TITLE PAGE

TITLE: Night shift work and risk of breast cancer in women: the Generations Study cohort

RUNNING TITLE: Night shift work and risk of breast cancer in women

AUTHORS:

Michael E Jones[1], Minouk J Schoemaker[1], Emily C McFadden[1,2], Lauren B Wright[1], Louise E Johns[1], Anthony J Swerdlow[1,3]

AUTHOR AFFILIATIONS:

1) Division of Genetics and Epidemiology, The Institute of Cancer Research, London, United Kingdom, SW7 3RP

2) Current Address: Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom, OX2 6GG

3) Division of Breast Cancer Research, The Institute of Cancer Research, London, United Kingdom, SW7 3RP

CORRESPONDING AUTHOR:

Dr Michael E Jones

Division of Genetics and Epidemiology

The Institute of Cancer Research

London

United Kingdom

SM2 5NG

Tel: +44 (0)20 8722 4254

Fax: +44 (0)20 8722 4019

E-mail: Michael.Jones@icr.ac.uk

ABSTRACT

BACKGROUND

It is plausible that night shift work could affect breast cancer risk, possibly by melatonin suppression or circadian clock disruption, but epidemiological evidence is inconclusive.

METHODS

Using serial questionnaires from the Generations Study cohort we estimated hazard ratios (HR) and 95% confidence intervals (95%CI) for breast cancer in relation to being a night shift worker within the last 10 years, adjusted for potential confounders.

RESULTS

Among 102 869 women recruited 2003–2014, median follow-up 9.5 years, 2059 developed invasive breast cancer. The HR in relation to night shift work was 1.00 (95%CI: 0.86–1.15). There was a significant trend with average hours of night work per week (*P*=0.035), but no significantly raised risks for hours worked per night, nights worked per week, average hours worked per week, cumulative years of employment, cumulative hours, time since cessation, type of occupation, age starting night shift work, or age starting in relation to first pregnancy.

CONCLUSIONS

The lack of overall association, and no association with all but one measure of dose, duration, and intensity in our data, does not support an increased risk of breast cancer from night shift work in women.

KEY WORDS: breast cancer, cohort study, night shift work, risk

BACKGROUND

Over 30 years ago it was proposed that suppression of the pineal hormone melatonin by exposure to electric light at night could increase risk of breast cancer (1). In 2007 an International Agency for Research on Cancer working group concluded that there was limited evidence in humans for the carcinogenicity of shift work that involves night work but overall shift work that involves circadian disruption is probably carcinogenic to humans (Group 2A) (2). There are biological reasons why night shift work may increase risk of breast cancer by suppression of melatonin (the 'melatonin hypothesis') (3) or disruption of internal 'body clocks' (circadian clocks) (4), however, findings from epidemiological cohort (5-16) and case-control (17-22) studies have been inconclusive. Most (17-21, 23-25), but not all (15), meta-analyses suggest night shift work may be associated with a modestly raised risk of breast cancer in women (26, 27). But the association is weaker when limited to cohort studies (18-21, 25, 27), the type of night shift work and exposure definitions have varied from study to study (28), and no clear dose-response relationship has been demonstrated (26, 27).

The most recent meta-analysis of all prospective studies including three previously unpublished cohorts concluded that night shift work has little or no effect on breast cancer incidence (15), but this has been challenged (29-31). It has been suggested that recent exposure (29-32), initiating night work at young ages (16, 30, 31) or before first pregnancy (33, 34), and risk among pre-menopausal women for estrogen receptor (ER) positive, progesterone receptor (PR) positive, or human epidermal growth factor-receptor 2 (HER2) positive tumours (14, 16, 34, 35) may be relevant, but the evidence is inconclusive. We therefore examined risk of breast cancer in relation to timing of night shift work and receptor status, in a large UK cohort study that has not been included in previous meta-analyses, using detailed questionnaire information at recruitment and during follow-up, with adjustment for potentially confounding factors.

MATERIALS AND METHODS

The Generations Study (GS) is a cohort study of >113 700 women aged 16 or older from the United Kingdom. Questionnaire information and informed consent was gained at recruitment since 2003 (36). The first follow-up questionnaire 2½ years after recruitment was completed by 99% of non-deceased participants, a second six years after recruitment by 97%, and a third 9½ years after recruitment by 96% of those recruited long enough ago to have entered this phase of follow-up.

Breast and other cancers occurring in the cohort were identified from recruitment and follow-up questionnaires and spontaneous reports to the study centre. Spontaneous reports occurred when a woman contacted us and told us about her cancer diagnosis. For those lost to questionnaire follow-up we ascertained cancers from linkage to National Health Service Central Registers (NHSCR) which provides information on vital status, cancer diagnosis and site (37). Confirmation of diagnosis was obtained from cancer registries in the United Kingdom, NHSCR linkage, pathology reports, and correspondence with patients' general practitioners.

Information on risk factors for breast cancer was obtained from recruitment and follow-up questionnaires. Because we had collected ages or dates at which certain events or changes in lifestyle occurred, we were able to conduct analyses using time-updated alcohol use, parity, oral contraceptive use, menopausal hormone therapy (MHT) use, and menopausal status, at the ages these events or changes occurred through to the second follow-up questionnaire. We also updated post-menopausal body mass index (BMI) at the date of the second follow-up questionnaire.

In relation to night shift work, women were asked in the recruitment questionnaire: "Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)", and we collected information on type of job, year starting and ending, average number of nights per week working at night or late evening, and average number of hours worked between 10pm and 7am for each such episode of work. The same information on night work, but covering the period from recruitment to the second follow-up questionnaire, was

collected at this follow-up six years after recruitment. When analysing type of occupation in which night shift work occurred, if a woman reported different types of night work occupation concurrently during a time period, we counted only the type of work that she had done the most, so that we could allocate her to a single occupation at any one time. If the hours per night or nights per week of night work changed during a period of night work, we took an average of these night work intensity measures weighted by the number of years at each intensity. We did not ask about night shift work in the next follow-up questionnaire, 9½ years after recruitment.

To analyse breast cancer risk in relation to being a night shift worker in the last 10 years we updated night shift work status, and cumulative duration and time since cessation in single year increments, through to the six year follow-up. After this point we assumed that women who had never been a night shift worker, or had ceased, did not commence new night work, and that women who were in current night work continued at the same intensity, frequency, and duration through to the end of analytic follow-up. Because our questionnaires only solicited information on night shift work history which, at least in part, had been undertaken in the last 10 years we did not count information from night shift histories that ended completely more than 10 years ago (*i.e.* when women volunteered more information than requested) because we deemed this would be incomplete or missing for some women. Therefore we were able to analyse comprehensive information on night shift exposures more than ten years ago that continued into the last 10 year period, but for exposures based on work history that ended before this 10 year period our analysis would be lesscomplete.

Statistical analysis

The current analytic cohort is based on all women who were recruited to the study during June 2003–December 2014 without prior invasive or *in-situ* breast cancer or other malignancy except non-melanoma skin cancer, or prior mastectomy, and who did not report being registered as blind or partially sighted because of the possible association between blindness, melatonin, and

breast cancer risk (38). The recruitment cut-off at December 2014 was selected because at the time of analysis the second follow-up was practically complete for this group of recruits and all women would have in principle been able to reach the minimum follow-up of 2½ years associated with the first follow-up questionnaire. Women entered risk at their date of recruitment and were censored at the earliest date of: invasive or *in-situ* breast cancer; other malignancy except non-melanoma skin cancer; death; or most recent follow-up questionnaire which was dependent on date of recruitment. If the most recent follow-up questionnaire was not completed the censoring date was the date the most recent follow-up questionnaire was due if cancer and vital status were known after this date from NHSCR linkage. If cancer and vital status were not known at this due date this was considered a loss to optimum follow-up and the censoring date was the date of the last completed questionnaire. The data for this analysis was extracted and frozen from our live database on 9-Jan-2019.

Left-truncated and right censored Cox proportional hazards regression (39) using attained age as the implicit time scale was used to estimate the hazard ratio (HR) and 95% confidence interval (95%CI) for night shift work and risk of first invasive breast cancer adjusted for potential confounding factors (see footnotes to Tables 2 and 3). We analysed primarily risk in relation to invasive breast cancer so that our results would be comparable with those from the Million Women Study, EPIC-Oxford, and UK Biobank (15), the Nurses Health Studies (16), and other prospective studies (9-11, 15), although we also compared HRs for invasive versus *in-situ* breast cancer.

