for the years 1990, 1995, 2000, 2005 and 2010 for all present and historical addresses using SoundPLAN, with implementation of NORD2000, which is a Nordic calculation method for prediction of noise propagating for railway traffic noise (www.soundplan.dk). The input variables for the noise model were point for noise estimation (geographical coordinate and height), railway links with information on annual average daily train lengths, train types, travel speed (information obtained from BaneDanmark, which is operating and developing the Danish state railway network); and building polygons for all Danish buildings. The daily train lengths are given for 1997 and 2012. We assumed that a flat terrain, and that urban areas and areas with water were hard surfaces, whereas all other areas were acoustically porous. All noise barriers along the railway are included in the model. Railway traffic noise was expressed as L_{den} at the most exposed facade of the dwelling.

The noise impact from all Danish airports and airfields was determined from information about noise zones (5 dB categories) obtained from local authorities. The programs DANSIM (Danish Airport Noise Simulation Model) and INM3 (Integrated Noise Model), which fulfill the joint Nordic criteria for air traffic noise calculations, were used.[38] The curves for aircraft noise were transformed into digital maps and linked to each address by geocodes.

Statistical analyses

Analyses were based on Cox proportional hazards model with age as underlying time, ensuring comparison of

Table 2. Incidence rate ratios (IRRs) of all breast cancers and subtypes of breast cancers according to estrogen receptor status, per 10 dB higher level of exposure to road traffic noise based on 22,453 cohort participants

Exposure to road traffic noise L_{den} (per 10 dB)	*N* cases	IRR (95% CI)	
		Crude	Adjusted[1]
All breast cancer			
L_{den} 1-year preceding diagnosis	1,219	1.07 (0.99–1.16)	1.04 (0.96–1.15)
L_{den} 5-years preceding diagnosis	1,219	1.05 (0.97–1.15)	1.02 (0.94–1.12)
L_{den} 10-years preceding diagnosis	1,219	1.05 (0.96–1.14)	1.02 (0.93–1.11)
ER+ breast cancer			
L_{den} 1-year preceding diagnosis	858	1.04 (0.95–1.15)	1.01 (0.92–1.12)
L_{den} 5-years preceding diagnosis	858	1.03 (0.93–1.14)	1.00 (0.90–1.10)
L_{den} 10-years preceding diagnosis	858	1.03 (0.93–1.14)	0.99 (0.90–1.10)
ER− breast cancer			
L_{den} 1-year preceding diagnosis	203	1.29 (1.06–1.57)	1.28 (1.04–1.56)
L_{den} 5-years preceding diagnosis	203	1.25 (1.02–1.53)	1.23 (1.00–1.51)
L_{den} 10-years preceding diagnosis	203	1.22 (0.99–1.50)	1.20 (0.97–1.48)

[1]Adjusted for age, parity, age at first birth, hormone replacement therapy (HRT) status and duration, age at menarche, length of school attendance, BMI, alcohol intake, smoking status, intake of vegetables, physical activity (MET score), calendar-year and railway and airport noise.
Abbreviations: IRR, incidence rate ratio; CI, confidence interval; dB, decibel.

individuals of the same age.[39] We used left truncation at age at July 1, 1997 (to ensure at least 10 years of exposure history), and right censoring at age of breast or other cancer, death, emigration or December 31, 2010, whichever came first. Exposure to road traffic noise was modeled as time-weighted averages for the preceding 1, 5 and 10 years, taking all present and historical addresses in that period into account. Exposure to railway noise was modeled as average yearly exposure at the current residence. These exposure windows were entered as time-dependent variables; thus, exposure was estimated for all cohort members who were at risk of diagnosis at exactly the same age as each case at diagnosis.

Incidence rate ratios (IRRs) for breast cancer in association with road traffic and railway noise were calculated crude and adjusted for parity (0, 1, 2, >2), age at first birth (years), hormone replacement therapy (HRT) status (never, former, present) and duration (years), age at menarche (years), length of school attendance (≤7, 8–10, >10 years), body mass index (BMI, kg/m^2), alcohol consumption (yes/no), alcohol intake (g/day), smoking status (never, former, current), intake of vegetables (g/day), physical activity (metabolic equivalent (MET) score), calendar-year (time dependent in 5 years intervals) and aircraft noise (≤45 dB (yes/no)). Potential modification of the association between road traffic noise and breast cancer by baseline characteristics and age at diagnosis were evaluated by introducing interaction terms into the model, and were tested by the Wald test.

