

1 **Descriptions of individual studies contributing to pooled case–control study by Cordina-**
2 **Duverger et al. (2018)**

3 See Table S2.1.

4 **The GENICA Study (Germany)**

5 The German GENICA study (Pesch et al., 2010), a population-based case-control study, also
6 contributed to the pooled case-control study (Cordina-Duverger et al., 2018). The study, which is described
7 in greater detail below (Rabstein et al., 2013) found no association of ever night work (compared to only
8 day work) with breast cancer risk (OR: 0.91; 95% CI: 0.55–1.49), no association of breast cancer risk with
9 long duration (20+ years) night work (OR: 2.48; 95% CI: 0.62–9.99; based on 12 and 5 exposed cases and
10 controls, respectively), and no association with total/cumulative number of night shifts worked (OR: 1.73;
11 95% CI: 0.71–4.22 for ≥ 807 cumulative nights worked).

12 [The Working Group noted that precision of the risk estimates from this study is limited by the small
13 number of cases and controls who had worked at night.]

14 Rabstein et al. (2013) extends the study by Pesch et al. (2010) by describing associations stratified by
15 hormone receptor status. It is reported here, based on very small case numbers for the hormone negative
16 breast tumours, that women with ER- breast cancer (who were, as expected, younger and more likely
17 premenopausal than women with ER+ breast tumours, see Table 1 in the paper), had a significantly higher
18 risk (OR: 4.73; 95% CI: 1.22–18.36) after 20+ years of night shift work. However, there were only 4
19 women in that group, and odds ratios for the lower categories of night work duration inconsistently varied
20 up and down, indicating that these results were unstable and that the study was not powered to address this
21 question properly.

22 **The BCEES study (Australia)**

23 This population-based case-control study (BCEES) (Fritschi et al., 2013) was conducted between
24 2009–2011 in Western Australia and comprised 1202 breast cancer cases and 1785 controls, and
25 contributed to the pooled case-control study (Cordina-Duverger et al., 2018). The initial publication from
26 2013 described no significantly elevated breast cancer risk among ever night shift workers (defined as
27 graveyard shift) (OR: 1.16; 95% CI: 0.97–1.38). Besides the study's main findings, which were largely
28 null or suggestively elevated in individuals with a mismatch between internal and external clock, it also
29 examined several sub analyses looking at rotation patterns, phase shift, stratified by chronotype (in Fritschi
30 et al., 2018), flexibility/rigidity, and languidness/vigorousness of the circadian rhythm, with little additional
31 evidence gleaned from these analyses. [The Working Group noted the low participation rate overall
32 including somewhat lower participation rate among controls (41%) versus cases (57.8%)]

33 **The CECILE study (France)**

34 The CECILE study (Menegaux et al., 2013), which was part of the pooled case-control study
35 (Cordina-Duverger et al., 2018), included 1232 breast cancer cases and 1317 controls. The OR associated
36 with ever having worked at night was 1.27 (95% CI: 0.99–1.64), and with overnight work was 1.35 (95%

1 CI: 1.01–1.80). Odds ratios were larger for longer total duration of night work (≥ 4.5 years: OR: 1.40; 95%
2 CI: 1.01–1.92; < 4.5 years: OR: 1.12; 95% CI: 0.78–1.60), and for the lowest frequency of night shifts per
3 week (< 3 nights/week: OR: 1.43; 95% CI: 1.01–2.03; ≥ 3 nights/week: OR: 1.14; 95% CI: 0.82–1.59).
4 The authors examined the impact of night work before first full-term pregnancy, and describe higher risks,
5 though these results are not entirely consistent. They interpret their findings as reflecting greater sensitivity
6 of breast tissue before first pregnancy.

7 The highest risk observed was among women who had worked 4+ years of night work with < 3 nights
8 per week before their first full-term pregnancy (OR: 3.03; 95% CI: 1.41–6.50), though this subgroup
9 finding is based on a small number of exposed cases ($n = 26$ cases) and controls ($n = 10$), which limits the
10 precision of the risk estimate and also should be interpreted in the context of the multiple statistical tests.

11 Cordina-Duverger et al. (2016) describe further analyses within the CECILE study, examining the
12 association of night work and risk by breast cancer risk subtypes. Among 975 cases and 1317 controls,
13 they found that premenopausal night workers were at higher risk of positive receptor subtypes of breast
14 cancer than were premenopausal women who had not worked at night. It provided suggestive evidence for
15 an association of night shift work with hormonally positive (ER+, as well as ER+/HER2+) breast tumours,
16 particularly among premenopausal women, with an OR of 3.30 (95% CI: 1.42–7.67) for ER or PR-positive
17 tumours that were also positive for HER2. There were no increased risks in the postmenopausal women of
18 this study. [For the Working Group, this, in conjunction with the pooled case-control study (Cordina-
19 Duverger et al., 2018), raises the question whether risk in premenopausal women, if they stop working
20 night shifts, would return to null, or whether the higher risk among premenopausal women is driven by
21 their greater hormonal sensitivity to the molecular effects of circadian disruption.]

22 [The Working Group noted that in both the Cordina-Duverger papers (Cordina-Duverger et al., 2016;
23 2018), only the participants' age range is provided (25–75), but the provision of an average/median age
24 among pre- versus postmenopausal women would have been informative, to gauge whether the
25 postmenopausal women were likely to have left their work life far behind or had only more recently
26 retired. The Working Group further noted that in Menegaux et al. (2013) (also from the CECILE study),
27 numbers per age range are provided in Table 1, but a direct reflection of their average age is not shown,
28 nor is an analysis provided regarding breast cancer risk according to time since last worked night shifts.]