Statistical trends for frequency, intensity, and duration of night work, and time since last night work, were based on discrete time-varying annually updated values. For example if at the time of recruitment a woman had been in night shift work for 5 years her cumulative exposure would be 5 years. If she continued night shift work then in the next year of follow-up her cumulative exposure would be updated to 6 years, and so on as long as she continued night shift work. Trends in these time-varying exposures and trend in risk with age starting night work, were assessed using the likelihood ratio test (40). For trend analyses, the groups defined by not being a night shift worker in

the last 10 years and current night shift worker in analysis of time since cessation were not assigned a zero magnitude but were treated as separate categorical terms, as was the group where the details of night shift work were missing (*i.e.* trends were only evaluated across those who were exposed but by using indicator variables we included the non-exposed and missing value group in the regression analysis). We stratified by breast cancer risk factors to examine interactions between these risk factors and night shift work, and by ever-use of melatonin supplements (reported at cohort entry). Heterogeneity in HRs by sub-type of breast cancer defined by receptor status, histology, or invasive versus *in-situ* breast cancer, was assessed using a data augmentation method (41) and Wald test (40). All statistical tests were two-sided and analyses were conducted using Stata/IC version 14.2 (42).

RESULTS

During 2003–2014 a recruitment questionnaire was completed by 102 869 women in the GS who had no previous invasive or *in-situ* breast cancer or other malignancy except non-melanoma skin cancer. By the censoring date, 1.1% of the women had died. Of the remainder, cancer and vital status was known for 95.3% who had completed the relevant follow-up questionnaire, and a further 3.2% from linkage to the NHSCR. The remaining 0.4% were lost to follow-up and censored at the date of an earlier returned questionnaire. The last follow-up and censoring date was 27th March 2018.

Table 1 presents descriptive characteristics, at recruitment, of the cohort members eligible for analysis, by night work status. The median age at recruitment was 45 years (inter-quartile range: 35–55). Among participants 17.5% reported being a night shift worker within the last 10 years. There were significant variations in the percentage of night shift workers in relation to all but one demographic or descriptive characteristic in the table (all $P_{heterogeneity}<0.0001$, except for pre-menopausal oral contraceptive use, $P=0.13$). The proportion reporting ever being a night shift worker in the 10 years before recruitment was greater for women who were younger, pre-menopausal, higher BMI at age 20, did not report family history of breast cancer or personal history of benign breast disease, lived in less affluent neighbourhoods, nulliparous, ex-drinkers of alcohol, current smokers, higher levels of physical activity, higher BMI at post-menopausal ages, current users of MHT, and those not reporting ever use of melatonin supplement.

During 880 864 person-years (median 9.5 years) of follow-up 2059 invasive breast cancers occurred, of which 2041 were confirmed through national cancer registration or medical records, and the remainder (n=18) were self-reported mostly with treatment or other details that implied breast cancer, *e.g.* information on receptor status. ER status data were available for 96.6%, and of these 84.3% were ER-positive. Invasive ductal carcinoma accounted for 78.2%, and lobular for

16.4%, of tumours. Further descriptive characteristics of the breast cancer cases are given in Supplementary Table 1.

The HR for invasive breast cancer in relation to being a night shift worker within the last 10 years was 0.98 (95%CI: 0.85–1.14; *P*=0.80) with adjustment only for attained age, and 1.00 (95%CI: 0.86–1.15; *P*=0.96) with adjustment for additional potentially confounding factors (Table 2). There were no significantly raised risks in relation to hours worked per night (P_{trend}= 0.62), nights per week on night shift (P_{trend}=0.066), cumulative years of employment as a night shift worker (P_{trend}=0.51), or cumulative hours of night shift work (P_{trend}=0.51), but there was a significant positive trend with average hours per week, adjusted for age only (P_{trend}=0.038) or fully adjusted (P_{trend}=0.035) (Table 2).

There were no significantly raised risks with being a night shift worker in the last 10 years by type of occupation nor was there evidence for heterogeneity (Table 3; *P*=0.20). There were no significant associations with age started night shift work (P_{trend}=0.89), whether night shift work started before (*P*=0.73) or after (*P*=0.90) first pregnancy, or by time since last worked night shifts (P_{trend}=0.38). When we restricted our analyses to women at recruitment who either reported being in a paid or self-employed job (n=69 942), student (n=3599), unemployed (n=789), or retired (n=15 711) our results were essentially the same (Supplementary Tables 2 and 3). We examined by stratification, interactions between risk of breast cancer and night shift work by selected risk factors for breast cancer, and for ever-use of melatonin supplement before recruitment, but found no significant associations or interactions (Supplementary Table 4).

We also stratified by menopausal status and examined risk in relation to being a night shift worker in the last 10 years and average hours per week on night shift but found no significant associations, trends, or interactions (Supplementary Table 5). Nor were there significantly raised risks in relation to night shift work by receptor status of breast cancer (ER, PR, HER2) or histological type (Supplementary Table 5). Further sub-division by menopausal status and sub-type of breast cancer is shown in Supplementary Table 6. No significantly raised risks were seen by sub-type for

pre-menopausal women, although there were some significant associations and trends seen in post-menopausal women for PR-positive, HER2-negative, and lobular tumours, but with no consistent pattern. Finally, when we analysed risk in relation to *in-situ* breast cancer (n=411 cases) the adjusted HR for night shift work in the last 10 years was 1.16 (95%CI: 0.85–1.57; *P*=0.35), with no significant heterogeneity between invasive and *in-situ* breast cancer (*P*=0.39).

DISCUSSION

In our detailed analysis of night shift work and risk of breast cancer we examined relative risks in relation to a number of aspects of being a night shift worker in the last 10 years, and with few exceptions, most were not statistically significant. We found no evidence for an overall increase in risk of breast cancer for women who had been night shift workers within the last 10 years, or by hours worked per night, nights worked per week, average hours worked per week, cumulative years of employment, cumulative hours, or time since cessation of such work. We found no significantly raised risks with type of night shift occupation, by age at starting night shift work, or by age starting in relation to first pregnancy. Increased risk has been reported previously for night shift work specifically among nurses (17), in particular those engaged in rotating night shift work (6, 7, 43), but we found no increased risk for nurses undertaking night shift work, nor did the Million Women Study (15), although neither we nor the Million Women Study explicitly examined rotating shift work.

The Nurses' Health Studies reported raised risks for night work of >20 years duration (6, 7), but this has not been seen in other cohorts (9, 11-13, 15) or the recent comprehensive meta-analysis of prospective studies (15). A previous dose-response meta-analysis of cohort and case-control studies did report a significant trend with duration (19) whereas another did not (17), so the literature is inconclusive on this. We found no association with duration in our study, although our data for long durations of night work was limited because our study was focussed on recent night shift work in the last 10 years. One potential interpretation for the raised risk seen with long duration in the Nurses' Health Studies is that this raised risk relates to night shift work during the period after puberty and before first childbirth, when the breast may be particularly susceptible to adverse changes (16). Such an association has been reported in a case-control study from France (33) but we, and the Nurses' Health Study-II (16), did not find increased risks with night shift work starting before first pregnancy. We also found no association with age started night shift work, similar to the one other cohort that has reported on this (9).

We did not find evidence for significant interaction (effect modification) between breast cancer risk factors and night shift work in relation to risk of breast cancer, similar to the Million Women Study (15). However, we found night shift work was positively associated with several characteristics that are associated with breast cancer risk therefore there is scope for confounding. In our study adjusting for these potential confounding factors made no material changes to the results, and adjustment for similar factors in other cohort studies (6, 7, 9, 10, 12, 14-16) generally made little difference to their conclusions (44). But if the confounding association is study specific, or women who engage in night shift work differ in other unidentified ways from those who do not, this may explain why results in the literature have been inconsistent.

The only statistically significant association observed in our main analyses in relation to breast cancer and night shift work was a dose-response trend with average hours per week on night shift. A significant trend has previously been reported in a case-control study for hours per week of 'graveyard' shift work (*i.e.* work between 7pm and 9am) in the 10 years before diagnosis (32), and raised risk for ;?20 hours per week in a pooled case-control analysis (22), whereas in a large record linkage cohort study based on Dutch Labor Force Surveys no significant association was seen with a metric based on contractual night working hours (11). There does not appear to be a strong rationale for hours per week on night shift being a risk factor for breast cancer. We found no significant overall association of risk of breast cancer with being a night shift worker. There was also lack of association with the other measures of dose, duration, and intensity that we analysed. These results from our study and the absence in the literature of an hypothesis for why there should be an association with hours per week but not with other measures of dose, duration, or intensity, and conflicting results from other studies (11, 22, 32) suggest it is possible this is a chance finding in our data. However, unlike traditional carcinogens where cumulative exposure and dose may supersede intensity as a requisite for cause-effect association it is still unclear which exposure 'domains' may be important in relation to night shift work (28).