In analyses considering ER status, the different types of breast cancer were treated as competing causes of failure. The assumption of linearity of L_{den} and covariates was evaluated visually and by formal testing with linear spline models.[40] We found no significant deviation from linearity. We used SAS version 9.2 (SAS Institute, NC). The graphical presentation of a functional form of an association between L_{den} and breast cancer was produced using restricted cubic spline in the design library (R 2.9.0 statistical software).

Results

Among 29,875 women, we excluded 338 women with cancer before enrolment, 4,798 who were premenopausal at enrolment, 1,083 with incomplete address history, 892 with missing covariates and 311 censored before July 1997 leaving a study cohort of 22,453 women. Breast cancer was diagnosed in 1,219 women during a mean follow-up time of 12.3 years.

Study population characteristics are summarized in Table 1. Breast cancer cases were more likely to be nulliparous, older at first birth, use HRT, be more educated and drink more alcohol as compared to the cohort. Women exposed to more than 58 dB road traffic noise were more likely to be nulliparous, use HRT, be less educated, drink less alcohol, smoke more and consume less vegetables as compared to women exposed to less than 58 dB. There was a very high correlation between L_{den} road and L_{night} road: Rs = 0.999. The correlation between L_{den} road and L_{den} railway among the participants exposed to railway noise (20% at start of follow-up) was very weak: Rs = 0.04.

We found no overall association between residential road traffic noise and risk of breast cancer for any of the three exposure windows 1-, 5- or 10-year mean noise exposure before breast cancer diagnosis (Table 2). In analyses of ER subtypes, a 10-dB higher level of road traffic noise during the previous 1, 5 and 10-years were associated with 28% (95% CI: 1.04–1.56), 23% (95% CI: 1.00–1.51) and 20% (95% CI: 0.97–1.48) higher risks of ER− breast cancer, respectively, in

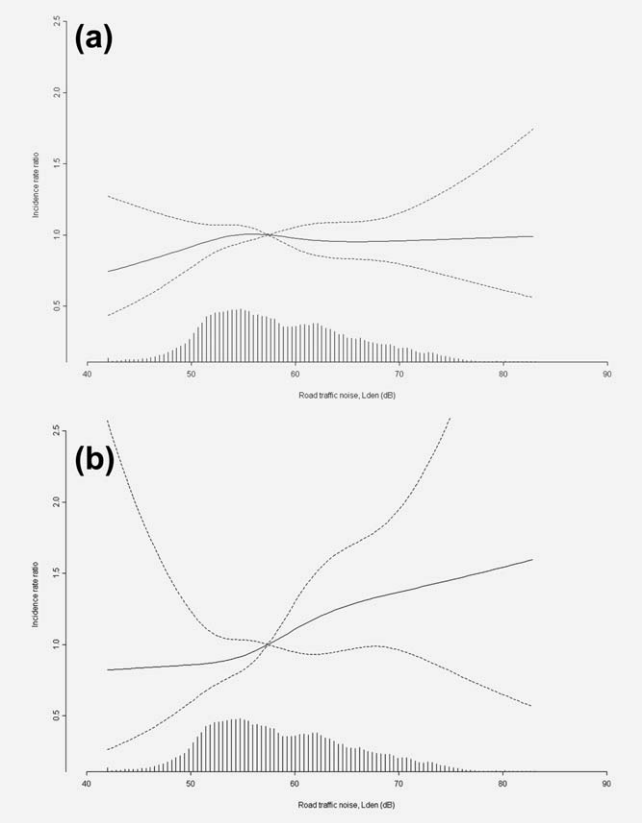

Figure 1. Association between residential exposure to road traffic noise (L_{den}, 1-year mean) and (*a*) estrogen receptor positive breast cancer and (*b*) estrogen receptor negative breast cancer. Analyses were adjusted for age, parity, age at first birth, hormone replacement therapy status and duration, age at menarche, length of school attendance, BMI, alcohol consumption, alcohol intake, smoking status, intake of vegetables, physical activity (MET score), calendar-year and railway and airport noise. Solid line: incidence rate ratio, dashed lines: 95% confidence interval. The median (57.4 dB) is the reference. The columns at the x-axis show the distribution of exposure to road traffic noise.

fully adjusted models (Table 2). The exposure-response curve seemed to indicate no associations between road traffic noise and risk for ER− breast cancer at exposures below 55 dB after which the risk seemed to increase in a dose-dependent manner (Fig. 1*b*). There was no association between road traffic noise and ER+ breast cancer (Table 2, Fig. 1*a*).

We found that a 10 dB increase in exposure to railway noise was associated with a statistically significant 38% increase in risk for ER negative breast cancer (95% CI: 1.01–1.89, Table 3). There was no association between railway noise and risk for all breast cancers and ER+ breast cancer.