29 **The British Columbia and Ontario Study (Canada)**

30 A population-based case-control study from Vancouver and Kingston, Canada (Grundy et al., 2013),
31 enrolled 1134 breast cancer cases and 1179 frequency-matched population controls, and described elevated
32 risks of breast cancer only among long-term (30+ years) night workers (OR: 2.21; 95% CI: 1.14–4.31; P
33 trend = 0.5), and particularly among those with health care occupations (OR: 3.11; 95% CI: 1.10–8.77).
34 This case-control study was also included in the larger pooled case-control study (Cordina-Duverger et al.,
35 2018). It had a relatively large proportion of premenopausal women (35%), but only a small proportion
36 among those with longer durations of shift work. The OR of premenopausal women working ≥ 20 years of

1 night work compared to non-night workers was 1.30 (95% CI: 0.66–2.58; based on 18 exposed cases) and
2 for postmenopausal women working ≥ 30 years of night work was 1.63 (95% CI: 0.80–3.35; based on 22
3 exposed cases), with no evidence of heterogeneity by menopausal status (P interaction by menopausal
4 status in women working ≥ 30 years of nights = 0.2), though with limited power to examine heterogeneity
5 due to the small number of cases working long-term night work. Though also based on very small numbers
6 (only 57, 30, 18, 11 and 5 exposed cases, respectively), breast cancer risk increased monotonically when
7 the proportion of evening or night shifts required for a job to be considered “night-shift” increased (20%,
8 40%, 60%, 80%, and 100% were considered), with very limited precision in the highest categories. For
9 example, the OR for working 30 years or more with at least 80% evening or night shifts is 3.73 (95% CI:
10 1.04–13.42). Lastly, positive findings were restricted to ER/PR+ breast tumours: the OR for ≥ 30 years of
11 shift work history (based on the 50% definition) was 2.37 (95% CI: 1.18–4.76) for ER/PR+ and 1.06 (95%
12 CI: 0.24–4.75) for ER/PR-. [This study had limited power to assess the association with hormonally
13 negative tumours (based on only 2 cases who had worked ≥ 30 years of nights).]

14 **MCC Study (Spain)**

15 A Spanish population-based study, the multicase–control (MCC) study (Papantoniou et al., 2016),
16 which also contributed to the five-studies pooled cases control study Cordina-Duverger et al. (2018),
17 examined associations between varying definitions of night shift work and breast cancer risk, enrolling
18 1708 breast cancer cases and 1778 population controls from 10 regions in Spain between 2008 and 2013.
19 The OR for breast cancer for ever having worked night shifts was 1.18 (95% CI: 0.97–1.43), and for
20 permanent and rotating nights, respectively, were 1.19 (95% CI: 0.89–1.60,) and 1.17 (95% CI: 0.91–
21 1.51). Working for 15 or more years, or working a higher number of cumulative night shifts, was
22 suggestive of higher risks, particularly among permanent night shift workers. There was no heterogeneity
23 in the association with night shift work by menopausal status (interaction p-value = 0.642).

24 [The Working Group considered that overall, this was an informative study and clear study design,
25 with a small possibility for recall bias, while also noting the low response rates in this study (below 70%).]

References

- Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, et al. (2016). 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.* 33(6):783–7. <https://doi.org/10.3109/07420528.2016.1167709> PMID:27078711
- Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, et al. (2018). Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol.* 33(4):369–79. <https://doi.org/10.1007/s10654-018-0368-x> PMID:29464445
- Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, et al. (2013). The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer.* 109(9):2472–80. <https://doi.org/10.1038/bjc.2013.544> PMID:24022188
- Fritschi L, Valérie Groß J, Wild U, Heyworth JS, Glass DC, Erren TC (2018). Shift work that involves circadian disruption and breast cancer: a first application of chronobiological theory and the consequent challenges. *Occup Environ Med.* 75(3):231–4. <https://doi.org/10.1136/oemed-2017-104441> PMID:28775132
- Grundty A, Richardson H, Burstyn I, Lohrisch C, SenGupta SK, Lai AS, et al. (2013). Increased risk of breast cancer associated with long-term shift work in Canada. *Occup Environ Med.* 70(12):831–8. <https://doi.org/10.1136/oemed-2013-101482> PMID:23817841
- Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. (2013). Night work and breast cancer: a population-based case-control study in France (the CECILE study). *Int J Cancer.* 132(4):924–31. <https://doi.org/10.1002/ijc.27669> PMID:22689255
- Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Ardanaz E, et al. (2016). Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol.* 31(9):867–78. <https://doi.org/10.1007/s10654-015-0073-y> PMID:26205167
- Pesch B, Harth V, Rabstein S, Baisch C, Schiffermann M, Pallapies D, et al. (2010). Night work and breast cancer - results from the German GENICA study. *Scand J Work Environ Health.* 36(2):134–41. <https://doi.org/10.5271/sjweh.2890> PMID:20039012
- Rabstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, et al.; GENICA Consortium (2013). Night work and breast cancer estrogen receptor status—results from the German GENICA study. *Scand J Work Environ Health.* 39(5):448–55. <https://doi.org/10.5271/sjweh.3360> PMID:23543199