257 We found overall no significantly raised risks by menopausal status for ER, PR, HER2, or
258 histological sub-types of breast cancer. Significantly raised risks have been reported for ER-positive
259 (16, 34, 35, 45), ER-negative (46), PR-positive (16, 34, 35, 45), HER2-positive (35), HER2-negative
260 (45), and lobular (34) breast cancer sub-types in particular among pre-menopausal women (14, 16,
261 34, 35) but we did not find any significantly raised risks in pre-menopausal women, overall or by sub-
262 type. We did see raised risks among post-menopausal women, but are uncertain about the
263 interpretation because these occurred in sub-group analyses subject to inflated type-I statistical
264 error. The evidence in the literature for risk by tumour sub-type, and menopausal status, is
265 inconsistent (14, 16, 34, 35, 45, 46) and this may be a reflection of small number of cases in
266 subgroups and lack of statistical power, or that there is no substantive difference by sub-type of
267 breast cancer in relation to night shift work.

268 Our night shift information was gained at recruitment and from follow-up questionnaire six
269 years later but our follow-up for breast cancer extended beyond the six year questionnaire. We
270 updated night shift work up to the six-year questionnaire, and then carried forward the exposure
271 status at that point in time until end of follow-up if this was >6 years. About one-third (31%) of
272 accrued person-years were after the six-year follow-up but 78% of the post six-year follow-up
273 person-years occurred soon after that, within the first three years after that follow-up. So the scope
274 for potential exposure misclassification was therefore less than in cohort studies that implicitly carry
275 forward exposure status from recruitment for everyone because the studies do not have any
276 updated exposure information. The only other study with updated night shift exposure information
277 using repeat questionnaires, The Nurses' Health Study-II (16), found a significantly raised risk with
278 cumulative duration ;?20 years, but we did not and other cohorts with updated night shift
279 information based on record linkage to employment databases did not find an association overall or
280 with duration (8, 13, 14).

281 Our questions on night shift work only ascertained periods of shift work that took place, or
282 at least ended, during the 10 years before recruitment. We did not collect lifetime history of night

283 shift work because we needed to contain the burden of data collection on the recruits to the study,
284 who at recruitment were completing a 44-page questionnaire covering a wide range of breast cancer
285 related topics. Some have suggested that any increased risk associated with night shift work may
286 diminish soon after exposure ceases (22, 30, 31) and as analysed here recent, rather than historic,
287 night shift work may be the most appropriate measure of exposure. However, to the extent that it is
288 longer term or earlier exposures that matter, our analyses would be limited and weaker.

289 An advantage of our study is that we were able to examine a wider range of night shift
290 exposures than most other prospective studies, which were often limited to analyses of duration of
291 night shift. There was little scope for bias from unascertained mortality or exits, or erroneous
292 reporting of breast cancer in our study, because follow-up for vital and breast cancer status was
293 obtained for 99% of participants and confirmation of reported breast cancers for over 99%. Our
294 breast cancer cases were particularly well characterised for histological type and ER status, allowing
295 for analyses by sub-type of breast cancer. Information on PR and HER2 status was less complete
296 because these tests have not been conducted routinely throughout the study period. As breast
297 cancer treatment has advanced, PR testing has become less common and HER2 testing become
298 more common in the UK, but it seems unlikely this would cause major bias in our analyses by sub-
299 type.

300 The interest in night shift work and risk of breast cancer springs from the hypothesis that
301 exposure to light at night may increase risk of breast cancer (1-3). Only this GS cohort (47) and a
302 cohort of California teachers (48) have examined directly, by prospective questionnaire, exposure to
303 indoor light at night in relation to breast cancer risk, rather than outdoor light at night from
304 ecological geographical correlation with environmental data (*e.g.* from satellite imagery), and both
305 studies fail to find significant associations with indoor light at night. However, the possible
306 association between night shift work and breast cancer remains a public health concern. A
307 substantial proportion of women in the general population are exposed to night shift work (28, 49)
308 and even a modestly increased risk could lead to considerable numbers of breast cancer cases (49-

309 51) if there were a causal association. We did find a statistically significant trend with average hours
310 per week on night shift. But in the absence of an association between breast cancer risk and night
311 shift work overall, or by other measures of dose, duration, or intensity, in our study, and no evidence
312 for association from the most recent and comprehensive meta-analysis (not including the
313 Generations Study) of prospective studies (15), our finding of a significant trend on its own does not
314 provide strong support for a real causal association. Our data overall do not provide evidence for an
315 increased risk of breast cancer with night shift work.

316 ADDITIONAL INFORMATION

317 ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The study was approved by the South East Multi-
318 Centre Research Ethics Committee (MREC 03/01/014) and conducted in accordance with the
319 Declaration of Helsinki.

320 CONSENT FOR PUBLICATION: No individually identifiable data is presented.

321 AVAILABILITY OF DATA AND MATERIAL: The datasets generated during and/or analysed during the
322 current study are not publicly available due to confidentiality reasons but anonymised versions may
323 be available from the corresponding author on reasonable request.

324 CONFLICT OF INTEREST: The authors declare no conflict of interest.

325 FUNDING: This work was funded by Breast Cancer Now and The Institute of Cancer Research.

326 AUTHORSHIP: AJS designed and obtained funding for the Generations Study. AJS, MEJ and MJS set
327 up and collected data in the Generations Study. MEJ, MJS, ECM, LBW, and LEJ collected and
328 prepared data for the analysis. MEJ conducted the analyses and drafted the manuscript. All authors
329 contributed to data interpretation and preparation of the final manuscript. All authors read and
330 approved the final manuscript.

331 ACKNOWLEDGEMENTS

332 We thank Breast Cancer Now and The Institute of Cancer Research for support and funding of the
333 Generations Study, and the study participants, study staff, and the doctors, nurses, and other health-
334 care providers and health information sources who have contributed to the study. The ICR
335 acknowledges NHS funding to the Royal Marsden/ICR NIHR Biomedical Research Centre.