We found no statistically significant effect modification by age at diagnosis and baseline characteristic (Table 4). There was, however, a tendency of a stronger association between road traffic noise and ER+ breast cancer among women above 65 years (1.08; 95% CI: 0.95–1.24) compared to women younger than 65 years (0.94; 95% CI: 0.81–1.09).

Table 3. Incidence rate ratios (IRRs) of exposure to railway noise and all breast cancers as well as subtypes of breast cancers according to estrogen receptor status

Railway noise, L_{den}	*N* cases	IRR (95% CI)[2]
All breast cancer		
Not exposed	956	1.00
<55 dB	181	0.94 (0.80–1.14)
≥55 dB	82	1.00 (0.79–1.11)
Linear (per 10 dB)[1]	1,219	1.02 (0.90–1.15)
ER+ breast cancer		
Not exposed	673	1.00
<55 dB	130	0.97 (0.81–1.18)
≥55 dB	55	0.95 (0.72–1.26)
Linear (per 10 dB)[1]	858	0.96 (0.83–1.10)
ER− breast cancer		
Not exposed	158	1.00
<55 dB	26	0.85 (0.56–1.29)
≥55 dB	19	1.38 (0.86–2.22)
Linear (per 10 dB)[1]	203	1.38 (1.01–1.89)

[1]Effect per 10 dB increase in railway noise among the exposed population.
[2]Adjusted for age, parity, age at first birth, hormone replacement therapy (HRT) status and duration, age at menarche, length of school attendance, BMI, alcohol intake, smoking status, intake of vegetables, physical activity (MET score), calendar-year and road traffic and airport noise.

Discussion

This first study on noise and breast cancer indicates that long-term exposure to road traffic noise increases the risk for ER− breast cancer in a dose-dependent manner, whereas there is no association with risk for ER+ breast cancers. Interesting, we found that also exposure to railway noise seemed associated with only ER− breast cancer. As we found no correlation between road traffic noise and railway noise, no effect of mutual adjustment and no effect modification of road traffic noise by railway noise, the effect of each of the two exposures on ER− breast cancer appears independent of each other.

Previous studies investigating effects of disturbance of the circadian rhythm have indicated that night work increases the risk for breast cancer,[11] whereas the few studies investigating effects of self-reported sleep duration on breast cancer risk are inconsistent.[14–19] Two studies on night work have investigated effect according to ER subtypes of breast cancer.[31,41] Similar to the present study one of these studies indicated an effect of night work only among women with ER− breast cancer,[31] whereas the other study reported an effect of night work on breast cancer risk but no modification according to ER subtype.[41] No studies have investigated the relationship between sleep disturbances and risk for breast cancer according to ER subtypes of breast cancer.

A potential mechanism for an effect of traffic noise on breast cancer risk is that traffic noise reduces sleep duration

Table 4. Modification of associations between yearly residential road traffic noise (per 10 dB) and breast cancer risk by baseline characteristics and age at diagnosis

	ER negative			ER positive		
Covariates	*N* cases	IRR (95% CI)[1]	*p*-interaction	*N* cases	IRR (95% CI)[1]	*p*-interaction
Age at diagnosis (years)			0.60			0.17
<65	101	1.35 (1.02–1.78)		396	0.94 (0.81–1.09)	
≥65	102	1.21 (0.91–1.60)		462	1.08 (0.95–1.24)	
Years of education (years)			0.55			0.44
≤7	61	1.12 (0.78–1.62)		260	0.96 (0.80–1.15)	
8–10	95	1.27 (0.95–1.69)		435	1.08 (0.94–1.25)	
>10	47	1.52 (1.02–2.29)		163	0.94 (0.75–1.19)	
HRT use			0.57			0.85
Never	77	1.19 (0.86–1.65)		318	1.03 (0.88–1.22)	
Ever	126	1.34 (1.04–1.72)		540	1.01 (0.90–1.15)	
Alcohol intake (g/day)			0.97			0.21
<10	102	1.27 (0.96–1.68)		393	0.95 (0.82–1.10)	
≥10	101	1.28 (0.97–1.70)		465	1.08 (0.94–1.24)	
Number of children			0.67			0.76
0	28	1.41 (0.84–2.39)		133	1.05 (0.82–1.35)	
≥1	175	1.25 (1.01–1.55)		725	1.01 (0.91–1.13)	
Railway noise (L_{den})			0.70			0.39
No railway noise	158	1.25 (1.00–1.56)		673	1.05 (0.94–1.18)	
<55 dB	26	1.60 (0.90–2.84)		130	0.88 (0.67–1.16)	
≥55 dB	19	1.18 (0.59–2.35)		55	0.88 (0.58–1.35)	