336 REFERENCES

337 1. Stevens RG. Electric power use and breast cancer: a hypothesis. American journal of
338 epidemiology. 1987;125(4):556-61.
339 2. Straif K, Baan R, Grosse Y, Secretan B, Ghissassi FE, Bouvard V, et al. Carcinogenicity of shift-
340 work, painting, and fire-fighting. The Lancet Oncology. 2007;8(12):1065-6.
341 3. Stevens RG, Davis S. The melatonin hypothesis: electric power and breast cancer. Environ
342 Health Persp. 1996;104 Suppl 1:135-40.
343 4. Blakeman V, Williams JL, Meng Q-J, Streuli CH. Circadian clocks and breast cancer. Breast
344 cancer research : BCR. 2016;18(1):89.
345 5. Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. Incidence of breast cancer in
346 Norwegian female radio and telegraph operators. Cancer Causes Control. 1996;7(2):197-204.
347 6. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, et al. Rotating
348 night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer
349 I. 2001;93(20):1563-8.
350 7. Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. Night work and risk of breast cancer.
351 Epidemiology (Cambridge, Mass). 2006;17(1):108-11.
352 8. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and
353 female shift workers. Scand J Work Environ Health. 2007;33(5):336-43.
354 9. Pronk A, Ji B-T, Shu X-O, Xue S, Yang G, Li H-L, et al. Night-shift work and breast cancer risk in
355 a cohort of Chinese women. American journal of epidemiology. 2010;171(9):953-9.
356 10. Knutsson A, Alfredsson L, Karlsson B, Akerstedt T, Fransson EI, Westerholm P, et al. Breast
357 cancer among shift workers: results of the WOLF longitudinal cohort study. Scand J Work Environ
358 Health. 2013;39(2):170-7.
359 11. Koppes LLJ, Geuskens GA, Pronk A, Vermeulen RCH, de Vroome EMM. Night work and breast
360 cancer risk in a general population prospective cohort study in The Netherlands. European journal of
361 epidemiology. 2014;29(8):577-84.
362 12. Akerstedt T, Knutsson A, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. Night work
363 and breast cancer in women: a Swedish cohort study. BMJ open. 2015;5(4):e008127.
364 13. Li W, Ray RM, Thomas DB, Davis S, Yost M, Breslow N, et al. Shift work and breast cancer
365 among women textile workers in Shanghai, China. Cancer causes & control : CCC. 2015;26(1):143-50.
366 14. Vistisen HT, Garde AH, Frydenberg M, Christiansen P, Hansen AM, Andersen J, et al. Short-
367 term effects of night shift work on breast cancer risk: a cohort study of payroll data. Scand J Work
368 Environ Health. 2017;43(1):59-67.
369 15. Travis RC, Balkwill A, Fensom GK, Appleby PN, Reeves GK, Wang X-S, et al. Night Shift Work
370 and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies. J
371 Natl Cancer I. 2016;108(12).
372 16. Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, et al. Rotating
373 Night-Shift Work and the Risk of Breast Cancer in the Nurses' Health Studies. Am J Epidemiol.
374 2017;186(5):532-40.
375 17. Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J. Night-shift work and risk of breast
376 cancer: a systematic review and meta-analysis. Breast Cancer Res Tr. 2013;138(1):291-301.
377 18. Ijaz S, Verbeek J, Seidler A, Lindbohm M-L, Ojajarvi A, Orsini N, et al. Night-shift work and
378 breast cancer--a systematic review and meta-analysis. Scand J Work Environ Health. 2013;39(5):431-
379 47.
380 19. Wang F, Yeung KL, Chan WC, Kwok CCH, Leung SL, Wu C, et al. A meta-analysis on dose-
381 response relationship between night shift work and the risk of breast cancer. Annals of oncology :
382 official journal of the European Society for Medical Oncology. 2013;24(11):2724-32.
383 20. Jia Y, Lu Y, Wu K, Lin Q, Shen W, Zhu M, et al. Does night work increase the risk of breast
384 cancer? A systematic review and meta-analysis of epidemiological studies. Cancer epidemiology.
385 2013;37(3):197-206.

21. He C, Anand ST, Ebell MH, Vena JE, Robb SW. Circadian disrupting exposures and breast cancer risk: a meta-analysis. Int Arch Occup Environ Health. 2015;88(5):533-47.
22. Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, et al. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. European journal of epidemiology. 2018;33(4):369-79.
23. Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: a systematic review and meta-analysis. European journal of cancer (Oxford, England : 1990). 2005;41(13):2023-32.
24. Lin X, Chen W, Wei F, Ying M, Wei W, Xie X. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. Sleep Med. 2015;16(11):1381-7.
25. Yuan X, Zhu C, Wang M, Mo F, Du W, Ma X. Night Shift Work Increases the Risks of Multiple Primary Cancers in Women: A Systematic Review and Meta-analysis of 61 Articles. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2018;27(1):25-40.
26. Lee H-E, Lee J, Jang T-W, Kim I-A, Park J, Song J. The relationship between night work and breast cancer. Ann Occup Environ Med. 2018;30:11.
27. Pahwa M, Labreche F, Demers PA. Night shift work and breast cancer risk: what do the meta-analyses tell us? Scand J Work Environ Health. 2018;44(4):432-5.
28. Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. Occupational and environmental medicine. 2011;68(2):154-62.
29. Hansen J. RE: Night Shift Work and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies. J Natl Cancer Inst. 2017;109(4).
30. Schernhammer ES. RE: Night Shift Work and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies. J Natl Cancer Inst. 2017;109(4).
31. Stevens RG. RE: Night Shift Work and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies. J Natl Cancer Inst. 2017;109(4).
32. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer I. 2001;93(20):1557-62.
33. Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. Night work and breast cancer: a population-based case-control study in France (the CECILE study). Int J Cancer. 2013;132(4):924-31.
34. Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Ardanaz E, et al. Breast cancer risk and night shift work in a case-control study in a Spanish population. European journal of epidemiology. 2016;31(9):867-78.
35. Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, et al. Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. Chronobiol Int. 2016;33(6):783-7.
36. Swerdlow AJ, Jones ME, Schoemaker MJ, Hemming J, Thomas D, Williamson J, et al. The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology. Br J Cancer. 2011;105(7):911-7.
37. Hawkins MM, Swerdlow AJ. Completeness of cancer and death follow-up obtained through the National Health Service Central Register for England and Wales. Br J Cancer. 1992;66(2):408-13.
38. Coleman MP, Reiter RJ. Breast cancer, blindness and melatonin. Eur J Cancer. 1992;28(2-3):501-3.
39. Cox DR. Regression Models and Life-Tables. J R Stat Soc B. 1972;34(2):187-220.
40. Buse A. The Likelihood Ratio, Wald, and Lagrange Multiplier Tests - an Expository Note. Am Stat. 1982;36(3):153-7.
41. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics. 1995;51(2):524-32.

437 42. StataCorp. Stata Statistical Software: Release 14. 14.2 ed. College Station, TX: StataCorp LP;
438 2015.
439 43. Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish
440 nurses: impact of shift systems. Eur J Cancer. 2012;48(11):1722-9.
441 44. Kolstad HA. Nightshift work and risk of breast cancer and other cancers--a critical review of
442 the epidemiologic evidence. Scand J Work Environ Health. 2008;34(1):5-22.
443 45. Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, et al. Night-shift work, sleep duration, daytime
444 napping, and breast cancer risk. Sleep Med. 2015;16(4):462-8.
445 46. Rabstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, et al. Night work and breast
446 cancer estrogen receptor status--results from the German GENICA study. Scand J Work Environ
447 Health. 2013;39(5):448-55.
448 47. Johns LE, Jones ME, Schoemaker MJ, McFadden E, Ashworth A, Swerdlow AJ. Domestic light
449 at night and breast cancer risk: a prospective analysis of 105000 UK women in the Generations
450 Study. Brit J Cancer. 2018;118(4):600-6.
451 48. Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, et al. Light at night and
452 breast cancer risk among California teachers. Epidemiology (Cambridge, Mass). 2014;25(5):697-706.
453 49. Purdue MP, Hutchings SJ, Rushton L, Silverman DT. The proportion of cancer attributable to
454 occupational exposures. Annals of epidemiology. 2015;25(3):188-92.
455 50. Carey RN, Hutchings SJ, Rushton L, Driscoll TR, Reid A, Glass DC, et al. The future excess
456 fraction of occupational cancer among those exposed to carcinogens at work in Australia in 2012.
457 Cancer epidemiology. 2017;47:1-6.
458 51. Slack R, Young C, Rushton L, British Occupational Cancer Burden Study G, Rushton L, Bagga S,
459 et al. Occupational cancer in Britain. Female cancers: breast, cervix and ovary. Brit J Cancer.
460 2012;107 Suppl 1:S27-32.

461

TABLE 1: Characteristics at recruitment of 102,869 women from the Generations Study, by night shift work* during the 10 years before recruitment to cohort