[1]Adjusted for age, parity, age at first birth, hormone replacement therapy (HRT) status and duration, age at menarche, length of school attendance, BMI, alcohol intake, smoking status, intake of vegetables, physical activity (MET score), calendar-year and railway and airport noise.

and thereby potentially reduces melatonin production.[4,5] Experimental studies have indicated that melatonin may inhibit breast carcinogenesis by various pathways, including antioxidant effects, enhancing DNA repair and reducing angiogenesis.[6–9] We found no associations with ER+ breast cancer though low melatonin has also been linked with increased estrogen levels.[10] A potential explanation suggested by other epidemiological studies on ER subtypes of breast cancer is that it might be easier to detect modest effects on ER− tumors than on ER+ tumors.[30,42] If the association between an exposure and breast cancer is modest, it might be difficult to identify in ER+ tumors where hormonal factors, in particular estrogen, already have a very strong influence. Conversely, the effect of an exposure on breast cancer may be more easily detectable in ER− tumors where hormonal factors are not so relevant.

In addition to its effect on sleep, exposure to traffic noise has also been associated with a stress response resulting in increased levels of the glucocorticoid cortisol.[43,44] Glucocorticoids are involved in a variety of cellular and physical processes that might promote tumor progression including apoptosis, immune response and angiogenesis.[21,22] Interestingly, in a meta-analysis by Pan *et al.* in 2011 consisting of 1,378 early stage breast cancer patients, activation of the glucocorticoid receptor was associated with poor prognosis among ER− cancer patients, whereas among cases with ER+ breast cancer high expression of the glucocorticoid receptor were associated with a better outcome relative to low expression of the glucocorticoid receptor.[45] Taking the study by Pan *et al.* into consideration, an explanation to our results might be that high cortisol levels induced by exposure to traffic noise could activate the glucocorticoid receptor which again could result in tumor progression among ER− breast cancers.[45] A potential explanation as to why ER+ breast cancer seems not related to traffic noise might be that activation of the ER inhibits glucocorticoid action as shown by Zang *et al.*[46] Also, we find that shorter term exposure to road traffic noise (1 year) seems slightly stronger associated with breast cancer than longer term exposure (10 years). A possible explanation might be that noise-induced stress affects progression of breast tumors and not tumor initiation, which corresponds to overall findings from epidemiological studies on psychosocial stress and breast cancer.[23–26]

The exposure-response curve suggested that, below approximately 55 dB, there was no association between road traffic noise and ER− breast cancer after which the risk

increased dose dependently. Studies on road traffic noise and risk for cardiovascular disease have also indicated a threshold limit of 55–60 dB,[1,2] suggesting that below this threshold effects of road traffic noise on sleep and stress are of minor importance with regard to health.

Strengths of our study include the prospective design, access to residential address histories and diagnosis of breast cancer and ER status using nationwide registers. Some limitations also need to be considered. Analyses of ER− breast cancer are based on a relatively modest number of cases. Also, noise exposure was estimated based on modeled values. The level of traffic noise varies over very short time periods due to *e.g.* movement of vehicles relative to the observer, and weather conditions also may strongly influence the propagation of traffic noise. It is therefore extremely difficult, if not impossible, to estimate reliable long-term noise exposure based on direct measurements. During the last four decades increasingly accurate and reliable prediction methods for traffic noise have been developed. Although the Nordic prediction method has been used for many years, estimation of noise is inevitably associated with some degree of uncertainty. One reason could be inaccurate input data, *e.g.* we lack information on noise barriers and road surface in the modeling of road traffic noise. This could have resulted in exposure misclassification. As the noise model does not distinguish between cases and noncases among cohort members, such misclassification is believed to be nondifferential, and, in most situations, this would influence the relative risk estimate toward the neutral value. Another limitation is that we had information only on residential addresses and not, for example, work or holiday addresses. Such an imprecision is, however, believed to have been similar for cases and the cohort and might therefore have attenuated the risk estimates. We also had no information on bedroom location, window-opening habits, noise from neighbors or hearing impairment, all of which might influence exposure to noise. Studies on traffic noise and cardiovascular diseases have found that the association with road traffic noise is stronger when these factors are considered[47] suggesting that the effect of noise might be underestimated in the present study. Finally, there might be residual confounding from risk factors not accounted for in the analyses, such as familiar history of breast cancer. However, adjustment of our analyses resulted in only minor changes in the estimates although we adjusted for many important risk factors for breast cancer and, therefore, residual confounding seems not to be a major issue in the present study.

In conclusion, our findings indicate that exposure to residential road traffic and railway noise is associated with a higher risk of ER− breast cancer. As this is the first study of its kind, the results need to be confirmed by other studies before any conclusions can be drawn.

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