Characteristic	Ever been a night shift worker during the 10 years before recruitment to cohort					Total	
	No		Yes		Yes		
	N	%	N	%	%†	N	%
Year of birth							
1908–1939	5771	*6.8*	136	*0.8*	*2.3*	5907	*5.7*
1940–1949	20174	*23.8*	1308	*7.3*	*6.1*	21482	*20.9*
1950–1959	21816	*25.7*	2930	*16.3*	*11.8*	24746	*24.1*
1960–1969	19066	*22.5*	4665	*25.9*	*19.7*	23731	*23.1*
1970–1998	18061	*21.3*	8942	*49.7*	*33.1*	27003	*26.2*
Year of recruitment							
2003–2005	27481	*32.4*	6272	*34.9*	*18.6*	33753	*32.8*
2006-–2007	40096	*47.2*	8293	*46.1*	*17.1*	48389	*47.0*
2008–2014	17311	*20.4*	3416	*19.0*	*16.5*	20727	*20.1*
Age at recruitment (years)							
16–34	15142	*17.8*	8037	*44.7*	*34.7*	23179	*22.5*
35–44	18295	*21.6*	4807	*26.7*	*20.8*	23102	*22.5*
45–54	21112	*24.9*	3281	*18.2*	*13.4*	24393	*23.7*
55–64	22277	*26.2*	1602	*8.9*	*6.7*	23879	*23.2*
65–74	7088	*8.3*	244	*1.4*	*3.3*	7332	*7.1*
75–102	974	*1.1*	10	*0.1*	*1.0*	984	*1.0*
BMI at recruitment (kg/m^2)							
<20.0	5398	*6.4*	1278	*7.1*	*19.1*	6676	*6.5*
20.0–<22.5	18074	*21.3*	3897	*21.7*	*17.7*	21971	*21.4*
22.5–<25.0	23022	*27.1*	4457	*24.8*	*16.2*	27479	*26.7*
25.0–<30.0	24817	*29.2*	4832	*26.9*	*16.3*	29649	*28.8*
;30.0	11177	*13.2*	2844	*15.8*	*20.3*	14021	*13.6*
Missing	2400	*2.8*	673	*3.7*	*21.9*	3073	*3.0*
BMI at age 20* (kg/m^2)							
<18.5	7075	*8.3*	1198	*6.7*	*14.5*	8273	*8.0*
18.5–<20.0	16275	*19.2*	2822	*15.7*	*14.8*	19097	*18.6*
20.0–<22.5	32370	*38.1*	6219	*34.6*	*16.1*	38589	*37.5*
22.5–<25.0	17435	*20.5*	4200	*23.4*	*19.4*	21635	*21.0*
;25.0	7817	*9.2*	2807	*15.6*	*26.4*	10624	*10.3*
age < 20 at entry	982	*1.2*	220	*1.2*	*18.3*	1202	*1.2*
Missing	2934	*3.5*	515	*2.9*	*14.9*	3449	*3.4*
Family history of breast cancer at recruitment							
None reported	71348	*84.0*	15592	*86.7*	*17.9*	86940	*84.5*
Yes	13540	*16.0*	2389	*13.3*	*15.0*	15929	*15.5*
History if benign breast disease at recruitment							
None reported	68014	*80.1*	15033	*83.6*	*18.1*	83047	*80.7*
Yes	16874	*19.9*	2948	*16.4*	*14.9*	19822	*19.3*
Living in affluent neighbourhood‡							
More affluent	38913	*45.8*	5723	*31.8*	*12.8*	44636	*43.4*
Less affluent	45987	*54.2*	12258	*68.2*	*21.0*	58233	*56.6*
Parity at recruitment							
Nulliparous	20798	*24.5*	8001	*44.5*	*27.8*	28799	*28.0*
Parous	64090	*75.5*	9980	*55.5*	*13.5*	74070	*72.0*

Premenopausal oral contraceptive use							
Post-menopausal §	39789	---	3251	---	---	43040	---
No	6364	*14.1*	2006	*13.6*	*24.0*	8370	*14.0*
Yes	38735	*85.9*	12724	*86.4*	*24.7*	51459	*86.0*
Regular alcohol consumption							
Never	16928	*19.9*	3204	*17.8*	*15.9*	20132	*19.6*
Current	57364	*67.6*	11959	*66.5*	*17.3*	69323	*67.4*
Ex-drinker	10596	*12.5*	2818	*15.7*	*21.0*	13414	*13.0*
Regular cigarette smoking							
Never	55236	*65.1*	10740	*59.7*	*16.3*	65976	*64.1*
Current	5847	*6.9*	2544	*14.1*	*30.3*	8391	*8.2*
Ex-smoker	23805	*28.0*	4697	*26.1*	*16.5*	28502	*27.7*
Physical activity (by quartile of MET)							
<30	21913	*25.8*	3871	*21.5*	*15.0*	25784	*25.1*
30–<51	21726	*25.6*	4145	*23.1*	*16.0*	25871	*25.1*
51–<83	21044	*24.8*	4275	*23.8*	*16.9*	25319	*24.6*
83+	20064	*23.6*	5669	*31.5*	*22.0*	25733	*25.0*
Missing	141	*0.2*	21	*0.1*	*13.0*	162	*0.2*
Postmenopausal BMI (kg/m^2)							
Pre-menopausal §	45099	---	14730	---	---	59829	---
<20.0	1511	*3.8*	96	*3.0*	*6.0*	1607	*3.7*
20.0–<22.5	6481	*16.3*	450	*13.8*	*6.5*	6931	*16.1*
22.5–<25.0	10715	*26.9*	769	*23.7*	*6.7*	11484	*26.7*
25.0–<30.0	13244	*33.3*	1092	*33.6*	*7.6*	14336	*33.3*
30.0+	5482	*13.8*	677	*20.8*	*11.0*	6159	*14.3*
Missing	2356	*5.9*	167	*5.1*	*6.6*	2523	*5.9*
Postmenopausal hormone therapy use							
Pre-menopausal §	45099	---	14730	---	---	59829	---
Never used	22696	*57.0*	1795	*55.2*	*7.3*	24491	*56.9*
Ex-user	9944	*25.0*	707	*21.7*	*6.6*	10651	*24.7*
Current user	6324	*15.9*	675	*20.8*	*9.6*	6999	*16.3*
User, status unknown	825	*2.1*	74	*2.3*	*8.2*	899	*2.1*
Ever used melatonin supplements before recruitment							
No	82010	*96.6*	17487	*97.3*	*17.6*	99497	*96.7*
Yes	2878	*3.4*	494	*2.7*	*14.7*	3372	*3.3*
Total	**84888**	***100.0***	**17981**	***100.0***	***17.5***	**102869**	***100.0***

BMI: Body Mass Index; MET: Metabolic Equivalent to Task

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)?

† Row percentage:

‡ Based on ACORN score, a socio-demographic neighbourhood based score

§ Not included in column percentage for distribution

TABLE 2: Relative risk of invasive breast cancer in relation to ever being a night shift worker* in last 10 years, by frequency, intensity, and duration of night shift work

	Cases†	Person-years (per 100,000)	Age adjusted			Full adjustment‡		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Being a night shift worker within the last 10 years								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
Yes	214	142.5	0.98	0.85–1.14	0.80	1.00	0.86–1.15	0.96
Average hours worked per night								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
<7 hours	91	66.4	1.05	0.85–1.30	0.66	1.04	0.84–1.28	0.74
7+ hours	103	65.1	0.93	0.76–1.14	0.48	0.96	0.78–1.17	0.68
Unknown	20	11.0	0.98	0.63–1.52	0.93	1.02	0.65–1.58	0.94
Trend§:					0.44			0.62
Average nights per week on night shift								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
<4	152	104.9	0.95	0.80–1.12	0.52	0.96	0.81–1.14	0.65
4–7	55	32.5	1.16	0.89–1.52	0.28	1.18	0.90–1.55	0.23
Unknown	7	5.1	0.70	0.33–1.48	0.35	0.70	0.33–1.47	0.35
Trend§:					0.073			0.066
Average hours per week on night shift								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
<10	70	56.3	0.88	0.69–1.12	0.31	0.88	0.69–1.12	0.29
10–<20	61	38.9	1.06	0.82–1.37	0.67	1.07	0.83–1.39	0.60
20–<30	35	20.5	1.02	0.73–1.43	0.90	1.05	0.75–1.48	0.76
30+	26	13.5	1.20	0.81–1.77	0.36	1.27	0.86–1.87	0.24
Unknown	22	13.3	0.88	0.58–1.34	0.54	0.91	0.60–1.38	0.65
Trend§:					0.038			0.035
Cumulative years of employment as night shift worker								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
<10	89	87.0	0.90	0.73–1.12	0.36	0.92	0.74–1.14	0.44
10–<20	65	33.7	1.07	0.83–1.37	0.61	1.09	0.85–1.40	0.51
20–<30	36	14.9	0.96	0.69–1.34	0.81	0.97	0.70–1.35	0.85
30+	24	6.9	1.12	0.75–1.67	0.59	1.12	0.75–1.69	0.57
Trend§:					0.49			0.51
Cumulative hours of night shift work (10,000 hours)								
None	1845	738.5	1.00	Baseline		1.00	Baseline	
0–<1	103	83.0	1.00	0.82–1.23	0.99	1.00	0.82–1.23	0.98
1–<2	36	18.7	1.01	0.73–1.41	0.95	1.04	0.74–1.44	0.83
2–<3	22	8.1	1.21	0.80–1.85	0.37	1.24	0.82–1.90	0.31
3+	21	7.4	1.05	0.68–1.61	0.84	1.07	0.70–1.66	0.75
Unknown	32	25.3	0.78	0.55–1.10	0.16	0.79	0.56–1.13	0.20
Trend§:					0.57			0.51

HR: Hazard Ratio; CI: Confidence Interval

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)?

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1-– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

§ Trend evaluated over those doing night shift work, based on time-varying annually updated values

TABLE 3: Relative risk of invasive breast cancer in relation to ever being a night shift worker* in last 10 years, by type of work, age started, timing of first pregnancy, and time since last night shift work

	Cases†	Person-years (per 100,000)	Age adjusted			Full adjustment‡		
			HR	95% CI	*P* -value	HR	95% CI	*P* -value
Type of night shift work in last 10 years								
None	1845	763.4	1.00	Baseline		1.00	Baseline	
Nurse	83	51.1	0.83	0.66–1.03	0.092	0.85	0.68–1.07	0.17
Waitress	10	24.5	0.60	0.32–1.13	0.11	0.61	0.33–1.15	0.13
Office/shops	29	14.3	1.32	0.92–1.91	0.14	1.35	0.93–1.95	0.11
Health Carer	22	9.1	1.29	0.85–1.97	0.23	1.42	0.93–2.17	0.11
Technical	18	8.4	1.37	0.86–2.18	0.18	1.28	0.81–2.05	0.29
Emergency services, armed forces, air crew	13	7.0	1.37	0.79–2.37	0.26	1.31	0.76–2.27	0.34
Manual work	8	4.6	1.10	0.55–2.21	0.79	1.12	0.56–2.25	0.74
Doctor/GP	7	8.3	0.85	0.40–1.78	0.66	0.78	0.37–1.65	0.52
Other	24	20.7	0.99	0.66–1.49	0.98	0.97	0.65–1.45	0.88
Heterogeneity:					0.18			0.20
Age started night work (years)								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
<25	71	72.7	1.02	0.80–1.31	0.86	1.03	0.80–1.32	0.82
25–34	45	36.1	0.82	0.61–1.11	0.20	0.84	0.62–1.14	0.26
35–44	63	20.7	1.21	0.94–1.56	0.13	1.24	0.96–1.60	0.095
45+	35	13.0	0.84	0.60–1.17	0.30	0.84	0.60–1.18	0.32
Trend:					0.86			0.89
Night work in relation to first pregnancy, parous women only								
Parous but no night work	1593	586.5	1.00	Baseline		1.00	Baseline	
Started night work before 1st pregnancy	58	41.3	1.00	0.77–1.31	0.99	0.95	0.73–1.25	0.73
Started night work after 1st pregnancy	111	47.0	0.97	0.80–1.18	0.75	1.01	0.83–1.23	0.90
Time since last night shift work (years)								
None	1845	738.4	1.00	Baseline		1.00	Baseline	
Current	84	54.7	0.98	0.79–1.23	0.88	1.01	0.80–1.26	0.96
0–<5	60	40.5	1.05	0.81–1.36	0.72	1.05	0.81–1.36	0.72
5–<10	70	47.3	0.93	0.73–1.18	0.55	0.94	0.74–1.20	0.64
Trend§:					0.34			0.38

HR: Hazard Ratio; CI: Confidence Interval

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1–– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

§ Trend evaluated over those who have ceased night shift work, based on time-varying annually updated values

SUPPLEMENTARY TABLE 1: Characteristics of incident invasive breast cancer cases arising in 102,869 women from the Generations Study, 2004–2017

Characteristic	N	%
Age at breast cancer diagnosis (years)		
24–44	269	*13.1*
45–54	536	*26.0*
55–64	689	*33.5*
65–74	471	*22.9*
74–95	94	*4.6*
Year of breast cancer diagnosis		
2004–2009	683	*33.2*
2010–2014	1177	*57.2*
2015–2017	199	*9.7*
Confirmation of breast cancer		
Confirmed*	2041	*99.1*
Self-reported only†	18	*0.9*
Histological type		
Ductal	1611	*78.2*
Lobular	337	*16.4*
Mucinous or colloid	23	*1.1*
Tubular	32	*1.6*
Adenocarcinoma, NOS	15	*0.7*
Other named types	20	*1.0*
Type unknown	21	*1.0*
Estrogen receptor status		
Positive	1677	*81.4*
Negative	313	*15.2*
Type unknown	69	*3.4*
Progesterone receptor status		
Positive	868	*42.2*
Negative	432	*21.0*
Type unknown	759	*36.9*
Human epidermal growth factor receptor 2 status		
Positive	273	*13.3*
Negative	1542	*74.9*
Type unknown	273	*11.9*
Total number of cases	**2059**	***100.0***

* Confirmation through national cancer registration or medical records

† Mostly with treatment or other details that implied breast cancer

SUPPLEMENTARY TABLE 2: Relative risk of invasive breast cancer in relation to ever being a night shift worker* in last 10 years, by frequency, intensity, and duration of night shift work in women who reported being in a paid or self-employed job, student, unemployed, or retired at recruitment

	Cases†	Person-years	Age adjusted			Full adjustment‡		
		(per 100,000)	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Being a night shift worker within the last 10 years								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
Yes	201	133.2	1.01	0.86–1.17	0.86	1.02	0.87–1.19	0.82
Average hours worked per night								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
<7 hours	86	61.7	1.09	0.88–1.36	0.44	1.08	0.87–1.35	0.49
7+ hours	98	61.4	0.95	0.78–1.17	0.78	0.98	0.80–1.21	0.86
Unknown	17	10.1	0.92	0.57–1.49	0.57	0.95	0.59–1.53	0.83
Trend§:					0.39			0.53
Average nights per week on night shift								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
<4	144	99.1	0.97	0.81–1.15	0.72	0.98	0.82–1.17	0.84
4–7	51	29.5	1.20	0.91–1.59	0.20	1.23	0.92–1.63	0.16
Unknown	6	4.6	0.68	0.30–1.52	0.35	0.66	0.30–1.48	0.32
Trend§:					0.058			0.052
Average hours per week on night shift								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
<10	67	52.9	0.92	0.72–1.18	0.31	0.92	0.71–1.172	0.49
10–<20	57	36.4	1.07	0.82–1.40	0.67	1.09	0.83–1.43	0.53
20–<30	33	19.4	1.04	0.73–1.47	0.90	1.07	0.75–1.51	0.72
30+	25	12.4	1.27	0.85–1.88	0.36	1.34	0.90–1.99	0.16
Unknown	19	12.1	0.84	0.53–1.32	0.54	0.86	0.55–1.35	0.51
Trend§:					0.03			0.027
Cumulative years of employment as night shift worker								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
<10	79	80.6	0.89	0.71–1.12	0.36	0.90	0.72–1.14	0.40
10–<20	63	31.6	1.13	0.87–1.45	0.61	1.15	0.89–1.48	0.28
20–<30	35	14.3	0.99	0.71–1.38	0.81	0.99	0.71–1.39	0.96
30+	24	6.7	1.18	0.78–1.76	0.59	1.18	0.79–1.77	0.43
Trend§:					0.31			0.35
Cumulative hours of night shift work (10,000 hours)								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
0–<1	97	77.3	1.04	0.84–1.28	0.99	1.04	0.84–1.29	0.71
1–<2	36	17.9	1.08	0.77–1.50	0.95	1.10	0.79–1.54	0.57
2–<3	21	7.7	1.23	0.80–1.89	0.37	1.25	0.81–1.93	0.31
3+	20	7.0	1.06	0.68–1.65	0.84	1.08	0.70–1.69	0.72
Unknown	27	23.2	0.73	0.50–1.07	0.16	0.75	0.51–1.09	0.13
Trend§:					0.67			0.62

HR: Hazard Ratio; CI: Confidence Interval

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)?

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1-– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

§ Trend evaluated over those doing night shift work, based on time-varying annually updated values

SUPPLEMENTARY TABLE 3: Relative risk of invasive breast cancer in relation to ever being a night shift worker* in last 10 years, by type of work, age started, timing of first pregnancy, and time since last night shift work in women who reported being in a paid or self-employed job, student, unemployed, or retired at recruitment

	Cases†	Person-years (per 100,000)	Age adjusted			Full adjustment‡		
			HR	95% CI	*P* -value	HR	95% CI	*P* -value
Type of night shift work in last 10 years								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
Nurse	81	48.6	0.86	0.69–1.08	0.19	0.88	0.71–1.11	0.29
Waitress	9	23.0	0.60	0.31–1.17	0.13	0.61	0.32–1.20	0.15
Office/shops	26	13.0	1.31	0.89–1.93	0.18	1.34	0.90–1.97	0.15
Health Carer	19	8.2	1.27	0.81–2.00	0.29	1.40	0.89–2.21	0.15
Technical	18	7.9	1.46	0.92–2.33	0.11	1.37	0.86–2.19	0.18
Emergency services, armed forces, air crew	11	6.5	1.26	0.70–2.29	0.44	1.21	0.67–2.20	0.53
Manual work	7	3.9	1.15	0.55–2.42	0.71	1.18	0.56–2.48	0.66
Doctor/GP	7	8.1	0.88	0.42–1.86	0.74	0.82	0.39–1.72	0.59
Other	23	14.0	1.07	0.71–1.62	0.74	1.05	0.69–1.58	0.83
Heterogeneity:					0.30			0.33
Age started night work (years)								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
<25	68	68.9	1.05	0.82–1.36	0.68	1.06	0.82–1.37	0.64
25–34	43	33.3	0.87	0.64–1.18	0.37	0.89	0.65–1.21	0.45
35–44	59	18.9	1.25	0.96–1.62	0.096	1.27	0.98–1.65	0.074
45+	31	12.1	0.81	0.57–1.15	0.24	0.81	0.57–1.16	0.25
Trend:					0.85			0.82
Night work in relation to first pregnancy, parous women only								
Parous but no night work	1341	491.2	1.00	Baseline		1.00	Baseline	
Started night work before 1st pregnancy	54	37.6	1.02	0.77–1.36	0.87	0.98	0.77–1.30	0.87
Started night work after 1st pregnancy	104	42.7	1.00	0.82–1.22	0.99	1.04	0.85–1.28	0.70
Time since last night shift work (years)								
None	1574	636.5	1.00	Baseline		1.00	Baseline	
Current	82	52.1	1.03	0.82–1.29	0.78	1.05	0.84–1.32	0.66
0–<5	56	37.9	1.06	0.81–1.39	0.65	1.06	0.81–1.39	0.65
5–<10	63	43.3	0.93	0.72–1.20	0.56	0.94	0.73–1.22	0.66
Trend§:					0.21			0.25

HR: Hazard Ratio; CI: Confidence Interval

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1-– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

§ Trend evaluated over those who have ceased night shift work, based on time-varying annually updated values

SUPPLEMENTARY TABLE 4: Relative risk of invasive breast cancer in relation to ever being a night shift worker* in last 10 years, stratified by risk factors for breast cancer, and ever use of melatonin supplements

	Cases†	Person-years (per 100,000)	HR for night shift work within the last 10 years					
			Age adjusted			Full adjustment‡		
			HR	95% CI	*P* -value	HR	95% CI	*P* -value
BMI at age 20 (kg/m^2) (excludes missing and those <20 years of age)								
<22.5	1437	563.9	1.05	0.88–1.25	0.61	1.04	0.87–1.24	0.66
;?22.5	557	278.8	0.88	0.68–1.15	0.36	0.90	0.69–1.17	0.44
		Interaction:		*P* =0.29			*P* =0.36	
Family history of breast cancer								
None	1552	745.6	1.01	0.86–1.19	0.87	1.02	0.87–1.20	0.82
Yes	507	135.3	0.90	0.66–1.23	0.51	0.92	0.67–1.25	0.58
		Interaction:		*P* =0.50			*P* =0.55	
History of benign breast								
None	1448	713.1	0.91	0.76–1.08	0.29	0.93	0.78–1.11	0.42
Yes	611	167.8	1.13	0.88–1.46	0.33	1.16	0.91–1.50	0.24
		Interaction:		*P* =0.16			*P* =0.15	
Living in affluent neighbourhood								
More affluent	1019	380.0	1.10	0.88–1.37	0.41	1.11	0.89–1.38	0.36
Less affluent	1040	500.8	0.92	0.76–1.11	0.37	0.92	0.76–1.11	0.38
		Interaction:		*P* =0.22			*P* =0.20	
Parity								
Nulliparous	297	206.0	0.98	0.71–1.36	0.91	0.99	0.71–1.37	0.95
Parous	1762	674.9	0.98	0.84–1.15	0.83	0.99	0.84–1.16	0.87
		Interaction:		*P* =0.99			*P* =0.98	
Alcohol consumption								
Never	172	80.5	1.43	0.93–2.20	0.11	1.46	0.95–2.26	0.086
Ever	1887	800.3	0.95	0.81–1.10	0.48	0.96	0.82–1.12	0.56
		Interaction:		*P* =0.089			*P* =0.080	
Smoking cigarettes								
Never	1223	564.3	0.97	0.80–1.17	0.73	0.98	0.81–1.19	0.86
Ever	836	316.6	0.98	0.79–1.21	0.85	1.01	0.82–1.26	0.90
		Interaction:		*P* =0.92			*P* =0.83	
Physical activity (MET) §								
<50	979	432.7	0.98	0.79–1.23	0.88	1.00	0.80–1.25	0.99
;?50	1078	446.8	0.98	0.82–1.19	0.87	0.99	0.82–1.20	0.93
		Interaction:		*P*= 0.99			*P* =0.96	
Postmenopausal hormone therapy use (only among post-menopausal women)								
Never	830	275.8	1.10	0.86–1.42	0.44	1.12	0.87–1.43	0.39
Ever	638	177.1	1.10	0.82–1.48	0.54	1.12	0.83–1.51	0.45
		Interaction:		*P* =0.98			*P* =0.97	
Postmenopausal BMI (only among post-menopausal women) §								
<25	574	191.9	1.20	0.87–1.65	0.28	1.21	0.88–1.68	0.24
;?25	679	193.5	1.07	0.81–1.41	0.64	1.12	0.85–1.48	0.43
		Interaction:		*P* =0.61			*P* =0.71	
Ever used melatonin supplements before recruitment								
No	1968	852.2	0.96	0.82–1.11	0.57	0.97	0.84–1.13	0.71

Yes	91	28.6	1.61	0.89–2.89	0.11	1.59	0.88–2.86	0.12
		Interaction:		*P* =0.11			*P* =0.13	

HR: Hazard Ratio; CI: Confidence Interval; MET: Metabolic Equivalent to Task

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)?

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1— <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing); unless part of stratification variable

§ Excludes strata for missing level of risk factor

SUPPLEMENTARY TABLE 5: Relative risk of invasive breast cancer in relation to being a night shift worker* in last 10 years, by menopausal status and type of breast cancer

	Night shift work within the last 10 years†		HR for night shift work within the last 10 years‡			Average hours per week on night shift‡								
	No	Yes	Yes vs No			<10		10–<20		20–<30		30+		Trend§
	Cases	Cases	HR	95% CI	*P-value*	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P-* value
Menopausal status														
Pre-	494	97	0.88	0.70–1.09	0.24	0.65	0.44–0.95	1.13	0.80–1.60	1.03	0.64–1.68	0.89	0.46–1.73	0.92
Post-	1351	117	1.10	0.91–1.34	0.31	1.12	0.82–1.52	0.97	0.66–1.44	1.06	0.66–1.69	1.58	0.98–2.56	0.099
		Interaction:		*P* =0.12					*P* =0.13					0.25
Estrogen Receptor (ER) Status														
ER+	1512	165	0.96	0.81–1.13	0.64	0.87	0.66–1.14	1.01	0.75–1.36	1.05	0.72–1.53	1.15	0.73–1.82	0.53
ER-	276	37	1.02	0.72–1.43	0.93	1.02	0.60–1.75	1.14	0.62–2.07	1.09	0.48–2.47	1.45	0.60–3.51	0.40
Unknown	57	12	1.82	0.89–3.74	0.10			(omitted: too few exposed cases for analysis)						
		Interaction:		*P* =0.23					*P* =0.96					0.64
Progesterone Receptor (PR) Status														
PR+	771	97	1.04	0.84–1.30	0.71	0.98	0.69–1.39	1.13	0.77–1.65	0.69	0.37–1.29	1.45	0.84–2.53	0.24
PR-	381	51	1.10	0.82–1.47	0.54	1.03	0.64–1.66	1.22	0.72–2.04	1.69	0.95–3.02	1.35	0.60–3.02	0.12
Unknown	693	66	0.88	0.68–1.14	0.32	0.65	0.40–1.03	0.90	0.56–1.45	1.11	0.64–1.92	0.96	0.46–2.04	0.48
		Interaction:		*P* =0.47					*P* =0.42					0.24
Human Epidermal Growth Factor-Receptor 2 (HER2) Status														
HER2+	242	31	0.88	0.61–1.29	0.52	0.68	0.35–1.30	1.48	0.86–2.56	0.57	0.18–1.78	1.20	0.44–3.27	0.85
HER2-	1384	158	1.02	0.86–1.21	0.82	0.98	0.74–1.28	0.93	0.67–1.28	1.24	0.86–1.79	1.21	0.76–1.93	0.27
Unknown	219	25	1.00	0.65–1.54	0.99	0.53	0.22–1.30	1.35	0.69–2.63	0.51	0.13–2.05	1.64	0.61–4.44	0.81
		Interaction:		*P* =0.79					*P* =0.38					0.95
Histological sub-type														
Ductal	1439	172	0.99	0.85–1.17	0.95	0.82	0.62–1.08	1.17	0.89–1.54	1.01	0.69–1.48	1.09	0.68–1.74	0.47
Lobular	301	36	1.24	0.87–1.78	0.24	1.52	0.91–2.55	0.66	0.27–1.60	1.52	0.72–3.23	2.14	0.95–4.83	0.072
Other	105	6	0.45	0.20–1.04	0.062			(omitted: too few exposed cases for analysis)						
		Interaction:		*P* =0.087					*P* =0.075					0.20

HR: Hazard Ratio; CI: Confidence Interval

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)?

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1-– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); age at menopause (trend, missing), and for analyses by receptor status and histological sub-type, menopausal status (pre- orpost-menopausal).

§ Trend evaluated over those doing night shift work, based on time-varying annually updated values (excludes missing hours per week)

SUPPLEMENTARY TABLE 6: Relative risk of invasive breast cancer in relation to being a night shift worker* in last 10 years, by type of breast cancer and menopausal status

	Night shift work within the last 10 years†		HR for night shift work within the last 10 years‡			Average hours per week on night shift‡								
	No	Yes	Yes vs No			<10		10–<20		20–<30		30+		Trend§
	Cases	Cases	HR	95% CI	*P-value*	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P-* value
Estrogen Receptor (ER) Status														
Pre-menopausal women														
ER+	394	70	0.81	0.62–1.04	0.099	0.57	0.36–0.90	1.04	0.69–1.56	1.15	0.69–1.94	0.50	0.19–1.36	0.27
ER-	81	24	1.18	0.75–1.84	0.48	1.12	0.57–2.22	1.59	0.80–3.17	0.68	0.17–2.76	1.61	0.51–5.05	0.63
Unknown	19	3	0.62	0.17–2.31	0.48			(omitted: too few exposed cases for analysis)						
	Interaction:			*P* =0.31					*P* =0.19					0.96
Post-menopausal women														
ER+	1118	95	1.12	0.90–1.39	0.30	1.19	0.85–1.66	0.97	0.63–1.50	0.97	0.56–1.68	1.77	1.06–2.96	0.078
ER-	195	13	0.85	0.49–1.49	0.57	0.91	0.38–2.19	0.52	0.13–2.10	1.66	0.62–4.46	1.30	0.32–5.27	0.93
Unknown	38	9	3.68	1.77–7.66	<0.001			(omitted: too few exposed cases for analysis)						
	Interaction:			*P* =0.0045					*P* =0.73					0.57
Progesterone Receptor (PR) Status														
Pre-menopausal women														
PR+	235	38	0.72	0.51–1.03	0.069	0.59	0.33–1.05	1.03	0.61–1.73	0.51	0.19–1.38	0.41	0.10–1.67	0.18
PR-	98	28	1.15	0.76–1.73	0.52	0.94	0.48–1.84	1.47	0.77–2.83	1.41	0.57–3.45	1.78	0.66–4.83	0.37
Unknown	161	31	0.88	0.60–1.30	0.52	0.51	0.24–1.09	1.03	0.54–1.95	1.50	0.73–3.07	0.93	0.30–2.96	0.86
	Interaction:			*P* =0.25					*P* =0.42					0.66
Post-menopausal women														
PR+	536	59	1.41	1.07–1.87	0.015	1.46	0.95–2.25	1.21	0.70–2.11	0.90	0.40–2.03	2.64	1.44–4.82	0.0044
PR-	283	23	1.07	0.70–1.63	0.75	1.17	0.60–2.25	0.92	0.38–2.23	2.07	0.98–4.38	0.93	0.23–3.74	0.44
Unknown	532	35	0.89	0.63–1.26	0.53	0.79	0.43–1.43	0.80	0.40–1.62	0.81	0.34–1.97	1.02	0.38–2.74	0.66
	Interaction:			*P* =0.12					*P* =0.24					0.13
Human Epidermal Growth Factor-Receptor 2 (HER2) Status														
Pre-menopausal women														
HER2+	86	21	0.97	0.60–1.57	0.91	0.59	0.25–1.41	1.83	0.97–3.46	0.64	0.16–2.60	1.52	0.47–4.87	0.89
HER2-	348	62	0.79	0.60–1.04	0.094	0.63	0.40–0.99	0.88	0.55–1.39	1.11	0.64–1.94	0.56	0.21–1.49	0.18
Unknown	60	14	1.12	0.61–2.04	0.72	0.82	0.29–2.31	1.44	0.58–3.57	1.03	0.25–4.29	1.73	0.42–7.17	0.33
	Interaction:			*P* =0.52					*P* =0.56					0.80
Post-menopausal women														
HER2+	156	10	0.77	0.40–1.46	0.42	0.85	0.32–2.26	0.90	0.29–2.86	0.48	0.07–3.49	0.77	0.11–5.55	0.96
HER2-	1036	96	1.24	1.00–1.54	0.048	1.32	0.95–1.84	0.95	0.60–1.51	1.39	0.86–2.25	1.81	1.07–3.08	0.016
Unknown	159	11	0.92	0.49–1.72	0.80			(omitted: too few exposed cases for analysis)						
	Interaction:			*P* =0.29					*P* =0.68					0.46
Histological sub-type														
Pre-menopausal women														
Ductal	403	84	0.90	0.71–1.14	0.39	0.66	0.44–0.99	1.20	0.83–1.73	0.94	0.54–1.63	0.92	0.46–1.87	0.19
Lobular	59	9	0.76	0.37–1.53	0.44			(omitted: too few exposed cases for analysis)						
Other	32	4	0.55	0.19–1.61	0.28			(omitted: too few exposed cases for analysis)						
	Interaction:			*P* =0.63										
Post-menopausal women														
Ductal	1036	88	1.08	0.87–1.35	0.49	1.02	0.70–1.47	1.13	0.75–1.71	1.11	0.65–1.88	1.24	0.66–2.33	0.26
Lobular	242	27	1.54	1.03–2.32	0.037	1.96	1.08–3.54	0.68	0.22–2.13	1.48	0.55–4.00	3.52	1.56–7.95	0.0053
Other	73	2	0.34	0.08–1.37	0.13			(omitted: too few exposed cases for analysis)						
	Interaction:			*P* =0.073					*P* =0.090					0.079

HR: Hazard Ratio; CI: Confidence Interval

* Night shift work: Over the last ten years, have you had any jobs that regularly involved work in the late evening or night (between 10pm and 7am)?

† Number of breast cancer cases

‡ HR adjusted for: attained age (Cox regression time scale); time since recruitment to cohort (0, 1–2, 3+ years); birth cohort (1908–39, 1940–49, 1950–59, 1960–69, 1970–96); benign breast disease (yes, no); family history of breast cancer in 1st degree relatives (yes, no); socio-economic score (ACORN score as trend, missing); birth weight (trend, missing); height at age 20 (trend, missing); age at menarche (trend, missing); body mass index at age 20 (trend, missing); age at first pregnancy (trend, missing); parity (trend, missing); breast-feeding (yes/no); current oral contraceptive use before menopause (yes, no); alcohol consumption (never regular, trend current drinker 1–– <60g/day, current drinker 60+g/day, past drinker, drinker with unknown details); age started smoking (never, <17, 17_9, 20+, unknown); physical activity (log(metabolic equivalent) trend, missing); post-menopausal body mass index (trend, missing); menopausal hormone therapy use (never used, ex-user, current estrogen only user, current estrogen plus progestogen user, current user of other types, missing); menopausal status (pre- or post-menopausal) and age at menopause (trend, missing).

§ Trend evaluated over those doing night shift work, based on time-varying annually updated values (excludes missing hours per week)